**The use of serum lactate levels to predict survival for patients with out of hospital cardiac arrest: a cohort study**

**ABSTRACT**

**Introduction** We examined the association of serum lactate levels and early lactate clearance with survival to hospital discharge for patients suffering an out-of-hospital cardiac arrest (OHCA).

**Methods** A retrospective cohort analysis was performed of patients with OHCA transported by ambulance to two adult tertiary hospitals in Perth, Western Australia. Exclusion criteria were: traumatic cardiac arrest, return of spontaneous circulation (ROSC) prior to the arrival of the ambulance, age less than 18 years and no serum lactate levels recorded. Serum lactate levels recorded for up to 48 hours post-arrest were obtained from the hospital clinical information system, and lactate clearance over 48 hours was calculated. Descriptive and logistic regression analyses were conducted.

**Results** There were 518 patients with lactate values, of whom 126 (24.3%) survived to hospital discharge. Survivors and non-survivors had different mean initial lactate levels (mean±SD 6.9±4.7 and 12.2±5.5 mmol/L, respectively; p<0.001). Lactate clearance was higher in survivors. Lactate levels for non-survivors did not decrease below 2 mmol/L until at least 30 hours after the ambulance call.

**Conclusion** In OHCA patients who had serum lactate levels measured, both lower initial serum lactate and early lactate clearance in the first 48 hours following OHCA were associated with increased likelihood of survival. However, the use of lactate in isolation as a predictor of survival or neurological outcome is not recommended. Prospective studies that minimise selection bias are required to determine the clinical utility of serum lactate levels in OHCA patients.

**Key words** cardiac arrest, out-of-hospital, lactate, clearance, survival

**Introduction**

Out-of-hospital cardiac arrests (OHCAs) account for a significant proportion of morbidity and

mortality in Australia. In 2010, cardiac arrests represented 7.1% of all-cause mortality in men and

6.8% in women.[1] There is growing interest in the identification of prognostic indicators of

neurologically intact survival after OHCA. Prehospital factors such as the initial cardiac arrest rhythm,

witnessed arrest and bystander cardiopulmonary resuscitation (CPR) have been shown to be

associated with improved outcomes.[2] In more recent times, the quality of CPR and post-resuscitation

care have been shown to be important.[3]

It has been suggested that serum lactate can be used as a surrogate marker for tissue perfusion in

patients suffering cardiac arrest after return of spontaneous circulation (ROSC).[4] There is evidence of

some utility of lactate in predicting survival to hospital discharge,[5,6] but another study found it to be

of limited value unless combined with other predictors such as ammonia levels.[6]

In addition to the initial levels of serum lactate following OHCAs, there has been interest in the rate

of clearance of excess serum lactate. Slow clearance of excess serum lactate has been associated

with both poor neurological outcomes and decreased survival after OHCAs,[7-9] but more research is

needed in this area because of inconsistent results and small sample sizes. We aimed to describe

cohort characteristics of OHCA patients with and without lactate values, and examine the association

of serum lactate levels and serum lactate clearance with survival to hospital discharge. We

hypothesised that lower lactate levels and increased serum lactate clearance were associated with

improved survival following an OHCA.

**Methods**

We conducted a retrospective cohort study for the period 1 January 2007 to 31 December 2012 in

Perth, Western Australia (WA). No formal sample size calculation was conducted. We considered that

the six-year period was sufficient to satisfy sample size requirements for the proposed adjusted

logistic regression analysis. Additionally, since measurement of lactate levels is a somewhat recent

practice in cardiac arrest management, collecting data from earlier patient episodes would have

been less resource efficient in obtaining appropriate cases for analysis. Ethics approval was obtained

from the relevant Human Research Ethics Committees (HR 2012-195, EC REG 13-131, HREC

RA/4/1/6163) and the study was approved by the St John Ambulance - Western Australia (SJA-WA)

Research Advisory Group. The STROBE checklist was used to guide reporting of this observational

data.[10] (Supplementary Table S1)

Adult patients (18+ years) who had suffered an OHCA were included if they were transported by SJA-

WA to the emergency department (ED) at two of the three adult tertiary-referral hospitals in the

greater metropolitan area of Perth. Perth is the capital city of WA, which comprises nearly a third of

Australia and has a population of 2 million people.[11] SJA-WA is the sole provider of emergency road

ambulance services in WA. Patients were identified from the SJA-WA cardiac arrest database, which

contains information on all OHCAs in WA.[12] Exclusion criteria were: trauma-related OHCAs; and ROSC

prior to ambulance arrival.

The SJA-WA OHCA database included demographic information about the patient, time event data,

characteristics of the arrest, prehospital clinical interventions and survival outcomes. The database

manager manually checked each case and where possible assigned the WA Department of Health

unique medical record number (MRN) for that patient. Serum lactate values were extracted by three

investigators (RM 50% of data collection, JK 25%, SA 25%) from the hospitals' Integrated Clinical

Information System, which used the same MRN system. For patients who did not have a MRN in the cardiac arrest database, demographic data and text descriptions were examined to identify patients. The MRN and serum lactate values were recorded in an Excel spread sheet (Microsoft® office excel® 2013) and then imported into SPSS Statistics Version 21.0 (IBM Corp. Released 2012. Armonk, NY: IBM Corp.) file. The lactate data were linked to the SJA-WA cardiac arrest database using the UMRN common to both data sets. Patient survival to hospital discharge status and neurological status on discharge were obtained through medical record review by a Research Nurse.

The serum lactate values used in this study were obtained from both arterial and venous blood samples.[13-15] Middleton et al.[14] and Mikami et al.[15] found high agreement between lactate and venous lactate values. While agreement was not perfect, Younger et al.[13] found the disagreement between venous and arterial values was at the high end of values and unlikely to impact on clinical decision-making.

Cohort characteristics, including demographic variables, variables related to the OHCA and serum lactate levels collected over the first 48 hours post-arrest, were described. Differences in characteristics between survivors and non-survivors within the groups with and without lactate values, and differences between those with and without lactate values, were tested using independent t-tests, Mann-Whitney U tests and chi-square tests, as appropriate.

The primary outcome was survival to hospital discharge. Neurological outcomes were also examined for patients with serum lactate levels: Cerebral Performance Category (CPC) scores of 1 and 2 were considered good neurological outcomes.[16] The association of survival to hospital discharge with the initial serum lactate level, taken from the time the emergency call was received by SJA-WA (0-2 hours), was investigated using unadjusted and adjusted logistic regression. The following variables were entered into the adjusted model: initial serum lactate level, patient age (years), sex, initial

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cardiac arrest rhythm (ventricular fibrillation/tachycardia, pulseless electrical activity/asystole), witnessed arrest (unknown, bystander-witnessed, paramedic-witnessed), bystander cardiopulmonary resuscitation (CPR), and ROSC on arrival to ED. A similar procedure was used to model the association between neurological outcome and initial serum lactate level.

Discrimination of the models for each of the 10 time periods: 0-2, >2-4, >4-6, >6-12, >12-18, >18-24 hours, >24-30, >30-36, >36-42 and >42-48 hours; was examined using the area under the receiving operating characteristic (AUROC) curve. The time periods were selected by consensus among the study team. Model discrimination was considered to be excellent if AUROC = 0.8-0.9.[17] We also used logistic regression to examine whether the odds of survival to hospital discharge differed according to whether or not patients had lactate values. We used two-sided comparisons, 95% confidence intervals (CIs), and statistical significance was set at < 0.05. No imputations were made for missing cases. Data were analysed with IBM SPSS v22 (IBM Corp, Armonk, NY, USA).

Graphs were used to illustrate the association between the rate of serum lactate clearance and survival to hospital discharge. Lactate clearance was calculated as the difference in percent serum lactate change from baseline (0 to 2 hours) to each time period up to 48 hours.[7,18]

**Results**

We identified 934 patients with OHCA during the six-year study period, of whom 518 patients (55%) had a serum lactate level (Figure 1). Cohort characteristics are shown in Table 1. Survival to hospital discharge for patients with a lactate level was 24.3% (126 patients). Survivors were younger than non-survivors (p<0.001) and more were male (p<0.01). There was a higher proportion of paramedic and bystander witnessed arrests (86% for survivors versus 59.9% for non-survivors p<0.01). Shockable rhythms (VF/VT) were the most common initial arrest rhythm in survivors (76%) and non-

survivors (36%) (Table 1). ROSC on arrival to ED was higher in survivors (92% for survivors versus 32% for non survivors; p<0.001). Of the 126 survivors, 94% had good neurological outcomes (CPC score of 1 or 2). Cohort characteristics of survivors and non-survivors among patients with no lactate values are also shown in Table 1.

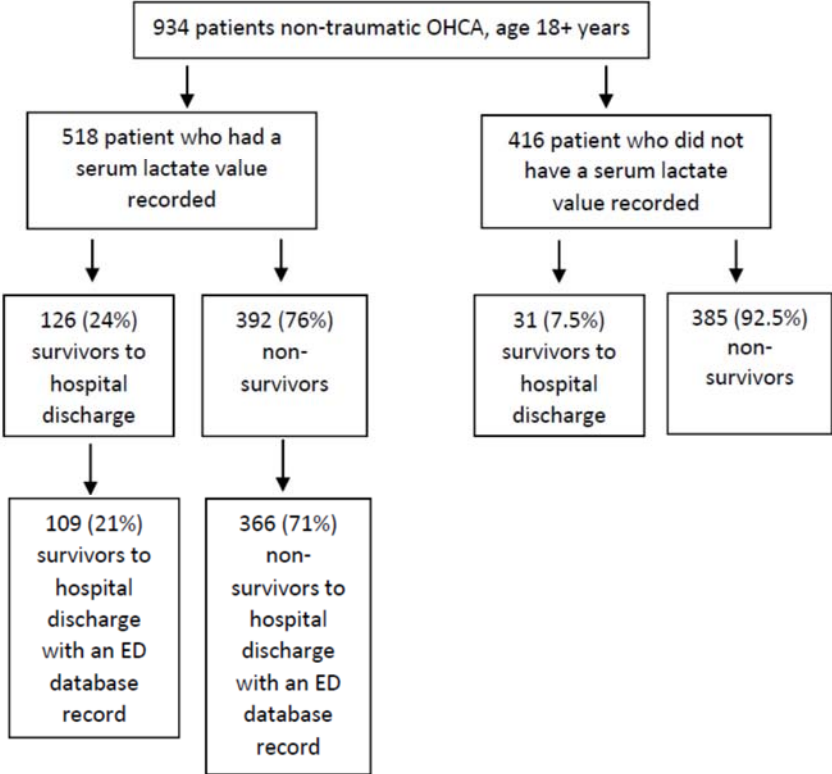Figure 1. Flow diagram of patient selection

Table 1. Characteristics of survivors versus non-survivors to hospital discharge and comparison

between patients with and without serum lactate values

| Characteristic | Serum lactate value recorded N=518 | | | No serum lactate value recorded N=416 | | | Comparison |
|---|---|---|---|---|---|---|---|
| | Survivors n=126 (24.3%) | Non-survivors n=392 (75.7%) | *P*-value[b] | Survivors n=31 (7.5%) | Non-survivors n=385 (92.5%) | *P*-value[b] | *P*-value[c] |
| Age, years, median (IQR) | 58 (49-67) | 67 (51-80) | <0.001 | 65 (58-74) | 72 (56-83) | 0.15 | <0.001 |
| Males, n (%) | 104 (82.5) | 277 (70.7) | <0.01 | 24 (77.4) | 274 (71.2) | 0.46 | 0.60 |
| *Collapse witnessed*, n (%) Unwitnessed Bystander witnessed Paramedic witnessed | 30 (24.0) 66 (52.8) 29 (23.2) | 156 (40.1) 175 (45.0) 58 (14.9) | <0.01 | 2 (6.9) 11 (37.9) 16 (55.2) | 183 (47.9) 161 (42.2) 38 (9.9) | <0.001 | 0.02 |
| *Initial cardiac rhythm*, n (%) VF/VT Pulseless electrical activity Asystole | 94 (76.4) 24 (19.5) 5 (4.1) | 140 (35.8) 128 (32.7) 123 (31.5) | <0.001 | 21 (77.8) 6 (22.2) 0 | 120 (31.4) 135 (35.2) 128 (33.4) | <0.001 | <0.01 |
| Bystander CPR, n (%) | 75 (59.5) | 181 (46.2) | <0.01 | 12 (38.7) | 185 (48.7) | 0.29 | 0.65 |
| Any return of ROSC, n (%) | 117 (95.1) | 141 (36.2) | <0.001 | 29 (93.5) | 28 (7.3) | <0.001 | <0.001 |
| ROSC on arrival to ED, n (%) | 112 (91.8) | 123 (31.8) | <0.001 | 29 (93.5) | 16 (4.2) | <0.001 | <0.001 |
| Initial lactate value recorded, mmol/L, mean (SD), median (IQR) | 6.9 (4.7) 5.9 (4.2-8.9) | 12.2 (5.5) 11.1 (8.1-15.0) | <0.001 | N/A | N/A | N/A | N/A |
| Time from call answered to ED[a], minutes, mean (SD) | 44.5 (15.2) | 47.5 (14.7) | 0.06 | 45.3 (12.9) | 51.2 (18.9) | 0.09 | <0.001 |

CPR=cardiopulmonary resuscitation; CI=confidence interval; ED=emergency department; IQR=interquartile range; n=number of patients; N/A=not applicable; ROSC=return of spontaneous circulation; SD= standard deviation; VF=ventricular fibrillation; VT=ventricular tachycardia.
Missing cases with lactate values: Cardiac rhythm: survivors=3, non-survivors=1; Collapse witnessed: survivors=1, non-survivors=3;
ROSC any: survivors=3, non-survivors=2; ROSC at hospital: survivors=4, non-survivors=5.
Missing cases for patients with no lactate values, n=777; Cardiac rhythm: survivors=7, non-survivors=3; Collapse witnessed: survivors=3, non-survivors=6;
ROSC any: survivors=5, non-survivors=5; ROSC at hospital: survivors=6, non-survivors=8.
[a] Time to ED calculated from time emergency call received by the St John Ambulance - Western Australia call centre to time ambulance arrived at ED.
[b] *P*-value from t-test or chi-squared test of whether the characteristic differed between survivors and non-survivors.
[c] *P*-value from t-test or chi-squared test of whether the characteristic differed between patients with and without serum lactate values.

Table 2 provides additional information about patients' initial serum lactate levels and the times they were collected. The highest initial lactate levels were those recorded at 0-2 hours for non-survivors (median 11.1 mmol/L). Twenty-nine (22.8%) survivors and 254 (64.8%) non-survivors only had one serum lactate value recorded within the first 24 hours after the ambulance call.

Table 2 Median and interquartile range (IQR) initial serum lactate levels (mmol/L)

| Time after the emergency call | Survivors | | Non-survivors | | $P$-value |
|---|---|---|---|---|---|
| | n | Median (IQR) | n | Median ( IQR) | |
| 0-2 hours | 109 | 5.7 (4.1-8.5) | 366 | 11.1 (8.1-15.0) | <0.001[a] |
| 2- 4 hours | 10 | 2.2 (1.5-3.4) | 12 | 4.6 (3.6-7.8) | <0.001[b] |

[a] *P*-value from independent *t*-test
[b] *P*-value from Man-Whitney *U* test

*Association of initial lactate value on hospital survival*

Table 3 presents the odds ratio (OR) estimates from logistic regression models of the association between survival to hospital discharge and each of the following: serum lactate levels, age, witnessed collapse, initial cardiac arrest rhythm, bystander CPR, ROSC on arrival to ED and sex; as well as the adjusted ORs (aORs) from a single model that contains all of the listed variables. After adjustment for the other variables, for each 1 mmol/L increase in initial serum lactate there is an 18% decrease in the odds of survival (aOR 0.82, 95% CI 0.75-0.89; p<0.001). The initial serum lactate level was also associated with good neurological outcome (CPC score 1 or 2) after adjustment for all other variables (aOR=0.84, 95% CI 0.77-0.91; p<0.001).

Table 3. The association of initial serum lactate values and other characteristics with survival to hospital discharge using unadjusted and adjusted logistic regression.

| Characteristic | Unadjusted analysis | | | Adjusted analysis[a] | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Initial lactate value per mmol/L increment | 0.77 | 0.72-0.82 | <0.001 | 0.82 | 0.75-0.89 | <0.001 |
| Age per year increment | 0.98 | 0.97-0.99 | <0.001 | 0.94 | 0.92-0.96 | <0.001 |
| *Collapse witnessed* | | | | | | |
| Unwitnessed | 1.00 | | | 1.00 | | |
| Bystander witnessed | 1.96 | 1.21-3.18 | <0.01 | 0.81 | 0.36-1.84 | 0.62 |
| Paramedic witnessed | 2.60 | 1.44-4.70 | <0.01 | 8.7 | 2.68-28.6 | <0.001 |
| *Initial cardiac rhythm* | | | | | | |
| Non-shockable rhythm | 1.00 | | | 1.00 | | |
| Shockable rhythm | 5.81 | 3.65-9.25 | <0.001 | 9.00 | 4.13-19.6 | <0.001 |
| *Bystander CPR* | | | | | | |
| No Bystander CPR | 1.00 | | | 1.00 | | |
| Bystander CPR performed | 1.71 | 1.14-2.58 | 0.10 | 2.88 | 1.24-6.68 | 0.14 |
| *ROSC at arrival to ED* | | | | | | |
| No ROSC | 1.00 | | | 1.00 | | |
| ROSC | 24.04 | 12.2-47.5 | <0.001 | 21.53 | 8.8-52.7 | <0.001 |
| *Sex* | | | | | | |
| Males | 1.00 | | | 1.00 | | |
| Females | 0.51 | 0.31-0.85 | <0.01 | 0.54 | 0.24-1.24 | 0.15 |

CPR=Cardiopulmonary Resuscitation; CI=confidence interval; ED=emergency department; OR=odds ratio; ROSC=Return of spontaneous circulation.
[a] All variables listed in table entered into the model.

The largest areas under ROC curves were 0.813 (95% CI 0.75-0.88; p<0.001) for the 2-4 hour period (Supplementary Figure S1) and 0.804 (95% CI 0.75-0.86; p<0.001) for the 0-2 hour period.

For survivors with more than one serum lactate value, the median serum lactate level had the greatest decrease within the first 4 hours (Figure 2). Between 0 and 2 hours it was 5.7 mmol/L for survivors compared to 11.1 mmol/L for non-survivors. Between 2 and 4 hours, the median serum lactate value decreased to 1.6 mmol/L for survivors, then remained steady over the next few hours. The serum lactate value almost halved for non-survivors (6.5 mmol/L) between 2 and 4 hours, then

declined steadily between 4 and 12 hours, but it did not decrease below 2.5 mmol/L until after 30 hours.

Figure 2. Median serum lactate values (mmol/L, solid line) and IQR (dashed line) for survivors (n=109) and non-survivors to hospital discharge (n=366) with initial serum lactate levels recorded in the time groups of 0-2 hours, >2-4 hours, >4-6 hours, >6-12 hours to >36-48 hours.
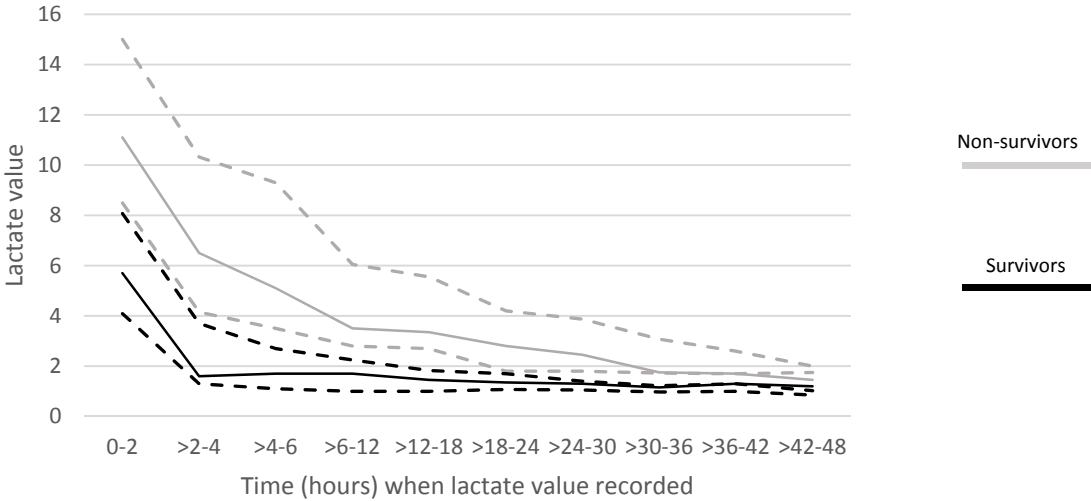


| Time group (hours) | 0-2 | >2-4 | >4-6 | >6-12 | >12-18 | >18-24 | >24-30 | >30-36 | >36-42 | >42-48 |
|---|---|---|---|---|---|---|---|---|---|---|
| Survivors | 5.7 | 1.6 | 1.7 | 1.7 | 1.5 | 1.4 | 1.3 | 1.2 | 1.3 | 1.2 |
| Non-survivors | 11.1 | 6.5 | 5.1 | 3.5 | 3.4 | 2.8 | 2.5 | 1.8 | 1.7 | 1.5 |

Median serum lactate clearances as percentages of patients' initial lactate values (absolute values to which it decreased from baseline) are illustrated in Figure 3. Survivors (n=65) had a more rapid lactate clearance than non-survivors (n=102): 69% by 4 hours versus 19%, respectively. Serum lactate clearance plateaued at 2-4 hours in survivors, but increased continuously in non-survivors. Median serum lactate clearance was similar for both survivors and non-survivors by 30-36 hours.

Figure 3. Median serum lactate clearance as a percentage of the initial serum lactate value for 475 patients with an initial serum lactate recorded between 0 and 2 hours.
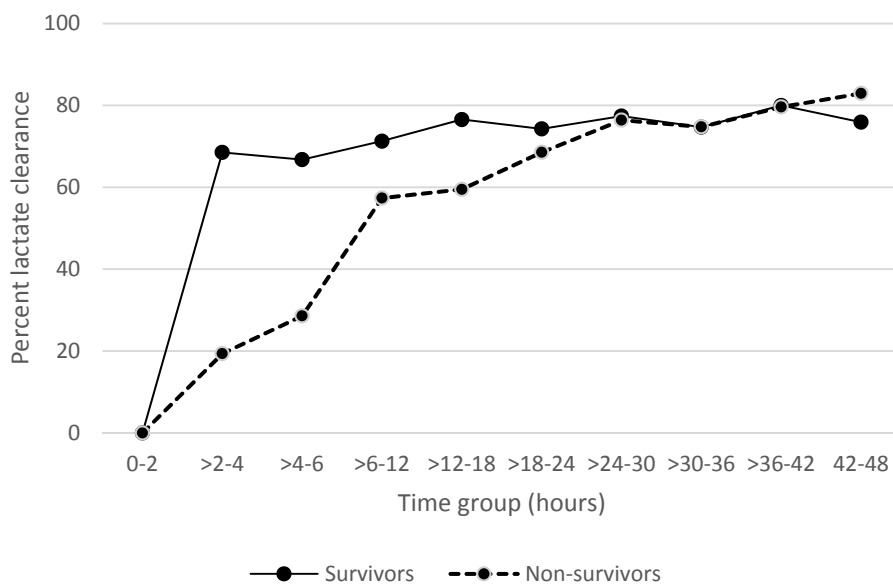


Due to the large number of patients without lactate levels we subsequently conducted a post hoc comparison between patients with and without lactate levels. The comparison of patients with and without lactate values indicated that patients with lactate values were younger and had significantly higher proportions of witnessed arrests, shockable rhythms and ROSC, and shorter time from their call to arrival at ED (*P*-values listed in Table 1). Although the unadjusted odds of survival to hospital discharge were higher for patients with lactate measures than those without (OR 3.99, 95% CI 2.63-6.06; p<0.001), after adjustment for other characteristics there was no difference in survival (aOR 0.98, 95% CI 0.47-2.05; p=0.96).

**Discussion**

Our study found that in patients whose physicians decided to measure serum lactate levels (about half of the OHCAs), both initial lactate level and lactate clearance were independently associated with survival to hospital discharge, even after adjusting for potential prehospital confounders. The highest serum lactate values occurred in the first 2 hours from the time the emergency call was received by SJA-WA, then rapidly decreased over the next 2 hours and continued to decrease over time. Non-survivors' serum lactate levels were higher and still above 2.0 mmol/L at 30 hours.

Previous research has shown a strong association between lactic acidosis and other conditions such as severe sepsis,[19,20] burns and trauma,[21] but studies investigating the association of serum lactate and hospital survival in cardiac arrest have been inconsistent.[5,6,8,9,22] The inconsistency may reflect the presence or absence of selection bias. Cocchi et al.[5] established a predictive link between survival and initial serum lactate levels when serum lactate was categorised into three groups: <5mmol/L, 5 to <10 mmol/L and >=10mmol/L. Kliegel et al.[23] Similarly, Donnino et al.[7,8] reported serum lactate was an independent prognostic factor of mortality and neurological outcome. However, Shinozaki et al.[6] did not find that initial serum lactate levels were statistically significant in predicting survival except when combined with ammonia levels. Lee[24] found no difference in the association of the initial serum lactate level on neurological outcomes in OHCA patients after therapeutic hypothermia but did find an association with increased serum lactate clearance.

Decreased serum lactate clearance, rather than initial serum lactate level, is arguably the stronger predictor for outcomes in cardiac arrest.[7] We found serum lactate clearance was highest in the first four hours and was a predictor of survival to hospital discharge. Several studies[1,7-9,22] reported patients with early serum lactate clearance were more likely to survive, supporting the results of our

study. The clearance of lactate is likely representative of improved tissue perfusion following the cardiac arrest.[7] Several mechanisms have been described that may explain how lactate and clearance is independent of other factors other than anaerobic metabolism in ICU patients.[25,26] These include severity of illness, exhaustion of energy supplies and impaired mitochondrial function.

### *Limitations*

Our study is the largest to date to examine the association between initial serum lactate levels and lactate clearance and outcomes after OHCA; but there are several limitations that may influence valid interpretation of the results. Firstly, this is a retrospective cohort study using secondary data but the data were collected prospectively and all cardiac arrest patient care records were checked manually for Utstein data elements by the cardiac arrest database manager. Data abstracted from the Clinical Information System were entered in the database by any one of the three data collectors and the accuracy of the lactate values was not verified by an independent data collector. Measurement of serum lactate levels was undertaken at physician discretion and not at prescribed times. We grouped serum lactate values into 2-hourly periods for the first 6 hours and thereafter within 6-hourly time periods. The highest serum lactate value was recorded during these time periods but when the event occurred within the 6 hour-period is unknown.

Forty-six percent of patients did not have any lactate levels measured, resulting in potential selection bias. These patients had a third of the survival to hospital discharge compared to those with serum lactate levels recorded. Possible reasons for not measuring lactate levels are that the patient died, or they survived and were either palliated or recovered quickly. In addition, lactate values may have been obtained but not recorded in the patient's medical record. We note, however, that after adjustment for age, collapse witnessed, initial cardiac rhythm, bystander CPR, ROSC at arrival, and sex, there was no difference in survival between patients with and without serum lactate measurements in this study cohort.

Survival to hospital discharge was much higher than those reported in previous studies involving our ambulance service.[27,28] In the PACA trial OHCA patients in VF/VT who reverted on the first or second shock would not have been included and hence the survival rate would have been low.[25] The exclusion of traumatic OHCA and patients with no lactate values, whose survival to hospital discharge (7%) was considerably lower than those patients with lactate values (24%), contributes to these differences and impacts on the study's external generalisability.

We conducted logistic regression analyses that adjusted for potential confounders but it is likely that unknown clinical confounders were not included. This may include the heterogeneity of OHCA aetiology. Treatments received, such as therapeutic hypothermia, mechanical ventilation and vasopressors may influence lactate levels,[7] but we did not have access to in-hospital treatment data. Nevertheless, important prehospital predictors for survival to hospital discharge were included in our models. An important consideration is the change in post-resuscitation care over time and the effect on outcomes. Prospective studies that minimise selection bias and prescribe measurement of serum lactate levels at specific time points are required to determine the impact of serum lactate clearance, which is arguably more important than the initial serum lactate level, on patients in the post-resuscitation phase of OHCA.[25]

**Conclusion**

In those OHCA patients who had lactate measurement(s) performed, both lower initial serum lactate and early lactate clearance in the first 48 hours following OHCA were associated with an increased likelihood of survival. Considering the limitations of our study, the use of lactate in isolation as a predictor of survival or neurological outcome is not recommended. To determine the clinical utility of serum lactate levels in OHCA patients, prospective studies that minimise selection bias are required.

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Supplementary Figure S1. Predictive effect on survival to hospital discharge of serum lactate levels taken between 2 and 4 hours