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Point-of-care testing on admission to the intensive care unit: lactate and glucose independently predict mortality

Abstract

Background: The aim of the study was to retrospectively investigate whether parameters of routine point-of-care testing (POCT) predict hospital mortality in critically ill surgical patients on admission to the intensive care unit (ICU).

Methods: Arterial blood analyses of 1551 patients on admission to the adult surgical ICU of the Technical University Munich were reviewed. POCT was performed on a blood gas analyser. The association between acid-base status and mortality was evaluated. Metabolic acidosis was defined by base excess (BE) <–2 mmol/L and, wherever applicable, subdivided into lactic acidosis by lactate >50% of BE, anion gap (AG)-acidosis by AG >16 mmol/L, hyperchloraemic acidosis by chloride >115 mmol/L. Metabolic alkalosis was defined by BE ≥3 mmol/L. Logistic regression analysis identified variables independently associated with mortality.

Results: Overall mortality was 8.8%. Mortality was greater in male patients (p=0.012). Mean age was greater in non-survivors (p<0.0005). Nine hundred and eighty-six patients showed no metabolic acid-base disorder (mortality 7.3%), thereof 26 patients with pCO_2 >55 mm Hg (mortality 23.1%). Three hundred and seventy-seven patients presented with acidosis (mortality 11.4%), thereof 163 patients with lactic acidosis (mortality 19%). Mortality for alkalosis (174 patients) was 12.1%. Mean blood glucose level for non-survivors was higher compared to survivors (p<0.0005). Logistic regression analysis identified lactate, glucose, age, male gender as independent predictors of mortality.

Conclusions: Lactate and glucose on ICU admission independently predict mortality. BE and AG failed as prognostic markers. Lactic acidosis showed a high mortality rate implying that lactate levels should be obtained on ICU admission. Prevalence of hyperchloraemic acidosis was low. Metabolic alkalosis was associated with an increased mortality. Further studies on this disturbance and its attendant high mortality are warranted.

Keywords: acid-base status; blood-gas analysis; critical illness; glucose; lactate; point-of-care testing.

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Introduction

The identification of critically ill patients at risk of further deterioration is of particular importance on admittance to an intensive care unit (ICU), a postoperative care unit or an emergency department. The benefit of biochemical markers of the metabolic status to identify these patients has long been addressed [1–5]. Numerous studies examined acid-base disturbances in critically ill patients, however, the discussion whether base excess (BE) is a prognostic indicator remains controversial [1–4, 6]. Studies focusing on differing aetiologies of acidosis found an association of elevated lactate levels on ICU admission and increased mortalities in patients with suspected lactic acidosis, in patients after vascular injury but also in mixed ICU populations [1, 3, 4, 6–8]. Physicochemical approaches quantifying unmeasured anions in patients with metabolic acidosis have also been used to predict mortality but yielded controversial results [4, 6, 9–13]. In contrast to acidosis, the effects of alkalosis on the outcome of critically ill patients have been evaluated to a lesser extent [14, 15].

Elevated glucose levels on ICU admittance were associated with increased mortality in trauma patients, in patients with intracerebral haemorrhage but not always uniformly in heterogeneous populations of critically ill patients [5, 16–20].

Point-of-care testing (POCT) to assess the metabolic status of patients on admittance may identify patients at risk of deterioration. As the identification of patients at risk is critical in terms of time and accuracy, modern blood gas analysers are ideal for clinician use providing rapid results with high accuracy and precision. Additionally, POCT provides the advantage of uncomplicated preanalytical processes, e.g., an immediately performed blood gas analysis avoids analytical errors generated by gas exchange phenomena, most important for the pCO_2 measurand. This study retrospectively investigates, in a large heterogeneous population of critically ill surgical patients, whether routine biochemical POCT on ICU admission identifies patients with an elevated mortality or independently predicts hospital mortality.

Materials and methods

The study was approved by the Institutional Ethics Committee. Informed consent was waived as this study utilised variables that were obtained as part of standard clinical practice. The study enrolment is shown in Figure 1. The time period between April 2004 and May 2007 was studied. The database of the POCT server of the central laboratory was reviewed for blood analyses by the ward-based blood gas analyser of the surgical adult ICU of the university hospital of the Technical University Munich, Germany. All analyses were performed on a Rapid-Lab 865 blood gas analyser, Siemens Medical Solutions (Eschborn, Germany), with automated sample delivery, automatic parameter calibration and daily quality control checks. The analyser comprised electrochemical sensors for the measurements of pH, oxygen tension (pO_2, mm Hg), carbon dioxide tension (pCO_2, mm Hg), sodium (Na^+, mmol/L), potassium (K^+, mmol/L), chloride (Cl^-, mmol/L), ionized calcium (Ca^{2+}, mmol/L), glucose (mg/dL), lactate (mmol/L) and a photometric diode array oximetry module to measure total haemoglobin concentration (ctHb, g/dL) and its Fe^{2+} and Fe^{3+} derivatives. Actual bicarbonate concentration (HCO_3^-) was calculated using Henderson-Hasselbalch's equation: HCO_3^- (mmol/L)=$0.03037\times pCO_2\times 10^{pH-6.105}$. Anion gap (AG) was calculated AG (mmol/L)=$(Na^+ + K^+)-(Cl^- + HCO_3^-)$. Base excess (BE) was calculated BE (mmol/L)=$(1-0.014\times ctHb)\times[(HCO_3^- - 24.8)+(1.43\times ctHb+7.7)\times(pH-7.40)]$. Networking and data handling between the blood gas analyser and the POCT server was done by Rapidlink server software (version 1.7c blood gas). The results of the analyses were extracted from the server by applying a structured query language script. Each data set adhered information on date and time of analysis, patient identification, type of blood sample, pH, pO_2, pCO_2, atmospheric pressure (pAtm), HCO_3^-, AG, BE, Na^+, K^+, Cl^-, Ca^{2+}, ctHb, glucose and lactate. A data merging process with the hospital information system (SAP AG, Germany) allowed the attribution of admission blood analyses to patient data on demographics, admission diagnostic category, length of stay and survival. This data merging process also enabled to exclude patients not treated on the ICU since the ward-based analyser was frequently used for patients treated outside the ICU. Patients without an arterial blood sample analysed on admission were excluded. The study cohort consisted of 1551 patients (Figure 1).

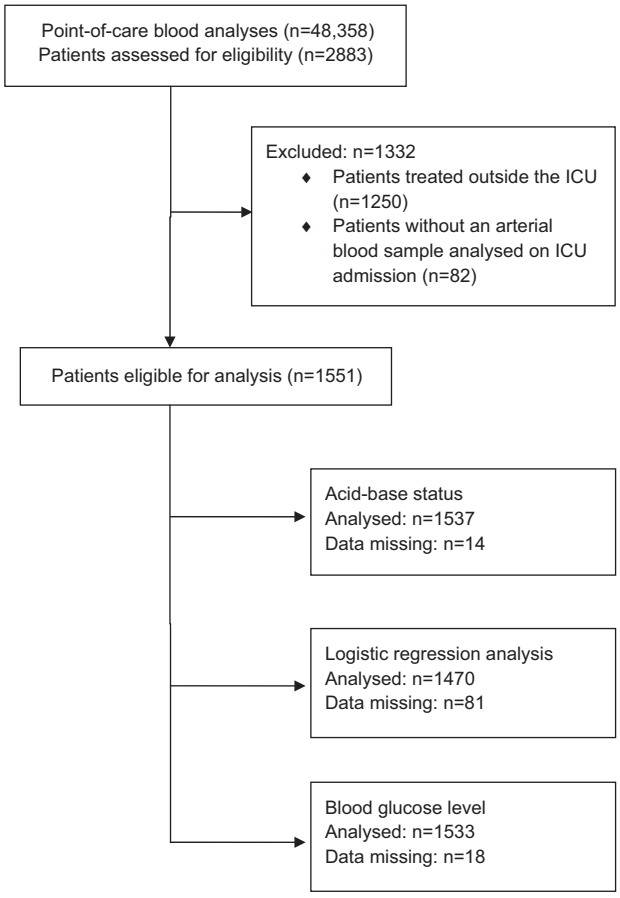

Figure 1 Study enrolment.

Patients were classified into different groups depending on the biochemical measurements to further describe the study population and identify groups with a high mortality. To assess the association between metabolic acid-base status on admission and hospital mortality, patients were classified according to a self-developed algorithm (Figure 2). Metabolic acidosis was defined by BE <–2 mmol/L. Patients with metabolic acidosis were then subdivided into different groups. Lactic acidosis was diagnosed if lactate accounted for more than 50% of BE. AG-acidosis was defined by an AG >16 mmol/L not explained by lactate. Patients with metabolic acidosis who did not meet the criteria for lactic acidosis or AG-acidosis were classified hyperchloraemic if the chloride level exceeded 115 mmol/L. In the remaining acidotic patients the anion contributing most to acidosis was not further defined. No metabolic disturbance was defined by a BE between –2 mmol/L and +3 mmol/L. In these patients, mortalities were also calculated for differing pCO_2 ranges (pCO_2 <35 mm Hg, pCO_2 35–45 mm Hg, pCO_2 >45 mm Hg, pCO_2 >55 mm Hg). Metabolic alkalosis was determined by a BE >3 mmol/L, and mortalities were calculated for the aforementioned pCO_2 ranges. To further classify

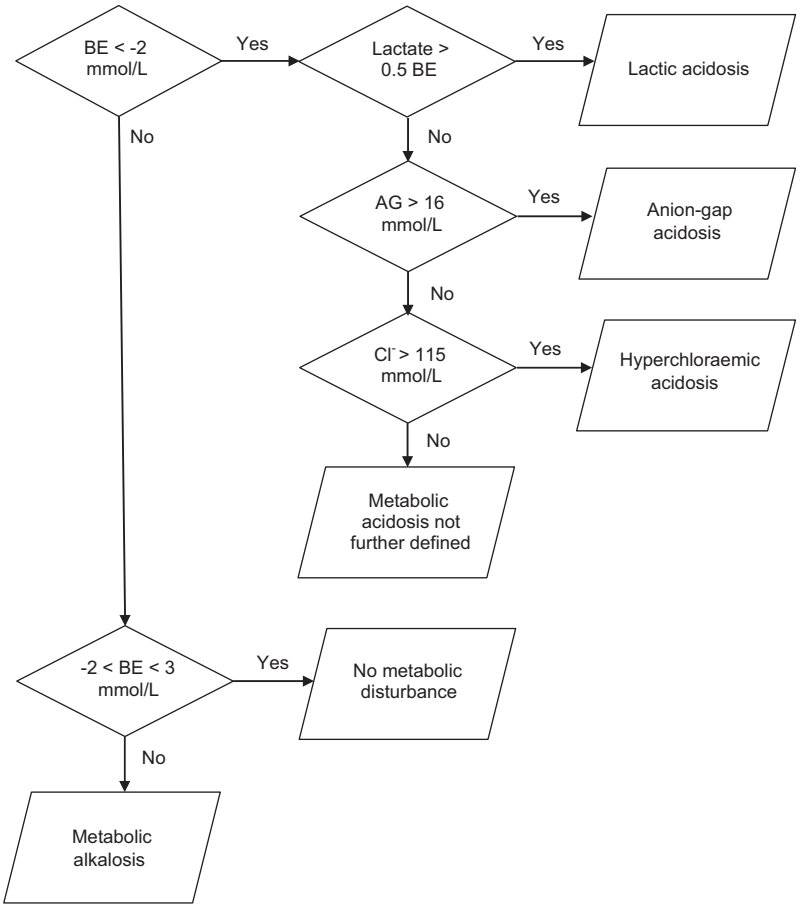

Figure 2 Classification algorithm of acid-base status.

the severity of alkalosis three ranges of admission blood pH were defined: mild alkalosis (pH<7.55), moderate alkalosis (7.55≤pH<7.60) and severe alkalosis (pH≥7.60). Patients were also stratified by their admission blood glucose level into four groups: hypoglycaemia (≤59 mg/dL), normoglycaemia (60–144 mg/dL), mild hyperglycaemia (145–179 mg/dL), or severe hyperglycaemia (≥180 mg/dL).

Multivariate logistic regression analysis was used to identify variables independently associated with mortality. The Student t-test was used to assess whether quantitative variables were related to survival. Categorical data were analysed with the Fisher exact test. Statistical significance was set at a $p<0.05$. All analyses were performed using SPSS 17.0.1 statistical calculation package (Chicago, IL, USA).

Results

The study cohort consisted of 1551 patients (mortality 8.8%), thereof 837 male patients (mean age 58.6 years, range 6.5–94.6, 88 non-survivors, mortality 10.5%) and 714 female patients (mean age 59.6 years, range 13.3–92.7, 49 non-survivors, mortality 6.9%). In-hospital mortality was significantly greater in male patients (two-sided Fisher's exact test: p=0.012; one-sided Fisher's exact test: p=0.007). Mean age of the overall cohort was 59.1 years (range 6.5–94.6) and significantly greater in non-survivors (64.1 years, range 18.5–91.3) compared to survivors (58.6 years, range 6.5–94.6; t-test: $p<0.0005$). Length of stay in hospital averaged 20.2 days for the overall cohort, for survivors 19.9 days, for non-survivors 23.7 days. Length of stay in ICU averaged 4.2 days for the cohort, for survivors 3.9 days, and for non-survivors 7.0 days. Admission diagnostic categories of the patients and the respective mortalities are presented in Table 1.

The prevalence of acid-base disorders on admission and the associated hospital mortalities are presented in Table 2. The cohort had an overall mortality of 8.8%. Of the 1551 patients, 986 patients showed no acid-base disorder with a mortality of 7.3%. The analysis of pCO_2 levels in this group yielded 580 patients with normocapnia (35 mm Hg<pCO_2<45 mm Hg, mortality 6.4%), 183 patients with hypocapnia (pCO_2 <35 mm Hg, mortality 9.3%) and 223 patients with hypercapnia (pCO_2 >45 mm Hg, mortality 8.1%). Hypercapnic patients

	n	Survivors/ non-survivors	Mortality[a]	95% CI
General surgery	96	89/7	7.3	3.0–14.5
Trauma surgery	42	40/2	4.8	0.6–16.2
Vascular surgery	25	18/7	28.0	12.1–49.4
Multiple trauma	28	25/3	10.7	2.3–28.2
Neurosurgery	186	174/12	6.5	3.4–11.0
ICH, aneurysmatic	70	62/8	11.4	5.1–21.3
ICH, non-aneurysmatic	55	43/12	21.8	11.8–35.0
Craniocerebral injury	69	59/10	14.5	7.2–25.0
Maxillofacial surgery	264	250/14	5.3	2.9–8.7
Gynaecology	122	114/8	6.6	2.9–12.5
Obstetrics	22	22/0	0.0	0–12.7
Opthalmology	88	88/0	0.0	0–31.2
Orthopaedics	134	122/12	9.0	4.7–15.1
Otorhinolaryngology	198	186/12	6.1	3.2–10.4
Urology	151	134/17	11.3	6.7–17.4
Neurology	51	44/7	13.7	5.7–26.3
Other	30	24/6	20.0	7.7–38.6
Total	1551	1414/137	8.8	7.5–10.4

Table 1 Admission diagnostic category with mortality rate.
[a]Hospital mortality (%). CI, confidence interval; ICH, intracranial haemorrhage.

with a pCO_2 level above 55 mm Hg (26 patients) showed a mortality of 23.1% (six non-survivors). We identified 377 patients with metabolic acidosis and an overall mortality of 11.4%. A high mortality (19.0%) was found in patients with lactic acidosis (mean lactate 3.9 mmol/L, range 1.1–25.2; mean BE –3.8 mmol/L, range –2.1 to –17.4). Patients with metabolic acidosis not classified lactic, nor hyperchloraemic nor AG-acidosis showed a low mortality (4.9%). Hyperchloraemic acidosis was diagnosed in seven patients, AG-acidosis in three patients, and these mortality rates result from one death in each group. In a combined cohort of patients with non-lactic metabolic acidosis (i.e., lactate <50% of BE, 214 patients), mean lactate was 1.3 mmol/L (range 0.1–6.1), mean BE –4.4 mmol/L (range –2.1 to –18.2). Mortality for the 174 patients with metabolic alkalosis was 12.1%, thereof 101 patients with normocapnia (mortality 13.9%), 17 patients with hypocapnia (one non-survivor) and 56 patients with hypercapnia (six non-survivors). Of the 174 patients with alkalosis, six patients showed a pH>7.55; all non-survivors showed a pH below 7.55.

Mean blood glucose level for survivors was 136 mg/dL (range 10–363), for non-survivors 154 mg/dL (range 48–441). Two-sided t-test revealed a significant difference ($p<0.0005$). A considerable higher mortality was seen in patients with severe hyperglycaemia (Table 3).

Logistic regression analysis identified lactate, glucose, age and male gender as independent predictors of mortality (Table 4).

Discussion

The early recognition of patients at risk of further deterioration may improve treatment and result in better outcomes. POCT may facilitate an early identification of these patients. Ease of access and rapid reliable results make onsite modern blood gas analysers ideal for an initial prompt assessment of the patient's metabolic status on admission to the ICU. Our study evaluates retrospectively, in a large heterogeneous population of critically ill surgical patients, whether routine POCT on ICU admission can independently predict mortality or identify patients with an elevated mortality. This investigation thus reflects a common clinical setting.

Acid-base status	n	%	Survivors/ non-survivors	Mortality[b]	Odds ratio	95% CI
Lactic acidosis	163	10.5	132/31	19.0	3.18	1.83–4.83
Anion gap-acidosis	3	0.2	2/1	33.3	6.35	0.22–90.46
Hyperchloraemic acidosis	7	0.5	6/1	14.3	2.12	0.09–18.04
Metabolic acidosis (other)[a]	204	13.2	194/10	4.9	0.65	0.31–1.34
Metabolic alkalosis	174	11.2	153/21	12.1	1.74	1.00–3.00
Data missing	14	0.9	13/1	7.1	0.98	0.04–7.30
No metabolic acid-base disorder[c]	986	63.6	914/72	7.3		
Total	1551	100	1414/137	8.8		

Table 2 Acid-base status on ICU admission: prevalence and mortality.
[a]Metabolic acidosis other than lactic acidosis, hyperchloraemic acidosis or anion gap-acidosis; [b]hospital mortality (%); [c]defined by –2 mmol/L <base excess <3 mmol/L. CI, confidence interval; ICU, intensive care unit.

Blood glucose, mg/dL	n	%	Survivors/non-survivors	Mortality[a]	Odds ratio	95% CI
≤59	3	0.2	2/1	33.3	5.85	0.525–65.208
60–144	1003	65.4	924/79	7.9		
145–179	335	21.9	311/24	7.2	0.90	0.562–1.451
≥180	192	12.5	161/31	16.1	2.25	1.439–3.524
Total	1533	100	1398/135	8.8		

Table 3 Blood glucose level on ICU admission: prevalence and mortality.
[a]Hospital mortality (%). CI, confidence interval.

Acidosis

Studies have long investigated the value of biochemical measurements on admission to the ICU or upon presentation to the emergency department focusing predominantly on BE and lactate [1–4, 21]. Several studies in patients on admission to the ICU showed that BE can discriminate between survivors and non-survivors [1, 12]. Also, in an investigation on outcome from major vascular injury base deficit was predictive [4]. In our study, patients with metabolic acidosis presented a higher mortality (11.4%) than patients with a BE in the normal range (7.3%). Logistic regression analysis, however, showed that pH and BE were not independently associated with hospital mortality (Table 4). Husain et al. analysed serial blood gas values in critically ill surgical patients and reasoned that initial base deficit was not useful in identifying patients in need of aggressive resuscitation and that base deficit remained inferior to simultaneously measured lactate levels [3]. Correspondingly, Rocktaeschel et al. studied retrospectively admission biochemical data of adult ICU patients and also found no strong correlation between mortality and pH or BE [13]. The results of our study are furthermore in accordance with a retrospective evaluation by Gunnerson et al. on the outcome of critically ill patients suspected of having lactic acidosis in which pH and BE were not predictive of mortality [6]. Gunnerson et al. argued that these findings could be attributed to the strong correlation of BE and pH with all forms of metabolic acidosis [6].

Further studies investigated whether different types of metabolic acidosis were associated with differing mortality rates [1–4, 6]. In this study, patients were classified according to the differing causes of acidosis pursuant to the technical capabilities of the POCT device (Figure 2).

Lactic acidosis was associated with a high mortality (19.0%, Table 2), and logistic regression analysis identified lactate as an independent predictor of mortality (Table 4). These findings are in agreement with other investigators who considered lactate an indicator of illness severity and a predictor of mortality [1, 6, 8, 22]. In our patients with lactic acidosis, mortality was high but lactate levels (mean 3.9 mmol/L) were not distinctly elevated given that these levels in patients with critical illness may be considered normal up to concentrations of 2–4 mmol/L [23]. The results of a recent investigation on "relative hyperlactaemia" also suggest that patients with lactate levels within the commonly accepted reference range are associated with increased hospital mortality [8]. Jansen et al. treated acidotic patients with a median lactate of 4.5 mmol/L and showed that lactate monitoring followed by targeted treatment reduced hospital mortality [24]. Thus, obtaining admission levels and monitoring the course of this metabolic parameter seems to be a reasonable approach for ICU patients.

For the diagnosis of metabolic hyperchloraemic acidosis, an arbitrary threshold of 115 mmol/L in patients with BE <–2 mmol/L was used. Hyperchloraemic acidosis was found in only seven patients although a rather large cohort of 1551 patients was evaluated. There were no patients with hyperchloraemia in the groups of patients with lactic

	p-Value	Odds ratio	95% CI
pH	0.240	0.000	0.000–269663.631
pCO_2	0.952	1.004	0.980–1.132
pO_2	0.679	1.001	0.998–1.003
Actual bicarbonate	0.708	0.405	0.004–45.709
Base excess	0.136	2.784	0.724–10.706
Sodium	0.992	1.025	0.010–104.801
Potassium	0.920	1.269	0.012–132.450
Calcium	0.674	1.518	0.218–10.598
Chloride	0.991	0.974	0.010–99.447
Anion gap	0.979	0.940	0.009–95.900
Glucose	0.001	1.007	1.003–1.011
Lactate	<0.001	1.238	1.122–1.366
Gender	0.034	1.525	1.032–2.254
Age	0.001	1.020	1.008–1.032

Table 4 Logistic regression analysis: independent predictors of mortality. CI, confidence interval.

acidosis or AG-acidosis. In a cohort study on patients suspected of having lactic acidosis, Gunnerson et al. found hyperchloraemic acidosis in 19% of the cohort with a mortality of 29% [6]. In comparison, we found notably fewer patients with hyperchloraemic acidosis, possibly due to the use of balanced rather than saline-based infusion solutions prior to admission. However, Gunnerson et al. did not measure chloride levels but defined hyperchloraemic acidosis as BE <–2 mmol/L not explained by lactate or the strong-ion gap [6]. Nevertheless, in our study group, hyperchloraemia appeared to play a minor role in view of the small number of patients identified. The associated mortality of 14.3% resulted from one non-survivor thus making assumptions on the influence of hyperchloraemia on mortality difficult. In the regression analysis chloride was not predictive (Table 4).

AG-acidosis was diagnosed in only three patients with non-lactic acidosis and seems to be of little avail in identifying patients at risk of deterioration. The associated mortality of 33.3% resulted from one death in this group. In contrast to lactate, AG did not predict mortality (Table 4). In previous studies concerning the usefulness of the AG to screen for lactic acidosis, AG was not an accurate tool [21, 25, 26].

Metabolic acidosis that was neither due to lactate, chloride or an elevated AG showed a rather low mortality of 4.9%. The mortality rate tempts to conclude that this group of acidotic patients is not at risk. Conclusions, though, are limited because POCT did not identify weak acid ions, often quantified by calculation of the strong-ion gap [4, 6, 12, 13].

Alkalosis

Metabolic alkalosis was found in 11.2% of the patients in this cohort affirming that alkalosis is a common acid-base disorder in critically ill patients. In the past, studies predominantly focused on the effects of acidosis while the consequences of metabolic alkalosis were rather slowly recognised [14, 27]. In a study on 1415 critically ill patients admitted to the emergency department, 12.5% presented with a pH >7.55 and demonstrated a rising mortality with increasing pH values [28]. A smaller study by Palange et al. evaluated 110 admissions to a general hospital and found metabolic alkalosis in 9% of the patients [29]. Although these data were not recently collected, the incidence of metabolic alkalosis upon presentation corresponds to our findings. In contrast to the findings by Wilson et al., our investigation did not demonstrate an increasing mortality with increasing pH values as almost all patients presented with a pH <7.55. Still, mortality was elevated for patients with metabolic alkalosis (12.1%) in comparison to patients without a metabolic acid-base disorder (6.9%) or the overall cohort (8.8%).

Glycaemia

Blood glucose level on ICU admission was a marker of mortality in our cohort. Mortality increased considerably when blood glucose level exceeded 180 mg/dL (Table 3). Logistic regression analysis identified glucose as an independent predictor of mortality (Table 4). Two-sided t-test was significant ($p<0.0005$) when analysing mean blood glucose levels of survivors and non-survivors. These results are in accordance with other investigations. Umpierrez et al. found an increased mortality in patients admitted to the hospital with hyperglycaemia [30]. Christiansen et al. studied non-cardiac critically ill surgical patients and found that high blood glucose level during the ICU stay was a marker of increased morbidity and mortality [17]. In patients with multiple trauma Kreutziger et al. demonstrated that admission blood glucose was an independent predictor of mortality [16]. Stead et al. also reported that hyperglycaemia in patients with intracerebral haemorrhage was predictive of early mortality [18]. Our results further show that the mortalities of patients with normoglycaemia (7.9%) and mild hyperglycaemia (7.5%) did not differ and were on par with the overall mortality of the cohort.

Limitations

In view of the comprehensive diagnostic capabilities of a central laboratory, the limitations of this study are inherent to the measurements available on a POCT device. Although modern POC blood gas analysers offer an increasing number of biochemical and oximetry measurands, critically ill patients may have complex metabolic disturbances that possibly remain inadequately diagnosed. Since traditional approaches often insufficiently explain acid-base derangements in critically ill patients there has been a resurgence of interest in physicochemical approaches to define the acid-base status, e.g., using the strong-ion gap methodology [9–11]. Irrespective of the differing results to predict mortality the required measurements of albumin, phosphate and magnesium are usually not available in a POC setting [2, 4, 6, 12, 13, 31, 32]. Ionised magnesium is forthcoming on a few systems. In our cohort, in more than half of the patients admitted

with metabolic acidosis the aetiology of acidosis remained undetermined. In the future, an increasing number of measurands analysed by POC systems should contribute to the value of POCT.

Conclusions

Lactate and glucose measured by routine POCT on admission to the ICU independently predicted mortality in a cohort of 1551 critically ill patients. A general surgical ICU population was studied. Consequently our findings should be broadly applicable. POCT thus facilitates an early identification of patients at risk. BE and AG failed as prognostic markers. Different types of acid-base disorders on ICU admission are associated with different mortality rates. Lactic acidosis had a high mortality rate implying that lactate levels should be obtained in all patients on ICU admission. The prevalence of hyperchloraemic acidosis was low. Metabolic alkalosis was also associated with an increased mortality. Its attendant high mortality should not be underestimated and warrants additional studies on this disturbance.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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References

1. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 2001;27:74–83.
2. Hucker TR, Mitchell GP, Blake LD, Cheek E, Bewick V, Grocutt M, et al. Identifying the sick: can biochemical measurements be used to aid decision making on presentation to the accident and emergency department. Br J Anaesth 2005;94:735–41.
3. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg 2003;185:485–91.
4. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med 2004;32:1120–4.
5. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med 2005;33:2772–7.
6. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care 2006;10:R22.
7. Juneja D, Singh O, Dang R. Admission hyperlactatemia: causes, incidence, and impact on outcome of patients admitted in a general medical intensive care unit. J Crit Care 2011;26:316–20.
8. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care 2010;14:R25.
9. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Resp Crit Care Med 2000;162:2246–51.
10. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: applications in biology and medicine. Resp Physiol 1993; 91:1–16.
11. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 1995;10:51–5.
12. Cusack RJ, Rhodes A, Lochhead P, Jordan B, Perry S, Ball JA, et al. The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. Intensive Care Med 2002;28:864–9.
13. Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: can they predict mortality? Crit Care Med 2003;31:2131–6.
14. Webster NR, Kulkarni V. Metabolic alkalosis in the critically ill. Crit Rev Clin Lab Sci 1999;36:497–510.
15. Demirjian S, Teo BW, Paganini EP. Alkalemia during continuous renal replacement therapy and mortality in critically ill patients. Crit Care Med 2008;36:1513–7.
16. Kreutziger J, Wenzel V, Kurz A, Constantinescu MA. Admission blood glucose is an independent predictive factor for hospital mortality in polytraumatised patients. Intensive Care Med 2009;35:1234–9.
17. Christiansen C, Toft P, Jorgensen HS, Andersen SK, Tonnesen E. Hyperglycaemia and mortality in critically ill patients. A prospective study. Intensive Care Med 2004;30:1685–8.
18. Stead LG, Jain A, Bellolio MF, Odufuye A, Gilmore RM, Rabinstein A, et al. Emergency department hyperglycemia as a predictor of early mortality and worse functional outcome after intracerebral hemorrhage. Neurocrit Care 2010;13:67–74.
19. Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;59:80–3.
20. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78:1471–8.
21. Berkman M, Ufberg J, Nathanson LA, Shapiro NI. Anion gap as a screening tool for elevated lactate in patients with an increased

risk of developing sepsis in the emergency department. J Emerg Med 2009;36:391–4.
22. Martin MJ, FitzSullivan E, Salim A, Brown CV, Demetriades D, Long W. Discordance between lactate and base deficit in the surgical intensive care unit: which one do you trust? Am J Surg 2006;191:625–30.
23. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
24. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Resp Crit Care Med 2010;182:752–61.
25. Adams BD, Bonzani TA, Hunter CJ. The anion gap does not accurately screen for lactic acidosis in emergency department patients. Emerg Med J 2006;23:179–82.
26. Chawla LS, Jagasia D, Abell LM, Seneff MG, Egan M, Danino N, et al. Anion gap, anion gap corrected for albumin, and base deficit fail to accurately diagnose clinically significant hyperlactatemia in critically ill patients. J Intensive Care Med 2008;23:122–7.
27. Galla JH. Metabolic alkalosis. J Am Soc Nephrol 2000;11: 369–75.
28. Wilson RF, Gibson D, Percinel AK, Ali MA, Baker G, LeBlanc LP, et al. Severe alkalosis in critically ill surgical patients. Arch Surg 1972;105:197–203.
29. Palange P, Carlone S, Galassetti P, Felli A, Serra P. Incidence of acid-base and electrolyte disturbances in a general hospital: a study of 110 consecutive admissions. Rec Prog Med 1990;81:788–91.
30. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978–82.
31. Abdulraof Menesi F, Verzola D, Villaggio B, Russo R, Sofia A, Fontana I, et al. Evaluation of metabolic acidosis in patients with a kidney graft: comparison of the bicarbonate-based and strong ion-based methods. Transplant Proc 2011;43: 1055–62.
32. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Acid-base disorders evaluation in critically ill patients: we can improve our diagnostic ability. Intensive Care Med 2009;35: 1377–82.