Routine Laboratory Indices as Predictor of Neurological Recovery in Post-Resuscitation Syndrome Patients Treated with Therapeutic Hypothermia

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ABSTRACT: **Background:** Hypothermia is associated with improved outcome in selected survivors of cardiac arrest but no single metric enables proper prediction of neurological outcome.

Objectives: To explored the association between routine laboratory indices of patients treated by hypothermia for cardiac arrest and their neurological outcome.

Methods: We retrospectively collected data from survivors of cardiac arrest treated with hypothermia for 24 hours and grouped them according to their neurological outcome, either "poor" or "favorable". Routine laboratory indices were collected at constant time intervals up to 1 week after admission. A comparison between the laboratory values of both groups was performed.

Results: The study group comprised 41 consecutive patients with a mean age of 54.3 ± 16.7 years who experienced cardiac arrest between May 2008 and November 2011. No significant correlation was found between routine laboratory indices and neurological outcomes. The temporal trend of decay in the serum glucose values and the ratio of polymorphonuclears to white blood cells during the first 72 hours after admission was steeper in the favorable outcome group (P for trend < 0.05).

Conclusions: No single routine laboratory index was associated with neurological outcome of survivors of cardiac arrest treated with hypothermia. The temporal trends in both serum glucose and polymorphonuclear ratio signaled a more intense inflammatory response associated with poor outcome.

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KEY WORDS: hypothermia, resuscitation, cardiac arrest, post-cardiac arrest syndrome, neurological recovery predictors

The prognosis of patients experiencing cardiac arrest is generally poor, with survival rate ranging from 6.4% in patients surviving an out-of-hospital event to 17% in an inpatient setting [1,2]. The neurological injuries and their late sequels are major determinants of mortality and morbidity in post-cardiac arrest patients [3]. Mild therapeutic hypothermia (TH) has become the standard of care treatment in selected post-cardiac arrest patients due to the ample evidence indicating improved patient outcome both in neurological sequelae and mortality [4-7]. Recently the aggressive hypothermia approach to reduce the corporal temperature to 33°C was reassessed to targeted temperature below 36°C [8,9]. At present, the ability to predict the neurological outcome by clinical or auxiliary metrics is limited [10]. The subcommittee of the American Academy of Neurology published a review manuscript that suggested a set of clinical neurological tests predicting a poor neurological outcome after cardiac arrest [11]. This manuscript mentioned that although data was from a small scale study, some laboratory indices (e.g., neuron-specific enolase) may predict outcome, but these tests are not readily available. Single routine laboratory indices (e.g., high base excess and serum ammonia) evaluated in the pre- and in-hospital care were also, sporadically, associated with favorable outcome [12,13] but none of the aforementioned parameters was explored for cardiac arrest patients with regard to TH. The aim of the present study was to explore connections of the routine laboratory indices for patients undergoing TH post-cardiac arrest to uncover associations between an index and outcome.

PATIENTS AND METHODS

This single-center study utilized data collected 3 years retrospectively from consecutive eligible patients who had undergone TH after surviving cardiac arrest. The criteria for TH were a determination of cardiac arrest based on first responder's monitor and immediate treatment with shockable rhythm, resulting in spontaneous circulation. The protocol was approved by the local institutional review board.

Mild TH (32–34°C) was implemented for 24 hours by utilizing standard protocol; induction was obtained by combining a high-rate of intravenous infusion of normal saline at 4°C with a designated hypothermia induction system (CureWrap™ and CritiCool™; Mennen Medical® group, Southhampton, PA, USA). After induction, hypothermia was maintained solely with a hypothermia suit. Body core temperature was monitored independently using three

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separate probes. Rewarming was initiated after 24 hours of hypothermia at a rate of 0.3°C per hour. All patients were sedated with midazolam and/or propofol combined with a muscle relaxant to prevent shivering. Timing of percutaneous angiography was irrespective of hypothermia therapy. Once normal body temperature was regained, sedation was halted. Neurological status was assessed independently both by cardiologists and neurologists during hospitalization and after neurological status stabilization (which ranged from a few hours to a few weeks in a minority of cases). The patients were grouped according to their neurological status by utilizing the Cerebral Performance Category (CPC) scale:

1. Conscious and alert with normal function or only slight disability
2. Conscious and alert with moderate disability
3. Conscious with severe disability
4. Comatose or persistent vegetative state
5. Brain dead or death from other causes

The outcome of patients with a CPC score of 1–2 was defined as "favorable" while those with a score of 3–5 were defined as "poor". Patients with a CPC score 1–2 underwent diagnostic analysis for sudden cardiac death as indicated (e.g., adenosine/epinephrine test, coronary catheterization).

During hospitalization, at least eight sets of routine blood samples for each patient were obtained as follows: three samples during the first day of admission (0–7 hours, 7–13 hours, 13–24 hours), every 12 hours during the next 2 days and once each day at days 6–10 after admission (referred to as "1 week after admission"). The following variables were studied: white blood cell count (WBC), percentage of polymorphonuclears (PMN) out of the WBC, pH, sodium (Na), potassium (K), glucose, calcium, creatine phosphokinase (CPK), international normalized ratio (INR), creatinine (Cr), urea, alanine transaminase (ALT), aspartate transaminase (AST) and troponinT (TnT). All laboratory tests were conducted in our central laboratory. A comparison of the laboratory indices of patients with favorable outcome to those of patients with poor outcome was performed.

STATISTICAL ANALYSIS

SPSS version 19 (IBM, Chicago IL, USA) was used for statistical analysis. Continuous variables were compared using Student's *t*-test and are expressed as mean ± standard deviation. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate, and are expressed as numbers and percentages. The independent samples *t*-test was used to detect possible differences between the two groups in normally distributed continuous variables. The mixed analysis of variance (ANOVA) test was used to compare each variable at different points in time during the first 72 hours of hospitalization. We used polynomial contrasts to compare the linear trends. A logistic regression model was used for analyzing the influence of several of the statistically significant parameters in the probability of a favorable outcome. Due to missing values, the analysis of a fraction of the variables was done after contracting the data into three values, each representing 24 hours out of the 72 hours of follow-up after admission. We used the paired samples *t*-test to compare the values of each variable at time of admission and 1 week after admission. The level of significance was set at $P < 0.05$.

RESULTS

The study comprised 41 consecutive patients. Six women (14.6%) and 35 men (85.4%) with mean age of 54.3 ± 16.7 years. As presented in Table 1, patients' baseline characteristics were similar, except for older age in the poor outcome group (61.0 ± 10.5 vs. 48.6 ± 19.0 years of age, $P < 0.05$). Although seven (30.4%) of the patients in the favorable group had undergone revascularization and 16 (69.5%) had an implantable cardioverter defibrillator (ICD), only two patients (11.11%) from the poor outcome group underwent revascularization and no ICD had been implanted in these patients.

No differences were noted in the laboratory indices between the patients with favorable and those with poor outcomes. Other biochemical laboratory indices differences (AST, ALT, TnT, pH, Na, K, urea, Cr, Urea/Cr ratio) were not significant as was their trend.

When the serum glucose values were compared at different time intervals from admission, a non-significant trend for lower values of glucose on admission was noted in the favorable outcome group (236.6 mg/dl vs. 303.1mg/dl, $P = 0.07$). During the following 13 hours, the group of patients with poor outcome had significantly higher glucose levels (157.8 vs. 219.1 mg/dl, $P < 0.05$). After this period of time, no significant differences were noted. However, when the temporal change in serum glucose values from admission to 72 hours after admission between the groups was calculated, a statistically significant trend was observed, as depicted in Figure 1. No significant difference was noted in the serum glucose 1 week post-admission (116.4 ± 37.1 vs. 148.8 ± 82.3 mg/dl, $P = 0.114$).

Table 1. Baseline patient characteristics

	All cohort (n=41)	Favorable outcome (n=23)	Poor outcome (n=18)	*P* value
Age (years)	54.3 ± 16.7	48.6 ± 19.0	61.0 ± 10.5	0.016
Gender, male	35 (85.4%)	19 (82.6%)	16 (88.9%)	0.57
Medical history				
History of smoking	18 (43.9%)	10 (43.5%)	8 (44.4%)	0.95
History of ischemic heart disease	10 (24.4%)	6 (26.1%)	4 (22.2%)	0.78
Chronic anti-arrhythmic therapy	6 (14.6%)	4 (17.4%)	2 (11.1%)	0.57
Hypertension	19 (46.3%)	8 (34.8%)	11 (61.1%)	0.093
Diabetes mellitus	9 (22%)	4 (17.4%)	5 (27.8%)	0.43
Hypercholesterolemia	17 (41.5%)	9 (39.1%)	8 (44.4%)	0.73

Figure 1. Temporal trend in serum glucose values during the first 72 hours after hospital admission

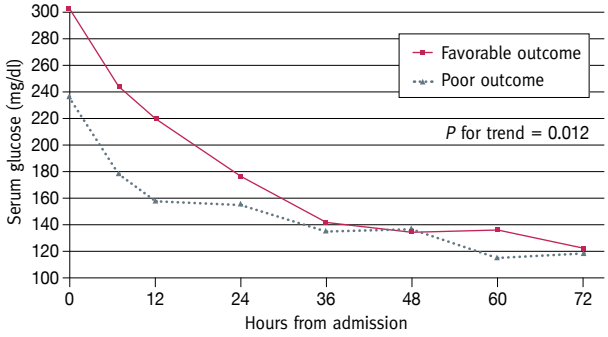
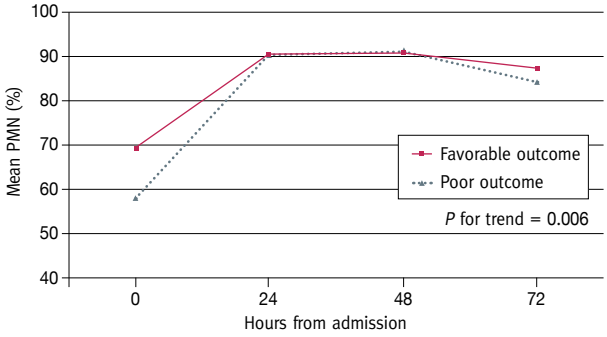


Figure 2. Temporal trend in mean percent of polymorphonuclears during the first 72 hours after hospital admission



PMN = polymorphonuclears

Serum CPK levels on admission were significantly higher in the poor outcome group (221.4 vs. 360.1U/l, $P < 0.05$). We noted a trend for lower troponin levels 24 hours after admission in the favorable group (0.11 µgr/dl favorable, vs. 0.33 µgr/dl poor, $P = 0.06$).

When blood count indices were scrutinized, both groups had high levels of WBC on admission (19.33 ± 10.273 10^3/µl poor, vs. 15.5 ± 5.726 10^3/µl favorable, $P = 0.207$), peaking at 24hours from admission (24.491 ± 9.694 10^3/µl, poor vs. 19.88 ± 5.626 10^3/µl, favorable, $P = 0.12$) with no statistically significant differences between the groups. When the PMN/WBC ratio was calculated, we noted a significant difference in the trend of the decay in the %PMN within the first 72 hours of admission [Figure 2].

Due to the relatively small cohort of patients, we were unable to establish a predictive logistic regression model.

DISCUSSION

Therapeutic hypothermia has recently been widely used as the standard treatment of care in appropriately selected patients after cardiac arrest. It was hypothesized that the outcome of post-cardiac arrest patients derive not only from the initial whole body ischemia but from the "second hit" reperfusion injury related to the inflammatory response [14]. Little data exists regarding the correlation between laboratory indices and the neurological outcome. We thus sought to explore this relationship by retrospectively comparing temporal association between routine laboratory indices and neurological outcome in patients undergoing therapeutic hypothermia.

The two groups of patients compared in the present study were mostly balanced albeit a noted difference in the average age with evidence of younger age in the favorable outcome group. This result is similar to previous studies that have shown that younger age is associated with improved outcome [5].

As opposed to earlier reports focusing mainly on laboratory indices on admission, we followed laboratory values from admission to the first days of hypothermia and re-warming, and up to 1 week after admission to evaluate the correlation between laboratory indices and outcome along this timeline. Although unable to correlate between most of the routine laboratory indices and outcome, a significant difference in the temporal trends in both serum glucose values and %PMN between the two groups of neurological outcome was noted.

Hyperglycemia at admission following cardiac arrest had previously been associated with reduced neurological recovery [15-17]. Although the exact mechanism is unclear, hyperglycemia is assumed to be a stress induced reaction [18], provoked by sympathetic activation and leading to insulin tolerance. These processes all act together to promote a sepsis-like syndrome [14]. The present study adds to the aforementioned data by acknowledging both the differences in serum glucose on admission (although not statistically significant) and the differences in the trend of serum glucose between the two groups in the critical time from admission to the post-re-warming period. This result may indicate that the higher glucose levels during the critical hours of hypothermia and re-warming in the poor outcome group is a more intense initial sepsis-like immunological reaction, indicating broader tissue damage that eventually translates into poor outcome.

PMN participate in virtually any inflammatory response. They are known for the beneficial role in accumulating in infected tissues promoting phagocytosis and microorganism killing [19]. Paradoxically, this beneficial role may be replaced by PMN-associated tissue damage. It has been demonstrated in both animal and human studies that PMN are major factors in inducting ischemia-reperfusion injury of various organs and thus serve as a target for suppression by pharmacological agents [20]. The rate of decrease in the %PMN in the present report differed significantly between the two groups with a steeper decline in PMN counts in patients with favorable outcomes. This result is probably in concordance with our assumption that patients who had sustained more

severe tissue damage would react with an intense inflammatory reaction which may lead to poor outcome.

The significantly higher CPK values at admission in the poor outcome group could have originated from either myocardial or striated muscle insult. The fact the no significant differences were noted between the serum troponin values at 24 hours from admission may indicate that the CPK did not originate from the myocardium and patients in the poor outcome group had sustained a more intense initial tissue damage, as was previously discussed.

STUDY LIMITATIONS

The following limitations should be acknowledged. The main limitation in this study lies in its relatively small number of patients. Although this is not a negligible cohort of patients, since large scale studies are scarce, the actual sample size limited us from establishing a more elaborate and reliable correlation between the laboratory indices and the neurological prognosis. Furthermore, larger cohorts and prospective studies are warranted for validation of our hypotheses.

CONCLUSIONS

No single routine laboratory index correlated well with neurological outcome in patients surviving cardiac arrest treated with hypothermia. The differences found between the temporal trend in serum glucose and %PMN may indicate a more intense inflammatory response that resulted in poor outcome.

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Capsule

Estimating transmission chains for dengue

Dengue virus (DENV) causes many asymptomatic infections, and therefore surveillance captures only a fraction of the cases. Salje et al. developed a method for identifying the number of transmission chains of DENV from sequence data and serology. They found that sequential transmission of DENV typically occurs between households in the same neighborhood. Within high-density urban localities, such as Bangkok, there are surprisingly few transmission chains. This results in epidemic spikes within a regional background of endemicity. Large urban settings may thus act as a source of diverse viruses that can be transported elsewhere.

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