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ORIGINAL RESEARCH ARTICLE

Time-weighted lactate as a predictor of adverse outcome in acute heart failure

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Abstract

Aims The role of dynamic changes in lactate concentrations on prognosis in acute heart failure has been poorly investigated. The aim of this study was to explore the predictive value of 24 h time-weighted lactate (LAC_{TW}) in patients with acute heart failure.

Methods and results Ninety-six consecutive acute heart failure patients presenting to the Emergency Department of San Paolo Hospital, Naples, Italy, were prospectively enrolled. Arterial blood lactate was measured at admission and during the following 24 h at random time intervals. LAC_{TW} was obtained by the sum of the average lactate values among consecutive time points multiplied by the intervals between consecutive time points and dividing the sum by the total time (24 h). The outcome was a composite of need of admission to the intensive care unit, hospitalization duration >7 days, or intra-hospital death. Admission lactate, maximum measured lactate, and LAC_{TW} were collected. Univariate and multivariate Cox regression analysis was applied to determine the hazard ratio (HR) of developing the outcome. Forty-three patients experienced the pre-specified outcome. In sex-adjusted and age-adjusted multivariable analysis, LAC_{TW} predicted the outcome occurrence (HR: 1.51, 95% confidence interval: 1.24, 1.84, $P < 0.001$). Risk stratification analysis based on LAC_{TW} tertiles demonstrated a gradual increase in risk of developing the outcome (HR: 17.32, 95% confidence interval: 2.30, 130.23, $P = 0.006$) for the highest LAC_{TW} tertile.

Conclusions In acute heart failure patients, 24 h LAC_{TW} had a significant independent predictive value for adverse intra-hospital outcome. LAC_{TW} could be a useful index at identifying high-risk patients who may require a more aggressive treatment during hospitalization.

Keywords Time-weighted lactate; Acute heart failure; Prognosis; Hospitalization; Intensive care

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Introduction

Acute heart failure (AHF) is a life-threatening medical condition that represents one of the most frequent causes of admission to the emergency department.[1] Beside its specific aetiology, AHF refers to a rapid onset or worsening of symptoms and/or signs of heart failure (HF), characterized by a mismatch between energy supply, oxygen demand, and consumption.[2] The detection of a high lactate concentration associated with a low blood pH (lactic acidaemia) is useful in describing the severity of such an imbalance.[3] In this regard, lactate concentration does not reflect the severity of heart dysfunction *per se*, but rather, it features the epiphenomenon of the metabolic consequences of the multiorgan insult driven by the acute circulatory decompensation.[4] Several studies have shown the usefulness of lactate concentration as a prognostic marker in acute myocardial infarction and cardiogenic shock.[5,6] Furthermore, it has been recently demonstrated that, in patients with AHF, elevated values of blood lactate on admission are associated with a higher risk of death.[7]

Beside single static lactate measurement upon admission, there is general agreement that in the acute setting,

prolonged high values of blood lactate concentration are associated with a worse prognosis.[8] The persistent increase in blood lactate concentration could be related to increase in its production, decrease in its clearance, or both conditions simultaneously.[9] Furthermore, even minimal fluctuation in lactate concentration above the normal value could reflect subtle phases of hypoperfusion due to a more severe underlying morbid condition, or insufficient response to therapeutic interventions, which could be related to a worse prognosis. In the absence of severe renal and/or hepatic dysfunction, dynamic changes in lactate concentration in the critically ill patient may predict prognosis more accurately than static indices.[10] Several dynamic parameters of lactate homeostasis are potentially measurable, but to date, no comparison has been performed among them. In the setting of cardiorespiratory failure, an earlier lactate clearance could help in the assessment of the metabolic response to therapy and in the identification of patients able to restore the oxygen debt rapidly.[11] Moreover, persistent hyperlactataemia within the first 24 h of hospitalization is a strong predictor of a worse outcome in AHF and is related to higher rates of in-hospital adverse events and 1 year mortality.[12] Recently, time-weighted (TW) average lactate (LAC_{TW}), an index of lactate homeostasis that takes into account the amount of time spent at each lactate concentration in relation to the total period of time observed, demonstrated to be superior to static indices of lactate concentration in outcome prediction in a large heterogeneous population of critically ill patients.[10] Until now, no prospective study has investigated the role of dynamic changes in lactate in predicting outcome in AHF. Here we aim at exploring the predictive value on adverse intra-hospital outcome of the TW average lactate during the first 24 h of hospitalization (LAC_{TW}) in comparison with static and other dynamic parameters of lactate homeostasis in patients admitted to the emergency department for AHF.

Some of the results of this study have been previously reported in abstract form.[13]

Methods

Patients and experimental design

Consecutive patients with AHF referred to the Emergency Department of San Paolo Hospital in Naples, Italy, were prospectively enrolled. All eligible patients were diagnosed with AHF according the following criteria[1]: signs and symptoms of congestion and/or hypoperfusion further confirmed by appropriate additional investigations: brain natriuretic peptide (BNP) values higher than 100 pg/mL when available, bilateral B-lines or comets on lung ultrasound, or typical findings on chest radiography. Exclusion criteria included clinical and laboratory signs of infection, BNP values lower than 100 pg/mL, malignant ventricular arrhythmias, cardiogenic shock, the need for intra-aortic balloon pump implantation, and electrocardiographic diagnosis of acute coronary syndrome upon admission. Moreover, to avoid clinical conditions potentially affecting lactate clearance regardless of HF itself, patients with end-stage renal disease or advanced liver failure were excluded. Patients were treated in accordance with the European Society of Cardiology guidelines.[1] Non-invasive ventilation, including both continuous positive airway pressure and bi-level positive pressure ventilation, was used when needed.[14] Step-down care from the emergency department (hospitalization on an ordinary inpatient ward or direct discharge to home with advice to be followed clinically in an outpatient clinic) was dictated by clinical stabilization. Patients with persistent, significant dyspnoea or haemodynamic instability were transferred to a more intensive ward (intensive care unit or coronary intensive care unit).

The study was performed in accordance with the Declaration of Helsinki on human research and the Good Clinical Practice standards. All participants gave their written informed consent, and the protocol was approved by the local ethics committee 'Campania Centro'.

Study procedures

Upon enrolment, all patients underwent the following study procedures: clinical history collection; physical examination; electrocardiogram; venous blood sample tests including troponin, urea, creatinine, electrolytes, glucose, complete blood count, and liver function tests; and arterial blood gas analyses. Bedside lung ultrasound for detection of bilateral anterior comets and transthoracic echocardiography for the assessment of left ventricular function through the measurement of ejection fraction (Simpson's method) were also performed.

Arterial blood samples were processed and instantly analysed trough a mobile point of care system (Cobas b 123, Roche, Basel, Switzerland). Lactate concentrations were measured at hospital arrival and during the following 24 h at random time intervals. Static [admission lactate (LAC_{START}) and maximum measured lactate (LAC_{MAX})] and dynamic [2 h clearance ($Cl_{2h}LAC$) and TW lactate (LAC_{TW})] indices of lactate homeostasis during hospitalization were recorded and included in the analyses. $Cl_{2h}LAC$ was calculated as the difference between lactate after 2 h and lactate on admission, divided by the lactate on admission and expressed as a percentage. LAC_{TW} was determined by the sum of the mean lactate values among consecutive time points multiplied by the period of time between consecutive time points and then dividing by the total time (24 h).[10]

Outcome definition

Outcome occurrence was defined by a composite of need of admission to a more intensive ward (intensive care unit or coronary unit), hospitalization duration of more than 7 days, and hospital mortality.

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Student's *t*-test for unpaired values was used to compare the means of groups for quantitative variables. Bonferroni correction was applied when indicated. Categorical variables were presented as frequencies and percentages and compared using χ^2 test with Yates correction. Correlations between variables were examined by determining Pearson's coefficient. Univariate and multivariate Cox regression analyses were used to determine the hazard ratio (HR) of experiencing the primary endpoint: composite endpoint was the dependent variable, whereas LAC_{START}, LAC_{MAX}, $Cl_{2h}LAC$, LAC_{TW}, and troponin were included as independent variables. The ability of TW lactate to predict the outcome was assessed by measurement of the area under the receiver operating characteristic (ROC) curve (or *c*-index). The best threshold of the ROC curve was chosen using bootstrap analysis and maximization of the Youden index. A *P*-value <0.05 was considered statistically significant.

All data were collected and entered in an Excel database (Microsoft Office 2016, Redmond, WA, USA), and statistical analyses were performed using SPSS (IBM SPSS Statistics Version 25, SPSS Inc., Chicago, IL).

Results

Characteristics of the study population

Among 121 screened patients, five patients were excluded because of the presence of acute coronary syndrome, one for a diagnosis of cardiogenic shock who required intra-aortic balloon pump, and two for ventricular fibrillation. In addition, 10 patients were excluded for a concomitant diagnosis of bacterial pneumonia, six for end-stage renal disease, and one for advanced liver failure.

Ninety-six patients were included in the final analysis. The characteristics of the study population including co-morbidities and arterial blood gas parameters are presented in *Table 1*.

The study population had a mean age of 76.3 ± 10.4 years, with a slightly higher prevalence of female sex (56%). Concerning the cardiological history, 67.7% of the patients had HF with reduced ejection fraction, 24% of them had HF with mid-range ejection fraction between 40% and 49%, and 8.3% had HF with preserved ejection fraction. The mean left ventricular ejection fraction value measured at bedside echocardiography performed upon admission was 33.3 ± 9.6%. From a clinical standpoint, 21 (21.9%) patients presented with signs of pulmonary congestion, 26 (27.1%) patients with signs of systemic hypoperfusion, and 49 (51%) patients with signs of both congestion and hypoperfusion. Details on chest X-ray findings are described in *Table 1*.

The most frequent suspected cause of AHF was hypertensive HF with reduced ejection fraction (36.4% of cases), followed by hypertensive HF with preserved ejection fraction (18.8%), acute coronary syndrome (18.8%), worsening HF (17.7%), and cardiogenic shock (8.3%).

The mean number of blood gas analyses performed during the first 24 h from admission for each patient was 3.7 ± 0.9. As shown in *Table 1*, blood gas analysis on admission showed low pH (7.2 ± 0.1) and pO_2 (52.3 ± 11.1 mmHg) with high level of pCO_2 (55.1 ± 20.8 mmHg) and lactate (5.3 ± 3 mmol/L). Troponin's mean value on admission was 0.14 ± 0.3 mg/L. BNP values were 777.6 ± 184.9 pg/mL.

Time-weighted lactate and intra-hospital outcome

Forty-three patients experienced the pre-specified primary composite endpoint. In particular, 18 patients were admitted to the intensive care unit for haemodynamic instability or need of tracheal intubation, 14 patients were admitted to the coronary intensive care unit for the development of acute coronary syndrome or end-stage HF, and finally, 11 patients died during the hospitalization.

Table 1 shows a comparison between patients that experienced the outcome and those who did not. Patients who experienced the outcome were significantly older with higher levels of troponin on admission and slightly lower values of both systolic and diastolic blood pressure. No differences were found in terms of self-reported co-morbidities. For indices of lactate homeostasis, we observed a statistically significant difference between the two groups for both static measures (LAC_{START} and LAC_{MAX}) and dynamic changes in lactate concentration ($Cl_{2h}LAC$ and LAC_{TW}) (*Table 1*).

As shown in *Table 2*, on multivariate Cox regression analysis adjusted for age and sex, LAC_{TW} was significant for developing the primary outcome (HR: 1.51, 95% confidence interval: 1.24, 1.84, $P < 0.001$). This was also observed for the other indices of lactate homeostasis (*Table 2*).

Risk stratification analysis based on LAC_{TW} tertiles demonstrated a gradual increase in risk of developing the primary endpoint across LAC_{TW} tertiles, with an HR of 17.32 (2.30, 130.23, $P = 0.006$) for the highest LAC_{TW} tertile (*Table 3* and *Figure 1*). In particular, no death was observed among the patients belonging to the first TW lactate tertile, two deaths

Table 1 Anthropometric characteristics and laboratory and clinical parameters of the whole study population divided according to outcome occurrence

Characteristics	Study population (N = 96)	No outcome (n = 53)	Yes outcome (n = 43)	P-value[a]
Sex (female), *n* (%)	54 (56)	27 (50.9)	27 (62.8)	ns
Age (years)	76.3 ± 10.4	74.1 ± 8.9	78.8 ± 11.5	0.02
Systolic blood pressure (mmHg)	171.8 ± 37.3	179.2 ± 35.6	162.4 ± 37.4	0.02
Diastolic blood pressure (mmHg)	96.4 ± 18.7	101.8 ± 16.4	90.1 ± 20.1	0.002
BNP (pg/mL)	777.6 ± 184.9	800 ± 188.3	749.4 ± 178.8	ns
Creatinine (mg/dL)	1.32 ± 0.68	1.36 ± 0.79	1.26 ± 0.52	ns
LVEF (%)	33.3 ± 9.6	34.3 ± 9.0	32.2 ± 10.2	ns
Troponin (mg/L)	0.14 ± 0.3	0.08 ± 0.1	0.22 ± 0.4	0.01
Respiratory rate (b.p.m.)	27.5 ± 5.5	26.7 ± 5.5	28.8 ± 5.3	ns
Clinical presentation				
Congestion, *n* (%)	21 (21.9)	16 (30.2)	5 (11.6)	0.016
Hypoperfusion, *n* (%)	26 (27.1)	9 (17)	17 (39.6)	
Congestion and hypoperfusion, *n* (%)	49 (51)	28 (52.8)	21 (48.8)	
Chest X-ray findings				
Cardiomegaly, *n* (%)	62 (64.6)	33 (62.3)	29 (67.4)	ns
Pulmonary congestion, *n* (%)	78 (81.2)	43 (81.1)	35 (81.4)	ns
Pleural effusion, *n* (%)	51 (53.1)	32 (60.4)	19 (44.2)	ns
Number of chest X-ray findings: 0/1/2/3, *n* (%)	2 (2.1)/22 (22.9)/47 (49)/25 (26)	2 (3.8)/10 (18.9)/25 (47.1)/16 (30.2)	0 (0)/12 (27.8)/22 (51.1)/9 (20.1)	ns
Co-morbidities				
Ischaemic heart disease, *n* (%)	74 (77.1)	40 (75.5)	34 (79.1)	ns
Atrial fibrillation, *n* (%)	22 (22.9)	12 (22.6)	10 (23.2)	ns
Valvulopathy, *n* (%)	11 (11.4)	7 (13.2)	4 (9.3)	ns
Hypertension, *n* (%)	85 (88.5)	47 (88.7)	38 (88.4)	ns
Type 2 diabetes, *n* (%)	45 (48.4)	26 (49.1)	20 (46.5)	ns
Chronic kidney disease, *n* (%)	40 (41.7)	23 (43.4)	17 (39.5)	ns
COPD, *n* (%)	16 (16.7)	10 (18.9)	6 (13.9)	ns
HFrEF, *n* (%)	65 (67.7)	35 (66.1)	30 (69.8)	ns
HFmrEF, *n* (%)	23 (24)	13 (24.5)	10 (23.2)	ns
HFpEF, *n* (%)	8 (8.3)	5 (9.4)	3 (7.0)	ns
ICD, *n* (%)	18 (18.7)	13 (24.5)	5 (11.6)	ns
Suspected cause of AHF				
Acute coronary syndrome, *n* (%)	18 (18.8)	0 (0)	18 (41.9)	<0.001
Cardiogenic shock, *n* (%)	8 (8.3)	1 (1.9)	7 (16.3)	
Worsening HF, *n* (%)	17 (17.7)	9 (17)	8 (18.5)	
Hypertensive HFpEF, *n* (%)	18 (18.8)	15 (28.3)	3 (7)	
Hypertensive HFrEF, *n* (%)	35 (36.4)	28 (52.8)	7 (16.3)	
Arterial blood gas parameters				
pH	7.2 ± 0.1	7.23 ± 0.15	7.19 ± 0.15	ns
pCO_2 (mmHg)	55.1 ± 20.8	57.3 ± 22.1	54.2 ± 22.5	ns
pO_2 (mmHg)	52.3 ± 11.1	52.9 ± 11.3	51.4 ± 10.9	ns
LAC_{START} (mmol/L)	5.3 ± 3.0	4.3 ± 2.6	6.5 ± 2.9	<0.001
LAC_{MAX} (mmol/L)	5.4 ± 2.9	4.4 ± 2.6	6.6 ± 2.9	<0.001
$Cl_{2h}LAC$ (%)	28.1 ± 30.8	37.2 ± 31.7	14.4 ± 25.0	<0.0001
LAC_{TW}	2.5 ± 1.6	1.59 ± 0.7	3.7 ± 1.6	<0.00001

AHF, acute heart failure; BNP, brain natriuretic peptide; $Cl_{2h}LAC$, 2 h clearance of lactate; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implanted cardioverter defibrillator; LAC_{MAX}, maximum lactate; LAC_{START}, lactate at admission; LAC_{TW}, time-weighted lactate; LVEF, left ventricular ejection fraction; ns, not significant.
Data expressed as mean ± standard deviation or frequencies and percentage as appropriate.
[a]*P*-value refers to the comparison between patients who experienced the outcome and patients who did not.

occurred among the patients belonging to the second TW lactate tertile, and nine deaths among the ones in the third TW lactate tertile.

Receiver operating characteristic curve analysis demonstrated an excellent ability of LAC_{TW} in predicting the outcome, with an area under the ROC curve of 0.928 (standard error 0.024, $P < 0.0001$, 95% confidence interval: 0.880, 0.976) (*Figure 2*). Using bootstrap analysis and maximization of the Youden index, the best cut-off was 2.2 (with a sensibility of 88% and a specificity of 83%).

Discussion

To our knowledge, this is the first prospective study that demonstrates that high overall levels of lactate during the first 24 h of hospitalization strongly predict the prognosis in patients presenting with AHF. We also show that LAC_{TW} has a greater predictive value than the other static and dynamic indices of lactate homeostasis. Moreover, we demonstrated that each tertile of LAC_{TW} identifies a different risk category in AHF patients.

Table 2 Cox regression analysis of primary composite outcome for lactate on admission, maximum measured lactate, and time-weighted lactate

	Univariate analysis		Multivariate analysis[a]	
Parameter	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
LAC_{START}	1.12 (1.01, 1.25)	0.033	1.16 (1.02, 1.31)	0.024
LAC_{MAX}	1.13 (1.01, 1.26)	0.031	1.16 (1.02, 1.32)	0.022
$Cl_{2h}LAC$	0.99 (0.98, 1.01)	ns	0.99 (0.98, 1.00)	ns
LAC_{TW}	1.40 (1.17, 1.68)	<0.001	1.51 (1.24, 1.84)	<0.001
Abnormal chest X-ray finding				
Cardiomegaly	1.06 (0.53, 2.11)	ns	1.04 (0.51, 2.10)	ns
Pulmonary congestion	1.31 (0.51, 3.41)	ns	1.31 (0.50, 3.43)	ns
Pleural effusion	0.78 (0.40, 1.53)	ns	0.72 (0.36, 1.45)	ns
BNP	1.00 (0.99, 1.00)	ns	1.00 (0.99, 1.00)	ns
Clinical presentation (congestion and/or hypoperfusion)				
Only congestion	Reference	—	Reference	—
Only hypoperfusion	1.78 (0.63, 4.97)	ns	1.78 (0.63, 5.07)	ns
Congestion and hypoperfusion	1.71 (0.63, 4.67)	ns	1.70 (0.62, 4.66)	ns
Troponin	5.52 (1.85, 16.42)	0.002	5.78 (1.91, 17.47)	0.002
LVEF	0.97 (0.93, 1.01)	ns	0.96 (0.93, 1.00)	ns
Systolic blood pressure	0.99 (0.98, 1.00)	ns	0.99 (0.98, 1.00)	ns
Diastolic blood pressure	0.99 (0.97, 1.01)	ns	0.99 (0.97, 1.01)	ns
Creatinine	0.59 (0.32, 1.07)	ns	0.58 (0.31, 1.08)	ns
Age	1.00 (0.97, 1.04)	ns	1.01 (0.97, 1.05)	ns
pH	0.98 (0.17, 5.53)	ns	0.99 (0.18, 5.58)	ns
pCO_2	1.00 (0.98, 1.01)	ns	0.98 (0.98, 1.01)	ns
pO_2	0.99 (0.95, 1.03)	ns	0.99 (0.95, 1.03)	ns

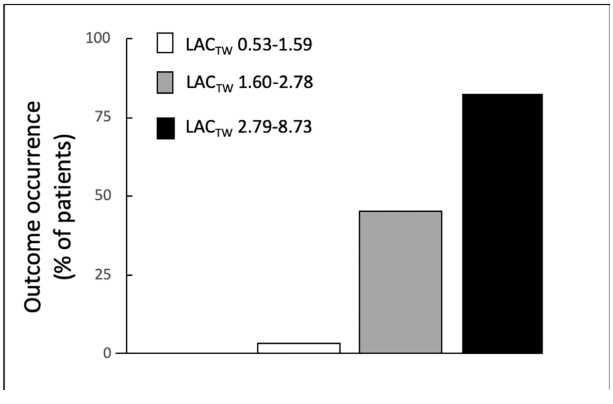
BNP, brain natriuretic peptide; CI, confidence interval; $Cl_{2h}LAC$, 2 h clearance of lactate; HR, hazard ratio; LAC_{MAX}, maximum lactate; LAC_{START}, lactate at admission; LAC_{TW}, time-weighted lactate; LVEF, left ventricular ejection fraction; ns, not significant.
[a]Adjusted for age and sex.

Table 3 Cox regression analysis of primary composite outcome according to time-weighted lactate LAC_{TW} tertile

	Univariate analysis		Multivariate analysis[a]	
Tertile (range)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
T1 (0.53–1.59)	Reference	—	Reference	—
T2 (1.60–2.78)	9.39 (1.21, 72.54)	0.032	9.20 (1.19, 71.28)	0.034
T3 (2.79–8.73)	17.32 (2.30, 130.23)	0.006	21.05 (2.73, 162.19)	0.003

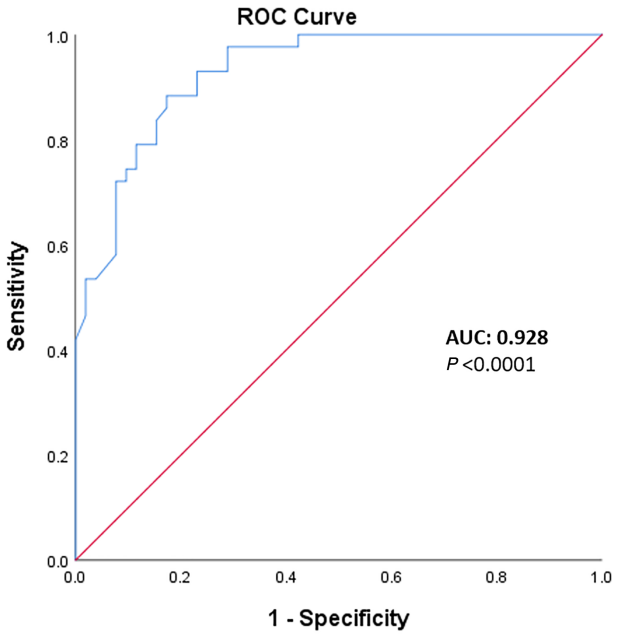
CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age and sex.

Figure 1 Relationship between adverse outcome occurrence and each tertile of time-weighted lactate (LAC_{TW}).



Several studies reported the prognostic role of lactate concentrations in critically ill patients, including those with septic shock[15] and trauma,[16] after cardiac arrest[17] or major surgery.[18] While in chronic HF the prevalence of increased levels of lactataemia is low and does not correlate with arterio-venous oxygen difference or cardiac index,[19] elevated blood lactate levels upon admission are associated with high mortality in AHF patients.[7] Lactate does not reflect the severity of heart dysfunction *per se* but rather reveals the metabolic consequences and the severity of the insult driven by the sudden HF.[4] Indeed, there are several different pathways that could potentially contribute to increase lactate levels during AHF: the insufficient supply of blood and oxygen to the peripheral tissues,[4] the neurohormonal activation,[20] and diaphragm fatigue.[21] Among these mechanisms, only

Figure 2 Receiving operating characteristic (ROC) curves of time-weighted lactate.*P*-values refer to the comparison of the area under the ROC curve (AUC) vs. 0.50 (i.e. no discrimination, red line).



the proportion of hyperlactataemia due to the activation of anaerobic metabolism following tissue hypoperfusion is directly related to the severity of the disease and to mortality rates.[22]

Some studies[23] have already underlined that serial evaluation of lactate concentrations may be more helpful than a single value, and dynamic changes of lactataemia may represent a useful monitoring tool of response to treatment. In this regard, a Cl_{2h}LAC demonstrated to be a good marker to guide the therapeutic approach in acute cardiorespiratory insufficiency.[11] Nevertheless, some concerns exist regarding the significance of lactate clearance and the best time to repeat lactate measurement.[23] In fact, during the first phases of hospitalization, blood lactate concentrations could have complex fluctuations above the normal value and persistent hyperlactataemia could identify further period of hypoperfusion due to a more severe underlying morbid condition or insufficient response to therapeutic interventions.[24]

Among the dynamic indices, we demonstrate that LAC_{TW} is more useful in predicting outcome than Cl_{2h}LAC in patients admitted with AHF. In this study, LAC_{TW} was significantly associated with mortality outcome as well as prolonged length of stay, therefore identifying patients with significant potential morbidity.

There are many advantages in the use of LAC_{TW}; this index describes not only the magnitude but also the duration and trend over time of lactate homeostasis. As demonstrated in this study, each tertile of LAC_{TW} had an increased risk of developing the primary endpoint in comparison with the lowest LAC_{TW} tertile. Furthermore, in this present study, a LAC_{TW} of more than 1.6 identified patients who had the worst outcome, as compared with subjects with a LAC_{TW} less than 1.6. Patients with LAC_{TW} more than 2.79 had an especially poor outcome. The prognostic significance of LAC_{TW} persisted after adjustment for age and sex. Thus, our results suggest that LAC_{TW} is a powerful predictor of patient adverse outcomes in AHF. Interestingly, according to Nichol *et al.*, relatively mild hyperlactataemia in AHF patients is independently associated with the negative outcome, such as in the middle tertile in our study.[24] Finally, to our knowledge, this is the first study in which LAC_{TW} was determined prospectively in a pure cohort of AHF patients.

Some limitations need to be accounted for in this study. First, the actual cause of increase in circulating lactate levels is still a matter of debate and it does not necessarily reflect organ hypoperfusion. Lactate is a complex, and highly volatile marker, with large fluctuations that are not only related to perfusion and anaerobic metabolism, but rather a complex and dynamic interplay between the sum of production and elimination in important organs such as muscle, heart, kidneys, and liver.[25] Furthermore, this was a single-centre experience with a relatively small sample size. The present study did not compare the different treatments and different aetiologies of AHF, and thus, optimal treatment of these patients remains elusive and requires further investigation. We chose a composite endpoint of intra-hospital morbidity and mortality; therefore, data on intermediate-term or long-term mortality are lacking. Finally, the clinical staff was not blinded to individual lactate measurements; nevertheless, lactate measurements did not influence *per se* the clinical management: all the clinical decisions were taken according to the current recommendations, taking into account the whole clinical picture and the results of the diagnostic work-up.

In conclusion, in patients presenting with AHF, LAC_{TW} concentrations collected during the first 24 h after emergency department admission had a significant independent predictive value of adverse outcomes. LAC_{TW} could be a useful index in identifying patients at higher risk of adverse outcomes, who may require more aggressive therapy during hospitalization. Further studies are needed in order to validate this index in the assessment of patients hospitalized for AHF.

Conflict of interest

None declared.

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Author contributions

G.B., V.M., G.G., F.G.N., C.G.T., and F.S. contributed in the conception and design of the study; G.B., A.P., G.P., E.A., C. S., and G.G. in the collection of data; G.B., V.M., and N.D. in the analysis and interpretation of data; G.B., V.M., and N.D. in drafting of the article; and G.B., V.M., N.D., A.P., G.P., E. A., C.S., G.G., F.G.N., C.G.T., and F.S. in the revision and final approval of the manuscript.

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