A raised serum lactate level is an independent predictor of in-hospital mortality in patients with isolated cerebral gunshot wounds

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Background. Cerebral gunshot wounds (CGSWs) represent a highly lethal form of traumatic brain injury, and triaging these patients is difficult. The prognostic significance of the serum lactate level in the setting of CGSWs is largely unknown.
Objectives. To examine the relationship between elevated serum lactate levels and mortality in patients with isolated CGSWs.
Methods. A retrospective review of the regional trauma registry was undertaken at the Pietermaritzburg Metropolitan Trauma Service, South Africa, over a 5-year period from 1 January 2010 to 31 December 2014. All patients with an isolated CGSW were included.
Results. A total of 102 patients with isolated CGSWs were identified. Of these, 92.2% (94/102) were male. The mean age (standard deviation) was 29 (8) years, and the in-hospital mortality rate was 21.6% (22/102). The mean serum lactate level was significantly higher among non-survivors than among survivors (6.1 mmol/L v. 1.3 mmol/L; $p<0.001$). Lactate levels among non-survivors were <2 mmol/L in 4.5%, 2 - 3.99 mmol/L in 9.1%, 4 - 5.99 mmol/L in 36.4% and ≥6 mmol/L in 50.0%. The odds ratio for mortality with a lactate level of 4 - 5.99 mmol/L was 67 (95% confidence interval (CI) 1.7 - 2 674.2), while for a lactate level of ≥6 mmol/L it was 1 787 (95% CI 9.0 - 354 116.1). The serum lactate level accurately predicted mortality even after adjustment for other variables. Based on a receiver operating curve analysis, an optimal cut-off of 3.3 mmol/L for serum lactate as a predictor for mortality was identified (area under the curve = 0.957).
Conclusions. CGSWs are associated with significant mortality, and a raised serum lactate level appears to be an independent predictor of in-hospital mortality. It is a potentially useful adjunct in the resuscitation room for identifying patients with a very poor prognosis.

Cerebral gunshot wounds (CGSWs) are a highly lethal form of traumatic brain injury (TBI), yet there are patients who survive these devastating injuries.[1-3] Triaging these patients is difficult, and accurate early prognostic indicators may help clinicians to make appropriate decisions.[1-5] The prognostic significance of a raised serum lactate level in torso trauma has long been appreciated. In this setting, it is able to guide resuscitation and to a certain extent predict clinical outcome.[6,7] However, the role of lactate in the context of an isolated TBI remains controversial [8-13]. Some authors have suggested that elevated serum lactate levels do not correlate with the extent of the cerebral cellular metabolic derangement in these patients, and that the predictive value of serum lactate in TBI is poor.[8-10]

Others, however, have shown that the serum lactate level correlates with the severity of TBI.[11,13]. Some have proposed that a raised serum lactate level is associated with improved neurological outcomes and lower mortality rates in patients with TBI. It has even been suggested that elevations in serum lactate due to anaerobic metabolism in trauma patients may in fact be neuroprotective.[8]

Objectives

To interrogate the relationship between serum lactate levels and mortality in patients with isolated CGSWs in order to improve prediction of mortality in these patients.

Methods
Clinical setting

This was a retrospective study undertaken at the Pietermaritzburg Metropolitan Trauma Service (PMTS) in Pietermaritzburg, South Africa (SA). Our electronic regional trauma registry was reviewed for the 5-year period from 1 January 2010 to 31 December 2014. Ethics approval for this study and for maintenance of the registry was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. BE 207/09 BCA 221/13). The PMTS provides definitive trauma care to the city of Pietermaritzburg, the capital of KwaZulu-Natal Province. It is one of the largest academic trauma centres in the province and serves as the referral centre for 19 other hospitals in the province, with a total catchment population of over 3 million. Approximately 4 000 trauma cases are admitted to the PMTS per annum, with over 50% being due to penetrating trauma. This is a direct reflection of the high incidence of firearm-related interpersonal violence and criminal activities throughout the entire province.

Criteria

All patients with single isolated CGSWs were included in the study. Those with concurrent gunshot wounds to other body regions (neck, chest, etc.) were excluded. All patients were managed in accordance with Advanced Trauma Life Support (ATLS) principles. Every patient

who has sustained a CGSW has a serum lactate level measurement performed as soon as practical after their arrival in the trauma resuscitation room.

Assessment

Basic demographic data, vital signs on arrival, physical examination findings, Glasgow Coma Score (GCS) and the final clinical outcome were reviewed. In accordance with ATLS, the conventional severity of TBI grading based on the GCS was used: mild (13 - 15), moderate (9 - 12) and severe (3 - 8). The serum lactate levels were arbitrarily divided into four categories, 0 - 1.99 mmol/L, 2 - 3.99 mmol/L, 4 - 5.99 mmol/L and ≥6 mmol/L, for the purposes of comparison.

Statistical analysis

The data were processed and analysed using Stata 13.0 (StataCorp, USA). Any associations between admission GCS category, serum lactate and categorical explanatory variables were assessed using Pearson's χ^2 test, or Fisher's exact test if an expected cell count was fewer than 5 observations. Comparison of means of continuous markers by GCS admission category was assessed using one-way analysis of variance. Correlations between GCS admission score and serum lactate were assessed using Spearman's rank correlation coefficient.

Results

Description of the patient cohort

During the 5-year study period, 102 patients with isolated CGSWs were treated at our institution. Of these, 92.2% (94/102) were male

and the mean (standard deviation (SD)) age was 29 (8) years. Most of the injuries (92.3%, 94/102) were related to interpersonal violence (assault). The remaining 7.8% (8/102) were attempted suicides; all these patients were male. The mean (SD) values of physiological parameters on arrival were as follows: heart rate 85 (24)/min, systolic blood pressure 124 (22) mmHg, temperature 36 (1)°C. The mean (SD) GCS on arrival was 12 (5). Thirty percent (31/102) of all patients had visible brain matter oozing from the wound. All 102 patients underwent computed tomography (CT) scans, of which 21.6% (22/102) revealed a bullet *in situ*. Neurosurgical intervention was required in 30.4% of cases (31/102); 28 (90.3%) of these 31 patients underwent debridement and/or elevation of a depressed skull fracture, and 3 required formal craniotomy for evacuation of a haematoma. Of the 102 patients, 21.6% (22/102) died during the admission. The remaining 80 patients (78.4%) survived to discharge. The mean (SD) GCS on discharge of all 80 survivors was 14.

CGCS v. lactate levels

Of the 102 patients, 19.6% (20/102) had a GCS of 3 - 8 on admission, 19.6% (20/102) a GCS of 9 - 12 and 60.8% (62/102) a GCS of 12 - 15. Table 1 summarises the demographics, clinical parameters and mean serum lactate level for each of these three severity groups. There was a significant difference in mean lactate level between the three groups, the level increasing as severity as determined by the GCS increased (mild: lactate 1.1 mmol/L, moderate: lactate 2.6 mmol/L, severe: lactate 5.6 mmol/L; $p<0.001$). This is shown in Table 2. A strong

Table 1. Comparison between mild, moderate and severe injury as determined by the GCS

	Mild: GCS 13 - 15 (N=62)	Moderate: GCS 9 - 12 (N=20)	Severe: GCS 3 - 8 (N=20)	*p*-value[†]
Demographics				
Age (years), mean (SD)	29 (8)	30 (7)	30 (9)	0.922
Gender, *n*				0.284
Male	55	19	20	
Female	7	1	0	
Clinical parameters				
Respiratory rate (per min), mean (SD)	18 (4)	19 (4)	17 (6)	0.501
Heart rate (bpm), mean (SD)	89 (21)	80 (18)	82 (33)	0.496
Systolic blood pressure (mmHg), mean (SD)	125 (20)	119 (18)	125 (27)	0.674
Temperature (°C), mean (SD)	37 (1)	36 (1)	36 (1)	<0.001*
Visible brain matter, *n*				<0.001*
Yes	6	7	18	
No	59	7	5	
Laboratory parameter				
Serum lactate (mmol/L), mean (SD)	1.0 (1.1)	3.3 (2.7)	5.2 (2.9)	<0.001*

GCS = Glasgow Coma Score; SD = standard deviation; bpm = beats per minute.
*Statistically significant (*p*<0.05).
[†]One-way analysis of variance for comparison of means by GCS group; Pearson's χ^2 test or Fisher's exact test (if expected cell count with fewer than 5 observations) used to test association between categorical variables and GCS category.

Table 2. The four categories of serum lactate levels in relation to GCS

Lactate level (mmol/L)	Mild: GCS 13 - 15 (N=62), *n* (%)	Moderate: GCS 9 - 12 (N=20), *n* (%)	Severe: GCS 3 - 8 (N=20), *n* (%)	*p*-value[†]
0 - 1.99	54 (87.1)	10 (50.0)	2 (10.0)	
2 - 3.99	4 (6.5)	5 (25.0)	3 (15.0)	<0.001*
4 - 5.99	3 (4.8)	3 (15.0)	5 (25.0)	
≥6	1 (1.6)	2 (10.0)	10 (50.0)	

GCS = Glasgow Coma Score.
*Statistically significant (*p*<0.05).
[†]Fisher's exact test.

inverse (negative) correlation was noted between serum lactate and admission GCS. The mean serum lactate level among non-survivors was significantly higher than that among survivors (6.1 mmol/L v. 1.3 mmol/L; $p<0.001$) (Fig. 1).

Serum lactate levels and mortality

There was a direct correlation between increasing serum lactate levels and mortality. Table 3 summarises the differences in demographi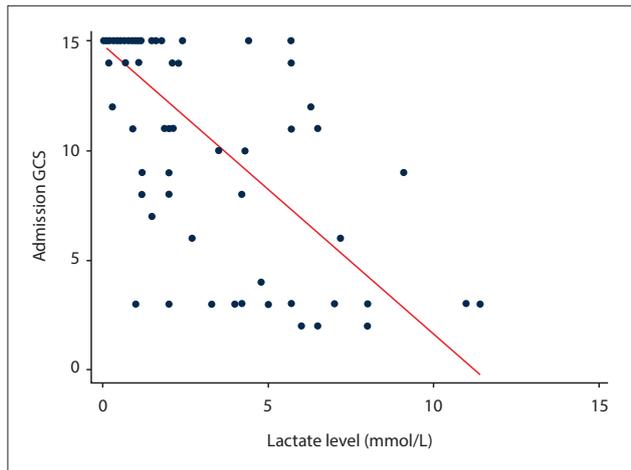cs, clinical parameters and serum lactate levels between survivors and non-survivors. This relationship is represented graphically in Figs 2 and 3. Both graphs demonstrate a direct relationship between increasing serum lactate levels and increasing mortality. An optimal breakpoint for serum lactate of 3.3 mmol/L for mortality prediction was identified using a positive predictive value (PPV) optimisation procedure for the receiver operating characteristic (ROC) curve (Fig. 4). The area under the curve for this cut-off was 0.957 (95% CI 0.913 - 1.001), which is well above the accepted cut-off of 0.8 for a good predictor. This optimal breakpoint yielded a high sensitivity (95%, 95% CI 77 - 99), specificity (94%, 95% CI 86 - 98), PPV (81%, 95% CI 63 - 99) and negative predictive value (99%, 95% CI 92 - 99). A direct comparison was made between survivors (80/102) and non-survivors (22/102). Table 4 shows how mortality increased with increasing serum lactate levels.

Fig. 1. Inverse correlation between serum lactate level and admission GCS. (GCS = Glasgow Coma Score.)

Discussion

CGSWs are a highly lethal form of TBI, and the severity of the injury strongly determines the outcome. The GCS is a highly successful and tried-and-tested clinical scoring system for blunt TBI. It is simple, elegant and repeatable, and separates TBI into the three broad categories of mild, moderate and severe. Although an elevated serum lactate level is a well-recognised marker of severity in torso trauma, its significance in TBI is unclear.[6-12] Our data suggested a close correlation between increased serum lactate levels and lower GCS. In addition, both these scoring systems correlate with increasing mortality.

Lactate is a waste product of anaerobic metabolism and reflects cellular disruption secondary to hypoperfusion and shock. It is a

Table 3. Baseline comparison between non-survivors and survivors

	Non-survivors (N=22)	Survivors (N=80)	*p*-value
Demographics			
Age (years), mean (SD)	30 (10)	29 (8)	0.7943
Gender, *n* (%)			0.196
Male	22 (100.0)	72 (90.0)	
Female	0 (0)	8 (10.0)	
Clinical parameters, mean (SD)			
Respiratory rate (per min)	17 (6)	18 (4)	0.3915
Heart rate (bpm)	76 (30)	87 (21)	0.0336*
Systolic blood pressure (mmHg)	124 (29)	124 (19)	0.608
Temperature (°C)	36 (1)	37 (1)	0.0012*
Visible brain matter			<0.001*
Yes	17 (77.3)	14 (17.5)	
No	5 (22.7)	66 (82.5)	
Admission GCS	4 (3)	14 (2)	<0.001*
Laboratory parameter, mean (SD)			
Serum lactate (mmol/L)	6.1 (2.5)	1.3 (1.3)	<0.001*

SD = standard deviation; bpm = beats per minute; GCS = Glasgow Coma Score.
*Statistically significant ($p<0.05$).

Table 4. Mortality according to serum lactate level

Lactate level (mmol/L)	Non-survivors (N=22), *n* (%)	Survivors (N=80), *n* (%)	OR (95% CI)†	*p*-value†
<2	1 (4.5)	65 (81.3)	1 (ref)	-
2 - 3.99	2 (9.1)	10 (12.5)	1.2 (0 - 84)	0.931
4 - 5.99	8 (36.4)	4 (5.0)	66.8 (1.7 - 2 674.2)	0.026*
≥6	11 (50.0)	1 (1.3)	1 786.9 (9.0 - 354 116.1)	0.006*

OR = odds ratio; CI = confidence interval; GCS = Glasgow Coma Score.
*Statistically significant ($p<0.05$).
†Adjusted for age, heart rate, systolic blood pressure, temperature, visibility of brain matter and low admission GCS (≤8).
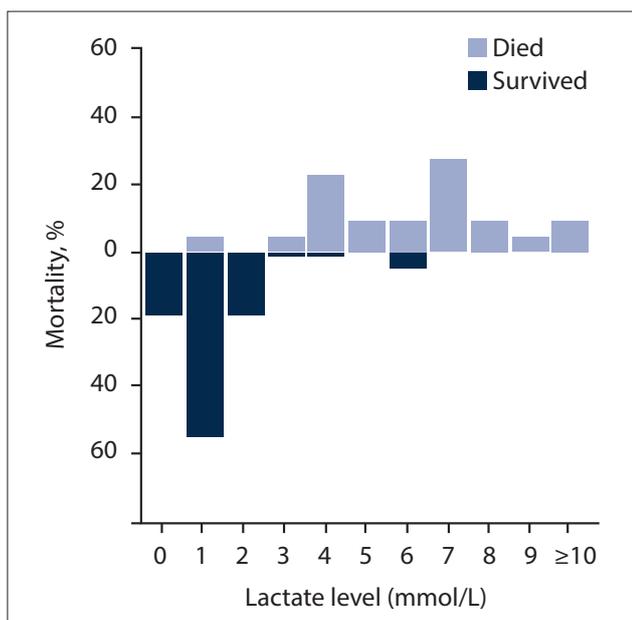
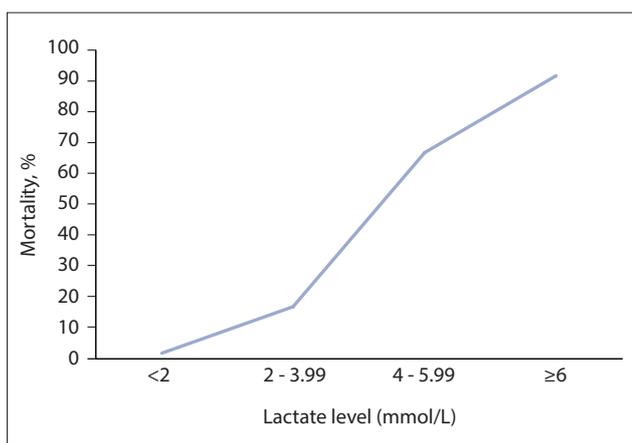*Fig. 2. Correlation between serum lactate level and mortality.*

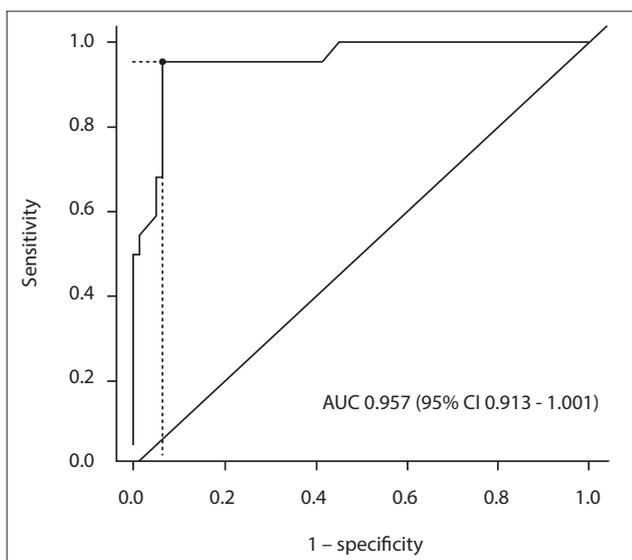*Fig. 3. Mortality rate according to increasing lactate level category.*

Fig. 4. ROC curve (criterion: ROC01) for optimal breakpoint identification of serum lactate level for mortality prediction. (ROC = receiver operating characteristic; AUC = area under the curve.)

better marker of shock states than vital signs, which may only become deranged late in the development of such a state.[6,7] In the context of TBI, some authors have suggested that elevated serum lactate levels reflect a general state of global hypoperfusion rather than cerebral metabolic derangement *per se*.[8-10] In a large series of 555 consecutive cases of isolated TBI, Cureton *et al*.[8] demonstrated that the serum lactate level was closely correlated with severity of TBI. However, they noted that a raised serum lactate level was associated with improved neurological outcomes and lower mortality rates. They went so far as to suggest that elevations in lactate due to anaerobic metabolism in trauma patients may be neuroprotective. Experimental data support this suggestion.[11-13]

The only study on the relationship between TBI and serum lactate in SA to date was from Milpark Hospital in Johannesburg.[5] In this study of 72 consecutive cases of isolated CGSWs, it was noted that the mean lactate level was higher in non-survivors than survivors (6.7 v. 2.7 mmol/L). In the present study, we have demonstrated that elevated serum lactate levels are predictive of increased in-hospital mortality. Using 3.3 mmol/L as a cut-off value, the odds of mortality are well over 300. We have also demonstrated that mortality increases dramatically as the serum lactate level rises. This remains significant even after adjusting for other variables and appears to be an independent predictor of in-hospital mortality. We consider that measurement of serum lactate levels in patients with a CGSW may potentially be useful as a predictor of mortality, especially if used in conjunction with other clinical features such as the GCS and the presence of exposed brain tissue. However, our sample sizes were small and the results should be interpreted with caution.

Conclusions

CGSWs are associated with significant mortality and a raised serum lactate level appears to be an independent predictor of in-hospital mortality. Serum lactate levels are closely correlated with the severity of penetrating TBI following a CGSW as determined by the GCS. There is an inverse relationship between admission GCS and serum lactate level. Serum lactate levels may well be a useful adjunct in determining the severity of TBI post CGSW. Further studies are required to assess the long-term neuropsychological outcomes in this injury subset in relation to our findings.

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