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Original Contribution

Blood lactate measurement within the emergency department: A two-year retrospective analysis

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ABSTRACT

We evaluate in this retrospective cohort, the clinical situations leading emergency physicians to take a blood lactate sample, the prevalence of hyperlactatemia and its impact on short-term adverse outcome. ED patients requiring a blood lactate measurement (BLM) during a two-year period were included. Early patients' outcomes were extracted and discharge diagnoses were classified into 12 diagnostic categories. A total of 118,737 patients were analyzed. A BLM was carried out in 13,089 of them. Surprisingly, the proportion of patients having a BLM was higher in those admitted for seizure (31.4%) than in those admitted for infection (27.9%). Ten percent of patients who had a blood lactate test had a lactate level >4 mmol/l (1,315). Among them, 23.2% were admitted for infections, 20% for seizures, and 11% for cardiovascular diseases. After excluding the patients older than 75 years from the analysis in order to prevent a selection bias, the patient's severity was independently associated to an age over 65 years (OR: 1.26), an arterial blood sampling (OR: 2.77) and the blood lactate level (OR: 1.31). The blood lactate level was very informative to detect the sicker patients in the infection group whereas its interest was poor in the group of patients admitted for seizures. In conclusion, blood lactate testing has become routine in emergency departments and a large proportion of patients have abnormal blood lactate levels. The most frequent causes of high blood lactate in the ED are infection and seizures but the prognostic value of blood lactate seems to be different from one diagnostic category to the other.

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1. Introduction

Serum blood lactate measurement is widely used in emergency departments (ED) to help physicians to improve their diagnostic process, prognosis and treatment in various clinical situations [1-3]. Current trauma guidelines recommend measuring lactate to stratify the risk of patients and guide fluid administration [4]. It is also recommended for the diagnosis and the prognostic staging of infection by the Surviving Sepsis Campaign [5]. Moreover, blood lactate has shown to be useful for both prognosis and diagnosis in many other clinical situations such as pulmonary embolism [6, 7], gastrointestinal bleeding [8, 9], acute abdominal pain [10, 11] or syncope [12].

It was initially recommended that the site of blood sampling for lactate measurement to be arterial, but several papers have reported that venous blood lactate can efficiently replace arterial sampling [13-15]. Accordingly, venous blood lactate measurement is currently the most frequently used in emergency medicine, as venous sampling is easier to perform and less painful.

Because of the broad indications and its ease of use, lactate is probably increasingly used in emergency departments. However, there is no study evaluating the clinical situations leading emergency physicians to measure blood lactate in a large cohort of ED patients.

In the present study, we aim at:

(i) describing the various clinical situations leading emergency physician to take a blood lactate sample in the ED
(ii) assessing hyperlactatemia prevalence in the ED and the main causes related to high blood lactate concentration
(iii) assessing the impact of high blood lactate concentration on short-term adverse outcome in unselected ED patients

2. Methods

2.1. Setting and selection of participants

This was a single center, retrospective cohort study conducted in a French ED of a university hospital with a current annual census of about 90,000. The research was approved by our institutional review board. Ethical and governance approval was provided by the "Commission Nationale Informatique et Liberté (CNIL)". According to French law, written consent was not required.

All patients presenting to the ED from January 2015 to December 2016 had their medical records examined via the hospital electronic

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health record. The inclusion criteria were: adult patients (minimum age 18 years) who were admitted to the ED and who required an initial blood lactate level drawn. When several lactate levels were measured from the same patient, we included only the first blood lactate concentration. Patients were classified into three groups depending on their baseline lactate concentration: "Normal Blood Lactate (NBL)" for a lactate concentration absolutely <2 mmol/l, "Intermediate Blood Lactate (IBL)" for a lactate concentration between 2 and 3.9 mmol/l, and "High Blood Lactate (HBL)" for a lactate concentration greater than or equal to 4 mmol/l.

2.2. Definition of diagnostic groups

Discharge diagnoses were noted from the patients' discharge summaries and ICD-10 coding. The varying diagnoses were classified into 12 categories representing the most frequent nosological classes encountered in emergency medicine: infections, shock states, acute abdominal syndrome, cardiovascular diseases, seizure/fainting, pulmonary diseases, metabolic disorders, traumatic injury/burns, toxicology, hematologic, neurological diseases, and other. The different diagnoses included for each category are presented in Table 1.

To detect the more severe patients, we elaborated a composite criterion that was defined by the presence of at least one of these parameters: ICU admission, requirement of emergent surgery or death within the ED. We eliminated the patients older than 75 from the severity analysis to limit the potential bias secondary to an eventual non-ICU admission for ethical reasons.

2.3. Data analysis

Because biological and clinical data were extracted from different files, it was necessary in a first time to match the right blood tests with the right patients. In order to do it, we performed a visual basic program on a MS Excel file that matched the lab data (family names, dates of birth and blood sampling day) with those derived from the ED registration. In case of several occurrences found for a same name at the same date or in case of date discrepancy, the corresponding data were systematically eliminated and not used for final analysis.

Depending on their distribution, data are presented as means ± SD or medians [extremes] for continuous variables and percentages for categorical ones. Medians of blood lactate concentration were compared using Mann and Whitney or Kruskall Wallis tests as appropriate. Percentages were compared using chi2 test. ROC curves were constructed to evaluate the capacity of lactate to discriminate some categories of patients. A multivariate analysis using a logistic regression by a backward method was used to determine the factors independently associated to a categorical dependent variable. The corresponding odds ratio with their 95% interval confidence were used to assess the weight of each factor to this association. All analyses were performed using the MedCalc statistical software (MedCalc software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

A p value of <0.05 was considered as statistically significant.

3. Results

3.1. Characteristics of study subjects

Between January 2015 and December 2016, 175,375 consecutive patients presented to the emergency department of Nice University Hospital. Among them, 43,410 were managed by other specialists than emergency physicians (psychiatrist, ophthalmologist, and dentist) and therefore excluded from analysis. Ten more percent of patients were excluded from analysis either because of discharge diagnoses lacking (n = 11,010) or because of uncertainty in the matching between the blood test and the medical file (n = 2218) (Fig. 1). Thus 118,737 patients were included in the final analysis. The average age of our population was 52 ± 23 years, with most of men (sex ratio = 1.12). The four diagnostic categories most represented in our population were: traumatic injury/burns (30.4%), acute abdominal syndrome (9.8%), infections (8.5%), and neurological diseases (6.2%) (Table 2).

3.2. Blood lactate measurement

During the study period, blood lactate was measured in 13,089 patients (11.0%). The patients who benefited the most frequently of a blood lactate measurement were infected patients (n = 2810, 21.5%), followed by patients with acute abdominal syndrome (n = 2087, 16%), patients with cardiovascular diseases (n = 1772, 13.5%) and patients admitted for fainting/seizures (n = 1397, 10.7%) (Table 2). The diagnostic categories during which blood lactate was the most frequently measured were metabolic disorders (45.4%), shock states (34.8%), pulmonary pathologies (32.9%), and fainting/seizures (31.4%) (Fig. 2). Blood lactate was measured in 28% of the patients with infection and 1.8% of the patients admitted for traumatic injury (Fig. 2). Blood lactate was measured much more often in admitted patients than in those discharged, (49.1% vs. 11.8% for infection, $p < 0.001$; 37.3% vs. 13.1% for acute abdominal syndrome, $p < 0.001$; 7.6% vs. 0.8% for traumatic injury, $p < 0.001$).

Lactate concentration was measured in the venous blood for the great majority of patients (n = 12,356 [94.4%]). Venous blood lactate concentration (1.66 mmol/l [0.21–28.07]) was not significantly different from arterial concentration (1.71 mmol/l [0.37–24.89], p = 0.077).

3.3. Prevalence of hyperlactatemia in the ED

The median blood lactate value in our population was 1.66 mmol/l, with extremes varying from 0.21 to 28.07 mmol/l. A total of 4922 patients (37.6%) had abnormally high lactate levels, of whom 10% (n =

Table 1
Presentation of the main pathologies for each diagnostic category.

Diagnostic categories	Pathologies
Infection	All kind of infections including abdominal ones, sepsis, septic shock.
Shock states	Anaphylactic shock, cardiogenic shock, Hemorrhagic shock, and hypovolemic shock.
Acute abdominal syndrome	Occlusive syndrome, hernia, renal colic, not specific abdominal pain, pancreatitis, gastrointestinal bleeding (without shock).
Cardiovascular diseases	Acute coronary syndrome, pulmonary embolism, rhythm disorders, ischemic stroke, acute limb ischemia, aortic dissection, acute mesenteric ischemia.
Seizure/fainting	All spontaneous loss of consciousness, epilepsy.
Pulmonary diseases	COPD, other respiratory failure, asthma, spontaneous pneumothorax.
Metabolic disorders	Diabetic ketoacidosis, ionic disorders (dyskalemia, dysnatremia…)
Traumatic injury/burns	Fractures, dislocations, contusions, traumatic hemo-pneumothorax, all burns (first, second and third degree)
Neurological pathologies	Cerebral Hemorrhage, myasthenia, neuropathy, headache, facial paralysis.
Hematology	Anemia, thrombocytopenia, leukemia, aplasia, lymphoma.
Toxicology	Acute alcoholic intoxication, drug poisoning.
Other	N/A

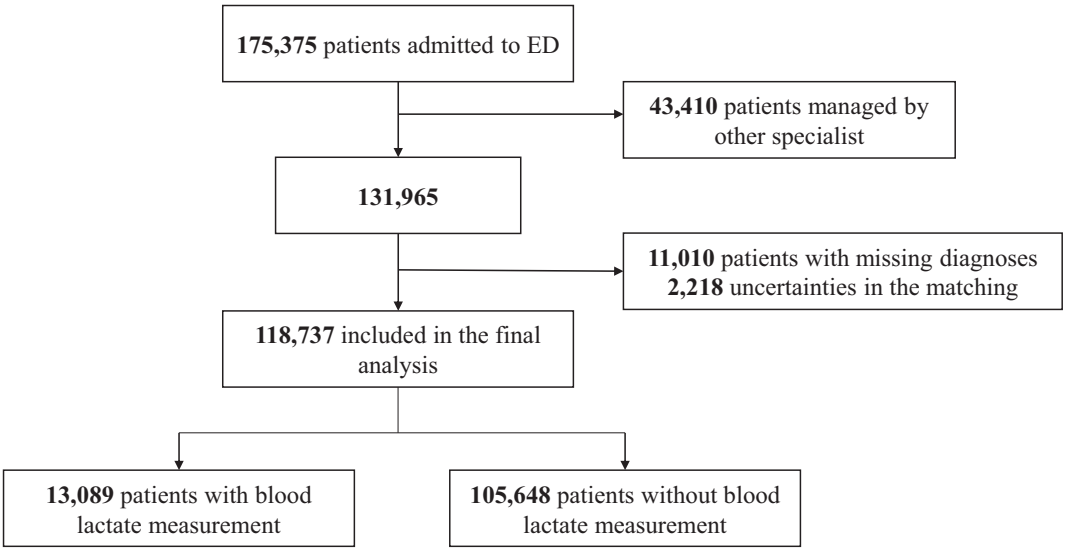

Fig. 1. Study Flowchart.

1315) had HBL and 27.6% (n = 3607) had IBL. Among the patients with HBL, the most frequently diagnostic categories were infections (23.2%), fainting/seizures (20%), cardiovascular diseases (11%) and acute abdominal syndrome (9.6%) (Table 3). The highest proportion of patients with HBL within the same diagnostic category was found to be shock states (29.3%), followed by fainting/seizures (18.8%).

3.4. Blood lactate concentration to evaluate patient's severity

3.4.1. Whole population (n = 13,089)

Patients who died during the ED stay (n = 78) had a significantly higher blood lactate value (6.75 mmol/l [0.71–25.76]) ($p < 0.005$) than those admitted (1.81 mmol/l [0.21–28.07], n = 8091, $p < 0.05$) and those discharged home (1.46 mmol/l [0.35–26.19], n = 4920) (Fig. 3).

Table 2
Characteristic of patients investigated.

Population	Total (n = 118,737)	BLM (n = 13,089)	No BLM (n = 105,648)	p value
Age (years) ± SD	52 (±23)	64 (±22)	50 (±23)	<0.0001
Sex ratio (M/F)	1.12	1.09	1.12	NS
Diagnostic categories				
Shock states	528 (0.4)	184 (1.4)	344 (0.3)	<0.0001
Fainting/seizures	4454 (3,8)	1397 (10.7)	3057 (2.9)	<0.0001
Infections	10,053 (8.5)	2810 (21.5)	7243 (6.9)	<0.0001
Pulmonary pathologies	2908 (2.4)	958 (7.3)	1950 (1.8)	<0.0001
Metabolic disorders	2201 (1.9)	999 (7.6)	1202 (1.1)	<0.0001
Acute abdominal syndrome	11,633 (9.8)	2087 (16)	9546 (9)	<0.0001
Cardiovascular diseases	11,854 (1)	1772 (13.5)	10,082 (9.5)	<0.0001
Neurological diseases	7402 (6.2)	657 (5)	6745 (6.4)	<0.0001
Toxicology	5410 (4.6)	460 (3.5)	4950 (4.7)	<0.0001
Traumatic injuries/burns	36,076 (30.4)	647 (5)	35,429 (33.5)	<0.0001
Hematology	694 (0.6)	126 (0.9)	568 (0.5)	<0.0001
Other	25,514 (21.5)	982 (7.5)	24,532 (23.2)	<0.0001
Outcomes				
Discharged	89,235 (75.2)	4920 (37.6)	84,315 (79.8)	<0.0001
Admitted	29,341 (24.7)	8091 (61.8)	21,250 (20.1)	<0.0001
Died during ED stay	161 (0.1)	78 (0.6)	83 (0.08)	<0.001
ICU transfer	2341 (2)	1156 (8.8)	1185 (1.1)	<0.0001

Data are presented as No (%) unless otherwise indicated. The p value provides the result of comparison between "BLM" (Blood lactate measurement) and "No BLM" (No Blood lactate measurement).

3.4.2. Population without the patients older than 75 (n = 7854)

The proportion of severe patients (evaluated by the presence of the composite criterion) was significantly different according to the initial blood lactate level (8.3% for NBL, 15.7% for IBL and 30.5% for HBL, $p < 0.0001$). For the overall diagnostic categories, a blood lactate ≥4 mmol/l had a specificity of 92.4% (95% CI: 91.7–93) and a sensitivity of 23.7% (95% CI: 21.1–26.5) to detect a severe patient.

A logistic regression including in the model the blood lactate concentration, the patient's age, the sample site (arterial or venous) and the diagnostic categories, showed that the factors associated to the patient's severity were the blood lactate concentration, an age over 65, an arterial sampling, and most of the diagnostic categories except the fainting/seizure that was associated to a lower risk (model AUC: 0.761, Table 4).

The discriminative power of blood lactate concentration to detect severe patients was compared for the patients admitted to the ED for fainting/seizures and those admitted for infection (Fig. 4). The median blood lactate was significantly different between the severe and the non-severe patients for both infection (1.43 mmol/l [1.48–10.06] vs. 2.73 mmol/l [0.58–23.98], $p < 0.0001$) and fainting/seizure (1.96 mmol/l [0.55–26.25] vs. 3.30 mmol/l [0.47–18.89], $p < 0.05$). However, the overlapping was major between the severe and the non-severe patients for the fainting/seizure group, the higher blood lactate values even being observed in the non-severe group of patients (Fig. 4).

4. Discussion

The prevalence, causes and outcomes associated to hyperlactatemia have largely been studied in patients admitted to intensive care unit but data on patients in the emergency department are really poor [16-18]. Our study, based on the largest cohort of unselected ED patients, attempted to describe the various pathologies associated to blood lactate measurement, to assess the incidence of hyperlactatemia and to evaluate its consequences on early morbi-mortality.

We found that about 11% of patients managed by ED physicians had a serum lactate measurement. This value is almost twice as important as that reported by Van den Nouland and al (5.8%) in their retrospective study conducted in Netherland between 2011 and 2014 [16]. This increase probably reflects the fact that emergency physicians currently measure blood lactate more often and in broader indications.

It is noteworthy that >30% of patients admitted to the ED for fainting or seizure had a blood lactate drawn. It is likely that physicians used blood lactate measurement in these patients to detect unwitnessed

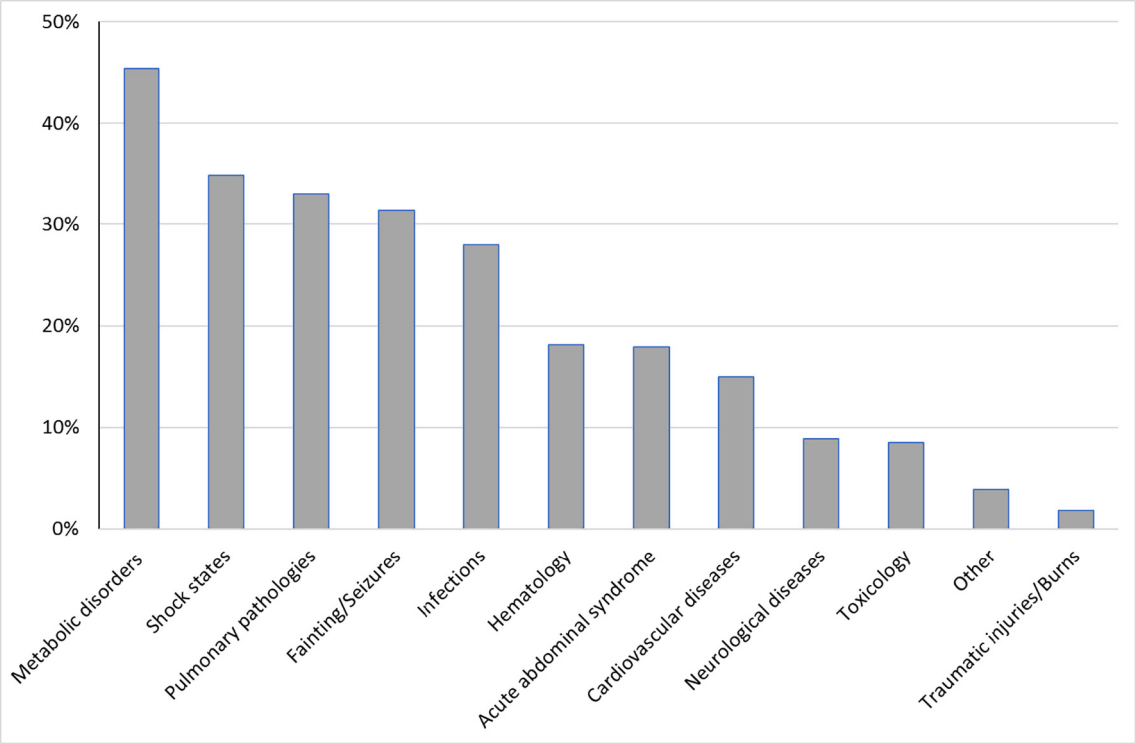

Fig. 2. Proportion of patients having a blood lactate measurement according the diagnostic category.

seizures, as already reported and suggested by several studies [12, 19, 20]. Seizure was one of the main causes of HBL concentration in our study and, since blood lactate measurement was widely used in this indication, this probably explains the higher percentage of HBL than those previously reported. For instance, Pedersen et al. reported 6.6% of HBL in their cohort that included much less patients than our study [21].

Even if infection was in absolute terms the first cause of blood lactate measurement in our cohort, only one in four infected patients had a lactate assay. This may appear surprising in regard to the current recommendations and to the importance of this biomarker in this clinical situation, as confirmed by our results. However, the patients with the infection label in our cohort included a wide variety of clinical situations, such as for instance benign viral infection or uncomplicated cystitis, during which even no blood tests were performed. When focusing on the infected patients needing to be admitted, this proportion of blood lactate measurement increased to almost 50%, which gives evidence to this assumption.

Table 3
Breakdown of diagnostic categories according to blood lactate level.

Population	Total	NBL (%)	IBL (%)	HBL (%)
N	13,089	8167	3607	1315
Diagnostic categories				
Shock states	184	72 (0.9)	58 (1.6)	54 (4.1)
Discomfort/seizures	1397	730 (8.9)	404 (11.2)	263 (20)
Infections	2810	1750 (21.4)	755 (20.9)	305 (23.2)
Pulmonary pathologies	968	613 (7.5)	258 (7.2)	97 (7.4)
Metabolic disorders	999	615 (7.5)	282 (7.8)	102 (7.8)
Acute abdominal syndrome	2087	1445 (17.7)	516 (14.3)	126 (9.6)
Cardiovascular diseases	1772	1099 (13.5)	529 (14.7)	144 (11)
Neurological diseases	657	438 (5.4)	181 (5)	38 (2.9)
Toxicology	460	248 (3)	157 (4.4)	55 (4.2)
Traumatic injuries/burns	647	386 (4.7)	204 (5.7)	57 (4.3)
Hematology	126	84 (1)	33 (0.9)	9 (0.7)
Other	982	687 (8.4)	230 (6.4)	65 (4.9)

Data are presented as No (%) unless otherwise indicated.
NBL (Normal Blood Lactate), IBL (Intermediate Blood Lactate), HBL (High Blood Lactate).

Blood lactate was measured in the venous blood for >94% of our patients, which confirms that ED physicians use preferentially venous blood lactate sampling. Surprisingly, the median blood lactate concentration was not significantly different between arterial and venous samples, whereas several papers have reported greater values in the venous blood [13, 22, 23]. This is probably the consequence that arterial sampling was rather done in the sickest patients, as demonstrated by the multivariate analysis, making the mean blood lactate value higher in this category of patients.

We evaluated the patient's severity using a composite criterion based on ICU admission, early death and emergent surgery requirement. We conducted the part of this analysis after excluding the elderly in order to minimize a potential bias linked to non-ICU admission for ethical reasons. Not surprisingly, we found that the proportion of severe

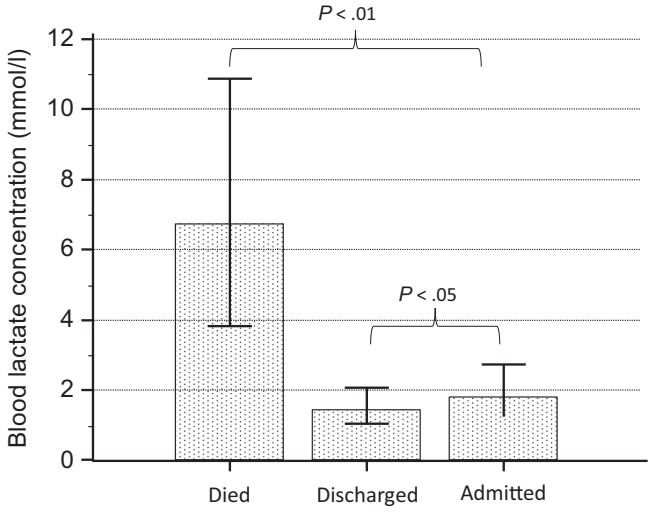

Fig. 3. Median blood lactate concentration according to patient's outcome. Error bars represent the 25th and the 75th percentiles.

Table 4
Results of the multivariate analysis showing the odds ratio (with their 95% confidence intervals) of the different parameters independently associated to the patient's severity. The patient's severity is evaluated by the presence or not of a composite criterion (early death or ICU admission or requirement of emergent surgery).

Variable	Odds ratio	95% CI	p value
Blood lactate concentration	1.31	1.27–1.35	<0.0001
Arterial blood sampling	2.77	2.13–3.62	<0.0001
Age > 65 years	1.26	1.08–1.48	<0.005
Diagnostic categories			
Infection	2.58	1.99–3.34	<0.0001
Pulmonary pathology	4.45	3.26–6.08	<0.0001
Metabolic disorder	3.55	2.61–4.83	<0.0001
Acute abdomen syndrome	2.15	1.61–2.81	<0.0001
Cardiovascular disease	4.94	2.66–9.17	<0.0001
Traumatic injury	3.71	2.66–5.18	<0.0001
Fainting/seizure	0.06	0.03–0.12	<0.0001

patients increased with the median blood lactate level. However, the discriminative power of blood lactate to detect the most severe patients was different from one diagnostic category to the other, as illustrated by the comparison between infection and fainting/seizure. Very high blood lactate levels are very common in seizing patients, but this is not clearly linked to the patient's severity, even if the median blood lactate value was significantly higher in the most severe seizing patients. This difference of the lactate prognostic power according to the diagnostic category has already been reported by others. For instance, Pedersen et al. [21] reported that blood lactate is useful in infections, cardiac diseases and trauma to predict 7-days mortality among ED patients whereas lactate is poorly informative in neurologic patients.

However, this study has some limitations. Firstly, it was a single retrospective study, and the management of our patients may be influenced by local work-up protocols that could promote blood lactate measurement. Furthermore, it is possible that some blood analyses were performed using point-of-care devices and these samples were not investigated in our study. This could underestimate the incidence of blood lactate measurement, especially in the most severe patients.

The diagnosis categories are based on patient discharge diagnoses. We cannot be sure that the ICD-10 discharge diagnoses are reliable enough to categorize patients in each diagnostic group. It remains besides a relatively large number of patients classified in “other” category, containing a lot of psychiatric disorders and other diagnoses making it impossible to determine a specific category.

The methodology that we used for the data linkage was a simple deterministic linkage depending on exact matches regarding the name, date of birth and blood sampling day. We could have used a more sophisticated methodology such as rules-based linkage, stepwise deterministic linkage or even probabilistic linkage in order to include much more data in the base [24]. However, our methodology produced a quite low missed match rate since <2% of the overall data were discarded from the analysis for a problem of data linkage.

Finally, we evaluated the patient's severity using a composite criterion that took into consideration only ICU admission, emergent surgery

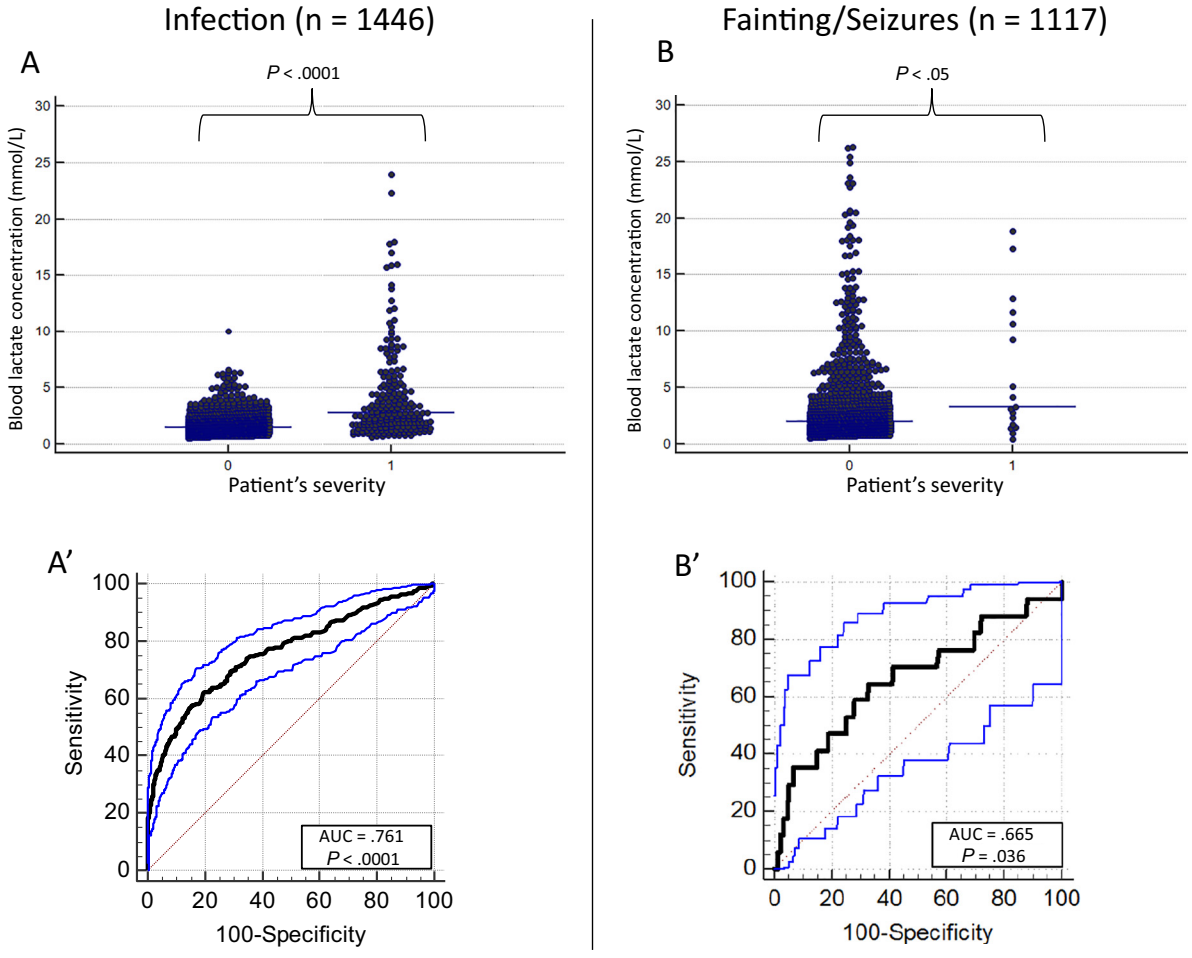

Fig. 4. Comparison of the effectiveness of blood lactate level to assess the patient's severity in two clinical situations: infection in the left panel (A) and fainting/seizure in the right panel (B). The top figures (A and B) show the blood lactate distribution with the medians (horizontal lines). The bottom figures (A' and B') show the ROC curves (bold line) with the 95% CI (thin blue lines) illustrating the capacity of blood lactate concentration to detect the patient's severity. The patient's severity is evaluated by the presence of a composite criterion (see Methods for details).

requirement and early death within the ED. We did not take into consideration the 28th day mortality, whereas it is a classical parameter used in the previously reported studies. Moreover, we eliminated the elderly from this analysis, which is highly questionable since most of the older people are not on palliative care. However previous studies or surveys have shown that older patients may be less likely to be admitted in ICU [25, 26] and we therefore decided to discard these patients in order to prevent that potential bias.

In conclusion, the present study describes the utilization of blood lactate measurement by emergency physicians in a large cohort of unselected ED patients. We report a high incidence of blood lactate measurement during broad clinical situations. This biomarker is now widely used by emergency physicians for both diagnostic and prognostic purposes and seems to be useful to predict bad outcomes in a broad population of ED patients. However, the utilization of blood lactate measurement is not an absolute tool and it requires, like all other biomarkers, to take into account the clinical context.

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