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ORIGINAL RESEARCH

Clinical significance of an elevated on-admission beta-hydroxybutyrate in acutely ill adult patients without diabetes

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Abstract

Objective: To determine the relationship between point-of-care β-hydroxybutyrate (BHB) concentration and outcomes in adult patients without diabetes admitted through ED.

Methods: This was a prospective study from 10 March to 2 July 2021. Admitted patients without diabetes had capillary BHB sampled in ED. Outcomes of length-of-stay (LOS), composite mortality/ICU admission rates and clinical severity scores (Quick Sepsis Organ Failure Assessment score/National Early Warning Score [qSOFA/NEWS]) were measured. BHB was assessed as a continuous variable and between those with BHB above and equal to 1.0 mmol/L and those below 1.0 mmol/L.

Results: A total of 311 patients were included from 2377 admissions. Median length-of-stay was 4.1 days (IQR 2.1–9.8), 18 (5.8%) died and 37 (11.8%) were admitted to ICU. Median BHB was 0.2 mmol/L (IQR 0.1–0.4). Twenty-five patients had BHB ≥1.0 mmol/L and five were >3.0 mmol/L. There was no significant difference in median LOS for patients with BHB ≥1.0 mmol/L compared to non-ketotic patients, 5.3 days (IQR 2.2–7.5) *versus* 4.1 days, respectively (IQR 2.0–9.8) ($P = 0.69$). BHB did not correlate with LOS (Spearman $\rho = 0.116$, 95% confidence interval: 0.006–0.223). qSOFA and NEWS also did not differ between these cohorts. For those 25 patients with BHB ≥1.0 mmol/L, an infective/inflammatory diagnosis was present in 11 (44%), at least 2 days of fasting in 10 (40%) and ethanol intake >40 g within 48 h in 4 (16%).

Conclusions: Routine BHB measurement in patients without diabetes does not add to clinical bedside assessment and use should be limited to when required to confirm a clinical impression.

Key words: *beta-hydroxybutyrate, emergency, ketosis, normoglycemic, outcomes.*

Key findings

- In this observational study of adult patients without diabetes requiring admission through the ED, there was no significant association of BHB concentrations with length-of-stay, mortality/ICU admission rates, qSOFA (Quick Sepsis Organ Failure Assessment) score and NEWS (National Early Warning Score).
- Ninety-two percent of patients presenting to ED had BHB concentrations of <1.0 mmol/L despite illness requiring hospital admission. Those who had a BHB ≥1.0 mmol/L usually had a history of decreased oral intake and/or excessive alcohol intake.

Introduction

Anorexia is frequently present in acute illness.[1] The ketone body β-hydroxybutyrate (BHB) is the primary alternative fuel source utilised in states of energy restriction. Serum BHB concentrations are maintained below 0.5 mmol/L during fed states[2] but may rise to over 6 mmol/L during starvation,[3] although BHB concentrations of ≥1 mmol/L are considered abnormal.[4]

In acute illness in children without diabetes, a strong correlation of BHB with decreased oral intake and fever is reported.[5] Elevated BHB has been observed in paediatric patients fasting in excess of recommended

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guidelines and is associated with haemodynamic instability.[6] In children with gastroenteritis and dehydration, elevated BHB correlated with both dehydration and magnitude of metabolic acidosis.[7] In contrast, the clinical relevance of elevated BHB in acutely ill adult patients without diabetes is yet to be explored.[8] In the absence of hyperglycaemic emergency, ketosis may reflect reduced carbohydrate intake; however, there is evidence that BHB also acts as a signalling substrate of the stress response.[3,9,10]

Euglycaemic ketoacidosis is known to occur in patients with diabetes on sodium glucose co-transporter 2 inhibitors (SGLT2i).[11] Given the increased use of SGLT2i in patients without diabetes with heart failure,[12] establishing expected degrees of ketosis during acute illness without SGLT2i is important. A recent systematic review identified only seven studies examining the relationship between at-presentation BHB and patient outcomes.[8] Of these, only one was conducted in adults and was limited to presentations with stroke.[13] This highlights a knowledge deficit regarding expected BHB concentrations in acutely ill adult patients without diabetes. Any clinical utility of BHB measurement in a general population of acutely ill patients is not yet determined. If a positive correlation is present, there is potential use of BHB as a marker of response to thiamine or nutritional supplementation or as an aid in the selection of treatment for acutely ill patients.

We hypothesise that BHB concentrations will be elevated in adult patients presenting with a higher severity disease state. The objective was to determine if BHB ≥1.0 mmol/L will be associated with a longer hospital stay (length-of-stay [LOS]), higher mortality/ICU admission rates and worse clinical severity scores.

Methods

Study design

This was a single-centre, prospective observational cohort study conducted at a metropolitan tertiary referral hospital in NSW Australia. There are approximately 58 000 yearly ED presentations. Inclusion criteria were patients aged 18 years and over, requiring a blood sample, and admission to hospital *via* ED between 16 March and 2 July 2021. Exclusion criteria were a history of diabetes or admission under psychiatry. The presence of diabetes was as documented in the admission or discharge summary and included new diagnoses made during that admission. A waiver of informed consent was granted by the South-Eastern Sydney Local Health District Human Research Ethics Committee, 2020/ETH01313.

Participant selection

BHB measurements were obtained by convenience sampling with sampling times varying throughout the day and across the entire week. Furthermore, all ED staff were urged to include point-of-care (POC) BHB measurements in addition to routine care even when not clinically indicated *via* online noticeboards, posters within the ED and word-of-mouth.

To ensure the cohort was representative of all ED admissions, general demographic information and outcome variables were also collected in patients without a BHB measurement, regardless of whether blood was sampled.

Independent measures

The primary independent variable was POC-measured BHB. Other secondary independent variables examined, if measured, were glucose, lactate and C-reactive protein (CRP) as derangements are associated with worse outcomes.[14–16]

BHB was measured on capillary blood *via* Nova Biomedical Glucose/Ketone Meter. Glucose was measured with the same monitor; missing values were substituted with blood gas values when available.

Outcome measures

The primary outcome was LOS. Secondary outcome was in-hospital mortality or ICU admission (combined binary outcome). The qSOFA (Quick Sepsis Organ Failure Assessment) score and NEWS (National Early Warning Score) were calculated, providing an indication of patient prognosis based on vital signs. The qSOFA score is ranked from 0 to 3 while the NEWS from 0 to 20. For both, higher scores denote worse prognosis (Table S1). The qSOFA is a predictor of 2-day mortality.[17] NEWS is now increasingly used as a validated pre-admission predictor of death or ICU escalation in adult populations.[18]

Patient demographics, medical history and most abnormal vital signs within 4 h of presentation were extracted from the electronic medical records (eMR) for calculation of qSOFA and NEWS score. Fasting duration and recent alcohol intake if documented in the eMR were collected from those with BHB ≥1.0 mmol/L. Data were stored within REDCap (Research Electronic Data Capture) software.

Data analysis

Analysis was carried out in R (version 1.4.1106) and SPSS (version 26.0.0.0). Univariate analysis of age, sex, vital signs, blood gases, blood chemistry and independent/outcome variables were performed. Continuous data were reported as a median and interquartile range (IQR) while categorical data was reported as counts and frequencies. Bivariate analyses were performed with $\alpha = 0.05$ and 95% confidence intervals. For comparison between cohorts with measured BHB *versus* no measurement, two-sample independent *t*-test or Mann–Whitney *U*-test for non-parametric data was performed. Fisher's exact test was used to assess for differences in mortality/ICU rate.

BHB was assessed as a continuous variable and as a dichotomous outcome < or ≥1.0 mmol/L. This was because hyperketonaemia has been previously defined at this threshold regardless of diabetic status.[4] Furthermore, previous studies have stated that BHB concentrations did not exceed 1.0 mmol/L in otherwise well patients with type 1 diabetes[19] and 0.9 mmol/L in well patients taking SGLT2i.[20]

To compare LOS between cohorts with normal and abnormal BHB measurements, Mann–Whitney *U* test was applied and quantified *via* Hodges-Lehmann estimator. For

mortality/ICU rates as well as NEWS >7 or ≤7, Fisher's exact test was used to report odds ratios. Chi-squared test was applied to comparisons with qSOFA scores with each score from zero to three as an individual category. Glucose, lactate and CRP were analysed as continuous variables and also compared pairwise between patients with normal and abnormal results. Cutoff limits were chosen based on local guidelines or published literature. The reference range of glucose in the present study was 4.0–7.8 mmol/L,[16] lactate <2.0 mmol/L[21] and CRP <5.0 mg/L (according to local laboratory cut-offs). NEWS over 7[22] was considered abnormal for the purposes of categorical analysis. Comparisons between BHB, glucose, lactate and CRP were achieved using Spearman's ρ test. Dunn's procedure and a Bonferroni correction were applied to significant results. Patients with missing observations for glucose or lactate were excluded during analysis of said variable.

The present study was deemed exploratory with few precedent studies to refer to. Therefore, a power calculation was not performed in advance.

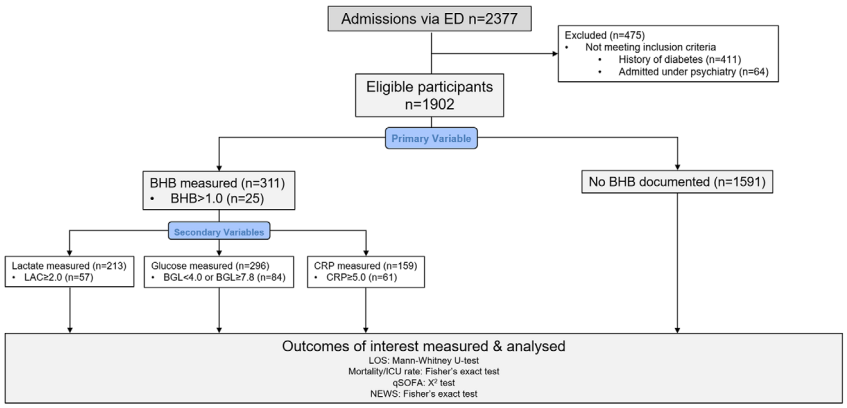

Figure 1. *Study cohort, variables and recruitment. Outcomes were compared between high and low values using the statistical tests listed. BGL, glucose; BHB, β-hydroxybutyrate; CRP, C-reactive protein; ICU, intensive care unit; LAC, lactate; LOS, length-of-stay;* N, *number measured.*

TABLE 1. *Baseline observations of study participants stratified by BHB result*

Clinical observations	BHB < 1.0 mmol/L ($n = 286$)	BHB ≥ 1.0 mmol/L ($n = 25$)
Age, median (IQR), years	70 (53–82)	50 (29–78)
Male, %	56.3	36
Surgical admission†, *n* (%)	90 (31)	10 (40)
Capillary glucose, median (IQR), mmol/L	6.40 (5.6–7.8)	5.65 (5.0–8.8)
Blood lactate, median (IQR), mmol/L	1.4 (1.1–2.1)	1.3 (1.1–1.9)
C-reactive protein, median (IQR), mg/L	2.7 (0.4–93.8)	0.6 (0.0–9.1)
pH, median (IQR)	7.38 (7.36–7.42)	7.36 (7.35–7.40)
HCO_3, median (IQR), mmol/L	25 (22.7–27.6)	24 (22.4–25.7)
Albumin, median (IQR), g/L	35 (31–38.25)	37 (31–41)
MAP, median (IQR), mmHg	87.3 (78–97.3)	82.3 (76.4–98.4)
RR, median (IQR), rpm	20 (18–24)	19.5 (18–21.8)
GCS, median (IQR)	15 (15–15)	15 (15–15)
Highest Temp, median (IQR),°C	36.9 (36.5–37.4)	36.8 (36.5–37.0)
Lowest temperature, median (IQR),°C	36.3 (36–36.7)	36.25 (36.0–36.5)
eGFR, median (IQR), mL/min/1.73 m^2	81 (58–90)	90 (82.5–90)
Haematocrit, median (IQR), %	39.5 (33.8–42.4)	40.9 (36.9–45.3)
White cell count, median (IQR), $\times 10^9$	8.9 (6.9–12.1)	9.6 (7.5–10.8)

All continuous values reported as medians (IQR) and categorical variables as number (frequency in %) except where specified. †As opposed to admission under a medical subspecialty. BHB, B-hydroxybutyrate; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; HR, heart rate; IQR, interquartile range; MAP, mean arterial pressure; N, number of available observations; RR, respiratory rate.

TABLE 2. *Pairwise comparisons of BHB, BGL, lactate and CRP stratified by severity and outcome variables*

BHB (n = 311)	BHB < 1.0 (*n* = 286)	BHB ≥ 1.0 (*n* = 25)	Test statistic
LOS†, median (IQR), hours	99.28 (48.75–236.15)	126.00 (53.94–180.70)	Median difference = 26.7, *P* = NS
Mortality/ICU‡, *n* (%)	49 (17.1)	5 (20.0)	OR = 1.14, 95% CI: 0.32–3.33, *P* = NS
qSOFA§, *n* (%)	—	—	*P* = NS
qSOFA = 0	149 (52.1)	11 (44.0)	
qSOFA = 1	99 (34.6)	11 (44.0)	
qSOFA = 2	34 (11.9)	2 (8.0)	
qSOFA = 3	2 (0.7)	1 (4.0)	
NEWS‡, *n* (%)	—	—	OR = 0.91, 95% CI: 0.29–2.45, *P* = NS
NEWS ≤ 7	215 (75.2)	19 (76.0)	
NEWS > 7	71 (24.8)	6 (24.0)	
BGL (*n* = 296)	4.0 ≤ BGL < 7.8 (*n* = 212)	BGL < 4.0 or BGL ≥ 7.8 (*n* = 84)	Test statistic
LOS†, median (IQR), hours	95.53 (46.85–201.15)	143.23 (63.80–303.90)	Median difference = 47.7, *P* = 0.0031*
Mortality/ICU‡, *n* (%)	37 (17.5)	17 (20.2)	OR = 1.19, 95% CI: 0.59–2.36, *P* = NS
qSOFA§, *n* (%)	—	—	*P* = NS
qSOFA = 0	113 (53.3)	36 (42.9)	
qSOFA = 1	83 (39.2)	25 (29.8)	
qSOFA = 2	16 (7.5)	20 (23.8)	
qSOFA = 3	0 (0.0)	3 (3.6)	
NEWS‡, *n* (%)	—	—	OR = 1.95, 95% CI: 1.08–3.50, *P* = NS
NEWS ≤ 7	165 (77.8)	54 (64.3)	
NEWS > 7	47 (22.2)	30 (35.7)	
LAC (*n* = 213)	LAC < 2.0 (*n* = 156)	LAC ≥ 2.0 (*n* = 57)	Test statistic
LOS†, median (IQR), hours	115.15 (53.38–245.27)	123.72 (67.15–291.53)	Median difference = 8.6, *P* = NS
Mortality/ICU‡, *n* (%)	30 (19.2)	14 (24.6)	OR = 1.47, CI: 0.72–2.91, *P* = NS
qSOFA§, *n* (%)	—	—	*P* = 0.012*
qSOFA = 0	66 (42.3)	19 (33.3)	
qSOFA = 1	71 (45.5)	21 (36.8)	
qSOFA = 2	17 (10.9)	16 (28.1)	
qSOFA = 3	2 (1.3)	1 (1.8)	
NEWS‡, *n* (%)	—	—	OR = 1.99, 95% CI: 1.02–3.91, *P* = NS
NEWS ≤ 7	110 (70.5)	31 (54.4)	
NEWS > 7	46 (29.5)	26 (45.6)	
CRP (*n* = 159)	CRP < 1.0 (*n* = 60)	CRP ≥ 1.0 (*n* = 99)	Test statistic
LOS†, median (IQR), hours	64.58 (41.54–170.54)	107.05 (60.79–247.30)	Median difference = 42.5, *P* = 0.0063*
Mortality/ICU‡, *n* (%)	4 (6.7)	14 (14.1)	OR = 2.29, 95% CI: 0.67–10.07, *P* = NS
qSOFA§, *n* (%)	—	—	*P* = NS
qSOFA = 0	39 (65.0)	43 (43.4)	

CRP ($n = 159$)	CRP < 1.0 ($n = 60$)	CRP ≥ 1.0 ($n = 99$)	Test statistic
qSOFA = 1	17 (28.3)	38 (36.4)	
qSOFA = 2	4 (6.6)	16 (16.2)	
qSOFA = 3	0	2 (2.0)	
NEWS‡, *n* (%)	—	—	OR = 6.56, 95% CI: 2.32–22.68, $P < 0.001$*
NEWS ≤ 7	55 (91.7)	62 (62.6)	
NEWS > 7	5 (8.3)	37 (37.4)	

*$P < 0.0125$ and is considered statistically significant. LOS reported as median (IQR); Mortality/ICU rates, qSOFA scores and NEWS reported as counts (% of total within each variable). Bonferroni adjusted $\alpha = 0.0125$. †Mann-Whitney *U*-test with Hodges-Lehmann estimate. ‡Fisher's exact test with odds ratio and 95% confidence intervals. §Chi-squared test. CI, confidence interval; *n*, number of available measurements; NS, not significant; OR, odds ratio.

Results

Characteristics of study subjects

The study cohort and recruitment process are outlined in Figure 1. Over the 108-day period, 2377 patients were admitted. Of these, 1902 did not have a diagnosis of diabetes and were admitted under a medical or surgical specialty, of which 311 (16.3%) had POC BHB measured. Out of these, 296 also received measurements for glucose, 213 lactate and 159 CRP.

Comparisons between patients with a BHB measurement and those without are found in Table S2. Combined mortality/ICU rate was higher in those with measured BHB (17.4%) *versus* unmeasured (12.4%) (odds ratio = 1.45, 95% confidence interval [CI]: 1.07–2.06), $P = 0.02$. There was no significant difference between median LOS of ketone-measured patients compared to unmeasured patients 4.1 days (IQR 2.1–9.8) *versus* 3.4 days (IQR 1.8–6.9), respectively, $P = 0.07$. The qSOFA and NEWS also did not differ.

Main findings (BHB)

Baseline characteristics of the study cohort, stratified by BHB result are given in Table 1. The study group of 311 patients had a median age of 69 years (IQR 50–81) and 176 (56.6%) were male. The median time to BHB measurement was 4.8 h (IQR 2.7–7.6). Median LOS was 99.6 h (4.1 days, IQR 49.5–235 h). Inpatient mortality was 18 (5.8%) and 37 (11.8%) were admitted to ICU.

The median BHB was 0.2 mmol/L (IQR 0.1–0.4), with the central 95% range between 0.0 and 1.6 mmol/L. BHB was ≥1.0 mmol/L in 25 (8.0%), and in 5(1.6%) ≥3.0 mmol/L (Table S3). There was no significant difference in median LOS for patients with a BHB ≥1.0 mmol/L compared to non-ketotic patients, 5.3 days (IQR 2.2–7.5) *versus* 4.1 days, respectively (IQR 2.0–9.8), $P = 0.69$. Figure S1 depicts this against logarithmic LOS. Three (12.0%) died as inpatients and two (8.0%) were admitted to ICU compared to 15 (5.2%) deaths and 35 (12.2%) ICU admissions in the ketotic *versus* non-ketotic cohorts, respectively. Overall, no statistically significant differences in LOS, mortality/ICU rates, qSOFA or NEWS were observed between the two cohorts (Table 2).

Of those with a BHB ≥1.0 mmol/L ($n = 25$), 16 (64%) were women with a median age of 50 years (IQR 29–78) and 11 (44%) had an infective or inflammatory (pancreatitis) diagnosis. Other risk factors included ethanol intake of at least four standard drinks in 48 h prior to presentation documented in 4 and at least 2 days of anorexia or fasting in 10 patients. Of those with a BHB ≥3.0 mmol/L ($n = 5$) the length of fasting was greater than 5 days in four with one reported being on a low carbohydrate diet for 1 month prior to the day of illness. Clinical details of those with BHB ≥3.0 mmol/L can be found in Table 3. Further descriptive information of the measured population can be found in Table S4.

As a continuous variable, BHB concentrations correlated very weakly with LOS (Spearman $\rho = 0.114$, 95% CI: 0.006–0.223), and not at all with glucose (Spearman $\rho = -0.090$, 95% CI: −0.206, 0.036), lactate (Spearman $\rho = -0.094$, 95% CI: −0.234, 0.052) and CRP (Spearman $\rho = 0.123$, 95% CI: −0.048, 0.296) (Table 4).

Secondary biomarkers (glucose, lactate, CRP)

The median lactate concentration for those with measured BHB was 1.4 mmol/L (IQR 1.1–2.0, $n = 213$); glucose 6.4 mmol/L (IQR 5.6–7.5, $n = 296$) and CRP 2.3 mg/L (IQR 0.4–9.5, $n = 159$). Comparisons between glucose, lactate and CRP with the outcomes of LOS, mortality/ICU rates, qSOFA and NEWS are shown in Table 2.

Those with abnormal glucose concentrations at presentation had a longer LOS of 5.9 days (IQR 2.7–12.7, $n = 84$) *versus* 4.0 (IQR 2.0–8.4, $n = 212$) in normoglycaemic patients ($P = 0.003$). As a continuous variable, this correlation was very weak (Spearman $\rho = 0.153$, 95% CI: 0.027–0.265). An elevated lactate ≥2.0 mmol/L ($n = 57$) was associated with higher qSOFA score ($P = 0.01$).

Those with CRP ≥5 mg/L had a longer median LOS of 6.1 days (IQR

TABLE 3. *Characteristics of study participants with BHB ≥ 3.0 mmol/L*

BHB (mmol/L)	Age (years)	Sex	Presenting complaint	Admitting team	Diagnosis	BGL (mmol/L)	LAC (mmol/L)	CRP (mg/L)	pH	HCO_3 (mmol/L)	Albumin (g/L)	LOS (days)	Mortality	ICU/HDU admission	qSOFA	NEWS	Risk factors
7.2	36	Female	Fever	Infectious diseases	Astrovirus infection	3.4	0.5	NA	7.28	13.6	29	3.1	No	No	2	7	Low carbohydrate diet (1 month) Anorexia (1 day)
7.1	35	Male	Abdominal pain	Urology	Obstructive uropathy	6.9	1.9	0.3	7.26	18.4	47	5.4	No	No	0	0	Anorexia (5 days)
5.7	53	Female	Hypothermia	Infectious diseases	Encephalopathy of unknown cause	2.6	1.1	NA	7.36	24.2	54	11.2	No	Yes	2	10	Fasting (1 week) due to delirium
4.6	73	Male	Trauma	Orthopaedics	Fracture	4.9	2.3	NA	7.42	28.2	25	20.1	No	No	0	1	Fasting (1 week) due to long lie
3.2	24	Female	Hypoglycaemia	Endocrinology	Starvation ketoacidosis	2.2	1.1	0.1	7.38	22.7	44	1.7	No	No	1	4	Fasting (2 weeks) due to acute social stressors

Missing values are due to study participants not receiving said measurements as part of their routine care. Risk factor data was only collected for fasting duration, alcohol usage in the last 24 h, pregnancy. Note all patients with BHB > 1.3 mmol/L had an extensive history of carbohydrate restriction or recent alcohol usage. BGL, blood glucose level; BHB, β-hydroxybutyrate; CRP, C-reactive protein; ETOH (stds), ethanol (1 standard drink = 10 g ETOH); GCS, Glasgow Coma Scale; LAC, serum lactate; LOS, length-of-stay; NA, not available.

3.2–11.7, $n = 99$) *versus* 3.0 days (IQR 1.7–6.8, $n = 60$), ($P < 0.001$). They also presented with higher qSOFA scores ($P = 0.002$) and greater odds of NEWS >7 (odds ratio = 4.35, 95% CI: 1.96–9.99, $P < 0.001$). CRP as a continuous variable had a weak correlation with an increased LOS (Spearman $\rho = 0.322$, 95% CI: 0.186–0.457).

Discussion

In this observational study of adult patients without diabetes requiring emergency hospital admission, there was no significant association of BHB concentrations with LOS, mortality/ICU admission rates, qSOFA scores or NEWS. Most (92%) had BHB concentrations of <1.0 mmol/L despite illness requiring hospital admission. Those who had a BHB ≥1.0 mmol/L usually had a history of fasting and/or significant alcohol intake.

There are few studies of BHB concentrations in adult patients without diabetes. Hamblin *et al.* examined BHB within 151 normoglycaemic patients undergoing colonoscopy, where the median BHB was 0.4 mmol/L (IQR 0.2–0.7) and range was 0.0–1.7 mmol/L. It was noted that 13 (9%) had BHB ≥1.0 mmol/L.[23] Burstal, Reilly and Burstal examined BHB in 100 fasted elective and emergency adult surgical patients, finding a median BHB of 0.2 mmol/L (IQR 0.1–0.4) specifically for the 42 requiring emergency surgery and a range of 0–1.8 mmol/L overall.[24] Their rate of BHB ≥1.0 mmol/L at 3% and zero for ≥3.0 mmol/L despite fasting and/or acute illness is similar to those rates in our population. These results are also congruent with results from landmark SGLT2i trials where ketoacidosis as an adverse event only occurred in those with diabetes.[25]

Our results suggest that in adults without diabetes, developing a BHB ≥1.0 mmol/L is rare. Acute illness is an insulin-resistant state and stress hyperglycaemia is common.[26] Hyperinsulinism may restrain the development of overt ketosis. In contrast, patients with diabetes have an absolute or relative lack of insulin. Acute illness in patients with diabetes in the absence of a diabetic emergency[27] is

TABLE 4. *Correlation analysis of continuous variables including BHB and LOS*

	BHB ($n = 311$)	BGL ($n = 296$)	Lactate ($n = 213$)	CRP ($n = 159$)	LOS ($n = 311$)
BHB ($n = 311$), Spearman ρ (95% CI)	NA	−0.09 (−0.21, 0.04)	−0.09 (−0.23, 0.05)	0.12(−0.05, 0.30)	0.11* (0.01–0.22)
BGL ($n = 296$), Spearman ρ (95% CI)	−0.09 (−0.21, 0.04)	NA	0.10 (−0.04, 0.22)	0.12 (−0.07, 0.29)	0.15* (0.03–0.27)
Lactate ($n = 213$), Spearman ρ (95% CI)	−0.09 (−0.23, 0.05)	0.10 (−0.04, 0.22)	NA	0.04 (−0.15, 0.23)	0.10 (−0.04, 0.24)
CRP ($n = 159$), Spearman ρ (95% CI)	0.12 (−0.05, 0.30)	0.12 (−0.07, 0.29)	0.04 (−0.15, 0.23)	NA	0.32** (0.19–0.46)
LOS ($n = 311$), Spearman ρ (95% CI)	0.11* (0.01–0.22)	0.15* (0.03–0.27)	0.10 (−0.04, 0.24)	0.32** (0.19–0.46)	NA

*Correlation is significant at $P < 0.05$ level (two-tailed). **Correlation is significant at $P < 0.01$ level (two-tailed). BGL, blood glucose level; BHB, β-hydroxybutyrate; CI, confidence interval; CRP, C-reactive protein; LAC, serum lactate; LOS, length-of-stay; *n*, number of measurements; NA, not applicable.

associated with higher rate of ketosis (BHB ≥1.0 mmol/L in this group was 14%), but no relationship between ketosis and LOS was seen. However, the notion of absolute insulin resistance being a prerequisite for ketoacidosis is being challenged by emerging case studies outlining the possibility of ketoacidosis without diabetes in SGLT2i users. Ongoing research can elucidate the frequency and degree of ketosis within these patients as SGLT2i usage increases.[28]

Our results in an adult cohort contrast to paediatric studies. Levy and Waltzmann's assessment of 188 patients younger than 6 years of age with dehydration and gastroenteritis found a median serum BHB of 3.1 mmol/L (IQR 1.2–4.6). There was weak correlation between BHB and clinical dehydration as well as BHB with metabolic acidosis.[7] In another population, however, BHB was correlated with risk of admission, but not LOS and varied greatly depending on presenting complaint, highest in those presenting with vomiting, anorexia and fever.[5]

Overall, our results confirm the associations between glucose, CRP and lactate with prognostic outcomes. In contrast, BHB was unrelated to LOS or ICU admission/in-hospital mortality. Of the 25 patients with BHB ≥1.0 mmol/L, the majority reported decreased oral intake or significant alcohol intake within the last 48 h. This denotes the importance of specific risk factors in the development of ketosis as opposed to general acute illness.

Limitations

Out of 1902 patients admitted *via* ED, only 311 BHB measurements were made. Those with measurements were older with higher mortality/ICU admission rate, potentially due to these patients being more likely to require blood samples and therefore a BHB measurement.

The use of convenience sampling may introduce bias compared to blinded random sampling; however it is validated for generating representative samples of the ED population with the amount of introduced bias being small.[29]

The present study population is highly heterogenous, so it is impossible to exclude relationships between BHB and outcomes in specific subgroups such as infection, given recent data suggesting a potential role of BHB in the T-cell response in patients infected with COVID-19.[30] LOS may be confounded by variables outside of the ED such as availability of imaging/theatres, involvement of allied health and discharge location. Ideally, future studies would control for these during analysis.

Conclusions

In adult patients without diabetes requiring hospital admission, ketosis was uncommon and not associated with increased LOS, ICU admission or mortality. Hence, routine BHB measurement provides little risk stratification in a general population and should be limited to confirmation of a clinical impression.

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Author contributions

AC and BD conceived the study and obtained research funding. The study was designed by SL, AC, BD, WV and SAH. SL undertook data collection and recruitment of patients alongside doctors and nurses of the ED where the present study took place. Data management, statistical analysis and manuscript draft were performed by SL; all other authors contributed substantially to its revision. SL takes responsibility for the paper as a whole.

Competing interests

AC is an Editorial Board member of the journal and co-author of this article. They were excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by members of the Editorial Board to minimise bias.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Figure S1. Logarithmic length of stay in high and low BHB cohorts.

Table S1. The qSOFA and NEWS scoring systems.
Table S2. Comparison of features between study participants with measured ketones and the overall ED cohort.
Table S3. Baseline distributions of predictor variables in patients with BHB measurement.
Table S4. Characteristics of study participants with BHB ≥ 1.0 mmol/L.