

Alactic Base Excess, New Potential Marker Associated for Circulatory Stress Due to Hemodialysis, a Pilot Study

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Abstract

Introduction: Circulatory stress increases mortality in patients with chronic kidney disease in renal replacement therapy by hemodialysis, the measurement of central venous saturation has been proposed as a useful tool for diagnosis but with limitations. We wanted to evaluate a new marker, the lactic base excess, to be applied in all types of hemodialysis patients to help diagnose this clinical condition.

Methodology: An observational, analytical, prospective and longitudinal study was carried out in hemodialysis of the Instituto Mexicano del Seguro Social, in León, Guanajuato from May 2020 to June 2021 by determining the lactic base excess. The association of lactic base excess as a marker of circulatory stress in hemodialysis was proposed as a primary end point and mortality at 12 months was evaluated as a secondary end point.

Results: An inverse association was found between the lactic base excess with the initial pH ($r = -0.303$, $p < 0.05$) and the final lactate ($r = -0.297$, $p < 0.05$), in addition to bicarbonate ($r = 0.593$, $p < 0.05$) and central venous saturation variability ($r = 0.304$, $p < 0.05$). In the analysis by subgroups, both lower tertiles had a higher risk of presenting the adverse event (HR= 0.817, [95% CI 0.21 to 3.05], $p = 0.763$). No association of mortality was found with the first (HR= 0.95, [95% CI= 0.73 to 1.2], $p = 0.687$) or final determination (HR= 1, [95% CI= 0.758 to 1.3], $p = 0.99$).

Discussion: In this study we found that the lactic base excess proposed to diagnostic different types of acidosis is capable of identifying small changes related to circulatory stress, regardless of the chronicity of kidney failure, hemodynamic status or hemoglobin concentration, but not related to mortality.

Conclusions: Lactic base excess is potentially useful to evaluate circulatory stress in conjunction with other tissue hypoperfusion markers, however it would be necessary to expand the sample size and introduce therapeutic variables to determine its clinical impact.

Background

The patient with chronic kidney disease has a high mortality (1), especially in patients with renal replacement therapy through hemodialysis (2), both due to the presence of multiple comorbidities and the high cardiovascular risk that define each of them, as well as variables typical of dialysis therapy such as ultrafiltrate volume and intradialysis hypotension(3). Circulatory stress associated with renal replacement therapy by hemodialysis was proposed as a result of the imbalance between the supply and consumption of oxygen in the tissues caused by the hemodialysis cycle; however, its pathophysiological mechanism has not been fully elucidated (4–6). Central venous saturation measurement has been the only marker studied with good predictive values for circulatory stress (7–9). The limitations of the use of central venous saturation are that its evaluation requires a correctly placed central vascular access in the vena cava and that the patient does not have significant anemia, which is uncommon in hemodialysis patients.

Just like in sepsis, circulatory stress from hemodialysis could cause damage to the microcirculation, activation of anaerobic cellular metabolism and release of free radicals or pro-inflammatory cytokines, resulting in increased lactate production (10, 11). In multiple clinical trials of critical ill patients, has been proposed the usefulness of lactate as an indirect marker of tissue hypoperfusion, being a therapeutic target for resuscitation with good results(12–14). In the patient with chronic kidney disease, a state of hyperlactatemia and chronic acidosis is recognized due to renal dysfunction for the elimination of non-measurable strong anions, so the evaluation of circulatory stress with these biochemical determinants is difficult. In 2019, Gattinoni et al. (15) in the only study published on alactic base excess, they propose this marker to discriminate between metabolic acidosis secondary to lactate or other fixed acids such as phosphates and sulfates, with results dependent on renal function. We study the behavior of lactate, acidosis and alactic base excess in patients with chronic kidney disease, undergoing hemodialysis therapy to assess whether this biochemical determinant can be used as a marker of circulatory stress in hemodialysis, being the first trial of its kind Worldwide.

Methods

Study design and approval

An observational, analytical, prospective and longitudinal study was carried out in hemodialysis of the Instituto Mexicano del Seguro Social, in León, Guanajuato from May 2020 to June 2021. The study was carried out with the approval of the local committee for health research 1001 (COFEPRIS 17 CI 11 020 146, CONNBOIETICA 11 CEI 0032018080) and the regulations of the 1964 Helsinki declaration; Prior to the inclusion of the study, an informed consent signature was requested for all participants.

Population

Adult patients in need of renal replacement therapy by hemodialysis were included, without discriminating between the presence of comorbid diseases or indications for renal replacement therapy. A central venous blood sample was taken through the vascular access for hemodialysis, from which a determination of lactate, pH, base deficit, bicarbonate and central venous saturation was obtained. The exclusion criterion was the diagnosis of respiratory failure due to COVID 19 and the elimination criteria included patients who could not complete a hemodialysis session without being possible to reprogram it.

Procedure for sampling.

Before being included in the study, the procedure to be carried out was explained and a request for informed consent was provided to all participants. Venous blood was taken from the central vascular access for hemodialysis, prior to the start of the session, at 90 minutes and at the end of the procedure. The lactate determination was carried out by a colorimetric test (Vitros 5600 from Ortho Clinical Diagnostics) and the analysis of gases in venous blood was carried out in the gasometer (GEM Premier 3000), later the determination of alactic base excess was obtained with the formula proposed by Gattinoni et al. (fifteen):

Alactic base excess (mmol/L) = standard base excess (mmol/L) + lactate (mmol/L)

Variables evaluated

During the procedure, demographic information was obtained from the participants, clinical data included blood pressure, heart rate, oxygen saturation, respiratory rate, temperature, weight, height and body surface area, indications for hemodialysis like ultrafiltrate volume, time of therapy, blood flow, dialysate flow, and filter size.

Statistical analysis

The results of the baseline characteristics of the study population are described in proportions for the categorical variables, means and standard deviation for continuous variables. As a primary end point, the association of alactic base excess with circulatory stress in hemodialysis was proposed, for which a hypothesis test was performed using Pearson's correlation, with an alpha value of 0.05, for the general analysis and by subgroups, which were classified into tertiles according to the central venous saturation level at the start of hemodialysis. To evaluate the variables by subgroups, a mean difference test (Student's T test) was performed, grouping the population into the upper tertile and the lower two tertiles in order to preserve the same proportion of patients. As a secondary end point, all-cause mortality was evaluated with a 12-month follow-up which was analyzed using the COX correlation, expressing results in Kaplan meier graphs. The statistical analysis was performed with the IBM SPSS Statics v23.0 Statistical Software.

Results

Baseline characteristics of the study population.

We enrolled 176 patients in hemodialysis of the Instituto Mexicano del Seguro Social from June to December 2020, in which it was not possible to determine central venous saturation in 96 of them secondary to vascular access other than the central one; 18 patients did not agree to participate in the study and 7 more were excluded due to additional peritoneal dialysis. Of the total of 55 patients who met the inclusion criteria, 5 patients from whom complete laboratory data could not be obtained were eliminated. Correlation analysis was performed on 50 of the remaining participants. For the mortality analysis, 11 participants were lost to follow-up.

In the demographic variables, a higher proportion of male users was found, with a mean age of 49 ± 16.7 years. 84% were on subsequent hemodialysis and only 10% presented an emergency for dialysis. The proportion of comorbid diseases and the indications for hemodialysis are exemplified in Table 1.

Table 1. Initial clinical characteristics of the general study population.

Variable	50 N (%)	Mean	SD	Minimum	Maximum
Demographic characteristics					
Age		49	± 16.7	24	79
males	27 (54)				
Comorbid:					
Diabetes	24 (48)				
Hypertension	43 (86)				
COPD	5 (10)				
Heart disease	5 (10)				
Kidney post-transplantation	4 (8)				
Indications for hemodialysis					
First-time hemodialysis	8 (16)				
Blood flow		319	± 36	250	400
Dialysate flow		566	± 49	500	800
Filter					
170	14 (28)				
190	20 (40)				
210	15 (30)				
Ultrafiltrate volume		1744	± 1025	300	3500
Dialysis urgency	5 (10)				
Clinical features					
Hemodynamic stability	43 (86)				
Intradialysis hypotension	10 (20)				
Systolic blood pressure initial		136	± 27.48	79	225
Systolic blood pressure 90 min		128	± 23.36	82	188
Systolic blood pressure final		131	± 23.03	87	178
APACHE II		12	± 4.6	4	32
Abbreviation SD= standard deviation, COPD: Chronic Obstructive Pulmonary Disease.					

Association between hemoglobin and lactic base excess

The mean hemoglobin level in our population was 9.7 ± 2.28 (95% CI 8.9 to 10.45) and the alactic base excess initial and final of hemodialysis are shown in Table 2. Pearson's analysis did not show a significant association with the determination of alactic base excess. And the statistical analysis by subgroups was evident the difference in hemoglobin means between the tertiles ($p = <0.05$, 95% CI 1.27 (0.07 to 2.47) table 3.

Table 2. General laboratory determinants

Variable	Mean (SD)	IC 95%
Initial Alactic base excess	-1.43 ± 4.09	-2.59 a -0.27
Final Alactic base excess	3.53 ± 3.27	2.6 a 4.4
Δ alactic base excess	0.45 ± 8.51	-1.96 a 2.87
Lactate Inicial	1.53 ± 0.69	1.34 a 1.73
Lactate Final	1.24 ± 0.48	1.1 a 1.37
Δ lactate	0.11 ± 0.34	0.01 a 0.21
Initial Central Venous Saturation	76.96 ± 9.32	74.31 a 79.61
Final Central Venous Saturation	74.84 ± 9.50	72.14 a 77.54
Δ Central Venous Saturation	0.23 ± 0.11	-0.00 a 0.05
Hemoglobin	9.70 ± 2.28	8.9 a 10.45
Initial pH	7.38 ± 0.06	7.37 a 7.41
Final pH	7.44 ± 0.05	7.42 a 7.46
Cretinin	9.49 ± 4.61	8.09 a 11.12
Initial base deficit	-2.32 ± 0.63	-3.61 a .1.03
Final base deficit	2.93 ± 0.50	1.90 a 3.96
Initial Bicarbonate	22.89 ± 0.45	21.96 a 23.82
Final Bicarbonate	26.58 ± 0.36	25.84 a 27.32
Abbreviation SD (standard deviation), IC (confidence interval), Δ Delta (variability)		

Association between pH, bicarbonate and alactic base excess.

The pH and bicarbonate quantity were evaluated to obtain global information on the acid-base equilibrium state in the study participants, whose means are shown in table 2. A significant difference in pH was found between the tertiles, being less in both lower tertiles of central venous saturation (Table 3), however, the state of metabolic acidosis was not reflected in the pH level in most of the participants. On

the other hand, the initial bicarbonate levels showed variability between patients, finding a negative association with the final lactate ($r = -0.326$, $p = <0.05$), but it was not possible to determine the cause responsible for lower levels of bicarbonate in each participant. The Pearson test showed an inverse association of the initial pH with the final lactate levels ($r = -0.303$, $p = <0.05$), association with the initial bicarbonate ($r = 0.593$, $p = <0.05$) and both values of alactic base excess (initial $r = 0.481$ and final $r = 0.548$, $p = <0.05$) (Figure 1a, b, c). Final pH and alactic base excess also had an association ($r = 0.382$, $p = <0.05$) (Figure 1d, e).

Table 3. Baseline clinical and laboratory characteristics by subgroups.

Variable	General Mean (SD)		Upper tertile Mean (SD)		Lower tertile Mean (SD)		Mean difference (IC 95%)	P value
	(50 n)		(28 n)		(22 n)			
Hemoglobin	9.7	± 2.28	9.14	± 2.6	10.41	± 1.57		0.038*
Creatinin	9.49	± 4.6	10.5	± 5.38	8.5	± 3.03	-2.31 (-5.27 a 0.64)	0.121
pH								
Initial	7.38	± 0.05	7.4	± 0.05	7.36	± 0.04		0.011*
Final	7.41	± 0.05	7.44	± 0.05	7.42	± 0.05	-0.02 (-0.05 a 0.007)	0.143
Bicarbonate								
Initial	22.4	± 2.95	22.57	± 3.3	22.18	± 2.48	-0.39 (-2.09 a 1.31)	0.64
Final	31.3	± 26.11	26.34	± 2.99	25.83	± 1.84	-0.51 (-1.97 a 0.95)	0.48
Alactic base excess								
Initial	-1.43	± 4.09	-1.62	± 4.52	-2.91	± 3.55	-1.28 (-3.65 a 1.07)	0.279
Final	3.53	± 3.27	3.61	± 3.81	2.13	± 2.61	-1.48 (-3.4 a 0.42)	0.125
Δ alactic base excess	0.45	± 8.51	0.86	± 7.92	3.14	± 5.60		0.452*
Lactate								
Initial	1.53	± 0.69	1.40	± 0.73	1.71	± 0.59		0.035*
Final	1.24	± 0.48	1.19	± 0.52	1.31	± 0.41	0.12 (-0.13 a 0.39)	0.340
Δ lactate	0.11	± 0.34	0.07	± 0.36	0.17	± 0.30		0.452*
Central venous saturation								
Initial	76.96	±	83.36	± 6.62	68.82	± 4.68	-14.53	< 0.05

		9.32					(-17.89 a -11.18)	
Final	74.84	± 9.50	79.36	± 6.50	69.09	± 9.71	-10.26 (-15.15 a -15.37)	< 0.05
Δ Central Venous Saturation	0.23	± 0.11	0.04	± 0.09	0.00	± 0.12	10.04 (-0.11 a 0.01)	0.131
Systolic blood pressure								
Initial	136	± 27.48	140.46	±28.46	130.82	±25.81	-9.64 (-25.30 a 6.01)	0.221
Final	131	± 23.03	133.75	±21.17	127.50	±25.26	-6.25 (-19.45 a 6.95)	0.346
Indications for hemodialysis								
Blood flow	319.4	± 36.05	312.14	± 34.67	328.64	± 36.42	16.49 (-3.15 a 36.80)	0.109
Dialysate flow	566	± 59.28	550	± 50.91	586.36	± 63.96	36.36 (3.71 a 69.01)	0.112
Ultrafiltrate volume	1744	± 1025	1721	±1056.67	2000	± 844.02	.318 (-276.73 a 833.87)	0.140
APACHE II	12.28	± 4.66	11.61	± 5.36	13.14	± 3.53		0.232*
Abbreviation SD (standard deviation), IC (confidence interval), Δ Delta (variability) * U Mann- Whitney								

Association between lactate and alactic base excess.

The mean lactate in our study population did not exceed the abnormal values, resulting in initial lactate 1.53 ± 0.69 and final lactate of 1.24 ± 0.48 , in which statistically significant difference was also found, with a higher value in both lower tertiles (1.71 ± 0.59 , $p= 0.035$). The baseline lactate values also showed an inverse relationship with the final bicarbonate ($r= -2.84$, $p= <0.05$) and the final lactate with both bicarbonate values (initial $r= -0.326$ and final $r= -0.439$, $p= <0.05$). The variability (delta) of lactate with respect to dialysis therapy was evaluated without obtaining a significant difference in the results.

The initial alactic base excess values were found to be negative (-1.43 ± 4.09) as well as positive at the end of therapy (table 2), this variable had no significant difference between the subgroups. The association study of the alactic base excess yielded significant results between the initial pH, the initial

bicarbonate ($r= 0.973$, $p <0.05$) and at the end of hemodialysis ($r= 0.660$, $p <0.05$), as well as the association of the alactic based excess with central venous saturation variability ($r= 0.394$, $p= <0.05$) (Figure 1f) and final lactate ($r= -0.297$, $p = <0.05$).

Association between central venous saturation and alactic base excess.

Although the central venous saturation levels were significant for the study and showed a significant difference between the subgroups, no significant association was found, except for the variability (delta) of central venous saturation ($r= 0.304$, $p= <0.05$).

Survival analysis

As a secondary end point, we evaluated all-cause mortality over a 12-month period, finding mortality in 5% of the participants. In the analysis by subgroups, those classified in both lower tertiles limited by central venous saturation level $\leq 74\%$ had a greater risk of presenting the adverse event (HR= 0.817, 95% CI= 0.21 to 3.05, $p=0.763$) in which, the significance was clinical (figure 2). No significant relationship between mortality was found with the determination of initial alactic base excess (HR=0.95, 95% CI= 0.73 to 1.2, $p=0.687$) and final alactic base excess (HR= 1, 95% CI=0.758 a 1.3, $p=0.99$) (figure 3).

Discussion

In the search for a simple and effective marker for the timely recognition of circulatory stress due to hemodialysis, other authors have proposed the measurement of indirect markers of tissue hypoperfusion such as central venous saturation and lactate (7,8). The utility of central venous saturation was evaluated in the pilot trial by Harrison et al. (7) in 2014, with the analysis of 18 patients on hemodialysis, obtaining baseline central venous saturation values of $63.5 \pm 13\%$ and final of $56.4 \pm 8\%$ ($p= 0.046$) which was inversely associated with the ultrafiltrate volume, proposed as one of the main mediators of circulatory stress. In the study by Cordtz et al.(9) the initial ScvO₂ was $52.2 \pm 6.7\%$ in patients prone to hypotension and $49.7 \pm 6.9\%$ in patients resistant to hypotension, however it only had 20 patients. Later in 2016 Chan et al. (8) takes up the research with the evaluation of the central venous saturation of 232 patients on hemodialysis and the risk of mortality dependent on the levels of intradialysis central venous saturation, in which higher mortality was associated with lower levels of saturation.

Conversely, the determination of lactate has been evaluated in multiple trials of patients in a critical environment (16,17), especially as a therapeutic objective of resuscitation (18-20), but its usefulness in the hemodialysis patient is unknown.

One of the limitations for the use of central venous saturation and lactate in the hemodialysis patient is the baseline state of metabolic acidosis and chronic hyperlactatemia due to renal dysfunction to achieve physiological balance, for which we wanted to evaluate the usefulness of the determination of alactic base excess first proposed by Gattinoni et al. (15) in 2019, in which the excess of alactic base, is a useful marker to differentiate a state of acidosis secondary to lactate from that of other types of acidosis due to

non-measurable strong ions, in this study lactate levels were independently elevated of the central venous saturation level and were directly proportional to renal function, more negative values were associated with the development of acute kidney injury. As proposed by these authors, in our study we found more negative levels of alactic base excess prior to the start of hemodialysis, being related to a state of acidosis secondary to non-measurable organic ions other than lactate, which means of the applicability of this marker, not only in the context of acute kidney injury.

The levels of excess alactic base were not related to the concentration of creatinine, bicarbonate or lactate, but they were related to the determination of pH, despite the fact that the mean pH in the population of our study was found within normality, which enhances the ability of excess alactic base to identify the origin of the acid base state. It should be noted that there was a significant difference between the tertiles, finding a lower pH in those patients with lower central venous saturation of 74%, so the utility of the alactic base excess could be even greater in patients with central venous saturation levels lower than this range. After hemodialysis therapy and due to its compensatory effect, the levels of base excess became very positive in both tertiles.

Another limitation of the applicability of central venous saturation in previous studies (7,8) is the dependence on hemoglobin concentration, losing its prognostic value in patients with anemia (11), one of the strengths of our study is that we consider essential the inclusion of all patients regardless of their hemoglobin levels, because the real clinical environment is that the patient with kidney disease has anemia, often severe (21). In our study we found that the determination of alactic base excess is not related to hemoglobin concentration but is related to central venous saturation, especially with saturation delta, so that together they could be used for the diagnosis of circulatory stress even in patients with severe anemia.

Another application that we found for alactic base excess is its ability to identify circulatory stress early in hemodialysis when the patient develops minimal changes in pH or bicarbonate, despite the severity of the metabolic acidosis with which hemodialysis therapy has been initiated. Hemodialysis, since it was not related to the concentration of these laboratory determinants, so it could be applied for the early detection of circulatory compromise in hemodialysis.

Limitations:

To avoid making a type II error, the sample size should be improved, obtaining the same variables, but this was not possible due to the epidemiological contingency due to COVID 19 and it was considered unethical to expose patients to infection by going to the hospital instance. In our study, no interventions were performed in the hemodialysis settings, because we cannot issue a recommendation on which indications would be best for each type of patient. Due to our methodological process, we cannot draw conclusions about the risk of mortality using this marker.

Strengths:

In our study, we consider all patients regardless of hemodynamic status, urgency for dialysis or baseline hemoglobin levels in order to find a marker applicable in all types of population and is feasible in daily clinical practice.

Conclusion

The determination of alactic base excess can favor the diagnosis of circulatory stress by hemodialysis together with other markers such as central venous saturation, even in patients with anemia or severe acidosis.

Declarations

* Declaration of conflict of interest: There is no conflict of interest on the part of any of the authors.

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Author contributions

Luevanos-Aguilera A: Principal investigator, research protocol design, mastermind, manuscript writer.

Lopez-Diaz J: academic advisor, physiological and scientific foundations of the nephropathy patient.

Sosa-Ramos J: Protocol director, methodological advisor, analysis and interpretation of results.

Pereyra-Nobara T: methodological advisor, analysis and interpretation of results, manuscript reviewer.

References

1. Valdez-Ortiz R, et al. (2018). Mortality in Patients With Chronic Renal Disease Without Health Insurance in Mexico: Opportunities for a National Renal Health Policy. *Kidney international reports*, **3**(5), 1171–1182. <https://doi.org/10.1016/j.ekir.2018.06.004>
2. Neovius M, Jacobson S.H, Eriksson J.K, Elinder C-G, Hylander B. (2014). Mortality in chronic kidney disease and renal replacement therapy: a population-based cohort study. *BMJ Open*, **4**: e004251. [doi:10.1136/bmjopen-2013-004251](https://doi.org/10.1136/bmjopen-2013-004251)
3. Burton JO, Jefferies HJ, Selby NM, McIntyre CW, (2009) Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol*, **4**:914–920. [doi: 10.2215/CJN.03900808](https://doi.org/10.2215/CJN.03900808).

4. McIntyre C.W, (2010) Recurrent Circulatory Stress: The Dark Side of Dialysis. *Seminars in Dialysis*, **Vol. 23, N.5** pp. 449–45. [doi: 10.1111/j.1525-139X.2010.00782.x](https://doi.org/10.1111/j.1525-139X.2010.00782.x).
5. McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker C.S, Camici PG, (2008) Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 2008;**3**:19–26. [doi: 10.2215/CJN.03170707](https://doi.org/10.2215/CJN.03170707).
6. Chirakarnjanakorn S, Navaneethan SD, Francis GS, Tang WH, (2017) Cardiovascular impact in patients undergoing maintenance hemodialysis: Clinical management considerations. *Int J Cardiol*. 2017 Apr 1;**232**:12-23. [doi: 10.1016/j.ijcard.2017.01.015](https://doi.org/10.1016/j.ijcard.2017.01.015).
7. Harrison LE, Selby NM, McIntyre CW (2014) Central venous oxygen saturation: a potential new marker for circulatory stress in haemodialysis patients? *Nephron Clin Pract*, **128**(1-2):57-60. [doi: 10.1159/000362557](https://doi.org/10.1159/000362557).
8. Chan L, Zhang H, Meyring-Wösten A, Campos I, Fuertringer D, Thijssen S, Kotanko P. (2017) Intradialytic Central Venous Oxygen Saturation is Associated with Clinical Outcomes in Hemodialysis Patients. *Sci Rep*, Aug **17**;7(1):8581. [doi: 10.1038/s41598-017-09233-x](https://doi.org/10.1038/s41598-017-09233-x).
9. Cordtz J, Olde B, Solem K, Ladefoged S. D, (2008) Central venous oxygen saturation and thoracic admittance during dialysis: new approaches to hemodynamic monitoring. *Hemodial Int* **12**, 369–377 DOI: 10.1111/j.1542-4758.2008.00283.x
10. Alexandre A, Pinto L, Silva E (2018) Monitoring Tissue Perfusion in Shock, From physiology to the bedside. Springer Nature, Ed 1st 2018; 93-121.
11. Pinsky M.R, Payen D (2005), Measurement of oxygen derived variables and cardiac performance: Functional hemodynamic monitoring Update in intensive care and emergency medicine Ed. Springer; 222- 281
12. Jansen T.C, Van Bommel J, Bakker J. (2009) Blood lactate monitoring in critically ill patients: a systematic health technology assessment. *Crit Care Med*, **37**(10):2827–39 DOI: 10.1097/CCM.0b013e3181a98899
13. Jones A. E, Shapiro N. I, Trzeciak S, Arnold R. C, Claremont H. A, Kline J. A, Emergency Medicine Shock Research Network (EMShockNet) Investigators (2010). Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*, **303**(8), 739–746. <https://doi.org/10.1001/jama.2010.158>
14. Levy MM, Evans LE, Rhodes A, The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med*. 2018 Jun;**44**(6):925-928. [doi: 10.1007/s00134-018-5085-0](https://doi.org/10.1007/s00134-018-5085-0).
15. Gattinoni L, et al. (2019) Understanding Lactatemia in Human Sepsis. Potential Impact for Early Management. *Am J Respir Crit Care Med*. Sep **1**;200(5):582-589. [doi: 10.1164/rccm.201812-2342OC](https://doi.org/10.1164/rccm.201812-2342OC).
16. Rello J, Valenzuela SF, Rodriguez RM, Moyano S. (2017) Sepsis: A review of advances in Management. *Adv Ther*, **34**(11): p. 2393-2411. DOI: 10.1007/s12325-017-0622-8
17. Labib A. Sepsis Care Pathway (2019). *Qatar Med J*. Nov **7**;2019(2):4. [doi: 10.5339/qmj.2019.qccc.4](https://doi.org/10.5339/qmj.2019.qccc.4).

18. Pan J, Peng M, Liao C, Hu X, Wang A, Li X. (2019) Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: A meta-analysis. *Medicine (Baltimore)*. Feb;**98**(8):e14453. doi: [10.1097/MD.00000000000014453](https://doi.org/10.1097/MD.00000000000014453).
19. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, The ANDROMEDA SHOCK Investigators and the Latin America Intensive Care Network (LIVEN), et al. (2019) Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA*. 2019 Feb 19;321(7):654-664. doi: [10.1001/jama.2019.0071](https://doi.org/10.1001/jama.2019.0071).
20. Ryoo SM, et al. (2018) Lactate Level Versus Lactate Clearance for Predicting Mortality in Patients With Septic Shock Defined by Sepsis-3. *Crit Care Med*. 2018 Jun;**46**(6):e489-e495. doi: [10.1097/CCM.0000000000003030](https://doi.org/10.1097/CCM.0000000000003030).
21. Cases A, Egocheaga MI, Tranche S, Pallarés V, Ojeda R, Górriz JL, & Portolés JM (2018). *Anemia of chronic kidney disease: Protocol of study, management and referral to Nephrology*. *Nefrología*, **38**(1), 8–12. doi:[10.1016/j.nefro.2018.01.007](https://doi.org/10.1016/j.nefro.2018.01.007)

Figures

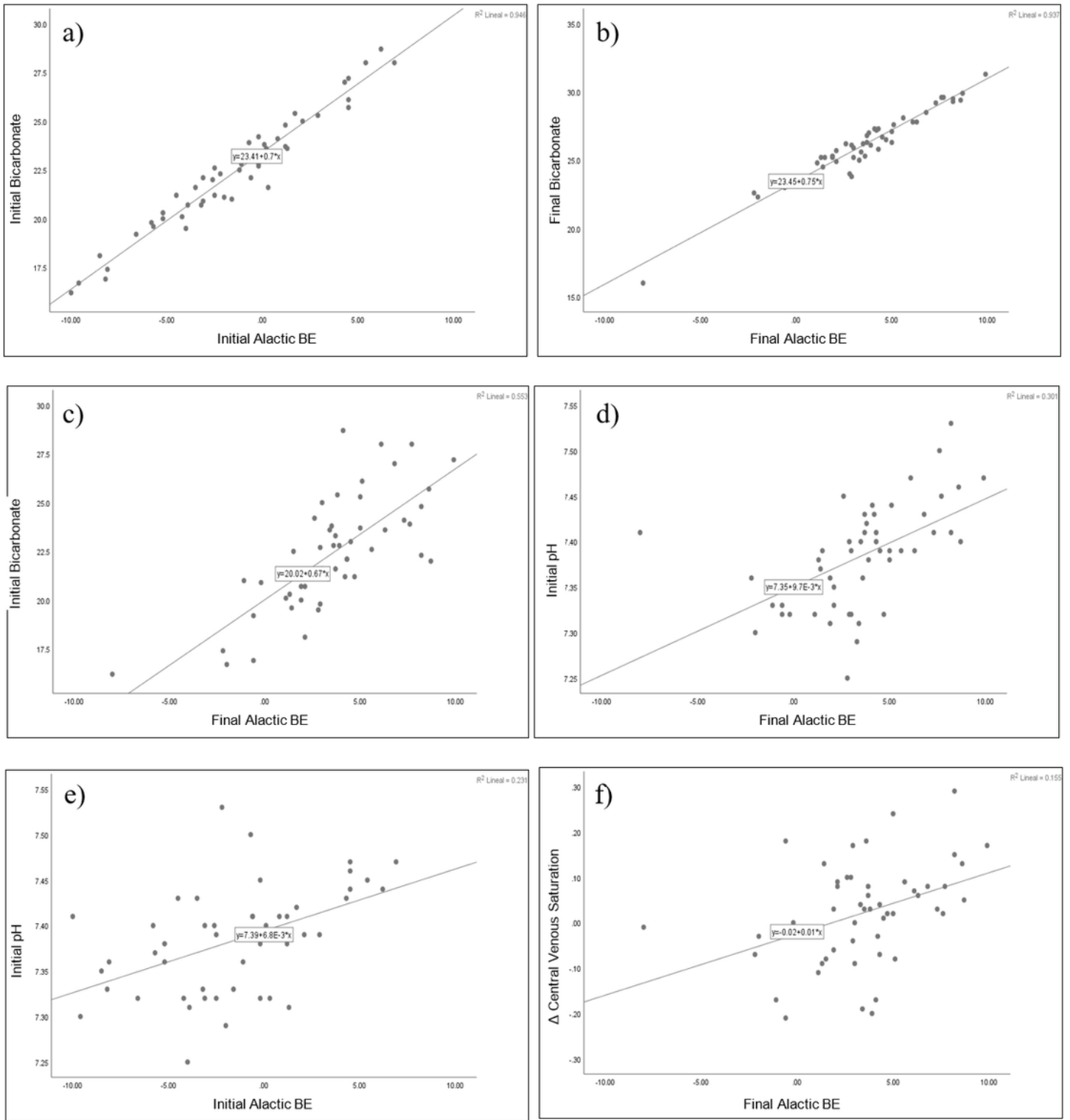


Figure 1

Dispersion graphs for association between variables: a) initial alactic base excess- initial bicarbonate, b) final alactic base excess- final bicarbonate, c) final alactic base excess- initial bicarbonate, d) final alactic base excess- initial pH, e) initial alactic base excess- initial pH, f) final alactic base excess- central venous saturation delta.

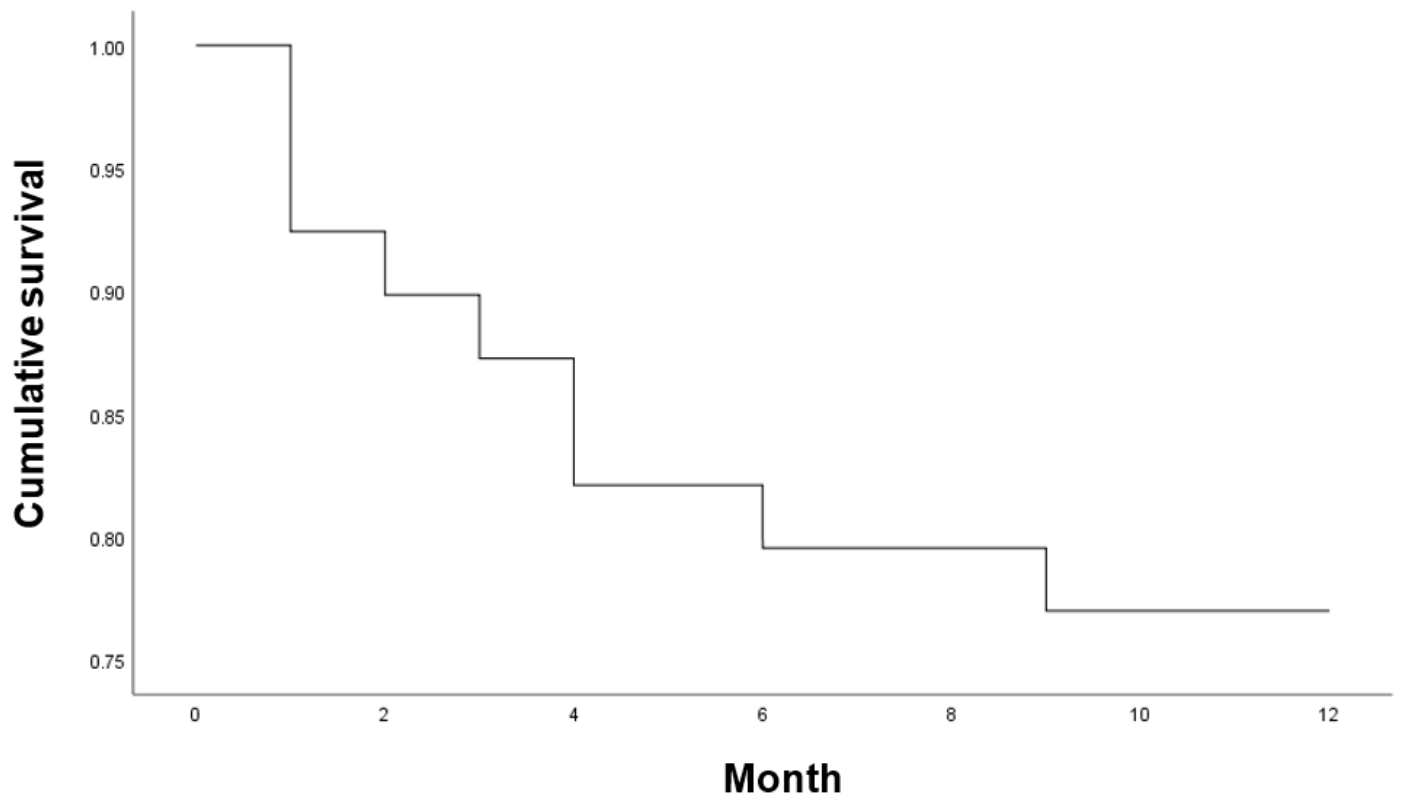


Figure 2

Kaplan meier survival curve all population. Kaplan meier survival curve based on follow-up of all patients included in the study over a 12-month period, the survival function of mean alactic base excess it shows.

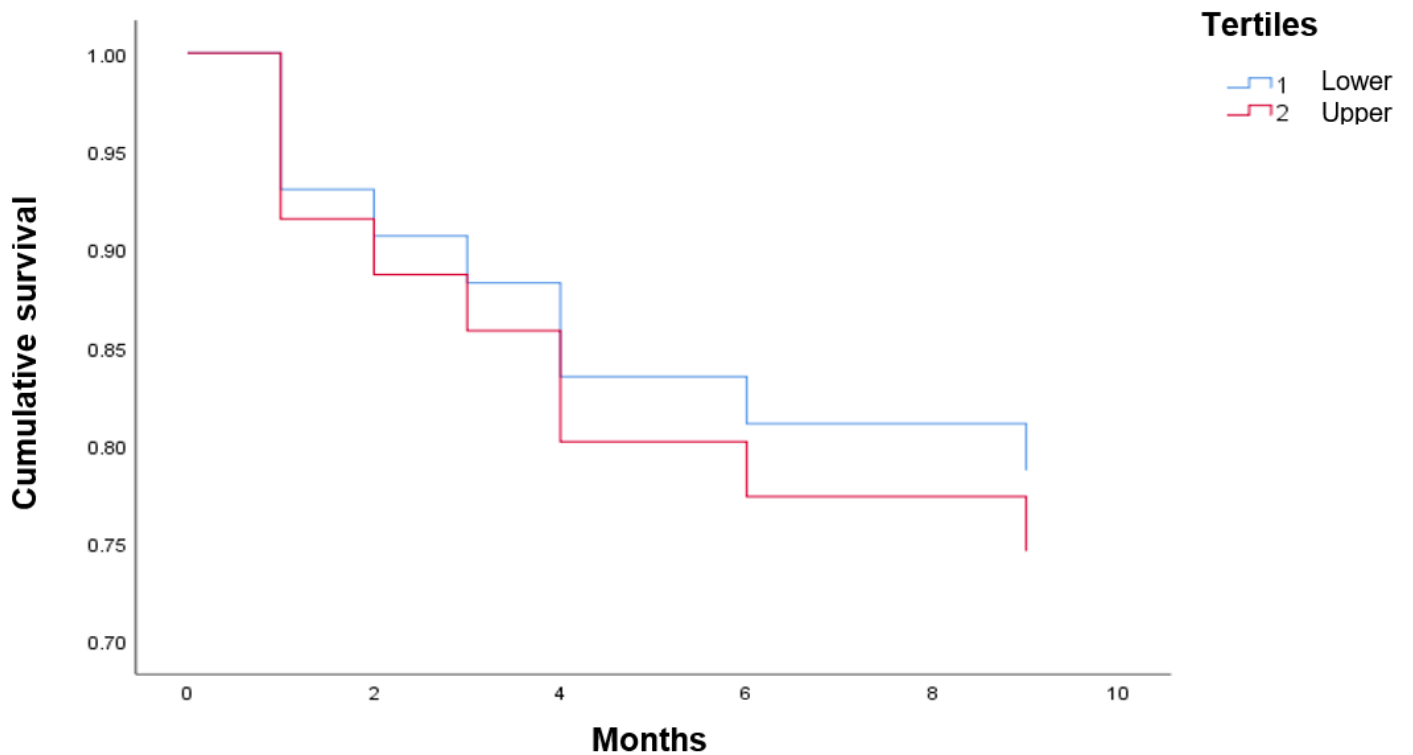


Figure 3

Kaplan meier curve for survival at 12 months of follow-up by subgroups. Kaplan-Meier estimates for survival probabilities in the lower two tertiles (blue) and the upper tertile (red), respectively. Median follow up for all population was 12 months, the risk of presenting the adverse event was higher in both lower tertiles (HR = 0.817, [IC 95% 0.21 a 3.05], p= 0.763).