Prognostic Significance of Blood Lactate and Lactate Clearance in Trauma Patients

Marie-Alix Régnier, M.D.,* Mathieu Raux, M.D., Ph.D.,† Yannick Le Manach, M.D.,‡ Yves Asencio, M.D. M.Sc,* Johann Gaillard, M.D.,* Catherine Devilliers, Pharm. D.,§ Olivier Langeron, M.D., Ph.D.,‖ Bruno Riou, M.D., Ph.D.#

ABSTRACT

Background: Lactate has been shown to be a prognostic biomarker in trauma. Although lactate clearance has already been proposed as an intermediate endpoint in randomized trials, its precise role in trauma patients remains to be determined.

Methods: Blood lactate levels and lactate clearance (LC) were calculated at admission and 2 and 4 h later in trauma patients. The association of initial blood lactate level and lactate clearance with mortality was tested using receiver-operating characteristics curve, logistic regression using triage scores, Trauma Related Injury Severity Score as a reference standard, and reclassification method.

Results: The authors evaluated 586 trauma patients (mean age 38 ± 16 yr, 84% blunt and 16% penetrating, mortality 13%). Blood lactate levels at admission were elevated in 327 (56%) patients. The lactate clearance should be calculated within the first 2 h after admission as $LC_{0-2\,h}$ was correlated with $LC_{0-4\,h}$ (R^2 = 0.55, P < 0.001) but not with $LC_{2-4\,h}$ (R^2 = 0.04, not significant). The lactate clearance provides additional predictive information to initial blood lactate levels and triage scores and the reference score. This additional information may be summarized using a categorical approach (*i.e.*, less than or equal to −20 %/h) in contrast to initial blood lactate. The results were comparable in patients with high (5 mM/l or more) initial blood lactate.

Conclusions: Early (0–2 h) lactate clearance is an important and independent prognostic variable that should probably be incorporated in future decision schemes for the resuscitation of trauma patients.

What We Already Know about This Topic

- Lactate, as a marker for tissue hypoperfusion, is an established biomarker for morbidity and mortality in patients with sepsis and trauma, but has limited clinical application

What This Article Tells Us That Is New

- In a study of 586 trauma patients, lactate clearance within 2 h of admission provided independent and significant prognostic information beyond a single value of lactate and other prognostic factors

TRAUMA is the third overall cause of death and the first before 40 yr of age, and is responsible for handicaps and high costs.[1] Most deaths (80%) occurred within 48 h and hemorrhage continues to be one of the two leading causes of death.[2] The main principles of trauma patient care are to recognize and treat hemorrhage early, limit the consequences of shock, and diagnose traumatic lesions. Hypoperfusion is still difficult to diagnose and remains so and favors adverse inflammatory and immunologic effects, coagulopathy, development of infection and organ failures, and finally precipitates to late mortality.[3]

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Jones AE: Lactate clearance in the acutely traumatized patient. ANESTHESIOLOGY 2012; 117:1162–4.

* Fellow, † Associate Professor, ‡ Staff Anesthesiologist, Department of Anesthesiology and Critical Care, § Staff Biologist, Department of Biology, Centre Hospitalo-Universitaire (CHU) Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France. ‖ Professor, Department of Anesthesiology and Critical Care, # Professor and Chairman, Department of Emergeny Medicine and Surgery, Université Pierre et Marie-Curie-Paris 6, Centre Hospitalo-Universitaire (CHU) Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France.

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Address correspondence to Dr. Raux: Département d'Anesthésie-Réanimation, CHU Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. mathieu.raux@psl.aphp.fr. Anesthesiology 2012; 117:1276-88

Shock is responsible for inadequate oxygen delivery, resulting in tissue hypoxia, anaerobic metabolism, and lactate production. Lactate is a diagnostic and prognostic biomarker in sepsis and trauma.[4–6] Even in patients with normal vital signs, blood lactate may be useful in differentiating major and minor injuries in trauma.[7] Lactic acidosis may persist despite control of hemorrhage, reflecting flow-demand mismatch or loss of appropriate capillary density as a consequence of shock, vasoconstriction, or other dysfunctional responses.[3] Lactate clearance (LC) has recently emerged as an important concept in septic shock, as part of the quantitative resuscitation concept that aims to reach predefined physiological goals to be achieved within the first hours.[8] Several studies have shown that poor lactate clearance is associated with increased mortality during septic shock[9–11] and after cardiac surgery.[12] Jones *et al.*[13] have shown that management to normalize lactate clearance as compared with management to normalize central venous oxygen saturation was not inferior in decreasing mortality in patients with septic shock. However, in septic patients, lactate clearance was usually measured over a prolonged time period (from 6 to 24 h), which may not be appropriate in trauma.

In trauma patients, there is a need for a rapid assessment of the resuscitation and of the diagnosis of occult hypoperfusion during its early phase. Moreover, there is also a need for both an early prognostic biomarker that may identify patients at high risk of death and a surrogate endpoint as mortality may not be appropriate to test therapeutic hypothesis, at least during the early phase of drug development.[14] Lactate clearance has already been used as a primary endpoint in a randomized trial assessing hemoglobin solutions in trauma patients.[15] Although this endpoint was a result of a consensus expert panel and might be considered as logical, no previous study supports this choice. Abramson *et al.*[11] observed that mortality was significantly lower in patients whose lactate normalized within 24 h as compared with others, but this variable does not really fit with the concept of early detection of hypoperfusion.

The purpose of this observational study was to understand the significance of blood lactate and lactate clearance in trauma patients. We aimed to answer the following questions: (1) Are blood lactate and lactate clearance independent and additional predictors of death, as compared with available scores? (2) How do these two variables evolve during the first hours of resuscitation? (3) Do these variables predict other clinically relevant endpoints, besides mortality?[16]

Materials and Methods

This prospective observational cohort study was conducted in a French academic trauma center (corresponding to a level-1 trauma center) from January 2010 to October 2011. Institutional approval was obtained from Comité pour la Protection des Personnes Pitié-Salpêtrière (Paris, France); waived written informed consent was authorized because the study was solely observational.

All these trauma patients were cared for by a mobile intensive care unit (ICU) because the severity of trauma was considered as high enough to warrant medical prehospital care after the alert had been received. The French mobile ICU system has been described elsewhere and its main characteristic is the presence of an emergency physician in each ambulance.[17] The onsite triage was based on the clinical assessment of the trauma patient. For each patient, the following data were recorded by a physician during the prehospital phase: age, sex, trauma characteristics, initial systolic arterial blood pressure, heart rate, respiratory rate, Glasgow coma scale, peripheral oxygen saturation, care provided during the prehospital phase, systolic arterial blood pressure, and heart rate at the time of arrival in the hospital. The total prehospital time was defined as the time interval between arrival of the emergency team on scene and its arrival in the hospital. The following scores were determined: Abbreviated Injury Scale,[18] Injury Severity Score (ISS),[19] Revised Trauma Score (RTS),[20] and Mechanism Glasgow Arterial Pressure and Mechanism (MGAP) score.[21] Then, the probability of survival was calculated using the Trauma Related Injury Severity Score (TRISS),[22] using updated regression coefficients.[23] Length of stay in the ICU and in the hospital were recorded. Survival was defined as survival within 30 days after trauma. Because hepatic trauma may interfere with LC processes, we identified patients with severe hepatic trauma (any hepatic trauma lesion coded with Abbreviated Injury Scale ≥2).

The RTS and MGAP scores were used as the scores that predict mortality and are available immediately and thus used in the prehospital phase triage. RTS is the most widely used score at least with its triage version[24,25] and MGAP has been recently shown as a more specific and easier-to-use score than RTS.[21] TRISS was used as the reference standard as it incorporates definite information about trauma lesions.[22] Although the TRISS score is calculated only when all information had been obtained concerning trauma lesions, it should be pointed out that all variables used to calculate it concerns phenomenon that occurred before hospital admission (age, type of trauma, RTS, ISS).

Endpoints

The primary endpoint was death. However, we also assessed the ability to predict the following secondary points: (1) early death, defined as death within 48 h,[2] and this was a *post hoc* hypothesis; (2) severe trauma defined by an ISS more than 15; (3) ICU length of stay more than 2 days and/or death within 30 days; (4) massive hemorrhage defined as blood transfusion more than 6 packed red cell units within 24 h and/or death from hemorrhagic shock; and (5) the requirement for an emergency procedure defined as the need for emergency thoracic drainage, emergency surgery, emergency embolization, or emergency transfusion (within the first hour after admission), as previously reported.[16]

Last, we considered the following subgroup analyses: (1) patients with high (>5 mM/l) initial blood lactate level; and (2) normotensive patients defined as those with arterial blood pressure >90 mmHg during the prehospital phase and at arrival in the hospital and without prehospital

administration of catecholamines. In the first subgroup of patients with high initial blood lactate level, we tested the hypothesis that lactate clearance provides some additional prognostic information in patients with the most severe lactic acidosis. In the second subgroup of patients, we tested the hypothesis that initial blood lactate and lactate clearance provides some additional information in normotensive patients, suggesting that these variables might detect occult hypoperfusion.[26]

Blood Lactate Measurements

At the admission to the trauma center, blood lactate concentration (Cobas Integra 400+; Roche Diagnostics, Meylan, France) was measured. The coefficients of variation of the measurement of blood lactate were 3.8% (at 1.15 mM/l) and 2.6% (at 4.5 mM/l) in our laboratory. We analyzed 16 previous studies describing the role of initial blood lactate in trauma patients and observed that the threshold for abnormal values was 2.2 mM\l (mean and median extremes 2.0 and 2.5 mM/l).[3,5–7,27–38] Thus, the normal range was considered as 2.2 mM/l or lower. Measurements were performed again 2 and 4 h after admission, whenever possible.

The lactate clearance was defined by the equation:

Lactate clearance = ([$Lactate_{initial}$ – $Lactate_{delayed}$]/$Lactate_{initial}$) × 100 × $Delay^{-1}$ (expressed as %/h)

The lactate clearance was calculated at the following time periods: 0–2 h ($LC_{0–2\ h}$), 0–4 h ($LC_{0–4\ h}$), and 2–4 h ($LC_{2–4\ h}$). The following *a priori* stratification of initial blood lactate was defined: normal values, 2.3–2.9, 3.0–4.9, 5.0–9.9, and 10 mM/l or higher. The following *a priori* stratification of lactate clearance was defined: −20 or lower, −19 to −11, −10 to 0, 1–9, 10–19, and 20% or higher per h. Because many trauma patients may have normal initial blood lactate values and it would make no sense to attempt to clear a value that is already normal,[13] we also calculated the $LC_{corrected}$ by assuming an arbitrary value (−30%/h, *i.e.*, the lowest value observed) in the following patients: (1) those having two consecutive normal lactate levels at 0 and 2 h; (2) those having two consecutive normal lactate levels (whatever the timing of the second one within the first 24 h);[13] and (3) those having an initial normal blood lactate without further blood lactate assessment but without further evidence of any deterioration as demonstrated by early discharge from the ICU within 24 h (patients with "extrapolated" values in fig. 1). Because this implies imputing multiple values, we performed a sensitivity analysis excluding these patients. Lastly, we *a posteriori* stratified the $LC_{corrected}$ as −20% or lower or more than −20 %/h.

Statistical Analyses

Data are mean ± SD or median (25–75 interquartile) for non-Gaussian variables (D'Agostino–Pearson Omnibus test). Comparison of two means was performed using the unpaired Student *t* test, comparison of two medians was performed using the Mann–Whitney test, and comparison of proportions was performed using Fisher exact method. Correlation between two variables was assessed using linear regression analysis. We used multivariate analysis of variance to compare blood lactate levels in patients with or without severe hepatic trauma, taking TRISS value as a covariate.

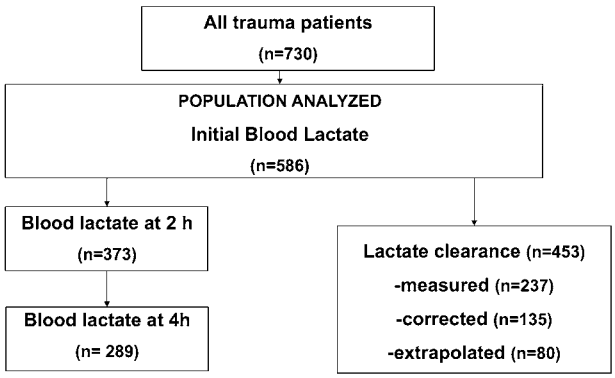

Fig. 1. Flow chart of the study. Lactate clearance (corresponding to $LC_{corrected}$, see Methods) was corrected (a value of −30%/h given) in patients with two normal blood lactates levels as it makes no sense to attempt to clear a value that is already normal. A value of −30%/h was extrapolated in patients who lacked blood lactate data at 2 h but with two consecutive normal blood lactate levels within 24 h after admission and in patients who had normal initial blood lactate levels and left the intensive care unit within 24 h.

Multiple logistic regressions were performed to assess the role of blood lactate and lactate clearance. We included initial blood lactate, lactate clearance, and either RTS, or MGAP, or TRISS scores. Discrimination of the final models was assessed by measurement of the area under the receiver-operating characteristic (ROC) curve (AUC or c-index) and their calibration by the Hosmer–Lemeshow statistic. Odds ratios and their 95% CI were calculated. Furthermore, an internal validation was also performed using 10-fold crossvalidation.[39] This method randomly assigns patients to 10 equally sized partitions. Subsequently, nine partitions were used as learning sets and one as a testing set. This operation was repeated 10 times until each partition was used as a testing set. Results of this internal validation are expressed as the difference of c-index between, in the entire population and in the cross-validated population (optimism).

Comparison of two AUCs was performed using a paired nonparametric technique.[40] The best threshold of an ROC curve was chosen as that which maximizes the Youden index (sensitivity + specificity − 1), as previously described.[41] ROC curves were obtained by averaging 1,000 populations bootstrapped (sampling with replacement) from the original study population. This method limits the impact of outliers and allows the provision of more robust presentations. CIs of the average ROC curve were depicted using box plots. Presented AUC and best threshold were the average of the 1,000 population, as previously reported.[42] As the comparison of ROC curves is recognized to be potentially insensitive, we assessed reclassification by calculating net reclassification improvement[43]

Table 1. Comparison of Patients Who Survived or Not

	Alive (n = 508)	Dead (n = 78)	*P* Value
Men	386 (76%)	52 (67%)	0.09
Women	122 (24%)	26 (33%)	
Age, yr	37 ± 15	45 ± 18	<0.001
Type of trauma			
Blunt	323 (82%)	69 (89%)	0.32
Penetrating	85 (17%)	9 (11%)	
Mechanism			
Fall	112 (22%)	35 (45%)	<0.001
Road crash	285 (56%)	32 (41%)	0.01
Gunshot	16 (3%)	7 (9%)	0.02
Stab wound	65 (13%)	2 (3%)	0.006
Other	25 (5%)	2 (3%)	0.56
Localization of trauma			
Head/neck	179 (35%)	65 (83%)	<0.001
Face	171 (34)	29 (37)	0.61
Thorax	262 (52%)	56 (78%)	<0.001
Abdomen/pelvis	152 (30%)	30 (38%)	0.15
Limb	340 (70%)	47 (60%)	0.25
Prehospital phase			
Systolic arterial blood pressure, mmHg	120 ± 25	92 ± 61	<0.001
Heart rate, beats/min	94 ± 22	72 ± 48	<0.001
Glasgow coma score	15 (13–15)	3 (3–7)	<0.001
Peripheral oxygen saturation, %	99 (96–100)	97 (85–98)	<0.001
Cardiac arrest	2 (0.4%)	22 (28%)	<0.001
Catecholamine administration	34 (7%)	30 (38%)	<0.001
Mechanical ventilation	130 (26%)	49 (63%)	<0.001
RTS	7.84 (7.11–7.84)	4.09 (2.01–5.97)	<0.001
MGAP	22 (20–24)	12 (10–17)	<0.001
Hospital phase			
Systolic arterial blood pressure, mmHg	123 ± 28	89 ± 56	<0.001
Heart rate, beats/min	89 ± 23	83 ± 42	0.08
Hemoglobin, g/dl	12.5 ± 2.4	9.8 ± 2.8	<0.001
Packed erythrocytes transfusion	122 (24%)	46 (59%)	<0.001
Packed erythrocytes transfusion (units)*	4 (2–11)	10 (6–18)	<0.001
Massive hemorrhage	52 (10%)	38 (49%)	<0.001
Emergency procedure	108 (21%)	33 (42%)	<0.001
Catecholamine administration	137 (27%)	72 (92%)	<0.001
Mechanical ventilation	211 (41%)	77 (99%)	<0.001
ISS	16 (9–26)	36 (26–43)	<0.001
ISS > 15	259 (51%)	73 (94%)	<0.001
TRISS	0.98 (0.95–0.99)	0.29 (0.05–0.62)	<0.001
Duration of hospitalization, days	12 (4–34)	2 (1–3)	<0.001
Duration of ICU, days	1 (1–8)	2 (1–3)	0.10
Duration of ICU stay > 2 d and/or death	168 (33%)	78 (100%)	—

n = 586. Data are mean ± SD, median (25–75 interquartile), or number (percentages).

* Values concern only transfused patients.

ICU = intensive care unit; ISS = Injury Severity Score; MGAP = Mechanism, Glasgow, Age, arterial Pressure score; RTS = Revised trauma score; TRISS = Trauma Related Injury Severity Score.

and providing graphical reclassification. All *P* values were two-sided, and *P* value less than 0.05 was considered significant. NCSS 6.0 software (Statistical Solutions Ltd, Corke, Ireland) and R 2.14 software** (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

**www.cran.r-project.org. Accessed February 2, 2012.

Table 2. Comparison of Blood Lactate and Lactate Clearance (LC) Levels in Patients with Complete Measurements (0, 2, and 4 h after admission)

	Normal Initial Blood Lactate Level (n = 121)	Elevated Initial Blood Lactate Level (n = 160)	All Patients (n = 281)
Blood lactate 0 h, mM/l	1.5 ± 0.5	5.0 ± 3.3*	3.5 ± 3.1
Blood lactate 2 h, mM/l	1.6 ± 0.9	4.2 ± 3.0*	3.1 ± 2.7
Blood lactate 4 h, mM/l	1.8 ± 1.1	4.1 ± 3.0*	3.1 ± 2.6
$LC_{0-2\,h}$, %/h	0 (–10;10)	–7 (–17;–1)*	–4 (–15;6)
$LC_{0-4\,h}$, %/h	6 (–8;25)	–10 (–22;1)*	–4 (–16;13)
$LC_{2-4\,h}$, %/h	1 (–3;8)	–1 (–5;3)*,†	0 (–4;5)
$LC_{corrected}$, %/h	–30 (–30;–30)	–7 (–17;1)*	–17 (–30;–2)

Data are mean ± SD or median (25;75 interquartiles). n = 281.

* *P* value less than 0.05 *vs.* patients with normal initial blood lactate. † *P* value less than 0.05 *vs.* $LC_{0-2\,h}$. For blood lactate levels, repeated measure two way analysis of variance showed that time was not significant (*P* = 0.58) in contrast to group effect (*P* value less than 0.001) and interaction effect (*P* value less than 0.001).

$LC_{corrected}$ = lactate clearance; see text for explanation.

Results

During the study period, 730 trauma patients were admitted to our trauma center. Blood lactate was measured at the admission in 586 patients (80%). Therefore, data from 586 patients were retained for analysis. In the excluded patient population (mean age 36 ± 16 yr), mortality rate was 8%. The main characteristics of our trauma population are shown in table 1. The percentage of missing values was 3.2% but no important data were lacking in this population. Severe hepatic contusion was diagnosed in 68 patients (12%). The total prehospital time was 65 (50–85) min.

Blood Lactate and LC

Blood lactate level at admission was elevated in 327 patients (56%). Blood lactate levels were significantly higher in patients with severe hepatic contusion (4.7 ± 3.8 *vs.* 3.2 ± 1.1 mM/l, *P* < 0.001) but these patients had more severe traumatic lesions (ISS: 29 [20–41] *vs.* 17 [9–27], *P* < 0.001) and a poorer prognosis (TRISS 0.94 [0.59–0.98] *vs.* 0.98 [0.89–0.99], *P* < 0.001). When adjustment on TRISS was performed using multivariate analysis of variance, there was no significant difference in blood lactate levels (*F* ratio 0.69, *P* = 0.41) between patients with and without hepatic contusion. There was no significant correlation between initial blood lactate levels and total prehospital time (R^2 = 0.004, *P* = 0.20).

Blood lactate level was measured again, 2 h after admission in 373 patients (64%), and 4 h after admission in 289 patients (49%). There were 281 patients (40%) with complete (0, 2, and 4 h) blood lactate measurements (table 2). The evolution of mean blood lactate level was significantly different in patients with normal *versus* abnormal initial blood lactate level (interaction: *P* < 0.001) (table 2). Therefore, the meaning of lactate clearance may not be the same in patients with

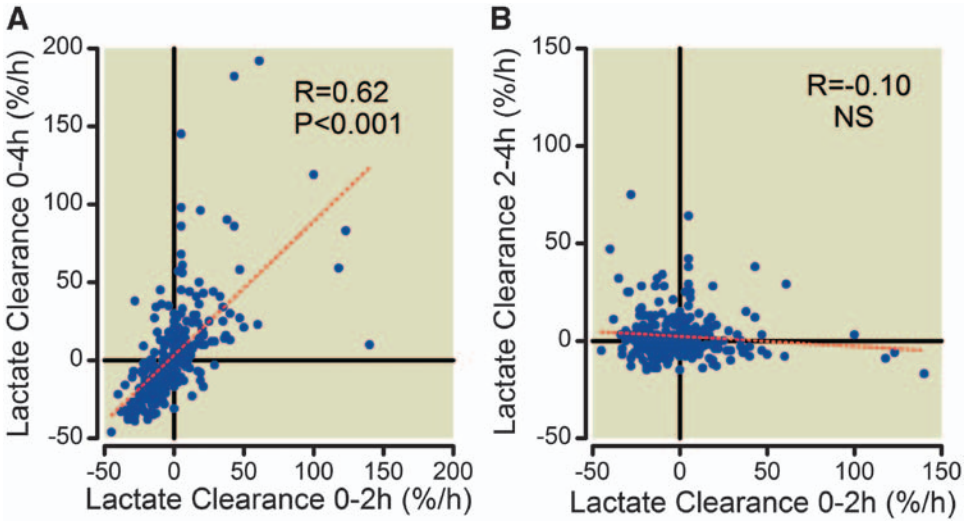

Fig. 2. Correlation between sequential measures of clearance lactate (LC) obtained between 0 and 2 h, 0 and 4 h, and 2 to 4 h after admission (n = 281). $LC_{0-4\,h}$ was significantly correlated with $LC_{0-2\,h}$ (*A*). In contrast, there was no significant correlation between $LC_{2-4\,h}$ and $LC_{0-2\,h}$ (*B*). The *dotted line* corresponds to the linear regression curve. NS = nonsignificant; R = coefficient of correlation.

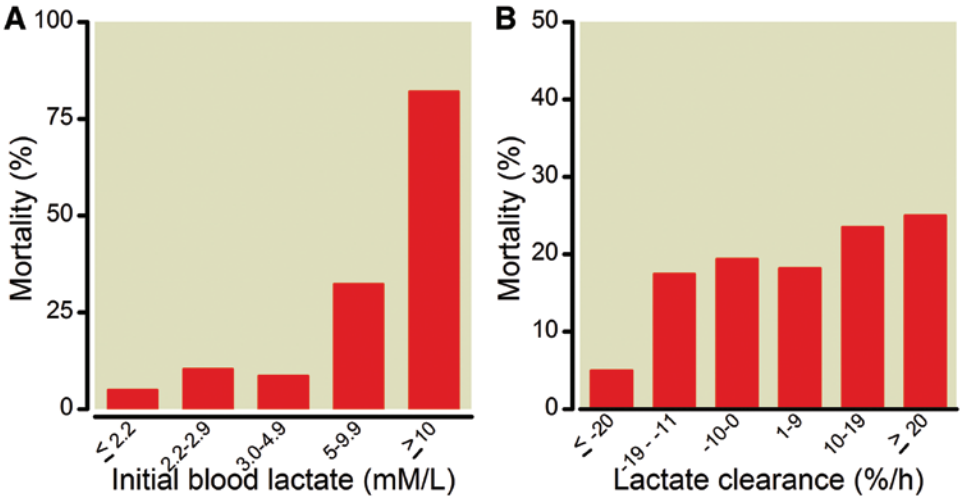

Fig. 3. Proportion of patients in the predefined categories of initial blood lactate (*A*, n = 586) and lactate clearance (*B*, n = 376). Lactate clearance is $LC_{corrected}$ (see Methods for definition).

normal initial blood lactate level. This was confirmed by the comparison of survivors and nonsurvivors in patients with normal initial blood lactate levels (n = 259): there was no significant differences in blood lactate levels initially (1.4 ± 0.4 *vs.* 1.5 ± 0.4 mM/l, $P = 0.77$) and after 2 h (1.6 ± 0.8 *vs.* 1.7 ± 0.8 mM/l, $P = 0.82$), and in $LC_{0-2\,h}$ (0 [−11 to 12] *vs.* 4 [0–13] %/h, $P = 0.98$). Therefore, to calculate the $LC_{corrected}$ we arbitrarily attributed the lowest value of $LC_{0-2\,h}$ observed (*i.e.*, −30%/h) to patients with two consecutive normal blood lactate levels (n = 135, mortality rate 7.4%). We also attributed a $LC_{corrected}$ value of −30%/h in 66 patients who lacked blood lactate data at 2 h but with two consecutive normal blood lactate levels within 24 h after admission and in 14 patients who had normal initial blood lactate levels and left the ICU within 24 h (total n = 80, mortality rate 1.2%). Thus, $LC_{corrected}$ was obtained in 453 patients (77%) (mortality rate 11%; fig. 1). In the remaining patients (n = 133), the mortality rate was 20%.

Figure 2 shows the correlation between $LC_{0-2\,h}$, $LC_{2-4\,h}$, and $LC_{0-4\,h}$. There was a significant correlation between $LC_{0-4\,h}$ and $LC_{0-2\,h}$ (fig. 2A). In contrast, there was no significant correlation between $LC_{2-4\,h}$ and $LC_{0-2\,h}$ (fig. 2B).

Prediction of Death

Figure 3 shows the relationship between mortality and the categories of initial blood lactate and lactate clearance ($LC_{corrected}$). There was an increase in mortality with increasing values of initial blood lactate over the whole range of categories (fig. 3A). In contrast, the increase in mortality observed with increasing values of lactate clearance was associated with a ceiling effect (fig. 3B).

Figure 4 shows the ability of initial blood lactate and lactate clearance to predict mortality in trauma patients. The global predictive properties of the initial blood lactate using ROC curve analysis (0.78, 95% CI: 0.73–0.83, $P < 0.001$) was significantly greater than that of lactate clearance (0.70,

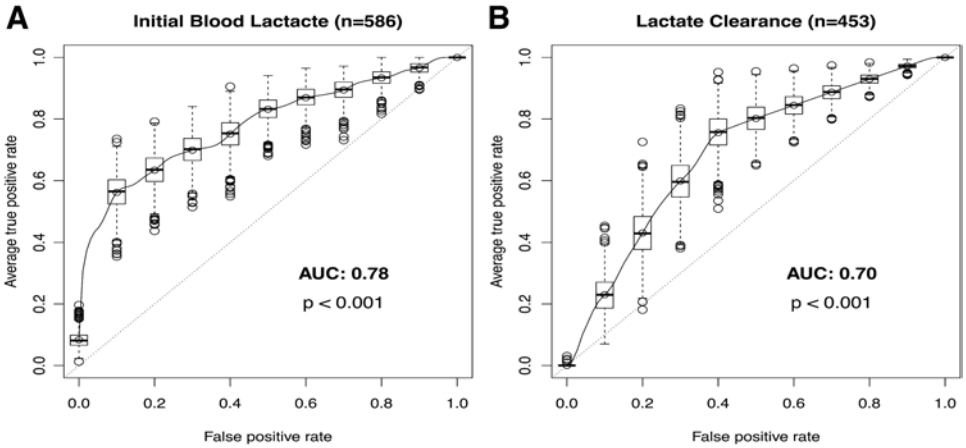

Fig. 4. Receiving operating characteristics (ROC) curves of initial blood lactate (*A*), and lactate clearance (*B*, $LC_{corrected}$ [see Methods for explanation]). *P* values refer to the comparison of the area under the ROC curve *versus* 0.50 (*i.e.*, no discrimination). The *dotted line* corresponds to the nondiscrimination curve. Bootstrap analysis (1,000 random populations) was performed to obtain average ROC curves and box plot. AUC = area under curve.

Table 3. Effects of Adding Initial Blood Lactate and Lactate Clearance to Revised Trauma Score, Mechanism, Glasgow, Age, Arterial Pressure Score, and Trauma Related Injury Severity Score in Predicting Mortality

Variables	Odds Ratio (95% CI)	*P* Value
Model 1 (n = 453; AUC = 0.88; HL *P* = 0.005, optimism = 0.005)		
RTS (per 1 point decrease)	2.06 (1.64–2.55)	<0.001
Initial blood lactate (per 1 mM increase)	1.21 (1.08–1.38)	<0.001
Lactate clearance (per 10%/h increase)	1.16 (1.01–1.31)	0.02
Model 2 (n = 453; AUC = 0.85; HL *P* = 0.23; optimism = 0.013)		
MGAP (per 1 point decrease)	1.21 (1.13–1.29)	<0.001
Initial blood lactate (per 1 mM increase)	1.29 (1.15–1.45)	<0.001
Lactate clearance (per 10%/h increase)	1.15 (1.00–1.30)	0.03
Model 3 (n = 453; AUC = 0.92; HL *P* = 0.005; optimism = 0.007)		
TRISS (per 0.1 point decrease)	1.72 (1.50–1.97)	<0.001
Initial blood lactate (per 1 mM increase)	1.13 (0.99–1.29)	0.054
Lactate clearance (per 10%/h increase)	1.14 (0.99–1.30)	0.054

Optimism is the difference of AUC between the entire population and the cross validated population.
AUC = area under the receiver-operating characteristic curve; HL = Hosmer–Lemeshow statistics; MGAP = Mechanism, Glasgow, Age, arterial Pressure score; RTS = Revised Trauma Score; TRISS = Trauma Related Injury Severity Score.

95% CI: 0.66–0.74, $P < 0.001$), but significantly lower than that of TRISS (0.95, 95% CI: 0.93–0.97, $P < 0.001$). Using bootstrap analysis and maximization of the Youden index, the best cutoffs were 4.7 mM/l (95% CI: 3.4–5.6 mM/l) for initial blood lactate level and −18%/h (95% CI: −28 to −6%/h) for lactate clearance. In contrast, $LC_{0-4\ h}$ (AUC_{ROC} 0.52, 95% CI: 0.41–0.62, $P = 0.54$) and $LC_{2-4\ h}$ (AUC_{ROC} 0.52, 95% CI: 0.39–0.61, $P = 0.86$) did not predict mortality better than chance.

We used a logistic regression model to assess the additional value of blood lactate and lactate clearance to predict mortality. Initial blood lactate and lactate clearance added significant information to that provided by RTS or MGAP and a trend ($P = 0.054$) was observed with TRISS (table 3). After 10-fold crossvalidation, the maximum difference in AUC between derivation and validation cohort (*i.e.*, optimism) was 0.01, suggesting that the presented models were robust and that their predictive values were not only related to several patients. Using a reclassification method, comparison of models including initial blood lactate and lactate clearance *versus* MGAP, RTS, and TRISS alone were significant, implying that these two variables significantly increase the ability of MGAP, RTS, and TRISS to predict mortality (fig. 5). Nevertheless, the graphical reclassification (fig. 5) shows that, although significant, this improvement remains clinically marginal for TRISS.

Because multiple imputations were performed for $LC_{corrected}$, we performed a sensitivity analysis including only patients with measured lactate clearance (n = 373). In this sensitivity analysis, the odds ratios of initial blood lactate (1.25 [1.10–1.45], $P = 0.002$) and lactate clearance (1.23 [1.00–1.20], $P = 0.007$) were significant, using the TRISS score as reference. Figure 6 illustrates the fact that additional information provided by lactate clearance mainly concerns trauma patients with high initial blood lactate levels.

Prediction of Secondary Endpoints

Early death (within 48 h) occurred in 53 patients (9%), representing 68% of all deaths. Initial blood lactate (AUC 0.84, 95% CI: 0.77–0.90, $P < 0.001$), and $LC_{corrected}$ (AUC 0.75, 95% CI: 0.66–0.82, $P = 0.001$) were significant predictors of early death. Using multivariate logistic regression, TRISS and lactate clearance were significant predictors of early death but initial blood lactate was not (table 4).

Initial blood lactate (AUC 0.61, 95% CI: 0.55–0.65, $P < 0.001$) and $LC_{corrected}$ (AUC 0.59, 95% CI: 0.54–0.64, $P = 0.001$) were significant predictors of severe trauma lesions defined as an ISS more than 15.

Initial blood lactate (AUC 0.86, 95% CI: 0.80–0.90, $P < 0.001$) and $LC_{corrected}$ (AUC 0.69, 95% CI: 0.62–0.74, $P < 0.001$) were significant predictors of massive hemorrhage.

Initial blood lactate (AUC 0.65, 95% CI: 0.59–0.70, $P < 0.001$) and $LC_{corrected}$ (AUC 0.64, 95% CI: 0.58–0.69, $P = 0.001$) were significant predictors of the need of an emergency procedure.

Initial blood lactate (AUC 0.70, 95% CI: 0.65–0.74, $P < 0.001$) and $LC_{corrected}$ (AUC 0.63, 95% CI: 0.58–0.68, $P < 0.001$) were significant predictors of the need for a stay in ICU more than 2 days or death.

Subgroup Analysis: High Blood Initial Blood Lactate

There were 90 patients with a high (5 mM/l or higher) initial blood lactate level of which 68 (76%) were men, aged 41 ± 16 yr, had ISS 33 (21–41), TRISS 0.618 (0.100–0.951), and death occurred in 43 (48%) of these patients. Table 5 shows the main comparison between patients who

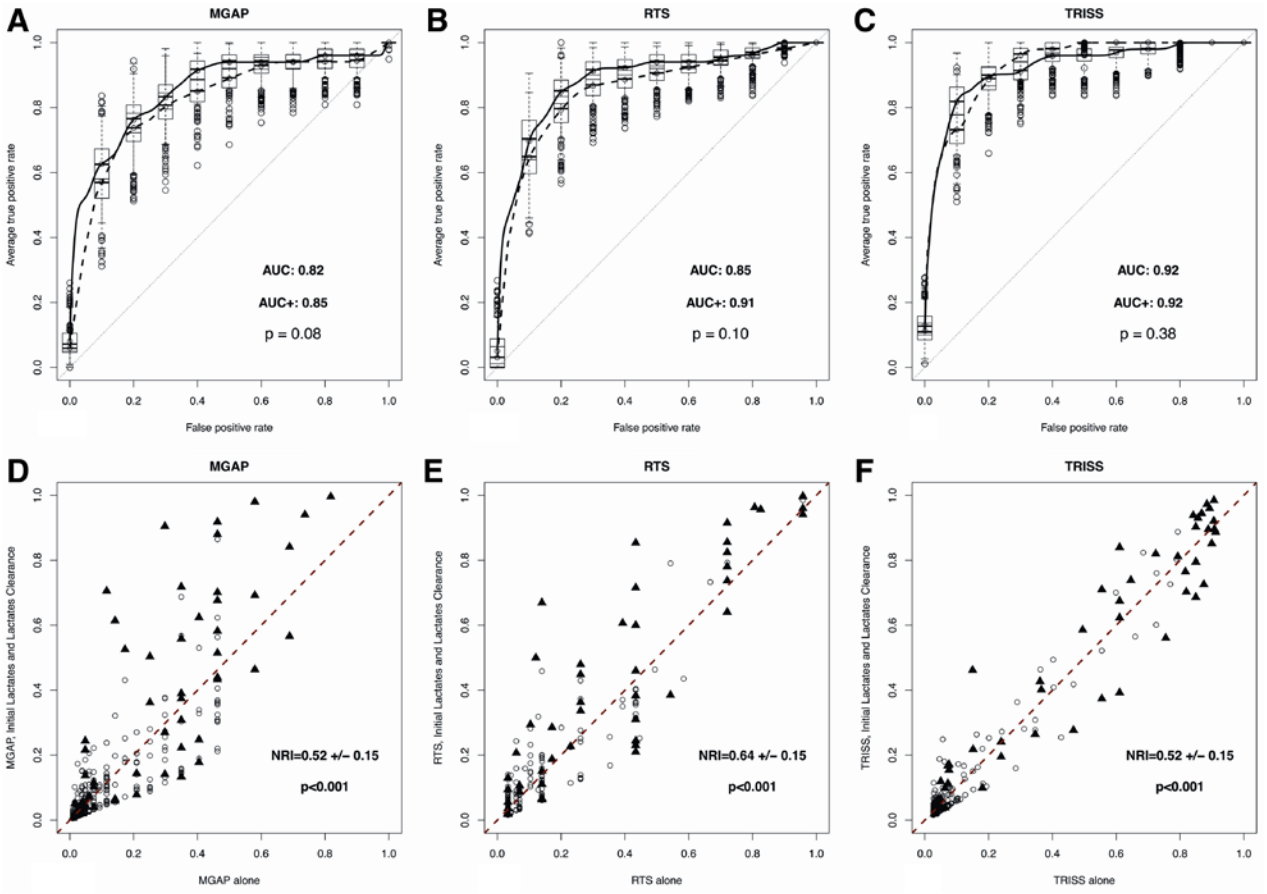

Fig. 5. Receiving operating characteristics (ROC) curves of Mechanism, Glasgow, Age, arterial Pressure score (MGAP) and the model including MGAP, initial blood lactate, and lactate clearance (*A*), Revised Trauma Score (RTS) and the model including RTS, initial blood lactate, and lactate clearance (*B*), and Trauma Related Injury Severity Score (TRISS) and the model including TRISS, initial blood lactate, and lactate clearance (*C*), *P* values refer to the comparison of the two areas under the ROC curves (AUC and AUC+). Bootstrap analysis (1,000 random populations) was performed to obtain average ROC curves and box plot. Graphical representation of reclassification provided by the inclusion of lactate and lactate clearance over MGAP (*D*), RTS (*E*), and TRISS (*F*). The *red dotted lines* correspond to the equality of the probability obtained by the models. Deceased patients (*filled triangles*) were expected to have a higher probability of death when initial blood lactate levels and lactate clearance were included. On the contrary, survivors (*open circles*) should have a lower probability of death when initial blood lactate level and lactate clearance were included. In case of perfect reclassification, all deceased patients would have been above the *red dotted line* and all survivors below it. NRI = net reclassification improvement.

survived and those who died. ROC curve analysis was performed and showed that the global predictive properties of the initial blood lactate (0.77, 95% CI: 0.60–0.87, $P < 0.001$), $LC_{corrected}$ (0.67, 95% CI: 0.51–0.78, $P = 0.015$), and TRISS (0.90, 95% CI: 0.79–0.95, $P < 0.001$) were significant. Only initial blood lactate added additional information to that provided by TRISS (table 6). In contrast, lactate clearance did not add significant information but the odds ratios were comparable to that observed in the whole population, suggesting an insufficient power (table 6). In this subgroup of patients, we confirmed the relationship observed between lactate clearance and mortality (fig. 6). Therefore, the results obtained in this subgroup of patients with severe lactic acidosis were comparable to those obtained in the whole cohort of trauma patients.

Subgroup Analysis: Normotensive Patients

There were 462 normotensive patients of whom 332 (77%) were men aged 37 ± 15 yr, who had ISS 14 (8–25) and TRISS 0.986 (0.953–0.994), and death occurred in 29 (6%) of these patients. ROC curve analysis was performed and showed that the global predictive properties of the initial blood lactate (0.63, 95% CI: 0.51–0.87, $P = 0.03$) and $LC_{corrected}$ (0.65, 95% CI: 0.53–0.75, $P = 0.007$) and TRISS (0.94, 95% CI: 0.90–0.97, $P < 0.001$) were significant. Using logistic regression, initial blood lactate and lactate clearance did not add significant additional information to that provided by MGAP, RTS, or TRISS (table 7). Using reclassification technique, adding initial blood lactate and lactate clearance did not add significant additional information to that provided by MGAP (net reclassification improvement 0.304 ± 0.216, $P = 0.16$), RTS

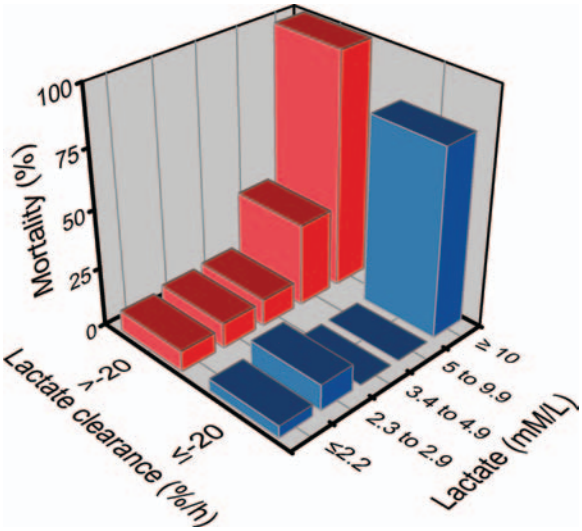

Fig. 6. Mortality in the predefined categories of initial levels and lactate clearance (n = 453). NRI = net reclassification improvement.

(net reclassification improvement 0.389 ± 0.216, P = 0.07), or TRISS (net reclassification improvement 0.337 + 0.218, P = 0.12). Therefore, the results obtained in this subgroup of normotensive patients were not comparable to those obtained in the whole cohort of trauma patients.

Discussion

The main findings of our study are the following: (1) lactate clearance provides additional predictive information to initial blood lactate levels and scores (MGAP and RTS available at admission and the reference standard TRISS); (2) lactate clearance should be calculated within the first 2 h after admission; and (3) this additional information provided by lactate clearance can be summarized using a categorical approach (*i.e.*, −20%/h or lesser) in contrast to initial blood lactate. Therefore, our study indicates that lactate clearance is a useful prognostic variable in trauma patients and explains to the physician how to measure and use it.

Lactate has been shown to be a prognostic biomarker in trauma, even in patients with normal vital signs.[3–6] This association has been confirmed in experimental studies.[44,45] In various types of shock, it has been shown that elevated blood lactate levels result from an increased production (lactic acidosis) without significant changes in lactate clearance processes.[46] In trauma patients, alcohol or drug use, which are frequently encountered conditions, do not modify the predictive accuracy of initial blood lactate levels.[47] Little information is available concerning the possible role of hepatic contusion on blood lactate levels. We observed that initial blood lactate levels were significantly higher in patients with hepatic trauma but this difference disappeared when adjustment to the global severity (TRISS) was performed. This result suggests that hepatic trauma does not play a significant role through a possible modification of lactate clearance processes in trauma patients.

Several arguments indicate that lactate clearance should be measured within the first 2 h after admission. Only early lactate clearance was able to predict death, as shown by significant AUC_{ROC} curve. We observed a significant correlation between $LC_{0–2\ h}$ and $LC_{0–4\ h}$ but not between $LC_{0–2\ h}$ and $LC_{2–4\ h}$ (fig. 2). Taken together, these results suggest that early lactate clearance contains most of the relevant information concerning the success of early resuscitation and thus final outcome. In septic patients, the lactate clearance has been calculated over a longer period (4–6 h, even 24 h) which is in line with the time course of septic disease, but is clearly not appropriate for trauma patients, whose evolution, as well as the impact of the emergency procedures done to stop the bleedings, is faster . In trauma, most deaths occur early, within the first 24 h[2] and thus physicians need accurate and very early indications concerning the prognosis. Our study strongly suggests that both initial blood lactate levels and early lactate clearance may be appropriate tools. A significant important proportion of trauma patients (44%) had normal initial blood lactate value and it would make no sense to attempt to clear a value that is already normal.[13] As a matter of fact, a slight, although not significant, increase in blood lactate levels was observed in patients with initial normal values, contrasting with a slight decrease in patients with elevated blood lactate levels (table 3). This trend was also noted when comparing alive and dead patients in the subgroup of patients with high initial blood lactate levels (table 4). Last, our sensitivity analysis without patients with normal blood lactate supports this hypothesis. Thus, we suggest that an arbitrary low value of lactate clearance should

Table 4. Effects of Adding Initial Blood Lactate and Lactate Clearance to Trauma Related Injury Severity Score in Predicting Early Deaths (within 48 h)

Variables	Odds Ratio (95% CI)	*P* Value
Model (n = 453; AUC = 0.95; HL *P* = 0.01; optimism = 0.001)		
TRISS (per 0.1 point decrease)	1.70 (1.46–2.00)	<0.001
Initial blood lactate (per 1 mM increase)	1.11 (0.98–1.27)	0.12
Lactate clearance (per 10%/h increase)	1.24 (1.06–1.43)	0.004

Optimism is the difference of AUC between the entire population and the cross-validated population.

AUC = area under the receiver-operating characteristic curve; HL = Hosmer–Lemeshow statistics. TRISS = Trauma Related Injury Severity Score.

Table 5. Comparison of Patients Who Survived or Not in the Subgroup of Patients with a High (≥ 5 mm/l) Initial Blood Lactate

	Alive (n = 47)	Dead (n = 43)	*P* Value
Blood lactate 0 h, mM/l	7.2 ± 2.0	11.7 ± 5.4	<0.001
Blood lactate 2 h, mM/l	5.3 ± 2.4	9.8 ± 4.3	<0.001
Blood lactate 4 h, mM/l	5.2 ± 2.3	9.5 ± 6.5	<0.001
$LC_{0-2h,}$ %/h	–14 (–23;–2)	–3 (–14;5)	0.03
$LC_{0-4h,}$ %/h	–13 (–25;2)	–13 (–24;0)	0.81
$LC_{2-4h,}$ %/h	–3 (–5;2)	–3 (–6;1)	0.66

Data are mean ± SD or median (–25; 75 interquartiles). Difference of area under the receiver-operating characteristic curve between the entire population and the cross-validated population. n = 90.

LC = lactate clearance.

be attributed to these patients with iterative normal blood lactates to predict mortality.

In our study, both initial blood lactate level and LC provided additional predictive information to scores used to predict mortality (table 3). RTS and MGAP scores are available immediately and thus are used in prehospital phase triage.[24,25] The MGAP score predicts mortality better than RTS does,[21] approaching the specificity of the reference standard, TRISS which incorporates definite information about trauma lesions and thus is used as a reference standard.[22] Because TRISS is already a very good predictor of mortality it is not surprising that the level of statistical significance is difficult to reach to demonstrate an improvement beyond that score (table 3). Nevertheless, when considering only early deaths, lactate clearance adds significant prognostic information over the TRISS score, whereas initial blood lactate did not. When using a more sensitive method such as reclassification, we were able to demonstrate that initial blood lactate level and lactate clearance also provided additional information to TRISS as shown by improvement in net reclassification improvement (fig. 5). However, the relationship between mortality and the categories of initial blood lactate and lactate clearance differed markedly (fig. 3). There was an increase in mortality with increasing values of initial blood lactate over the whole range of categories (fig. 3A) and thus a dichotomic approach may not be appropriate. In contrast, the increase in mortality observed with increasing values of lactate clearance was associated with a ceiling effect for all categories (fig. 3B), indicating that a dichotomic approach may appropriately summarize the information provided by this variable (*i.e.*, –20%/h or lesser or not). In fact, the additional information provided by the LC mainly concerned trauma patients with a high initial blood lactate level (fig. 7).

The initial blood lactate level and LC were also able to predict early deaths, severe traumatic lesions (ISS > 15), need for emergency procedure, and prolonged ICU duration. This is important because, besides mortality itself, the duration of ICU stay might be a clinically and economically relevant criterion to assess morbidity of trauma patients. The initial blood lactate level and LC were also able to predict massive hemorrhage and this prediction was comparable to those previously reported in casualties arriving at combat support hospital for RTS and Field Triage score.[48] These prehospital scores are obviously less accurate than more specific scores that incorporate biological variables performed at admission.[49] Because of their relatively weak accuracy in predicting massive hemorrhage, we cannot rule out that this capacity to predict is only related to the well-known link between massive hemorrhage and mortality.[21,50]

In contrast, in normotensive patients, initial blood lactate and lactate clearance did not add significant additional information to that provided by MGAP, RTS, or TRISS (table 7), even when a powerful technique such as reclassification was used. This important negative result suggests that, although

Table 6. Effects of Adding Initial Blood Lactate and Lactate Clearance to Trauma Related Injury Severity Score in Predicting Mortality in Patients with High (≥ 5 mm/l) Initial Blood Lactate Level

Variables	Odds Ratio (95% CI)	*P* Value
Model (n = 64; AUC = 0.92; HL *P* = 0.38; optimism = 0.03)		
TRISS (per 0.1 point decrease)	1.49 (1.21–1.93)	<0.001
Initial blood lactate (per 1 mM increase)	1.46 (1.09–2.20)	0.03
Lactate clearance (per 10%/h increase)	1.44 (0.91–2.36)	0.13

Optimism is the difference of AUC between the entire population and the cross-validated population.

AUC = area under the receiver-operating characteristic curve; HL = Hosmer–Lemeshow statistics; TRISS = Trauma Related Injury Severity Score.

Table 7. Effects of Adding Initial Blood Lactate and Lactate Clearance to Revised Trauma Score, Mechanism, Glasgow, Age, Arterial Pressure Score, and Trauma Related Injury Severity Score in Predicting Deaths in Normotensive Patients (See Text for Definition)

Variables	Odds Ratio (95% CI)	*P* Value
Model 1 (n = 361; AUC = 0.90, HL *P* < 0.001, optimism = 0.01)		
RTS (per 1 point decrease)	2.50 (1.85–3.49)	<0.001
Initial blood lactate (per 1 mM increase)	0.99 (0.77–1.26)	0.93
Lactate clearance (per 10%/h increase)	1.13 (0.93–1.33)	0.14
Model 2 (n = 361; AUC = 0.83, HL *P* = 0.24, optimism = 0.02)		
MGAP (per 1 point decrease)	1.21 (1.10–1.32)	<0.001
Initial blood lactate (per 1 mM increase)	1.20 (0.99–1.44)	0.05
Lactate clearance (per 10%.h^{-1} increase)	1.11 (0.93–1.29)	0.17
Model 3 (n = 361; AUC = 0.93, HL *P* < 0.001, optimism = 0.02)		
TRISS (per 0.1 point decrease)	1.94 (1.61–2.40)	<0.001
Initial blood lactate (per 1 mM increase)D	0.98 (0.78–1.23)	0.84
Lactate clearance (per 10%/h increase)	1.14 (0.92–1.34)	0.15

Optimism is the difference of AUC between the entire population and the cross-validated population.

AUC = area under the receiver-operating characteristic curve; HL = Hosmer–Lemeshow statistics; MGAP = Mechanism, Glasgow, Age, arterial Pressure score; RTS = Revised Trauma Score; TRISS = Trauma Related Injury Severity Score.

lactate clearance may be useful to assess the initial resuscitation provided to the trauma patients, it is probably not appropriate to diagnose occult hypoperfusion. Our results support the conclusion of several authors who considered that other variables such as renal artery or microcirculation blood flow should be measured to detect occult hypoperfusion in normotensive trauma patients.[26,51]

Some limitations in our study deserve consideration. First, this study was performed in an adult population and thus may not apply to pediatric patients.[52] Second, our study was observational and we demonstrated an association but cannot infer causality. Thus, further studies are required to demonstrate that interfering with lactate clearance using therapeutics actually modifies prognosis. The recent results obtained with new hemoglobin solutions are in favor of this hypothesis.[15] These authors observed that normalization of blood lactate within 8 h or clearance of more than 20% within 2 h (*i.e.*, corresponding to –40%/h) correlates with outcomes from traumatic hemorrhagic shock with high (more than 5 mM/l) initial blood lactate levels.[53] This might provide a very interesting surrogate endpoint to mortality because mortality is a very difficult endpoint in the population of trauma patients, mainly because of its bimodal distribution.[14] To be a valid surrogate endpoint, lactate clearance should be strongly and independently associated with mortality and our study supports that hypothesis. But any intervention targeting clearance lactate should also modify mortality, which remains to be demonstrated.[54] We look at blood lactate levels after admission to the hospital. Because several studies have recently emphasized the interest of measuring blood lactate levels during the prehospital phase,[38,55] further studies are needed to assess the possible role of the measurement of lactate clearance during this very early phase. Last, our study was conducted in a prehospital system in which intensive medical treatment is administered on scene by physicians, which can both slightly delay hospital admission and modify the prognosis,[56] thus potentially interfering with timing and prognostic value of initial blood lactate and lactate clearance measurements. However, in our study, there was no significant correlation between initial blood lactate and prehospital time.

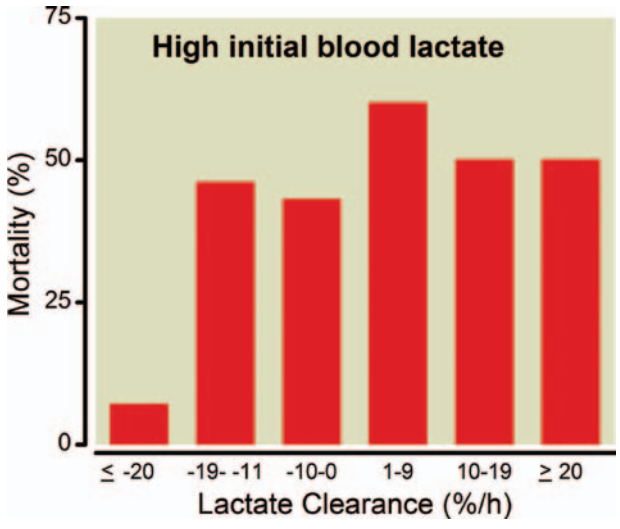

Fig. 7. Mortality according to initial blood lactate level and/or lactate clearance (n = 453).

Conclusions

Lactate clearance should be calculated within the first 2 h after admission of a trauma patients and an arbitrary low value should be given to patients with two consecutive

normal blood lactate levels. The lactate clearance provides additional predictive information to initial blood lactate levels and scores and this information can be summarized using a categorical approach (*i.e.*, –20%/h or lower, or not). Lactate clearance should probably be incorporated in future decision scheme in the resuscitation of trauma patients and might be considered as a relevant surrogate endpoint in randomized clinical trials.

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