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Comparison of the Prognostic Significance of Initial Blood Lactate and Base Deficit in Trauma Patients

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Anesthesiology

Comparison of the prognostic significance of initial blood lactate and base deficit in trauma patients --Manuscript Draft--

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Abstract:	<p>Background: Initial blood lactate and base deficit have been shown to be prognostic biomarkers in trauma but their respective performances have not been compared.</p> <p>Methods: Blood lactate levels and base deficit were measured at admission in trauma patients in three level 1 trauma centers. This was a retrospective analysis of prospectively acquired data. The association of initial blood lactate and base deficit with mortality was tested using receiver operating characteristics curve, logistic regression using triage scores (Revised Trauma Score, and Mechanism Glasgow scale and Arterial Pressure score) and Trauma Related Injury Severity Score as a reference standard. We also used a reclassification method.</p> <p>Results: We evaluated 1,075 trauma patients (mean age 39 + 18 years, with 90% blunt and 10 % penetrating injuries, and a mortality of 13%). At admission, blood lactate were elevated in 425 (39%) patients and base deficit was elevated in 725 (67%) patients. Blood lactate was correlated with base deficit ($R^2=0.54$, $P<0.001$). Using logistic regression, blood lactate was a better predictor of death than base deficit when considering its additional predictive value to triage scores and Trauma Related Injury Severity Score. This result was confirmed using reclassification method but only in the subgroup of normotensive patients ($n=745$).</p> <p>Conclusions: Initial blood lactate should be preferred to base deficit as a biological variable in scoring systems built to assess initial severity of trauma patients.</p>

RESPONSE TO THE EDITOR

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2 We thank the Editor and the reviewer for their helpful comments. We would like to offer the
3 following responses to the comments from the Reviewers. Any modification within the
4 manuscript has been quoted in “red” characters.
5

6
7 *Anesthesiology journal style calls for figures to be cited within the text in numerical order:*
8 *Figure 1A, Figure 1B, Figure 2A, Figure 2B, etc. Once a figure has been cited it can then be*
9 *re-cited again in any order. If the entire figure is cited first (Figure 1), then subsequent*
10 *citations can be Figure 1B, Figure 1A. Figure 2 is cited out of order (see page 12); please*
11 *correct.*
12
13

14
15 Correction done.
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19 *Please provide the academic degrees of each member of the TraumaBase Group listed in the*
20 *Appendix*
21

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23 Information provided.
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MS # ALN-D-16-00529R2

Fifth revision

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4 **Comparison of the prognostic significance of initial blood**
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7 **lactate and base deficit in trauma patients**
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17 Bruno Riou, M.D., Ph.D., for the TRAUMABASE® Group
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1 **Abstract**
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4 **Background:** Initial blood lactate and base deficit have been shown to be prognostic
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9 **Methods:** Blood lactate levels and base deficit were measured at admission in trauma
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13 acquired data. The association of initial blood lactate and base deficit with mortality was
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17 (Revised Trauma Score, and Mechanism Glasgow scale and Arterial Pressure score) and
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19 Trauma Related Injury Severity Score as a reference standard. We also used a reclassification
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45 **Conclusions:** Initial blood lactate should be preferred to base deficit as a biological
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47 variable in scoring systems built to assess initial severity of trauma patients.
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INTRODUCTION

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4 Most trauma deaths occur within 48h of injury and half of them are related to
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6 hemorrhage.¹ In trauma patient care, it is crucial to recognize and treat hemorrhage early and
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8 limit the consequences of hemorrhagic shock which results in tissue hypoxia, anaerobic
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10 metabolism and lactic acidosis. Lactic acidosis reflects flow-demand mismatch or loss of
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12 appropriate perfused capillary density as a consequence of shock, vasoconstriction, or other
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14 dysfunctional responses, and may persist despite control of hemorrhage.² Beside clinical
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16 examination and imaging procedures, biological measurements (hemoglobin, blood gases,
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18 lactate, hemostasis) are important to assess hemorrhage and its consequences and thus are
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20 measured on arrival of the trauma patients at the hospital, or even earlier in the prehospital
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22 phase.³ Initial blood lactate and base deficit are both considered as useful biomarkers in
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24 trauma patients.^{4,5} However, these two biomarkers are not completely equivalent, at least from
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26 a physiological point of view. Base deficit reflects the acid-base status and thus may be
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28 increased during metabolic but also respiratory acidosis and modified by therapeutic
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30 resuscitation such as fluid loading (chloride-induced acidosis).⁶ Blood lactate mainly reflects
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32 lactic acidosis in trauma patients but might be also influenced by other factors such as
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34 decreased hepatic clearance, alcohol or other toxic insults, or increased muscular activity
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36 during seizures.⁷ Although numerous studies have assessed the prognostic values of these two
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38 biomarkers separately, very few studies have compared them.⁸⁻¹¹ However, these studies have
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40 included few patients and did not appropriately compare the additive prognostic value of these
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42 two biomarkers.¹²

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53 The purpose of this observational cohort study was to compare the prognostic value of
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55 initial blood lactate and base deficit in trauma patients. We aimed to answer the following
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57 questions: (1) which of these two variables is the best additional predictor of death, as
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59 compared with available scores? (2) Are there differences in predicting other clinically
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relevant outcome (early death, severe trauma, prolonged intensive care unit (ICU) stay,
massive hemorrhage, requirement for an emergency procedure) besides mortality ?¹³

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MATERIALS AND METHODS

This observational cohort study was conducted from January 1st, 2013 to April 15th 2014, in three French academic trauma centers with a full range of specialists and equipment available 24 hours a day. These centers provide the highest level of care for trauma patients and correspond to the comprehensive service (*i.e.* level I) from the American College of Surgeons. Regarding the observational nature of the study, waived written informed consent was authorized by institutional review board (Comité pour la Protection des Personnes – CPP PARIS VI - Pitié-Salpêtrière, Paris, France). In accordance with the French Law, the registry was approved by the Advisory Committee for Information Processing in Health Research (CCTIRS, Paris, France) and the French National Commission on Computing and Liberty (CNIL, Paris, France). Although data were prospectively acquired for a research purpose, the study should be considered as a retrospective study.

Study population

During the study period, all trauma patients older than 18 years were included. After the alert had been received, on-site triage was based on patients' clinical assessment. Medical prehospital care needs were determined regarding the severity of the trauma. Medical mobile intensive care units carried all trauma patients admitted to the study centers. For each patient admitted to a study center, the following data were recorded by a physician during the prehospital phase: age, sex, trauma characteristics, systolic arterial blood pressure, heart rate, respiratory rate, Glasgow coma scale, peripheral oxygen saturation. The details of the care provided during the prehospital phase were also recorded. On arrival at the hospital, hemodynamic, neurologic and respiratory status were re-evaluated and recorded.

The following scores were determined: Abbreviated Injury Scale (AIS),¹⁴ Injury Severity Score (ISS),¹⁵ Revised Trauma Score (RTS),¹⁶ and Mechanism (of trauma) Glasgow

1 scale Age and Arterial Pressure (MGAP) score,¹⁷ and the Trauma Related Injury Severity
2 Score (TRISS) score,¹⁸ using updated regression coefficients, AIS and ISS being required to
3 calculate the TRISS score.
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7 Length of stay in the ICU and in the hospital were recorded. The RTS and MGAP
8 score were used as these scores are available immediately and thus used in the prehospital
9 phase triage. RTS is the most widely used score at least with its triage version^{19,20} and MGAP
10 has been recently shown as a more specific and easier to use score than RTS.¹⁷ TRISS was
11 used as the reference standard since it incorporates definite information about trauma
12 lesions.²¹
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25 **Data monitoring**

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27 The registry included all trauma patients from the study centers. Algorithms for
28 automatic detection data inconsistency were used centrally to generate verification queries. In
29 addition, a set of 35 variables that cannot be missing was pre-defined, data completeness was
30 regularly checked at both local and central levels.²²
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43 **Blood lactate and Base Deficit Measurements**

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45 Arterial blood gases and lactate concentrations were measured simultaneously at the
46 admission to the trauma center. The normal range of blood lactate was defined as ≤ 2.2
47 mM/l.⁵ Stratification of blood lactate was performed as following: ≤ 2.2 , 2.2 to 4.9, 5.0 to
48 9.9, and ≥ 10 mM/l since these strata have been shown to be associated to different mortality
49 level.⁵ Base deficit was calculated using the following equation:
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58 Base deficit = $125.58 - (13.77 \times \text{arterial pH}) - (0.02786 \times \text{carbon dioxide partial pressure} \times$
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60 $10^{\text{pH}-6.1})$
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2 Any values ≤ 2.0 mM/l were considered as normal. Stratification of base deficit was defined
3 as previously reported:²³ ≤ 2.0 , 2.0 to 5.9, 6.0 to 9.9, and ≥ 10 mM/l.
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8 **End points**

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11 The primary endpoint was in-hospital mortality, defined as death occurring within 30
12 days after hospital admission or prior to discharge when discharge occurred within 30 days.
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14 Deaths occurring after hospital discharge were not considered and for the purpose of the
15 analyses were censored, the patients being recorded as alive.
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21 Secondary endpoints included: 1) early death, defined as death within 48h; 2) severe
22 trauma defined by an ISS >15 ; 3) ICU length of stay > 2 days and/or death within 30 days; 4)
23 massive hemorrhage defined as blood transfusion > 6 packed red cell units within 24 h and/or
24 death from hemorrhagic shock; 5) the requirement for an emergency procedure defined as the
25 need for emergency thoracic drainage, emergency surgery, emergency embolization, or
26 emergency transfusion (within the first hour after admission).⁸
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39 **Statistical Analyses**

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42 This analysis followed the recommendations for reporting risk marker,²⁴⁻²⁶ adapted to the
43 clinical setting of multiple trauma. Assuming a mortality rate of 13% (95% confidence
44 interval (CI) 11-16%),⁴ and considering that at least 100 events (*i.e.* in-hospital deaths) were
45 required to perform a robust analysis,¹⁸ we calculated that at least 909 patients should be
46 included in our study. All analyses were *a priori* decided, except those specifically labelled as
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54 *a posteriori*.
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57 Data are expressed as mean \pm SD or median [25-75 interquartile] for non-Gaussian
58 variables (D'Agostino-Pearson omnibus test). Comparison of two means was performed using
59 the unpaired Student t test, comparison of two medians was performed using the Mann-
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Whitney test, and comparison of proportions was performed using Fisher's exact method. Correlation between two variables was assessed using linear regression analysis.

Predictive performances of both initial lactate and initial base deficit for the study primary endpoint were first evaluated using not adjusted averaged receiver operating characteristic curves 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, as previously reported.²⁷ Paired non-parametric technique (bootstrap, 2000 replicates) were then used to compare them.^{12,28}

To assess additional predictive values, multiple logistic regressions were then performed to assess the predictive performances of blood lactate and base deficit knowing either RTS, or MGAP, or TRISS scores. Model performances were evaluated by assessing the calibration and discrimination. Calibration was assessed graphically by plotting observed outcome against the predicted in-hospital mortality probability. A smooth, non-parametric calibration line was created with the LOESS algorithm (*i.e.* a locally weighted scatterplot smoothing) to estimate the observed probabilities of in-hospital mortality in relation to the predicted probabilities.²⁹⁻³¹ Discrimination was quantified by calculating the concordance statistic (*c*-statistic) completed with optimism, which relates to both model coefficients estimation and over-fitting (*e.g.* selection of predictors; categorization of continuous predictors). Variable performances were reported (odd ratios (OR), 95% CI and p values) and models discrimination comparison were conducted using paired non-parametric technique. As the comparison of receiver operating characteristic curves is recognized to be potentially insensitive, we conducted reclassification by calculating the net reclassification index³² and providing graphical reclassification in which we made the assumption that biomarkers have to modify the probability of death given by the clinical score by at least 30% to be clinically relevant.

1 We pre-defined a subgroup analysis in normotensive patients, defined as those with
2 systolic arterial blood pressure >90 mmHg during the prehospital phase and at the arrival in
3 the hospital and without prehospital administration of vasopressors. This subgroup of patients
4 was chosen because biological variables might be more important to detect occult
5 hypoperfusion.^{5,33} We also performed a post hoc analysis of the subgroup of patients with a
6 high probability of survival (i.e. TRISS > 0.90).²¹
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14 All P values were two-sided and $P < 0.05$ was considered significant. NCSS 6.0
15 software (Statistical Solutions Ltd, Corke, Ireland) and R 3.2.3 software³⁴ were used for
16 statistical analyses.
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RESULTS

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3 During the study period, 1,680 trauma patients were admitted to the three trauma
4 centers. Arterial blood lactate and base deficit were measured at the admission in 1,075 (64%)
5 patients who were retained for analysis. In the excluded patient population (mean age 37 ± 18
6 years, ISS 9 [4-17]) the mortality rate was 7%, indicating that missing values were from low
7 risk patients. The main characteristics of the study population are reported in Table 1. The
8 proportion of missing values was 1.7%.
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Blood lactate and Base deficit

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25 Blood lactate at admission was elevated (*i.e.* greater than the predefined threshold) in
26 425 (39%) patients and base deficit in 725 (67%) patients. Initial blood lactate and base
27 deficit were both normal in 278 (26%) patients; and both were increased in 353 (33%)
28 patients. Discrepancies were thus observed in 444 (41%) patients: blood lactate was increased
29 whereas base deficit was normal in 72 (7%) patients, and base deficit was increased whereas
30 blood lactate was normal in 372 (35%) patients. Although significant correlation between
31 blood lactate and base deficit ($R^2 = 0.55$, $P < 0.001$) was observed (Fig. 1), the coefficient of
32 regression suggested that blood lactate and base deficit were not fully interchangeable. In fact,
33 when considering only patients with discrepancy between blood lactate and base deficit
34 (Table 2), patients with increased base deficit but normal blood lactate had lower arterial pH,
35 bicarbonate, and arterial carbon dioxide partial pressure, suggesting that ventilation play a
36 role in the observed difference. Further, they also presented lower hemoglobin and fibrinogen
37 concentrations and received more fluids during the prehospital phase although the incidence
38 of massive hemorrhage and blood transfusion were not significantly different (Table 2),
39 suggesting that hemodilution was more pronounced in that group.
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Prediction of death

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3 We first evaluated initial blood lactate and base deficit as continuous variables. The
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5 area under the averaged receiver operating characteristic curve (Fig. 2) of the initial blood
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7 lactate was not significantly different from that of base deficit (respectively. 0.77, 95% CI
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9 0.72 to 0.81 and 0.75, 95% CI 0.70 to 0.80; P=0.33), but was significantly lower than those of
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11 RTS (0.89, 95% CI 0.85 to 0.92, P<0.001), MGAP (0.90, 95% CI 0.87 to 0.92, P<0.001), or
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13 TRISS (0.91, 95% CI 0.87 to 0.93, P<0.001). When considering the predefined class of both
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15 biomarkers, a visual subjective analysis suggests that blood lactate categories were associated
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17 with a more linear relationship with mortality rate than base deficit (Fig. 3).
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22 The additional predictive values of initial blood lactate and base deficit to predict
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24 mortality were then estimated using logistic regression models. In all models c-statistic
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26 optimism was lower than 0.01, suggesting that the observed predictive performances were not
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28 only related to several patients. When initial blood lactate and base deficit were entered
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30 separately as linear predictor in models including one of the three predefined baseline
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32 predictions (*i.e.* MGAP, RTS and TRISS), they were significant predictors of mortality.
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34 However, when they were entered simultaneously in models (*i.e.* as competitors), initial blood
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36 lactate was a significant predictor of mortality in all models (*i.e.* MGAP, RTS and TRISS),
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38 whereas base deficit was a significant predictor in none of the three models (Table 3). When
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40 added to the baseline models, initial blood lactate increased the c-statistic of the models based
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42 on RTS (from 0.890 to 0.913, P=0.01) and MGAP (from 0.900 to 0.923, P=0.01), but not
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44 TRISS (from 0.906 to 0.913, P=0.44). Adding initial base deficit to models based on MGAP
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46 was associated to an increased c-statistic ((from 0.900 to 0.920, P=0.03) but not when added
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48 to RTS (from 0.890 to 0.902, P=0.17) or TRISS (from 0.906 to 0.898, P=0.46).
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51 Discrimination of the models including initial blood lactate and initial base deficit were not
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53 different from those of the models including only initial blood lactate.
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Using reclassification methods, we demonstrated that adding separately initial blood lactate and base deficit to MGAP, or RTS, or TRISS was associated to a net reclassification index significantly different from zero (Table 4), implying that these two variables significantly increase the ability of MGAP, RTS, and TRISS to predict mortality. The graphical reclassification depicted the individual variation in prediction when initial blood lactate, or when base deficit, were added to models including MGAP or TRISS (Fig. 4).

Prediction of secondary end-points

Early death (≤ 48 h) occurred in 83 (8%) patients, representing 59% of all deaths. Blood lactate (area under the receiver operating characteristic curve 0.83, 95% CI: 0.77 to 0.88, $P < 0.001$), and base deficit (area under the receiver operating characteristic curve 0.82, 95% CI: 0.75 to 0.87, $P = 0.001$) were significant predictors of early death, but they were not significantly different ($P = 0.60$). In multivariate logistic regression, blood lactate (OR 1.22, 95% CI 1.07 to 1.42, $P = 0.004$) was a significant predictor of early death but not base deficit (OR 1.07, 95% CI 0.99 to 1.16, $P = 0.09$).

Severe trauma lesions defined as an ISS > 15 occurred in 555 (52%) patients. Using area under the receiver operating characteristic curve analysis, blood lactate (0.66, 95% CI: 0.63 to 0.70, $P < 0.001$), and base deficit (0.67, 95% CI: 0.63 to 0.70, $P = 0.001$) were significant predictors of severe trauma lesions, but they were not significantly different ($P = 0.91$). In multivariate logistic regression, blood lactate (OR 1.14, 95% CI 1.02 to 1.27, $P = 0.02$) was a significant predictor of severe trauma but not base deficit (OR 1.05, 95% CI 0.99 to 1.11, $P = 0.06$).

Massive hemorrhage occurred in 139 (13%) patients. Using area under the receiver operating characteristic curve analysis, blood lactate (0.83, 95% CI: 0.78 to 0.86, $P < 0.001$), and base deficit (0.85, 95% CI: 0.81 to 0.89, $P < 0.001$) were significant predictors of massive

1 hemorrhage and these two areas were not significantly different (P=0.19). Using multivariate
2 logistic regression, blood lactate (OR 1.25, 95% CI 1.10 to 1.42, P<0.001) and base deficit
3 (OR 1.21, 95% CI 1.13 to 1.29, P<0.001) were significant predictors of massive hemorrhage.
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7 The need for an emergency procedure occurred in 89 (10%) patients. Using area under
8 the receiver operating characteristic curve analysis, blood lactate (0.72, 95% CI: 0.65 to 0.77,
9 P<0.001), and base deficit (0.74, 95% CI: 0.68 to 0.80, P=0.001) were significant predictors
10 of the need for an emergency procedure and these two areas were not significantly different
11 (P=0.36). Using multivariate logistic regression, base deficit (OR 1.12, 95% CI 1.04 to 1.20,
12 P=0.003) was a significant predictor of severe trauma but not blood lactate (OR 1.14, 95% CI
13 1.00 to 1.30, P=0.05).
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24 The need for a stay in ICU > 2 days or death occurred in 775 (72%) patients. Using
25 area under the receiver operating characteristic curve analysis, blood lactate (0.65, 95% CI:
26 0.62 to 0.69, P<0.001), and base deficit (0.70, 95% CI: 0.67 to 0.73, P<0.001) were
27 significant predictors of the need for a stay in ICU > 2 days or death and these two areas were
28 significantly different (P=0.001). Using multivariate logistic regression, base deficit (OR
29 1.20, 95% CI 1.12 to 1.27, P<0.001) was a significant predictor of the need for a stay in ICU
30 > 2 days or death but not blood lactate (OR 1.06, 95% CI 0.93 to 1.20, P=0.39).
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46 **Subgroup analysis: normotensive patients**

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49 There were 749 normotensive patients of which 564 (81%) were male, age was $38 \pm$
50 17 years, ISS 12 [8 to 18], TRISS 0.992 [0.970 to 0.995], and death occurred in 41 (4%) of
51 these patients. Using receiver operating characteristic curve analysis, the global predictive
52 properties of the blood lactate (0.68, 95% CI 0.59 to 0.76, P=0.02) was significant whereas
53 that of base deficit was not (0.58, 95% CI 0.45 to 0.69, P=0.16). Using multivariate logistic
54 regression, blood lactate was a significant predictor of death but not base deficit (Table 5).
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1 Using the net reclassification index, base deficit did not add significant additional information
2 to that provided by MGAP (0.299 ± 0.160 , $P=0.06$), RTS (0.231 ± 0.160 , $P=0.15$) or TRISS
3 (0.018 ± 0.155 , $P=0.91$). Lactate added significant additional information to that provided by
4
5 (0.468 ± 0.160 , $P=0.003$), RTS (0.425 ± 0.160 , $P=0.007$) or TRISS (0.284 ± 0.158 ,
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10 $P=0.007$).

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17 **Subgroup analysis: patients with a high probability of survival**

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20 There were 807 patients with a high probability of survival (TRISS >0.90) of which
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22 641 (79%) were male, age was 36 ± 16 years, ISS 12 [8 to 18], TRISS 0.991 [0.974 to 0.995],
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24 and death occurred in 28 (3.5%) of these patients. Using area under the receiver operating
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26 characteristic curve analysis, the global predictive properties of the blood lactate (0.74, 95%
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28 CI 0.62 to 0.82, $P<0.001$) and base deficit (0.64, 95% CI 0.56 to 0.79, $P<0.001$) were both
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30 significant, without significance between these two values ($P=0.34$). Using multivariate
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32 logistic regression, blood lactate was a significant predictor of death but not base deficit
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34 (Table 5). Using the net reclassification index, base deficit did not add significant additional
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36 information to that provided by MGAP (0.299 ± 0.160 , $P=0.06$), RTS (0.231 ± 0.160 , $P=0.15$)
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38 or TRISS (0.018 ± 0.155 , $P=0.91$). Lactate added significant additional information to that
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40 provided by MGAP (0.468 ± 0.160 , $P=0.003$), RTS (0.425 ± 0.160 , $P=0.007$) or TRISS
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42 (0.284 ± 0.158 , $P=0.007$).

DISCUSSION

The main findings of our study are the following: 1) blood lactate predicts mortality better in trauma patients than base deficit; 2) the superiority of blood lactate is confirmed when considering most other relevant clinically end point, except the need for emergency procedures and the need for prolonged mechanical ventilation, and when considering normotensive trauma patients; 3) two factors may at least partly explain the difference observed between blood lactate and base deficit, hemodilution with crystalloids and the ventilatory component of the acid-base equilibrium. Therefore, our study indicates that initial blood lactate should be preferred to base deficit as a biological variable in scoring systems built to assess initial severity of trauma patients.⁵ In our study, we used three scores, RTS, MGAP, and TRISS. The RTS and MGAP scores are available immediately and are used in prehospital phase triage.^{17,35} The MGAP score predicts mortality better than RTS,¹⁷ approaching the specificity of the reference standard, TRISS which incorporates definite information about trauma lesions.¹⁸

Both initial blood lactate and base deficit have been shown to be prognostic biomarkers in trauma, even in patients with normal vital signs.³⁻⁶ Surprisingly, very few studies have compared them,⁸⁻¹¹ and some studies limited the comparison to elderly patients,³⁵ torso injury,⁹ or vascular injury.¹¹ Unfortunately, none of them appropriately compared the additive prognostic value of these two biomarkers.¹² This might be important since acid-base based variables are recognized as important variables beside clinical variables to identify high-risk trauma patients.^{5,23} Moreover, their variation over time may guide early resuscitation as shown by the concept of lactate clearance which represents an independent prognostic factor providing additional critical information to initial blood lactate. In our study, several arguments support the choice of blood lactate as a predictor of mortality: 1) although the area under the receiving operating characteristic curves were similar, increased blood lactate

1 occurred less frequently than increased base deficit (39% and 67%) and discrepancies
2 between increased blood lactate and base deficit were more frequently related to base deficit
3 than blood lactate (35% vs 7%); 2) using multivariate analysis, blood lactate was a significant
4 predictor of mortality in all models whereas base deficit was not (Table 3); 3) using
5 reclassification methods and in both normotensive patients and those with a high probability
6 of survival, adding blood lactate significantly modified the predictive performances whereas
7 base deficit did not.
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17 To identify the possible mechanisms involved in the different capacities of blood
18 lactate and base deficit to predict mortality, we considered patients with discrepancy between
19 these two biomarkers and identified two mechanisms that may play a role, ventilation and
20 prehospital fluid loading (Table 2). Ventilation may modify the acid-base equilibrium through
21 modification of carbon dioxide pressure and prehospital fluid loading may act through various
22 processes including hyperchloremic acidosis induced by saline,³⁶ colloid-related
23 administration of nonvolatile weak acid,³⁷ and lastly hemodilution which modifies protein
24 concentration and thus acid-base equilibrium.³⁸ Nevertheless, in these two subgroups of
25 patients with discrepancy, base deficit and lactate levels were not very high and differences
26 between groups had limited magnitude (Table 2). However, we cannot rule out the hypothesis
27 that other mechanisms may explain why base deficit is less accurate than blood lactate in
28 predicting mortality in trauma patients. Our mechanistic analysis remains subjective and
29 further studies should be performed to better understand this point and several hypotheses can
30 be evoked such as modification of lactate clearance, strong ion difference, phosphate or
31 albumin concentration and the role of unmeasured anions.³⁹
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53 Blood lactate was also superior to base deficit in predicting early deaths, severe
54 traumatic lesions (ISS > 15), and massive hemorrhage. In contrast, base deficit was superior
55 to blood lactate in predicting the need for emergency procedure and prolonged ICU duration.
56 We have previously demonstrated that all scores (RTS, MGAP, TRISS) are very poor
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1 predictors of the need for emergency procedures, probably because these emergency
2 procedures may be life-saving and thus may not be systematically linked with a poor outcome
3 and sometimes they may not be attempted in moribund patients.¹³ We previously identified
4 some clinical variables which can predict the need for emergency procedures (systolic arterial
5 pressure, heart rate, fluid loading, penetrating trauma), but the accuracy of the model was
6 relatively weak.¹³ Some biological variables may be useful, but base deficit might be more
7 suitable than blood lactate for that purpose. Base deficit was better than blood lactate in
8 predicting a prolonged stay in the ICU. This may be related to the fact that ICU length of stay
9 might be affected by excessive fluid loading. This might be important since the duration of
10 ICU stay might be also a clinically and economically relevant criterion in assessing morbidity
11 of trauma patients beside mortality itself.

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In normotensive patients, blood lactate was also superior to base deficit in predicting mortality. This result contrasts with our previous report indicating that blood lactate and lactate clearance did not add significant additional information to that provided by MGAP, RTS, or TRISS.⁵ This discrepancy is probably explained by the limited power of our previous study which included only a relatively small sample size of normotensive patients (n=361 vs n=749), but who had more severe trauma than the actual sub-population (median ISS 14 vs. 12). Anyway, although biological variables (blood lactate, lactate clearance, and base deficit) may be useful to assess the initial severity of trauma patients, other variables such as renal artery or microcirculation blood flow might be more appropriate to diagnose occult hypoperfusion in normotensive trauma patients.^{33,40}

Some limitations in our study deserve consideration. First, this study was performed in an adult population and thus may not apply to pediatric patients.⁴¹ Second, our study was observational and we demonstrated an association but cannot infer causality. Third, our result cannot be generalized to minor trauma since many of these patients were excluded from our analysis because of missing values of lactate and/or base deficit. Fourth, our study was

1 conducted in a prehospital system in which intensive medical treatment is administered on
2 scene by physician, especially normal saline, which can both slightly delay hospital admission
3 and modify the prognosis,⁴² thus potentially interfering with timing and prognostic value of
4 initial blood lactate and lactate clearance measurements. However, we have previously
5 demonstrated that there is no significant correlation between initial blood lactate and
6 prehospital time.⁵ We did not test other acid-base variable such anion gap, and strong ion gap
7 since they are less routinely performed than blood lactate and base deficit. Although, strong
8 ion gap was more predictive of mortality in patients with vascular injury,¹¹ no data are
9 available concerning the additional predictive value of these acid-base variables. Future
10 studies could help to investigate whether such a metabolic analysis (*i.e.* strong ion gap) could
11 add relevant information for outcome prediction in trauma patients since this metabolic
12 assessment needs more elaborate methods at a time the physician needs easy to use
13 markers. A subgroup analysis of patients according to the mechanism of injury could have
14 been interesting since the value of base deficit as a predictor of mortality appears less useful
15 for patients sustaining stab wounds.⁴³ However, the small number of deaths (n=7) observed in
16 this category precludes any valid analysis. Our study cannot definitely identify the
17 mechanisms involved in the prognostic differences observed between blood lactate and base
18 deficit and we could have missed some other important mechanisms. Lastly, it should be
19 pointed out that the additional prognostic values provided by these two biomarkers remains of
20 relatively low magnitude (as shown by small increase in c-statistics or small odds ratio in
21 logistic regression).

54 CONCLUSION

57 In a large observational study (n=1075), we observed that initial blood lactate should
58 be preferred to base deficit as a biological variable to assess initial severity of trauma patients.
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This might be important since acid-base based variables are recognized as important variables
beside clinical variables to identify high-risk trauma patients and guide early
resuscitation.^{5,23,44}

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Table 1. Comparison of patients who survived or not (n=1,075).

	ALIVE (n=934)	DEAD (n=141)	P value
Men	732 (78%)	111 (79%)	1.00
Women	202 (22%)	30 (21%)	
Age, yr	38 ± 17	48 ± 21	<0.001
Type of trauma			
Blunt	838 (90%)	127 (90%)	1.00
Penetrating	96 (10%)	4 (10%)	
Mechanism:			
Fall	252 (27%)	62 (44%)	<0.001
Road crash	553 (59%)	62 (44%)	<0.001
Gunshot	23 (2%)	7 (5%)	0.10
Stab wound	73 (8%)	7 (5%)	0.30
Other	33 (3%)	3 (2%)	0.61
Localization of Trauma			
Head/neck	428 (46%)	122 (86%)	<0.001
Face	204 (22%)	39 (28%)	0.13
Thorax	450 (48%)	91 (64%)	<0.001
Abdomen	324 (35%)	45 (32%)	0.57
Limb	538 (58%)	57 (40%)	<0.001
Prehospital Phase			
Systolic arterial blood pressure, mmHg	123 ± 24	99 ± 39	<0.001
Heart rate, bpm	95 ± 22	101 ± 34	<0.001
Glasgow Coma Score	15 [13-15]	4 [3-9]	<0.001
Peripheral oxygen saturation, %	98 [96-100]	96 [90-100]	<0.001
Cardiac arrest	12 (1%)	35 (25%)	<0.001
Catecholamine administration	75 (8%)	64 (45%)	<0.001
Mechanical ventilation	243 (26%)	123 (87%)	<0.001
Crystalloids, ml	500 [500-1000]	1000 [500-1500]	<0.001
Crystalloids >500 ml	392 (42)	82 (58)	<0.001
Colloids, ml	0 [0-0]	0 [0-500]	<0.001
Colloids >500 ml	37 (4%)	17 (12%)	0.001
RTS	7.84 [7.11-7.84]	4.09 [3.46-6.27]	<0.001
MGAP	27 [23-27]	15 [13-20]	<0.001
Hospital Phase			
Systolic arterial blood pressure, mmHg	123 ± 24	108 ± 36	<0.001
Heart rate, bpm)	90 ± 21	91 ± 32	0.51
Hemoglobin, g/dl)	12.8 ± 2.0	10.6 ± 2.8	<0.001
Erythrocyte transfusion within 24h	122 (25%)	78 (57%)	<0.001
Erythrocyte transfusion within 24h, units*	4 [2-8]	7 [4-12]	0.001
Massive hemorrhage	84 (9%)	46 (33%)	<0.001
Emergency procedure	63 (8%)	26 (20%)	<0.001
Catecholamine administration	156 (17%)	86 (61%)	<0.001
ISS	13 [8-22]	32 [24-41]	<0.001
ISS > 15	425 (45%)	130 (92%)	<0.001
TRISS	0.99 [0.96-0.99]	0.53 [0.24-0.89]	<0.001
Duration of hospitalization, days	11 [5-25]	2 [1-7]	<0.001
Duration of ICU, days	5 [2-14]	2 [2-7]	<0.001
Duration of ICU stay > 2 d and/or death	634 (68%)	141 (100%)	-
Base deficit and blood lactate			
Base deficit, mM/l	3.6 ± 3.6	9.4 ± 7.4	<0.001
Blood lactate, mM/l	2.2 ± 1.7	5.4 ± 4.4	<0.001

Data are mean \pm SD, median [25-75 interquartile], or number (percentages). 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; *: values concern only transfused patients;

Table 2. Comparison of patients with elevated base deficit and normal blood lactate (n=372) and patients with elevated blood lactate and normal base deficit (n=72)

	Elevated Base Deficit Normal Lactate (n=372)	Elevated Lactate Normal Base Deficit (n=72)	P values
Men	268 (72%)	59 (82%)	0.11
Women	104 (28%)	13 (18%)	
Age, yr	39 ± 18	44 ± 18	0.05
Body mass index, kg.m ⁻²	24.5 ± 3.9	24.7 ± 3.6	0.72
Type of trauma			
Blunt	337 (91%)	167 (93%)	1.00
Penetrating	35 (9%)	5 (7%)	
Prehospital Phase			
Systolic arterial blood pressure, mmHg	116 ± 23	119 ± 25	0.30
Heart rate, bpm	93 ± 21	97 ± 24	0.19
Glasgow coma score	15 [11-15]	15 [13-15]	0.62
Peripheral oxygen saturation, %	98 [96-100]	98 [96-100]	0.65
Cardiac arrest	6 (2%)	0 (0%)	0.60
Catecholamine administration	35 (10%)	3 (4%)	0.17
Mechanical ventilation	120 (32%)	19 (26%)	0.34
Crystalloids, mL	500 [500-1000]	500 [500-500]	<0.001
Crystalloids >500 mL	146 (46%)	13 (22%)	<0.001
Colloids, mL	0 [0-0]	0 [0-0]	0.14
Colloids > 500 mL	48 (15)	5 (8)	0.22
Hospital Phase			
Systolic arterial blood pressure, mmHg	123 ± 23	128 ± 24	0.08
Heart rate, bpm	88 ± 19	95 ± 23	0.004
Body temperature, °C	36.4 ± 1.0	36.5 ± 1.3	0.56
Erythrocyte transfusion within 24h	89 (25%)	12 (17%)	0.17
Erythrocyte transfusion within 24h, units*	4 [2-5]	4 [2-7]	1.00
Massive hemorrhage	84 (9%)	46 (33%)	1.00
Emergency procedure	21 (7%)	6 (10%)	0.42
Catecholamine administration	66 (18%)	9 (13%)	0.35
Biology			
Hemoglobin, g/dl	12.6 ± 1.7	13.3 ± 2.3	0.006
Creatinin, μM/l	76 ± 27	76 ± 22	0.89
Arterial pH	7.36 ± 0.06	7.38 ± 0.08	0.005
PaCO ₂ , mmHg	38 ± 7	43 ± 7	<0.001
PaO ₂ , mmHg	198 ± 124	177 ± 124	0.19
Bicarbonates, mM/l	21.6 ± 2.7	23.4 ± 3.0	<0.001
Fibrinogen, mg/dl	237 ± 85	272 ± 115	0.005
Base deficit, mM/l	4.2 ± 1.9	0.5 ± 1.4	-
Blood lactate, mM/l	1.4 ± 0.5	3.3 ± 1.5	-

Data are mean ± SD, median [25-75 interquartile], or number (percentages). 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. PaCO₂: arterial carbon dioxide partial pressure; PaO₂: arterial oxygen partial pressure; *: values concern only transfused patients.

Table 3. Effects of adding initial blood lactate or base deficit to Revised Trauma Score (RTS), Mechanism, Glasgow, Age, arterial Pressure score (MGAP), and Trauma Related Injury Severity Score (TRISS) in predicting mortality.

Variables	Odds ratio [95% CI]	P value
<i>Model (n=1034; AUC=0.88, optimism<0.01)</i>		
RTS (per 1 point decrease)	2.55 [2.18-2.99]	<0.001
Blood lactate (per 1 mM/l increase)	1.21 [1.05-1.39]	0.007
Base deficit (per 1 mM/l increase)	1.00 [0.93-1.08]	0.96
<i>Model (n=1033; AUC=0.88, optimism<0.01)</i>		
MGAP (per 1 point decrease)	1.37 [1.30-1.44]	<0.001
Blood lactate (per 1 mM/l increase)	1.18 [1.03-1.35]	0.018
Base deficit (per 1 mM/l increase)	1.06 [0.98-1.13]	0.13
<i>Model (n=1033; AUC=0.85, optimism<0.01)</i>		
TRISS (per 0.1 point decrease)	1.76 [1.60-1.94]	<0.001
Blood lactate (per 1 mM/l increase)	1.22 [1.07-1.39]	0.003
Base deficit (per 1 mM/l increase)	1.03 [0.96-1.10]	0.39

Blood lactate and base deficit were forced into the models and should be considered as competitors, explaining low odds ratio values. AUC: area under the receiver-operating characteristic curve; CI, confidence interval. Optimism is the difference of AUC between the entire population and the cross validated population.

Table 4: Net reclassification index (NRI) when adding initial blood lactate or base deficit to Revised Triage Score (RTS), Mechanism Glasgow scale and Arterial Pressure (MGAP) score, and the Trauma Related Injury Severity Score (TRISS).

	Clinical score with lactate		Clinical score with base deficit	
	NRI	<i>P</i> value	NRI	<i>P</i> value
RTS	0.36±0.10	0.001	0.20±0.10	0.03
MGAP	0.41±0.10	<0.001	0.36±0.09	<0.001
TRISS	0.40±0.09	<0.001	0.35±0.09	<0.001

Data are mean ± SD

Table 5. Effects of adding initial blood lactate or base deficit to Revised Trauma Score (RTS), Mechanism, Glasgow, Age, arterial Pressure score (MGAP), and Trauma Related Injury Severity Score (TRISS) scores in predicting deaths in normotensive patients and in patients with a high probability of survival (See text for definition)

NORMOTENSIVE PATIENTS	Odds ratio [95% CI]	P value
<i>Model (n=742; AUC=0.79, optimism<0.01)</i>		
RTS (per 1 point decrease)	3.06 [2.36-3.96]	<0.001
Blood lactate (per 1 mM/l increase)	1.36 [1.09-1.68]	0.005
Base deficit (per 1 mM/l increase)	1.05 [0.93-1.17]	0.45
<i>Model (n=742; AUC=0.81, optimism<0.01)</i>		
MGAP (per 1 point decrease)	1.39 [1.29-1.51]	<0.001
Blood lactate (per 1 mM/l increase)	1.31 [1.08-1.61]	0.01
Base deficit (per 1 mM/l increase)	1.07 [0.96-1.20]	0.21
<i>Model (n=742; AUC=0.70, optimism<0.01)</i>		
TRISS (per 0.01 point decrease)	2.07 [1.72-2.51]	<0.001
Blood lactate (per 1 mM/l increase)	1.34 [1.08-1.65]	0.007
Base deficit (per 1 mM/l increase)	1.03 [0.98-1.15]	0.62
PATIENTS WITH A HIGH PROBABILITY OF SURVIVAL		
<i>Model (n=807; AUC=0.73, optimism<0.01)</i>		
RTS (per 1 point decrease)	3.37 [2.30-4.93]	<0.001
Blood lactate (per 1 mM/l increase)	1.64 [0.99-1.64]	0.06
Base deficit (per 1 mM/l increase)	1.01 [0.87-1.17]	0.88
<i>Model (n=807; AUC=0.80, optimism<0.01)</i>		
MGAP (per 1 point decrease)	1.39 [1.26-1.54]	0.002
Blood lactate (per 1 mM/l increase)	1.23 [0.92-1.55]	0.09
Base deficit (per 1 mM/l increase)	1.06 [0.97-1.21]	0.43
<i>Model (n=807; AUC=0.77, optimism<0.01)</i>		
TRISS (per 0.01 point decrease)	1.41 [1.23-1.61]	<0.001
Blood lactate (per 1 mM/l increase)	1.25 [1.02-1.53]	0.03
Base deficit (per 1 mM/l increase)	1.09 [0.97-1.22]	0.16

Blood lactate and base deficit were forced into the models and should be considered as competitors, explaining low odds ratio values. AUC: area under the receiver-operating

characteristic curve; CI: confidence interval. Optimism is the difference of AUC between the entire population and the cross validated population.

Appendix

The following investigators belong to the TraumaBase Group®: Pr. Jacques Duranteau MD, PhD (Le Kremlin-Bicêtre, France), Pr. Olivier Langeron MD, PhD (Paris, France), Pr. Jean Mantz MD, PhD (Paris, France), Pr. Catherine Paugam-Burtz MD, PhD (Clichy, France), and Dr. Bernard Vigue MD (Le Kremlin-Bicêtre, France).

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Figure legends

Figure 1: Correlation between initial blood lactate and base deficit (n=1,075, $R^2=0.55$, $P<0,001$). The black dotted line corresponds to the linear regression curve, the red dotted lines to normal range thresholds (2.2 mM/l for lactate and 2.0 mM/l for base deficit).

Figure 2: Averaged receiving operating characteristics curves of initial blood lactate (Panel A), and base deficit (Panel B). The outcome is in-hospital mortality, defined as death occurring within 30 days after hospital admission or prior to discharge when discharge occurred within 30 days. P values refer to the comparison of the area under the receiving operating characteristics curves (AUC) vs 0.50 (i.e. no discrimination). The dotted line corresponds to the non-discrimination curve.

Figure 3: Proportion of patients (n=1,075) in the predefined categories of initial blood lactate (Panel A) and base deficit (Panel B).

Figure 4: Graphical reclassification: Probabilities of death obtained with blood lactate (Panels A and C) and base deficit (Panels B and D) knowing Mechanism, Glasgow, Age, arterial Pressure (MGAP) score (Panels A and B) or Trauma Related Injury Severity Score (TRISS) (Panels C and D) in the whole population (n=1,075). The outcome is in-hospital mortality, defined as death occurring within 30 days after hospital admission or prior to discharge when discharge occurred within 30 days. Deceased patients (red dot) were expected to have a higher probability of death when initial blood lactate levels or base deficit were included (i.e. correct reclassification) and be in the red sector. On the contrary survivors (green dot) should have a lower probability of death when initial blood lactate level or base deficit were included and be in the green sector. For patients in the grey sector (i.e. less than 30% difference between both

probabilities), blood lactate or base deficit did not change significantly the probability given by either MGAP or TRISS (not clinically relevant reclassification). Color mismatches (e.g. red patients in green sector) represent significant misclassification.







