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Original Article

Arterial pH and short-term mortality in adult non-traumatic acute patients

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ABSTRACT

INTRODUCTION. Acid-base disturbances are common in the emergency department, with acidosis and alkalosis being associated with an elevated risk of mortality and morbidity. Understanding the relationship between pH and mortality may serve to optimise patient outcomes.

The primary objective was to describe the association between arterial blood pH and 0-2-day mortality in adult non-traumatic acute visits. The secondary objective was to describe this association for 3-7-day mortality.

METHODS. This population-based, multicentre cohort study included all adult non-traumatic acute visits in the Region of Southern Denmark between 2016 and 2018 who had an arterial blood gas (ABG) drawn within four hours of arrival. We described 0-2- and 3-7-day mortality stratified by pH level, controlled for confounding factors and reported as hazard ratio (HR) compared to normal pH.

RESULTS. A total of 64,725 acute visits in 31,650 individuals with an ABG were included. The overall mortality rate for index visits was 2.4% on days 0-2 and 2.1% on days 3-7. Patients with severe acidosis (pH < 7.20) had 20.8% and 8.9% mortality rates (HR = 9.6 and 5.2), whereas patients with acidosis (pH 7.20-7.34) had mortality rates of 7.4% and 5.2% (HR = 4.1 and 2.7) on day 0-2 and 3-7, respectively. Our secondary analysis found a 0-2-day mortality rate of nearly 60% in patients with a pH < 6.90.

CONCLUSION. The short-term mortality rates increased with the severity of acidosis. The highest mortality rate was found in patients with a pH < 6.90.

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The association between arterial blood pH and short-term mortality is important to emergency department (ED) patient care [1]. Acidosis and alkalosis are associated with increased morbidity and mortality [2, 3]. Acidosis, in particular, affects multiple organ systems and correlates with diseases that present with various signs and symptoms, including tachycardia, arrhythmias, dyspnoea, altered mental status and seizures [4, 5]. The diversity of patients who arrive at EDs with acid-base disturbances necessitates a thorough understanding and timely intervention to optimise patient outcomes.

The prevalence of acid-base disturbances is high, and some studies imply that they occur in more than half of intensive care unit (ICU) patients during the first 24 hours after admission [6, 7]. Common medical diagnoses include pneumonia, sepsis or neurological disorders, where pneumonia is more common in patients who have acidosis, and neurological disorders are more common in patients with alkalosis [6]. In addition, hypertension and diabetes are among the most common comorbidities in patients with acidosis as well as alkalosis [6]. Most studies were conducted in an ICU where treatment may have influenced the results, causing iatrogenic acidosis or alkalosis [2, 7, 8].

As pH is used to prioritise treatment for acute patients, our objective was to examine the association between arterial blood pH, 0-2-day mortality and 3-7-day mortality in adult non-traumatic acute visits.

METHODS

Study design and setting

This study was a population-based, multicentre cohort study of all adult non-traumatic acute patient visits in the Region of Southern Denmark between 1 January 2016 and 19 March 2018. Seven departments were included in this study, five EDs and two smaller acute departments, covering a population of approx. 1.2 million people. The dataset was previously described by Arvig et al. [9]. The EDs/acute departments provided 24-hour acute care. All patients were referred to the EDs/acute departments by a primary care physician or the ambulance service. In Denmark, healthcare and emergency services are tax-paid and free for all citizens. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) [10].

Selection of participants

This study included all registered non-traumatic acute patient visits by patients aged 18 years or older who arrived alive at the ED/acute department and had an arterial blood gas (ABG) drawn within four hours after arriving.

Data sources and variables

Information regarding ABG and primary presenting symptoms was obtained from the electronic patient administrative and laboratory information systems. Information about each patient visit was linked to the Danish Civil Registration System and the National Patient Registry [11, 12]. Collected data included patient demographics, comorbidities and discharge diagnosis (based on the International Classification of Diseases, 10th Rev. (ICD-10)) assigned by the attending physician. In the Danish EDs/acute departments, ABG is a frequently used tool used on clinical indications in severely ill patients (e.g., in respiratorily distressed patients or patients with suspected sepsis). ABG was obtained by a physician or a nurse and analysed within five minutes. The results of the ABG were divided into intervals, with severe acidosis defined as pH < 7.20, acidosis as pH 7.20-7.34, normal (physiological) as pH 7.35-7.45 and alkalosis as pH > 7.45 [2, 7, 13].

The primary outcome of this study was short-term mortality, defined as death within two days. The secondary outcome was death within 3-7 days. Day 0 was defined as the arrival day. The 0-2-day mortality period was chosen based on clinical experience and literature stating that mortality in ED patients is highest within two days after admission [14]. We measured comorbidity using the Charlson Comorbidity Index (CCI) based on discharge diagnoses recorded ten years before the index date. Discharge diagnoses were identified from the National Patient Registry and reported by the main ICD-10 category.

Statistical methods

Demographic data, vital values, PaO_2, $PaCO_2$ and HCO_3 for all acute visits with an ABG were summarised using

medians and interquartile range. Symptoms, comorbidity, mortality, discharge diagnosis and pH intervals were described as numbers and percentages of the total sample and included all acute visits with an ABG. We handled missing values regarding symptoms as independent variables in a separate group. In patients with more than one acute visit registered, the date of the first visit was used as the index date for calculating mortality. Patients were followed to death or seven days after their index date, whichever occurred first. Mortality was described as the proportion of those who died on days 0-2 and, for those who survived to day 3, the proportion who died on days 3-7. A multivariable Cox regression model adjusted for age, sex, comorbidities and pH levels was used to determine the association between mortality and obtain the crude hazard ratio (cHR) and adjusted hazard ratio (aHR). Covariates were selected based on clinical judgment and existing literature. A 95% confidence interval was used to determine statistical significance. We performed a sensitivity analysis for the acute visits with acidosis and subdivided them into respiratory, metabolic and mixed disorders and compared the mortality rates to determine if they were influenced by the type of acidosis. All statistical analyses were done with STATA version 18.0 (StataCorp, College Station, TX, USA).

Ethics

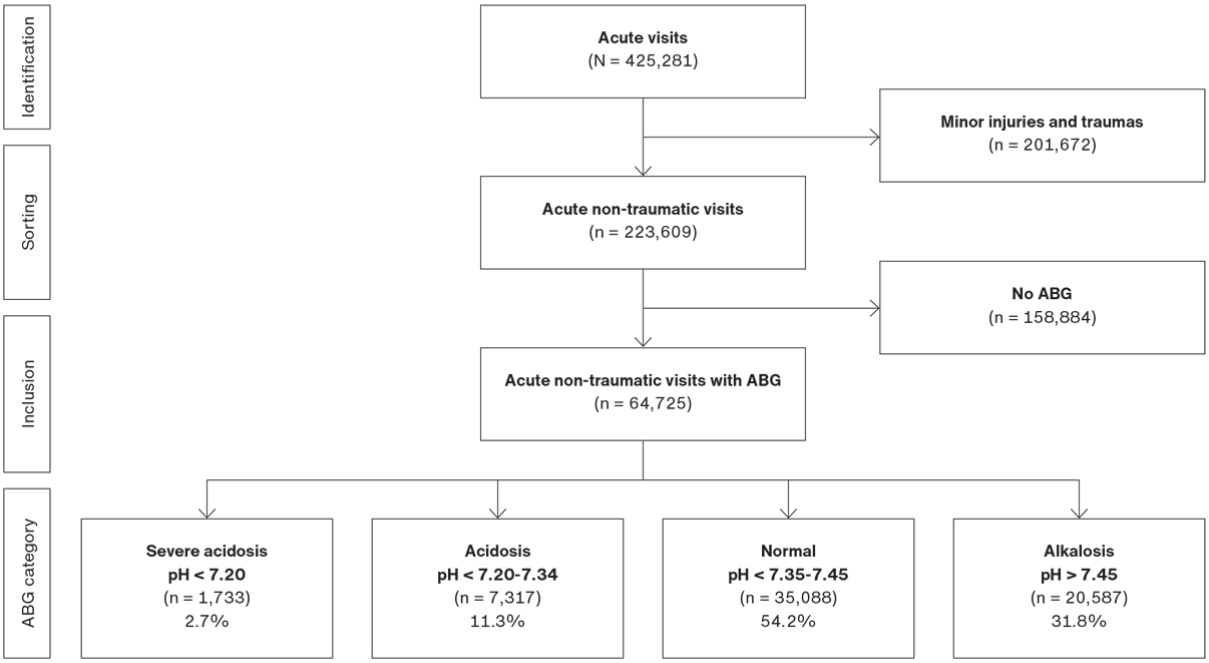
The regional authorities granted permission to obtain and store data (identifier 3-3013-2272/1 and identifier 17/24904, amendment identifier 20/24502). All data were stored, secured and managed according to the General Data Protection Regulation [15] and the Danish Data Protection Act [16]. According to the Act on Research Ethics Review of Health Research Projects, register-based studies do not require approval from the research ethics committee system in Denmark [17].

Trial registration: not relevant.

RESULTS

Among 425,281 acute visits, 64,725 had an ABG performed within four hours, distributed on 31,650 individual patients (**Figure 1**). The distribution of males and females among all acute visits with an ABG was even; the highest proportion of individuals was in the 65-84-year age group (48.3%) (**Table 1**). Acute visits with an ABG had an ABG within normal pH (54.2%), followed by alkalosis (31.8%), acidosis (11.3%) and severe acidosis (2.7%). Patients frequently arrived with dyspnoea (31.5%), unspecific symptoms (18.1%) and other symptoms (16.2%). The most common symptom in patients with severe acidosis was dyspnoea (29.5%), and more than 60% were 65 years or older. Patients with no comorbidities represented the largest group regardless of the type and severity of acid-base disturbance (44.8%), followed by two or more comorbidities (35.1%). Median vital signs were close to normal in all pH subgroups, except for respiratory and heart rate, which was higher in the severe acidosis group. Half of the patients with severe acidosis and one-quarter of those with acidosis were transferred to the ICU. The most frequent discharge diagnoses, regardless of acid-base disturbance, were diseases of the respiratory system (29.2%), symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (18.6%), and diseases of the circulatory system (12.4%) (Table S1). For the severe acidosis group, most patients were discharged with diseases of the respiratory system (35.8%), diseases of the circulatory system (19.4%), and endocrine, nutritional and metabolic diseases (12.5%). Diseases of the respiratory system were the most frequent conditions in all pH groups.

FIGURE 1 Flow diagram of the selection of adult non-traumatic acute patients arriving at an emergency/acute department in the Region of Southern Denmark between 2016 and 2018 and their arterial blood gas categories.



ABG = arterial blood gas.

TABLE 1 Baseline characteristics for adult non-traumatic visits with an arterial blood gas at an emergency/acute department in 2016-2018 in the Region of Southern Denmark.

	Severe acidosis pH < 7.20 (N_{sac} = 1,733)	Acidosis pH 7.20-7.34 (N_{aci} = 7,317)	Normal pH 7.35-7.45 (N_{nor} = 35,088)	Alkalosis pH > 7.45 (N_{alk} = 20,587)	Total (N_{tot} = 64,725)
Sex, n (%)					
Female	815 (47.0)	3,467 (47.4)	16,370 (46.7)	10,207 (49.6)	30,859 (47.7)
Male	918 (53.0)	3,850 (52.6)	18,718 (53.3)	10,380 (50.4)	33,866 (52.3)
Age, median (IQR), yrs	71 (59-80)	72 (61-81)	70 (55-80)	72 (58-81)	71 (57-81)
Age groups, n (%)					
18-44 yrs	201 (11.6)	633 (8.7)	2,590 (12.6)	5,002 (14.3)	8,446 (13.1)
45-64 yrs	408 (23.5)	1,676 (22.9)	4,575 (22.2)	8,503 (24.2)	15,162 (23.4)
65-84 yrs	891 (51.4)	3,802 (52.0)	10,117 (49.1)	16,432 (46.8)	31,242 (48.3)
≥ 85 yrs	233 (13.4)	1,206 (16.5)	3,305 (16.1)	5,131 (14.6)	9,875 (15.3)
CCI, n (%)					
0	662 (38.2)	2,402 (32.8)	16,090 (45.9)	9,869 (47.9)	29,023 (44.8)
1	411 (23.7)	1,887 (25.8)	7,242 (20.6)	3,416 (16.6)	1,2956 (20.0)
≥ 2	660 (38.1)	3,028 (41.4)	11,756 (33.5)	7,302 (35.5)	22,746 (35.1)
Symptoms, n (%)					
Abdominal pain	66 (3.8)	461 (6.3)	2,764 (7.9)	1,645 (8.0)	4,936 (7.6)
Chest pain	25 (1.4)	187 (2.6)	2,780 (7.9)	1,311 (6.4)	4,303 (6.6)
Dyspnoea	512 (29.5)	2,746 (37.5)	11,154 (31.8)	5,969 (29.0)	20,381 (31.5)
Fever	58 (3.3)	466 (6.4)	3,546 (10.1)	3,704 (18.0)	7,774 (12.0)
Missing registration	335 (19.3)	593 (8.1)	1,833 (5.2)	980 (4.8)	3,741 (5.8)
Neurologic	57 (3.3)	183 (2.5)	777 (2.2)	354 (1.7)	1,371 (2.1)
Others	333 (19.2)	1,215 (16.6)	5,984 (17.1)	2,949 (14.3)	10,481 (16.2)
Unspecific	347 (20.0)	1,466 (20.0)	6,250 (17.8)	3,675 (17.9)	11,738 (18.1)
Vital parameters, median (IQR)					
sBP, mmHg	133 (110-157)	132 (114-151)	134 (119-152)	132 (117-149)	133 (118-151)
dBP, mmHg	74 (59-91)	75 (62-87)	76 (66-87)	75 (65-85)	75 (65-87)
HR, bpm	101 (83-119)	94 (78-110)	88 (75-102)	90 (78-105)	89 (76-104)
RR, brpm	24 (19-30)	21 (18-27)	20 (16-24)	20 (16-24)	20 (16-24)
SaO_2, %	96 (91-100)	96 (91-98)	96 (93-98)	96 (94-99)	96 (93-98)
Temp., °C	37 (36-37)	37 (36-37)	37 (37-38)	37 (37-38)	37 (37-38)
GCS	15 (13-15)	15 (15-15)	15 (15-15)	15 (15-15)	15 (15-15)
PaO_2, kPa	14 (10-20)	11 (9-15)	10 (9-12)	10 (9-12)	10 (9-12)
$PaCO_2$, kPa	9 (5-12)	6 (5-8)	5 (5-6)	4 (4-5)	5 (4-6)
HCO_{3^-}, mmol/l	16 (10-21)	22 (19-26)	25 (23-26)	26 (24-28)	25 (23-27)
Transferred to the ICU, n (%)	892 (51.5)	1,359 (18.6)	1,671 (4.8)	910 (4.4)	4,832 (7.5)

bpm = beats/min.; brpm = breaths/min.; CCI = Charlson Comorbidity Index; dBP = diastolic blood pressure; GCS = Glasgow Coma Scale; HR = heart rate; ICU = intensive care unit; IQR = interquartile range; RR = respiratory rate; sBP = systolic blood pressure; temp = temperature.

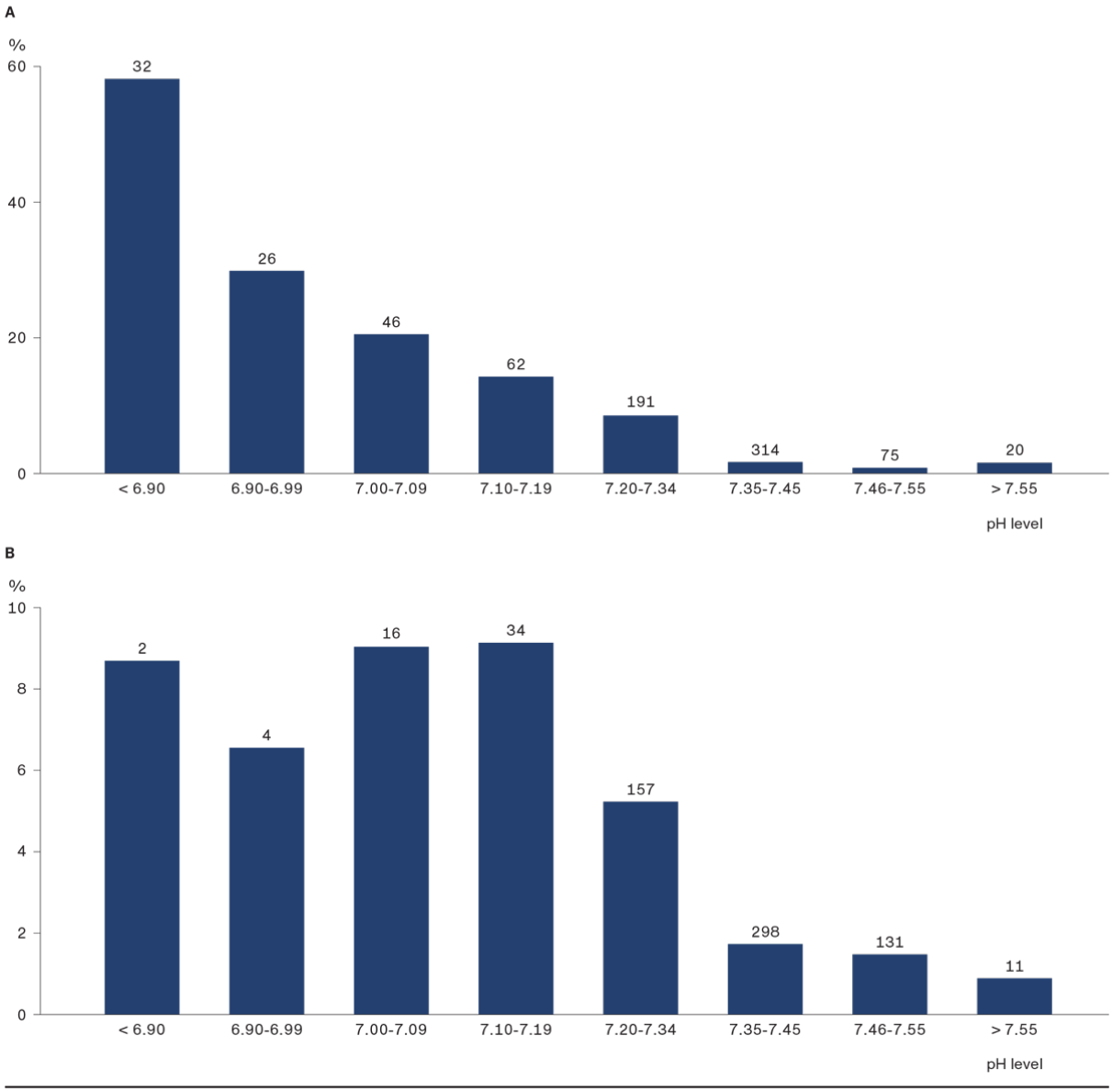
Mortality was 2.4% on days 0-2 and 2.1% on days 3-7 (**Table 2**). Patients with severe acidosis had the highest 0-2-day mortality (20.8% (cHR = 10.0 and aHR = 9.6)) and 3-7-day mortality (8.9% dying (cHR and aHR = 5.2)). In the relationship between severe acidosis and mortality, the 0-2-day mortality was nearly 60% (32 patients) when pH dropped below 6.90 and 9% (two patients) for 3-7-day mortality (**Figure 2**). Patients with acidosis, normal pH and alkalosis had 0-2-day mortality rates of 7.4%, 1.5%, and 0.9%, respectively, whereas the corresponding 3-7-day mortality rates were 5.2%, 1.7%, and 1.4%, respectively. In the multivariable analysis, lower pH, higher CCI and higher age were associated with increased short-term mortality risk. A sensitivity analysis revealed that patients with respiratory acidosis had a three-fold higher risk of dying than patients with metabolic or mixed disorders (Table S2).

TABLE 2 Univariate and multivariable analyses of the variables pH, sex, age and comorbidities as a function of 0-2-day and 3-7-day mortality among first-time acute visits in 2016-2018 in the Region of Southern Denmark.

	0-2-day mortality				3-7-day mortality			
	N	n, died (%)	cHR (95% CI)	aHR (95% CI)	n	n, died (%)	cHR (95% CI)	aHR (95% CI)
Total	31,650	766 (2.4)	-	-	30,883	653 (2.1)	-	-
pH								
Severe acidosis	800	166 (20.8)	10.0 (7.7-13.0)	9.6 (7.4-12.5)	633	56 (8.9)	5.2 (3.9-7.0)	5.2 (3.9-7.0)
Acidosis	3,241	241 (7.4)	4.6 (3.8-5.7)	4.1 (3.3-5.1)	3,000	157 (5.2)	3.1 (2.5-3.7)	2.7 (2.2-3.3)
Normal	17,443	264 (1.5)	1	1	17,179	298 (1.7)	1	1
Alkalosis	10,166	95 (0.9)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	10,071	142 (1.4)	0.8 (0.7-1.0)	0.8 (0.6-1.0)
Sex								
Female	15,197	350 (2.3)	1	1	14,847	319 (2.2)	1	1
Male	16,453	416 (2.5)	1.1 (0.9-1.3)	1.2 (1.0-1.4)	16,036	334 (2.1)	1.0 (0.8-1.1)	1.0 (0.9-1.2)
Age								
18-44 yrs	5,005	14 (0.3)	1	1	4,991	13 (0.3)	1	1
45-64 yrs	7,948	100 (1.3)	4.8 (2.3-10.1)	4.4 (2.1-9.1)	7,847	67 (0.9)	3.3 (1.8-6.0)	3.0 (1.6-5.4)
65-84 yrs	14,473	400 (2.8)	11.6 (5.8-23.5)	9.7 (4.8-19.6)	14,073	324 (2.3)	8.9 (5.1-15.5)	7.3 (4.2-12.7)
≥ 85 yrs	4,224	252 (6.0)	26.2 (12.9-53.2)	22.2 (10.9-45.3)	3,972	249 (6.3)	24.6 (14.1-43.0)	20.5 (11.7-36.0)
CCI								
0	18,464	357 (1.9)	1	1	18,106	276 (1.5)	1	1
1	5,117	109 (2.1)	1.1 (0.9-1.5)	0.8 (0.6-1.0)	5,008	106 (2.1)	1.4 (1.1-1.7)	1.0 (0.8-1.3)
≥ 2	8,069	300 (3.7)	1.9 (1.6-2.3)	1.2 (1.0-1.5)	7,769	271 (3.5)	2.3 (2.0-2.7)	1.5 (1.2-1.7)

aHR = adjusted hazard ratio; CCI = Charlson Comorbidity Index; cHR = crude hazard ratio; CI = confidence interval.

FIGURE 2 The absolute risk of mortality as a function of different pH categories, as percentages. The numbers above the bars indicate how many died within each category. **A**. 0-2-day mortality. **B**. 3-7-day mortality.



DISCUSSION

In this multicentre study, we found that severe acidosis and advanced age were the most significant risk factors for short-term mortality during acute visits. Notably, only 40% survived a pH of 6.90 or lower within two days. Severe acidosis had the highest 0-2-day and 3-7-day mortality, followed by acidosis. However, mortality declined after two days, implying that the first two days are the most critical.

Regardless of arterial blood pH, higher age and comorbidity index were associated with increased mortality in both periods. This observation contradicts a previous study, where age and comorbidities were more detrimental in the later stages than in the acute phase [14]. In addition, a large proportion of patients with severe acidosis was discharged with diagnoses correlating to endocrine, nutritional and metabolic diseases (12.5%). Part of the survival rate may potentially have been affected by conditions with relatively good prognoses, such as diabetic

ketoacidosis and metformin-associated lactate acidosis, as revealed in our sensitivity analysis and observed in another study [18].

This study revealed a mortality of nearly 60% within two days in patients with an arterial blood pH < 6.90. A recent study, which specifically focused on extreme acidosis (pH < 6.90), found a comparable mortality rate of about 70% within the first 24 hours after ED admittance [19]. The similarity in mortality rates confirms the reproducibility of the findings and highlights extreme acidosis as a critical mortality predictor.

Other studies have focused on acidosis in an ICU setting. A small study in the ICU examined pH below 7.0 and found an overall mortality of 67.5% while reporting a mortality of 29% in cases with metformin-associated lactate acidosis [2]. Another small ICU study with patients with a pH below 7.0 found an overall hospital mortality of 42.8%, where none of the diabetic ketoacidosis patients died [20]. Although comparing studies from an ICU setting with those from an ED setting is difficult, the strong relationship between a low pH and mortality seems comparable. In addition, our study revealed that half and one-quarter of the patients with severe acidosis and acidosis, respectively, were transferred to the ICU and thereby also treated in a more specialised unit.

None of the previously mentioned studies included patients with alkalosis. However, one small study only including acute heart failure patients in the ED showed that alkalosis was the most common acid-base disturbance in acute heart failure patients (44%) [1]. In that study, alkalosis was not associated with increased short- or long-term mortality, but acidosis was a significant predictor of mortality. The authors also found that significant predictors of death in addition to acidosis were advanced age, previous congestive heart failure, low systolic blood pressure and higher pro-B-type natriuretic peptide, the latter especially when combined with pH level [1].

From a clinical perspective, it should be emphasised that even though our results show a high mortality rate when pH drops below 6.90, 40% survive this extreme pH level. This challenges the consensus that extreme levels of acidosis are incompatible with life. With this high potential for survival, prompt assessment and aggressive treatment should be initiated to identify the aetiology and correct the acid-base disturbance. This knowledge may assist the emergency physician in assessing short-term mortality risk based on pH levels, age and comorbidities. Doing so may ensure a more efficient allocation of healthcare resources and cost savings.

Further studies should examine the prognostic value of blood gas parameters, considering more patient data, e.g., comorbidities, age and other influencing risk factors, such as smoking, Body Mass Index (BMI) and alcohol consumption. With the development of new and sophisticated artificial intelligence (AI) systems, data collection could be used to determine individual prognosis.

This study had various limitations. First, it was based on Danish EDs/acute departments. Although this is a limitation, the study population was large, with a wide variety of patients who typically present to an ED. This makes it applicable in most Western countries owing to similarities in disease burden. Second, ABG was obtained on the attending physician's decision alone. This may have caused some acid-base disturbances not to be discovered. For instance, we might have overlooked terminally ill patients, for whom an ABG might not be indicated, or patients deemed stable upon triage and thus receiving an ABG after a delay exceeding four hours. However, ABG is a frequently used tool in Danish ED/acute departments. Additionally, the lack of rigid criteria for ABG results in a broader range of patients with different clinical presentations and conditions, increasing the generalisability of the study. Third, registration of comorbidities in the hospital setting may potentially have excluded comorbidities treated by general practitioners and/or have introduced misclassification bias.

CONCLUSION

Lower pH, comorbidities and older age are linked to a higher short-term mortality risk in the ED. Even though severe acidosis is closely related to a high risk of short-term mortality, 40% of severe acidotic patients survive the acute phase.

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