Venous bicarbonate and creatine kinase as diagnostic and prognostic tools in the setting of acute traumatic rhabdomyolysis

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Background. Myorenal or crush syndrome often develops following soft-tissue traumatic injury. It is a spectrum of disease that may result in severe renal dysfunction and kidney injury requiring renal replacement therapy.

Objectives. To review a large cohort of patients with so-called myorenal or crush syndrome and assess the biochemical markers of venous bicarbonate and creatine kinase as predictors for the development of acute kidney injury (AKI).

Methods. All patients with myorenal syndrome who presented to Khayelitsha District Hospital, Cape Town, South Africa (SA), and Ngwelezana Hospital, Empangeni, KwaZulu-Natal, SA, between January and December 2017 were identified and reviewed.

Results. A total of 212 patients were included in the study. At both hospitals, 94% of the patients were male. Using the Pearson correlation coefficient, we compared creatinine kinase (CK) against serum creatinine. The mean CK level was 5 311.8 U/L and the mean creatinine level 133.457 µmol/L. The *r*-value was 0.2533. Although this is a technically positive correlation, the relationship between the variables is weak. Using the Pearson R Calculator, we inserted the *r*-value to calculate the *p*-value. The *p*-value was 0.000208. When comparing venous bicarbonate (HCO_3) against creatinine, the mean HCO_3 level was 22.296 mmol/L and the mean creatinine level 162.053 µmol/L. The *r*-value was –0.3468. Although this is a technically negative correlation, the relationship between the variables is weak. Using the Pearson R Calculator, we inserted the *r*-value to calculate the *p*-value. The *p*-value was 0.000013. The inverse ratio shown with HCO_3 v. creatinine, although still a weak correlation, is significantly better in predicting an increase in creatinine compared with the weak positive correlation of CK v. creatinine.

Conclusions. Although both venous HCO_3 and CK showed a weak correlation with creatinine, the former performed significantly better in predicting AKI. In a resource-constrained system, we recommend that HCO_3 be measured to assess patients with crush injury and that CK be regarded as a complementary modality.

S Afr Med J 2021;111(4):333-337. https://doi.org/10.7196/SAMJ.2021.v111i4.14915

Myorenal syndrome following significant soft-tissue injury remains a common presentation in South Africa (SA).[1,2] The pathophysiology of massive soft-tissue disruption has been well described and involves myoglobin deposition in the proximal renal tubules.[3-5] The mainstay of therapy involves judicious rehydration to ensure adequate diuresis.[6,7] If not managed, myorenal syndrome can progress to acute kidney injury (AKI), which may require renal replacement therapy (RRT). If RRT is required, there is significant associated morbidity and mortality.[8] Identifying patients at risk for the development of AKI requiring RRT is important, as it can prompt the appropriate degree of clinical concern.[1,2] In SA there are regional differences in the diagnostic modalities used to grade these injuries and in the management protocols. In Western Cape Province there is a tendency to use creatinine kinase (CK) levels, whereas in KwaZulu-Natal (KZN) Province the use of venous bicarbonate (HCO_3) has been widespread since it was first popularised by Muckart *et al.*[2] three decades ago.

Objectives

To compare the spectrum and outcome of myorenal syndrome between two busy centres, namely Khayelitsha District Hospital (KDH) in Cape Town, Western Cape, and Ngwelezana Hospital (NH) in Empangeni, KZN. It is hoped that this may help provide some clarity in the ongoing controversy as to which method of grading is most appropriate and effective.

Methods

The study involved a retrospective chart review of all patients presenting to KDH and NH with myorenal syndrome from January to December 2017. Demographic information as well as injury mechanism and the weapons used were noted. All cases of trauma-related myorenal syndrome at each hospital for a year were included, the only cases excluded being those related to medical conditions such as epilepsy and myopathies, and drug-related cases. All blood samples were taken on admission, prior to any treatment for the related injuries.

Definitions

Myorenal syndrome severity was determined using both the HCO_3 and CK classifications. The validity of CK was determined, and a severity scale of HCO_3 values was weighed against the need for RRT and fluids. Management, general morbidity and myorenal-specific morbidity were determined and weighed against outcomes. The management of specific grades was reviewed and weighed against outcomes. All values for HCO_3 are given in mmol/L and those for CK in U/L.

Statistical analysis

Descriptive statistics were initially done to describe the basic features of the data at hand and to indicate the dispersion of the data. These descriptive methods were also used to indicate the skewness and kurtosis of the data. In cases where outliers were evident, rank and percentile tests were done to measure the true dispersion. Descriptive analysis was also used to aid trend analysis of the historical data in order to make meaningful inferences. Mortality rate, age, sex and mechanism of injury are commonly measured with this method. When comparing certain characteristics between the samples (non-paired), or within the samples themselves (paired), parametric tests such as paired or unpaired *t*-tests were done. Non-parametric tests were the Wilcoxon matched-pair test or Mann-Whitney *U*-test. Using the Pearson correlation coefficient, we compared CK and HCO_3 with renal function (creatinine). Using the Pearson R Calculator, we inserted the *r*-value to calculate the *p*-value. A *p*-value <0.05 was considered statistically significant.

Results

Demographics

Over a 1-year period, 98 patients with myorenal syndrome were admitted to NH and 114 patients were admitted to KDH. At both hospitals, 94% of these patients were male. The mean age was 27 years at KDH and 29 years at NH, with an overall mean of 28 years.

Mechanism of injury

At NH, 4 patients (4%) sustained penetrating injuries and 94 (96%) blunt-force injuries. At KDH, 10 patients (9%) sustained penetrating injuries and 104 (91%) blunt-force injuries. Overall, 14 injuries (7%) were due to penetrating trauma and 198 (93%) to blunt-force trauma. Of the patients who sustained penetrating injuries, 71% were stabbed with a knife, 21% were stabbed with an unknown sharp object, and 7% were shot. All 4 patients from NH were stabbed with a knife.

Of total blunt-force injuries, 191 (96%) were due to assault, 4 (2%) were secondary to a pedestrian-vehicle accident and 1 (0.5%) to a motor vehicle accident, and 2 (1%) were secondary to burns. At NH, 99% of blunt-force injuries were secondary to assault and 1% to a pedestrian-vehicle accident.

At NH, the most common weapons that had been used were sticks ('knobkierie') (*n*=67 patients; 64%), followed by metal rods (*n*=13; 13%), sjamboks (*n*=5; 5%) and stones (*n*=3; 3%), with other weapons used in 5 cases (5%); 1 patient (1%) had been involved in a pedestrian-vehicle accident. At KDH, 98 blunt-force injuries (94%) were secondary to assault, 3 patients (3%) had been involved in a pedestrian-vehicle accident and 1 (1%) in a motor vehicle accident, and 2 patients (2%) had sustained burns. The most common weapons used were metal rods (*n*=21 patients; 20%), followed by sticks (*n*=13; 13%), sjamboks (*n*=12; 12%) and stones (*n*=7; 7%); in 45 cases (43%) the weapon was unknown. Overall, the most common weapon used was sticks ('knobkieries') (*n*=80 patients; 77%).

Presenting physiology

For the patients in total (*N*=212), the median respiratory rate was 18 breaths per minute, the median heart rate 91 bpm (range 47 - 166) and the median systolic blood pressure 124 mmHg. A total of 20 patients (18%) were shocked on presentation, of whom 12 were at NH and 8 at KDH. The median Glasgow Coma Score (GCS) was 15/15. The lowest GCS recorded at KDH was 3/15 and the lowest at NH 9/15. The median temperature was 36.2°C, pH 7.34, base excess 0.10 mmol/L, lactate 2.15 mmol/L and haemoglobin 12.9 g/dL.

Concurrent injuries

The median Injury Severity Score (ISS) was 12 at NH and 5 at KDH. The median ISS for both hospitals combined was 9. With regard to the most common body regions injured, at NH there were 56 lower limb injuries (57%), 53 upper limb injuries (53%), 53 head injuries (53%)and 32 abdominal injuries (33%). At KDH there were 81 head injuries (71%), 79 facial injuries (69%), 79 upper limb injuries (69%) and 55 lower limb injuries (48%). The percentages do not equate to 100%, because some patients sustained injuries to more than one regional system and the percentage is based on regional body injury per number of patients. All injuries were graded from 1 to 5 using the Abbreviated Injury Scale (AIS).

Renal function v. CK

Potassium, urea and creatinine levels were compared against CK intervals of <3 000, 3 000 - 8 000 and >8 000. At both NH and KDH, the mean potassium, urea and creatinine levels increased consistently as CK increased (Table 1).

Renal function v. HCO_3

Potassium, urea and creatinine levels were compared against HCO_3 intervals of ≤18, 19 - 21 and >22. At NH, the median potassium level showed an initial increase with a decrease in HCO_3 interval from ≥22 to 19 - 21, followed by a decrease in potassium with HCO_3 ≤18. Mean urea and creatinine levels increased consistently with decreasing HCO_3 intervals. At KDH, the mean potassium levels showed a decrease with decreasing HCO_3 intervals. The mean urea and creatinine levels increased consistently with decreasing HCO_3 intervals. For the patients in total, the mean potassium level showed minimal to no change between HCO_3 intervals. The mean urea and creatinine levels increased consistently with decreasing HCO_3 intervals. These findings are summarised in Table 2.

Renal function v. CK and HCO_3 comparison

Using the ANOVA (analysis of variance) calculator, we compared CK and HCO_3. The mean (standard deviation (SD)) CK level was 5 311.8 (9 351.95) and the mean (SD) HCO_3 level 22.296 (3.76). The *f*-ratio of 48.58877 shows that these two variables have no correlation, which is to be expected.

Using the Pearson correlation coefficient, we compared CK and HCO_3 against renal function (creatinine, µmol/L). When comparing CK against creatinine, the mean CK level was 5 311.8 and the mean creatinine level 133.457. The *r*-value was 0.2533. Although this is a technically positive correlation, the relationship between the

Table 1. Summary of renal function v. CK

CK intervals	K⁺ (mmol/L)			Urea (mmol/L)			Creatinine (µmol/L)		
(U/L)	<3 000	3 000 - 8 000	>8 000	<3 000	3 000 - 8 000	>8 000	<3 000	3 000 - 8 000	>8 000
Min.	3.10	3.30	3.60	0.90	1.90	2.30	46.00	55.00	67.00
Q1	3.70	3.90	4.03	3.20	4.10	5.20	64.00	78.25	91.25
Q2	4.10	4.20	4.40	4.20	5.25	7.65	75.50	96.50	135.00
Q3	4.30	4.50	4.88	5.83	6.53	13.30	96.00	123.00	301.75
Max.	5.60	6.00	6.50	32.60	62.30	43.90	583.00	1 300.00	1 244.00
Mean	4.09	4.23	4.56	4.86	6.76	10.98	88.86	136.01	270.00
Median	4.10	4.20	4.40	4.20	5.25	7.65	75.50	96.50	135.00
Range	2.50	2.70	2.90	31.70	60.40	41.60	537.00	1 245.00	1 177.00
IQR	0.60	0.60	0.85	2.63	2.43	8.10	32.00	44.75	210.50

CK = creatine kinase; K^+ = potassium; Q = quartile; IQR = interquartile range.

Table 2. Summary of renal function v. HCO_3

	K⁺ (mmol/L)			Urea (mmol/L)			Creatinine (µmol/L)		
HCO_3 intervals (mmol/L)	≤18	19 - 21	≥22	≤18	19 - 21	≥22	≤18	19 - 21	≥22
Min.	3.10	3.30	3.10	0.90	2.20	1.20	56.00	57.00	52.00
Q1	3.73	3.90	3.80	4.13	3.60	3.38	102.00	87.00	71.50
Q2	4.25	4.20	4.20	6.85	5.35	5.05	140.00	109.50	89.00
Q3	4.40	4.73	4.33	16.25	6.50	6.65	411.50	148.25	107.75
Max.	6.00	6.50	5.40	43.90	19.50	62.30	1 244.00	397.00	1 300.00
Mean	4.26	4.34	4.13	12.42	6.48	6.19	339.58	138.45	123.58
Median	4.25	4.20	4.20	6.85	5.35	5.05	140.00	109.50	89.00
Range	2.90	3.20	2.30	43.00	17.30	61.10	1 188.00	340.00	1 248.00
IQR	0.68	0.83	0.53	12.13	2.90	3.28	309.50	61.25	36.25

HCO_3 = venous bicarbonate; K^+ = potassium; Q = quartile; IQR = interquartile range.

variables is weak. Using the Pearson R Calculator, we inserted the *r*-value to calculate the *p*-value. The *p*-value was 0.000208.

When comparing HCO_3 against creatinine, the mean HCO_3 level was 22.296 and the mean creatinine level 162.053. The *r*-value was –0.3468. Although this is a technically negative correlation, the relationship between the variables is weak. Using the Pearson R Calculator, we inserted the *r*-value to calculate the *p*-value. The *p*-value was 0.000013.

The inverse ratio shown with HCO_3 v. creatinine, although still a weak correlation, is significantly better in predicting an increase in creatinine compared with the weak positive correlation of CK v. creatinine.

Management

The majority of patients were managed with intravenous fluids and analgesia only. At NH, 12 patients also received electrolyte replacement. Of the 12 patients, 1 had a CK level <3 000, 6 a level of 3 000 - 8 000 and 5 a level >8 000. In comparison, 4 patients had an HCO_3 level ≥22, 1 a level of 19 - 21 and 7 a level ≤18.

A total of 11 patients required RRT, all of whom had sustained blunt-force trauma. The 11 patients were classified as Kidney Disease Improving Global Outcomes (KDIGO) 3. Of these 11 patients, 4 had a CK level of 3 000 - 8 000 and 7 a level >8 000, while 2 had a HCO_3 level ≥22, 2 a level of 19 - 21 and 7 a level ≤18 (Figs 1 and 2).

Outcomes

At NH, mean length of stay (LoS) in hospital showed an initial decrease from 6 days to 5 days in patients with CK levels of <3 000 and 3 000 - 8 000, respectively, followed by an increase to 9 days in those with a level >8 000. LoS increased from 5 days to 11 days with HCO_3 levels ≥22 and ≤18, respectively. At KDH, mean LoS increased from 3 days to 7 days in patients with CK levels <3 000 and >8 000, respectively, and decreased from 7 days to 6 days in those with HCO_3 levels ≥22 and ≤18, respectively. Overall, LoS increased in tandem with increasing CK intervals. LoS showed an initial decrease with an HCO_3 level of 19 - 21, followed by an increase with a level ≤18.

Of the total sample, 12 patients were intubated and ventilated. Of these, 5 had a CK level <3 000, 3 had a level of 3 000 - 8 000 and 4 had a level >8 000; 5 patients had an HCO_3 level ≥22, 4 had a level of 19 - 21 and 3 a level ≤18. At NH, a total of 4 patients were intubated and ventilated. Of these, 3 had a CK level >8 000 and 1 a level between 3 000 and 8 000, while 2 had an HCO_3 level of 19 - 21 and 2 a level ≤18. At KDH, a total of 8 patients were intubated and ventilated, of whom 5 had a CK level <3 000 and an HCO_3 level ≥22, 2 had a CK level of 3 000 - 8 000 and an HCO_3 level of 19 - 21, and 1 had a CK level >8000 and an HCO_3 level ≤18.

At NH, 5 patients were admitted to the intensive care unit (ICU), of whom 3 had a CK level >8 000 and an HCO_3 level ≤18, and 2 a CK level of 3 000 - 8 000 and an HCO_3 level of 19 - 21. In comparison, of 5 patients admitted to the ICU at KDH, 1 had a CK level >8 000, 2 a level of 3 000 - 8 000 and 2 a level <3 000. Four of the 5 patients had an HCO_3 level ≥22 and 1 a level ≤18. Of the total of 10 patients, 4 had a CK level >8 000, 4 a level of 3 000 - 8 000 and 2 a level <3 000, while 4 had an HCO_3 level ≤18, 2 a level of 19 - 21 and 4 a level ≥22.

There were 2 deaths at KDH. Both these patients had sustained blunt-force injuries secondary to assault. One had a CK level in the 3 000 - 8 000 range (4 179) with an HCO_3 level ≤18 (17.2), and the other a CK level >8 000 (15 080) and an HCO_3 level in the 19 - 21

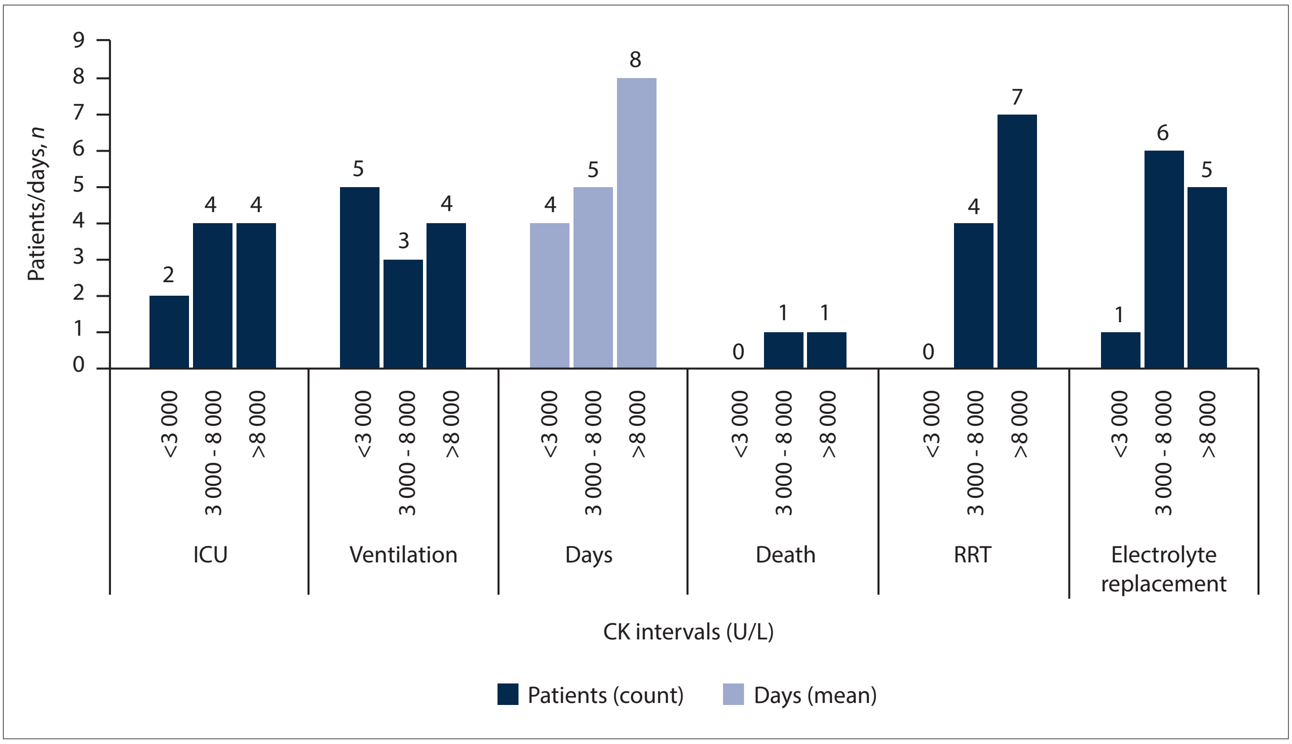

Fig. 1. CK overview. (CK = creatine kinase; ICU = intensive care unit; RRT = renal replacement therapy.)

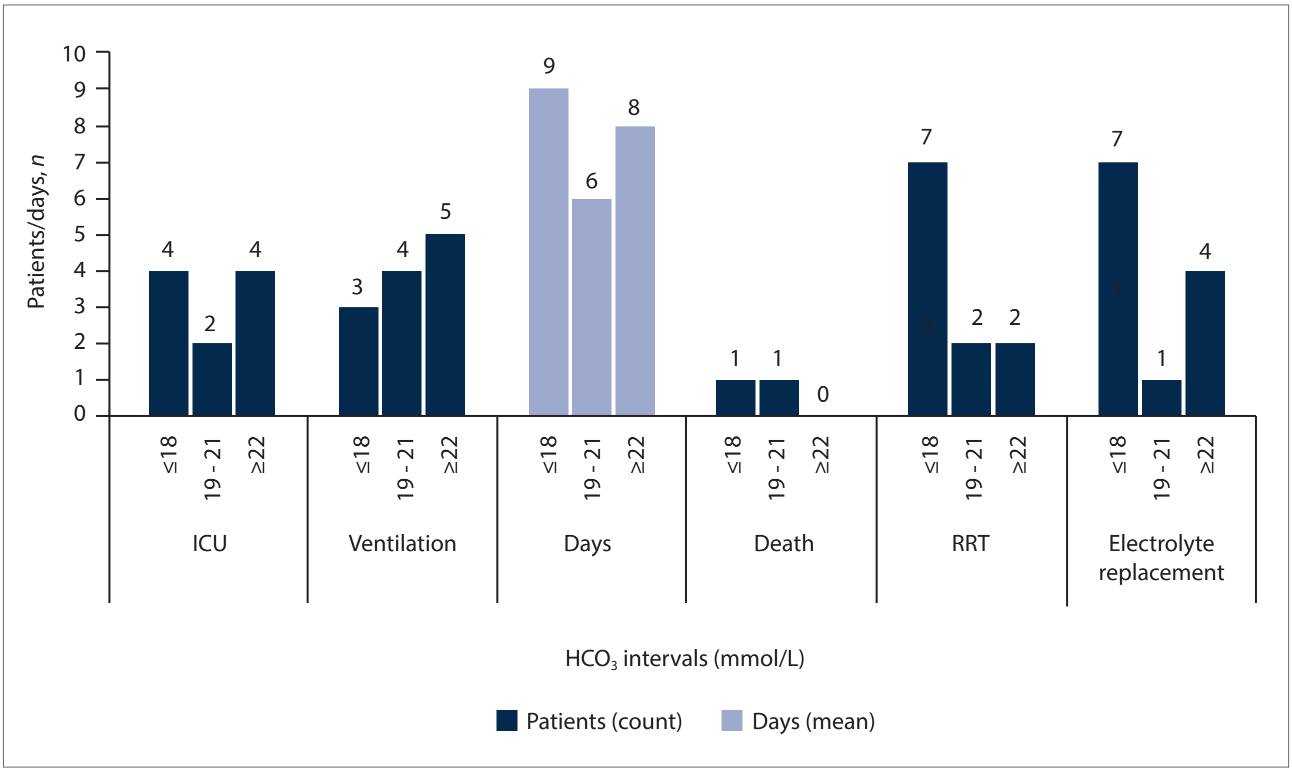

Fig. 2. HCO_3 overview. (HCO_3 = venous bicarbonate; ICU = intensive care unit; RRT = renal replacement therapy.)

range (20). No deaths were recorded at NH. The first death was non-renal related; the patient had a traumatic brain injury (TBI), AIS 4, and died of hospital-acquired pneumonia secondary to prolonged ventilation. The second death was also non-renal related. This patient also had a TBI (AIS 1) with hospital-acquired pneumonia secondary to prolonged ventilation; however, he developed nephrotoxicity due to treatment of his pneumonia with amikacin, and developed a new AKI with a potassium level of 6,5 mmol/L. The cause of death was still considered to be pneumonia.

Discussion

Myorenal syndrome is a common presentation in SA.[1,6] It is associated with long durations of hospital stay and significant morbidity, as evidenced by the need for ICU admission and for

RRT.[2,9] However, the mortality rate is low. The plethora of scoring systems in use reflects a degree of controversy and means that there are regional differences in our assessment and management strategies.[10-12] This is not an ideal situation.

Smith and Hardcastle[1] showed in a cohort of 334 patients that a CK level >8 500 predicted renal failure, and that CK >5 000 had a worse outcome compared with lower levels.[1] Simpson *et al*.[13] found that CK >5 000 is useful as a screening tool for further assessment of risk of renal failure; however, CK in their study was followed up daily and peaked at 3 days after admission. In the present study, CK was done on admission only; it is not common practice in our units to do daily CK testing.

Muckart *et al*.[2] showed in a cohort of 64 patients that an HCO_3 level <17 is highly predictive of acute renal failure. These findings were validated by Skinner *et al*.[9] in a retrospective study of 310 patients. Their results showed that decreasing levels of HCO_3 correlated with an increased tendency to require RRT. HCO_3 was statistically significant in predicting the need for RRT (p<0.001), whereas CK was not (p=0.052).[9]

In our study, although the inverse ratio of HCO_3 v. creatinine showed a weak correlation, it performed significantly better in predicting an increase in creatinine compared with the weak positive correlation of CK v. creatinine.

HCO_3 testing has several advantages over CK testing. First, serum CK may be useful as a screening tool for the presence of crush injury; however, in most cases clinical examination should provide sufficient suspicion, making CK testing superfluous. Second, blood gas testing is a routine adjunct to the primary survey in trauma, and hence HCO_3 (arterial or venous) should be readily at hand at the bedside, while CK testing is done in the laboratory and could lead to delays in decision-making. When HCO_3 has already risk-stratified a patient at the bedside, the additional value of the delayed CK level is questionable, and it would appear to be an unnecessary additional expense to the institution. Third, blood gas testing at the bedside provides not only HCO_3 levels but also a number of other important markers including lactate and potassium levels. Fourth, HCO_3 gives an indication of what is occurring at the renal level in real time, while CK is a surrogate marker.

Study limitations

This was a retrospective study, which in itself is considered a weakness. Another weakness of this study was that we do not have any indication of the amount of fluids the patients received prior to hospital admission. However, all blood samples were taken on admission. All non-trauma-related myorenal cases were excluded in this study. The study not only validates the current body of literature on this topic, but supports the fact that HCO_3 is the more accurate predictor; however, CK should not be seen as competitive but rather as complementary.

Conclusions

Although both venous HCO_3 and CK showed weak correlations with the development of renal failure in this study, venous HCO_3 was shown to be a more powerful predictor. For this reason, as well as in view of the practical and cost considerations mentioned, we recommend the measurement of venous HCO_3 for patients with crush injury, with the measurement of CK regarded as a complementary modality.

Declaration. None.

Acknowledgements. Stellenbosch University Department of Surgery, Khayelitsha District Hospital, Ngwelezana Hospital.

Author contributions. JJPB and SV: writing of the manuscript and data overview. MP, JF, BM: data collection. DLC, GVO and AG: review of manuscript and supervision.

Funding. None.

Conflicts of interest. None.

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Accepted 15 November 2020.