Pan-Asian Resuscitation Outcomes Study (PAROS): Rationale, Methodology, and Implementation

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Abstract

Disease-based registries can form the basis of comparative research to improve and inform policy for optimizing outcomes, for example, in out-of-hospital cardiac arrest (OHCA). Such registries are often lacking in resource-limited countries and settings. Anecdotally, survival rates for OHCA in Asia are low compared to those in North America or Europe, and a regional registry is needed. The Pan-Asian Resuscitation Outcomes Study (PAROS) network of hospitals was established in 2009 as an international, multicenter, prospective registry of OHCA across the Asia-Pacific region, to date representing a population base of 89 million in nine countries. The network's goal is to provide benchmarking against established registries and to generate best practice protocols for Asian emergency medical services (EMS) systems, to impact community awareness of prehospital emergency care, and ultimately to improve OHCA survival. Data are collected from emergency dispatch, ambulance providers, emergency departments, and in-hospital collaborators using standard protocols. To date (March 2011), there are a total of 9,302 patients in the database. The authors expect to achieve a sample size of 13,500 cases over the next 2 years of data collection. The PAROS network is an example of a low-cost, self-funded model of an Asia-Pacific collaborative research network with potential for international comparisons to inform OHCA policies and practices. The model can be applied across similar resource-limited settings.

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O ut-of-hospital cardiac arrest (OHCA) is a global health concern.¹ Asia-Pacific's (Continental Asia and Australasia) population is still increasing and is expected to age progressively in the next 10 to 15 years.² Emergency medical conditions in the elderly, including OHCA, are anticipated to increase, and many emergency medical services (EMS) systems in Asia are

experiencing strain from increasing workload and limited resources. $\!\!\!^3$

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Table 1

(ROC) of North America¹ are examples of regional registries that have produced research affecting policy in this important area. There is a need for countries and regions with fewer resources to learn from these databases, to pool data, and to derive meaningful information for comparison with established registries to improve outcomes of OHCA through EMS systems, hospital policies, and public and community education.

Some key questions for the Asia-Pacific and other developing regions are as follows: How can we increase survival from OHCA in the most cost-effective, evidence-based way, given limited resources? How can the heterogeneity across systems be addressed when designing future policy? What intervention strategies will give the most benefit for investment? There is an urgent need for high-quality data collection to promote research on OHCA in the Asia-Pacific region.

We aim to understand OHCA as a disease in Asia, as well as describe current prehospital systems in the Asia-Pacific area. An Asia-Pacific cardiac arrest registry will help provide international benchmarking and study of best practices in Asian EMS. Our long-term aim is to affect community awareness and change attitudes toward prehospital emergency care and to improve survival by future implementation and objective evaluation of system- and community-level interventions. The large sample size and international nature of this registry provides a unique opportunity for analysis of the preventable risk factors and systemic predictors of survival for OHCA.

This article describes the conceptualization, processes of implementation, short- and long-term aims, potential benefits, and identified obstacles and solutions for a newly established Asia-Pacific network to improve OHCA outcomes. The goal is to provide a future framework for others in the field and to increase international dialogue and collaboration for OHCA research.

BACKGROUND

The Asian Emergency Medical Services Council was established in 2009 as a voluntary, participation-based group promoting education and advocacy of EMS issues in the Asia-Pacific region. It has adopted the PAROS study as one of its core activities for the next 5 years. A working group of interested prehospital and emergency care providers in the Asia-Pacific region (see Table 1) was formed in 2009 to discuss establishing a prehospital and emergency care collaborative research group. This group had regular quarterly meetings as well as additional Web-based and telephone conferences. The PAROS clinical research network was inaugurated in 2010 and adopted a constitution with an executive committee comprising a chair, three co-chairs, and two nominated representatives per participating country. The executive committee is elected for a 3-year term. More information about the PAROS network, constitution, methodology, and data variables can be found at the PAROS website: http://www.scri. edu.sg/index.php/paros-clinical-research-network.

The PAROS mission is to establish a resuscitation clinical research network in the Asia-Pacific region that will provide baseline information about OHCA prevalence, management, and outcomes; describe variations among

List of Participating Regions by Countr	ý
Countries Using Batch Download from National Registries	Participating Regions/Agencies
Japan	• Aichi • Osaka
Korea	• Tokyo • Daegu • Gwangju
	• Goyang • Incheon • Jeju • Seoul
Taiwan	• Taipei • Taoyuan
Countries Using Electronic Capture System	Participating Regions/Agencies
Australia Malaysia	 New South Wales Johor Kedah Kelantan KL/Selangor Negeri Sembilan Pahang Penang Sarawak
Singapore Taiwan Thailand	 Terengganu Singapore Tainan Ayutthaya Bangkok Nakhon Nayok Ratchaburi Chonburi Phitsanulok Prachinburi Songkla Yala
Turkey United Arab Emirates	• Izmir • Dubai

emergency medical systems in the region; and compare systemic and structural interventions to address OHCA. Once the core data entry system is in place, the network will serve as a platform to support research into the cost-effective strategies to improve survival from sudden cardiac arrest and other prehospital emergency conditions.

We have collaborated with CARES⁴ to develop a unified taxonomy and data dictionary for the study. We have standardized all definitions across the PAROS network by adopting a consensual common taxonomy and data collection methodology. This will allow valid comparison of population-based incidence and outcomes across network sites and create an opportunity for comparison of data across the globe.

This effort is a unique, low-cost, self-funded model of a collaborative research network. Each participating country is responsible for administering its own data collection process. All data are input via secured shared Internet electronic data capture system hosted by the Study Coordination Centre (SCC) in Singapore. The SCC is supported by grants from the Singapore Clinical Research Institute, Singapore Health Services, and the National Medical Research Council (Singapore).

REGISTRY DATA COLLECTION PROTOCOL

The study was reviewed and approved by national institutional review boards (IRBs) of participating EMS sites, having met the criteria for minimal risk research.⁶ Each participating site is responsible for obtaining and maintaining its IRB approvals for the study. In addition, the PAROS network has a data sharing agreement that protects the confidentiality of patients enrolled in the study. A register of all IRB approvals is kept by the coordination center.

Inclusion/Exclusion Criteria

The PAROS study will include all OHCAs conveyed by EMS or presenting at emergency departments (EDs), as confirmed by the absence of pulse, unresponsiveness, and apnea. This will include cardiac arrests of both presumed cardiac and noncardiac etiology. We exclude patients who are immediately pronounced dead and for whom resuscitation is not attempted, including those with decapitation, rigor mortis, and dependent lividity. Patients with known "do not attempt resuscitation" orders will also be excluded.

Data Collection

Data from members are collected via a standardized survey form (Data Supplement S1, available as supporting information in the online version of this paper). It includes a dictionary of EMS definitions, which is available online at http://www.scri.edu.sg/index.php/parosclinical-research-network. Data entry is done using the electronic data capture (EDC) system, an online data registry system that has been set up with assistance from CARES/CDC. EMS data are collected both from EMS dispatch and from ambulance personnel. EMS times are automatically recorded by the respective dispatch systems, with computerized system timings where available. Prospectively collected data are verified by local coordinators before and after entry into the EDC. Each participating site or EMS system has a designated local coordinator, who is responsible for ensuring the accuracy of data entry and verifying records. In addition, each local coordinator must respond to any data queries or verification requests from the SCC within 2 weeks.

Every case created in the EDC is assigned a unique identifier based on country, EMS site, date, time, and a site survey number. Each site is responsible to maintain a separate trial log, which links the trial numbers to identifiable national patient identity numbers. This trial log is kept secure locally and is only accessible by the site principal investigator. The SCC has no access to patient identifiers. Cases recruited by EMS will generate a notice with the case number to the local coordinator to follow-up on hospital outcomes. Hospital data are collected from the EDs, intensive care units, and wards. Inpatient discharge summaries and death certificate information are also assessed. For survivors, quality of life is assessed with the European Quality of Life- 5 Dimensions (EO-5D), a standardized instrument used in measuring quality of life.

All patient identifiers are removed from the dataset to protect patient confidentiality. The EDC has inherent quality assurance checks and validations. This includes inbuilt validation rules that cross-check data fields, as well as mandatory fields that must be completed to complete a case. The system will also flag missing fields for the coordinator's attention. In addition, the SCC maintains a stringent data quality review and audit process including verification with local coordinators and source documents. All data entries go through two levels of screening, at the local and SCC levels. Based on our initial collection of data, we estimate that >90% of eligible cases are collected in the registry, with complete data capture of mandatory fields.

Variables Measured

Definitions follow Utstein recommendations⁷ and include information on bystander cardiopulmonary resuscitation (CPR), public access defibrillation, response times, advanced life support (ALS; e.g., intravenous drugs, advanced airway management like endotracheal intubation, or alternative airway devices), and specialized postresuscitation care (hypothermia, extracorporeal membrane oxygenation [ECMO]). We also collect data on the geographical location of OHCA, which will be mapped using ArcView GIS (ESRI, Redlands, CA). System variables are collected as stated in Figure 1. To increase compliance, we identified a list of core variables that are mandatory for data entry, while the others have been designated optional fields. We have included our data dictionary as an additional online resource for this article (Data Supplement S2, available as supporting information in the online version of this paper).

All case record forms (CRFs) and electronic data sent to the SCC are in English. However, at the local level, some of the CRFs have been translated into the local languages for entry by service providers. These CRFs were all validated by back-translation to the original English language. The translated CRFs share common data fields and coding, thus facilitating entry into the EDC system.

Outcome Measures

The primary outcome data collected are survival to hospital discharge or survival to 30 days post-cardiac arrest for those who have not yet been discharged from the hospital by the 30th day postarrest. This was chosen as our primary outcome as it is the most consistently captured outcome across countries. The secondary outcomes collected include return of spontaneous circulation, survival to hospital admission, and neurologic status on hospital discharge or on the 30th day postcardiac arrest, if not discharged. Neurologic status will be assessed using the Glasgow Outcome Score⁷ (Cerebral Performance Category and Overall Performance Category). Quality-of-life assessment for survivors is done using the EQ-5D Health Dimensions and Visual Analog Scale, which provides a descriptive profile of health status in five dimensions. The EQ-5D has been extensively used to assess patient quality of life in trials of treatments within the cardiovascular field⁸ and is

Mode of Transport*	Disposition
 Brought in by: EMS/Non-EMS 	 Final status at scene*
Incident Information	 Cause of arrest*
 Date of incident* 	 Level of destination hospital
 Location of incident (Zip/Postal code) 	 Destination hospital
- Location type	 Patient's status at ED arrival*
Patient Information	ED Resuscitation Information
 Date of birth* 	 Date of arrival at ED*
- Age*	 Time of arrival at ED
- Sex*	 Patient status on arrival at ED
- Race	 Cardiac rhythm on arrival at ED
 Medical history 	 ED defibrillation performed
Dispatch Information	 Mechanical CPR device used at ED
 Time call received at dispatch center* 	 Advanced airway used at ED
 Time first responder dispatched 	 Drug administered at ED
- Time ambulance dispatched	 Return of spontaneous circulation at ED*
 Time first responder arrived at scene 	 Emergency PCI performed
 Time ambulance arrived at scene* 	 Emergency CABG performed
 Time EMS arrived at patient side* 	 Hypothermia therapy initiated
 Time ambulance left scene* 	 ECMO therapy initiated
 Time ambulance arrived at ED* 	 Cause of arrest*
Prehospital Event and Resuscitation Information	 Reason for discontinue CPR at ED
 Estimated time of arrest 	 Outcome of patient*
 Arrest witnessed by* 	Hospital Outcome
- Bystander CPR*	 Patient status*
 First CPR initiated by 	 Date of discharge or death
- Bystander AED applied	 Patient neurological status on discharge or at 30th day post arrest
 Resuscitation attempted by EMS/Private ambulance* 	Patient Health and Quality of Life
 First arrest rhythm* 	 EQ-5D Health Dimensions
 Time CPR started by EMS/Private ambulance 	 EQ-5D Visual Analog Scale (VAS)
 Time AED applied by EMS/Private ambulance 	
 Prehospital defibrillation* 	
 Defibrillation performed by 	
 Mechanical CPR device used by EMS/Private ambulance 	
 Advanced airway used by EMS/Private ambulance 	
 Drug administered by EMS/Private ambulance 	
 Return of spontaneous circulation at scene/en-route* 	
 CPR discontinued at scene/en-route 	
*Denotes Core Variable	

EMS = emergency medical services; CPR = cardiopulmonary resuscitation; AED = automated electronic defribrilator; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; ECMO = extracorporeal membrane oxygenation; EQ-5D = European Quality of Life - 5 Dimensions; VAS = visual analog scale

Figure 1. PAROS data variables.

useful for modeling of health utilities and economic evaluations within the cardiovascular area.

Sample Size

The PAROS OHCA study is intended as a long-term OHCA registry. However, we have set an initial aim of identifying the factors (and thus the related interventional strategies) associated with better survival outcome among OHCA patients in the Asia-Pacific region. To compute the sample size, we looked at each potential risk factor for poor outcome and identified the one that would require the largest sample size to assess. A previous study from Canada had reported that the probability of exposure among controls (nonsurvivors) was 0.05.5 To detect an odds ratio (OR) for disease in exposed subjects relative to unexposed subjects of 1.4, we will need to study 13,447 OHCA patients to be able to reject the null hypothesis (using an uncorrected chisquare statistic) that the OR equals to 1, with type I error of 0.05 and power of 90%.⁹

In addition, applying the approach recommended by Peduzzi et al.,¹⁰ assuming we have 20 potential risk factors to evaluate, the minimum sample size required would be given by $n = 10 \times$ (the number of risk factors)/(the smallest proportion of positive or negative cases in the population) = 7,407. Hence 13,447 OHCA patients will be sufficient to also meet these criteria. We expect that we will be able to achieve a sample size of 13,500 cases over 2 years of data collection.

Planned Data Analysis

Descriptive statistics including frequencies, means and their standard deviations, medians, and quartiles will be obtained for the sociodemographic and other independent variables as appropriate. For independent variables with more than two categories, dummy variables will be created. The categories of variables having sparse data will be grouped together in biologically meaningful ways. The category with minimum level of potential risk (hazard) of survival will be taken as the reference group for each risk (prognostic) factor. Univariate analysis will be carried out and ORs and corresponding 95% confidence intervals will be computed to estimate the associations between the dependent variable (survival status) and each factor.

Multivariate logistic regression modeling will be employed using the direct/standard method, with a priori selection of clinically important covariates. We will also cross-validate the final model to further strengthen the findings (using "leave-one-out" validation). The overall significance of the independent variables in the model will be assessed by the likelihood ratio test. Confounding will be assessed by $\geq 10\%$ change in the estimated coefficient for the particular variable. After developing the main effect model to uncover any multicollinearity, the association among independent variables will be assessed by using the appropriate test, and plausible interactions between the independent variables will also be assessed. The Pearson's chisquare test will be applied to check for the goodnessof-fit of the final model. Site-specific covariates will also be modeled as random effects to account for any within-subject correlation, thereby allowing for more accurate modeling of the effect of these covariates on the outcome.

PROGRESS TO DATE

A total of nine countries across the Asia-Pacific region are participating in this study (Figure 2). Together, the study sites represent a population base of 89 million, which is the aggregated population base of all the EMS systems participating in the study, not the total population of the participating countries (Table 2).

Characteristics of the PAROS member sites are listed in Table 2, including population base of participating sites, EMS system type, number of participating hospitals, and level of EMS providers. In general, the EMS systems involved represent a mix of fire-based, hospital-based, and independent service EMS providers. A majority of ambulances are manned by crews roughly equivalent to North American EMT-Intermediate level providers. They are able to provide basic life support and defibrillation with automated external defibrillators and limited symptom relief medication like intravenous adrenaline (epinephrine), dextrose, and saline infusions. They are less likely to perform endotracheal intubation compared to North American systems, but some use alternative airway devices such as the laryngeal mask airway in cardiac arrest.

Characteristics of PAROS sites pertaining to OHCA management are elaborated in Table 3.^{11–25} In general,



Figure 2. Map of PAROS member sites.

Table 2

Characteristics of Participating EMS Sites

Site	Regions	Population base of Participating Sites	EMS System Type	Number of Participating Hospitals	Level of Providers	
Korea	6	20 million	Single tier	232	 Basic and intermediate life support 	
Singapore	1	5 million	Single tier	7	 Basic life support Intermediate life support 	
Taiwan	3	8 million	Single tier	45	Intermediate life supportALS	
Japan	3	24 million	Single tier	346	 Basic life support Emergency Life-saving Technician (ALS) 	
Thailand	9	10 million	Single tier	13	 Basic life support ALS 	
Malaysia	10	10 million	Single tier	10	 Basic life support 	
Australia	1	6 million	Two tier	119	 Basic life support Advanced life support (intensive care paramedic) 	
Turkey	1	4 million	Single tier	47	 Basic life support 	
United Arab Emirates	1	2 million	Single tier	11	Basic life supportALS	

ALS = Advanced life support.

*Based on a survey of all participating EMS systems.

Table 3
Characteristics of PAROS Sites ^{11–25}

Site	Bystander CPR (%)	PAD*	EMS Response Times (Minutes)	ALS*	Post Resuscitation Care Hypothermia/ECMO*	Reported OHCA Survival, %
Singapore	20.6 ¹³	Rare ¹⁴ Bare	10.4 ¹³ 6 ¹⁵	Rare	Rare Moderate	2.0 ¹³ 2.3 ¹⁵
Taiwan	4.2 ¹⁶	Rare ¹⁷	4.89 ¹⁸	Moderate	Moderate	6.0 ¹⁶
Japan	36 ¹⁹	Wide ¹¹	5 ²⁰	Moderate	Wide	2.619
Thailand	—	—	12.6 ²¹	Rare	—	7.7 ²¹
Malaysia	8.7 ²²	_	25.6 ²³	_		_
Australia	36.7 ¹²	Moderate	8 ¹²	Wide	Wide	3.8 ¹²
Turkey	1.7 ²⁴	_	11.3 ²⁵	Rare	_	11.2 ²⁴
United Arab Emirates	—	Moderate	11.5	Wide	—	—

Rare, moderate, and wide refer to the degree of implementation in the study participant areas.

ALS = advanced life support; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; EMS = emergency medical services; OHCA = out of hospital cardiac arrest; PAD = public access defibrillation; PAROS = Pan-Asian Resuscitation Outcomes Study.

*Based on a survey of all participating EMS systems.

countries in the Asia-Pacific region have EMS systems that are still developing. Bystander CPR and public access defibrillation (PAD) rates (excluding Japan¹¹ and Australia¹²) are low, and few Asian EMS systems have prehospital ALS.

DISCUSSION

There is currently little evidence from randomized controlled trials to guide the best policies for improving outcomes of OHCA.²⁶ Because of the prevalence and setting of OHCA, it would present an ethical and resource challenge to conduct large-scale clinical trials comparing competing strategies and interventions, especially across countries. Furthermore, many EMS practices are rooted in local structures and systems with historical contexts that make traditional clinical trials approaches impractical. A registry approach allows for a longitudinal cohort approach, which has been demonstrated in previous studies²⁷ and provides a more feasible framework for addressing core issues.

An international cohort study, taking advantage of the inherent variations in Asia-Pacific EMS systems, provides a unique opportunity for analysis of the modifiable risk factors and systemic predictors of survival for OHCA. An analysis of the local costs involved in implementing any potential strategy will also be important in assessing incremental cost-effectiveness. This will enable us to answer the policy questions facing us, in the most evidence-based manner available.

To date (March 2011), our registry has accumulated a total of 9,302 patients in the preliminary database, with a clear protocol for data collection and entry. The database is expected to reach a critical mass of 13,500 cases, for potential statistical analysis by 2012.

We hypothesize that there are several major modifiable factors for OHCA survival. From a systemic point of view, North American studies have identified several modifiable factors that predict survival from OHCA.^{5,28} These include bystander CPR, defibrillation, EMS response time, and postresuscitation care, among others.

What is unclear is the relative importance of these factors compared with each other in an Asian setting.

We hypothesize that there are differences in the population demographics, underlying disease burdens, and the incidence of primary ventricular fibrillation in Asian populations compared to Western ones. The priorities of interventional strategies for OHCA in Asia will also be different from those in Western countries. For example, a primary strategy to increase bystander CPR might have a much greater effect in the Asia-Pacific region, where the baseline bystander CPR rate is low compared to North America or Europe. The cost environment for interventions in EMS will also be different in the Asia-Pacific region compared to the West.

Based on our literature review, we have identified five potential strategies for improving survival rates for OHCA in the participating Asia-Pacific nations, namely:

- 1. Widespread community-based and systemic efforts to increase bystander CPR.
- 2. Investing in PAD.
- 3. Having a basic life support EMS system, but investing in reducing response times.
- 4. Developing ALS EMS systems.
- 5. Investing in hospital-based postresuscitation care (cardiac arrest centers).

In an ideal world, with no funding constraints, one could argue that EMS systems could pursue all of these strategies simultaneously. In practice, resources are limited, and policy decisions must be made regarding priority of investment in a particular strategy. Which strategy or combination of strategies will give the maximum survival benefit for the most cost-effective investment? This is a very real policy question that is being asked. We hope that through the PAROS registry, identifying the incremental cost-effectiveness of these strategies for OHCA survival will allow prioritization and selection among these interventional strategies.

LIMITATIONS AND BARRIERS TO IMPLEMENTATION

A problem in the current literature and in practice is that different countries and EMS systems use different denominators for reporting outcomes. This may partially account for differences in reported survival rates in the literature.^{26,29} Depending on the report or community, the denominator may consist of only cases initially presenting with ventricular fibrillation, EMStreated cases regardless of presenting rhythm, or all cases of EMS-attended arrest including those where resuscitation is not attempted. It is thus crucial to establish common data definitions and a universal taxonomy for this registry. This will allow valid comparison and aggregation of data across the different countries and EMS systems. The International Liaison Committee on Resuscitation advocates a standardized reporting in the "Utstein style."⁷ The taxonomy that has been adopted by PAROS is compatible with the Utstein style.

Another difficulty is that we need to account for various system and demographic factors in interpreting outcome differences for OHCA between study sites, hence the importance of conducting a systemwide survey of participating sites to be able to describe country and EMS system–specific population and structural factors. This will be planned as part of the initial phase of our study and will allow a baseline understanding for describing subsequent findings for OHCA and making valid comparisons of differences.

Limitations will also be the risk of missing or incomplete data and confounding due to unrecognized variables. We have tried to minimize this risk by implementing quality assurance data checks built into the data entry system, as well as having a system for data verification at both the local sites and the SCC level. Finally, we acknowledge that in an observational study, we can only suggest relationships between system factors and outcomes, rather than prove causality.

Significant potential barriers to successfully conducting this project include language, political, cultural, and financial issues. The working language adopted by PA-ROS is English, and great pains have been taken to use a consensus-building approach to agree on a constitution with equal representation across participating countries. The executive committee meets three to four times yearly, with regular conference calls coordinated by the SCC, which maintains a permanent network manager. Support of local EMS and hospitals is a prerequisite for PAROS membership. In addition, the PA-ROS Executive Committee is served by two additional subcommittees: a Publication Committee and an Operations Committee, which have representation across all participating countries. The constitution includes agreements for data sharing, ethical research, study procedures, and publication procedures.

Many of the participating EMS systems in the study are from developing countries with limited financial resources and scientific grants to tap into. Through the help of the Singapore Clinical Research Institute, and CARES (CDC), we have been able to build a low-cost, Internet-based, electronic data collection platform that is able to meet the needs of our participating sites. The infrastructure costs of setting up the SCC are supported by grants from Singapore. With this in place, the only additional costs to participating sites are for data collection and entry. This is usually performed by clinical providers using data forms standardized across the network. These forms are integrated into routine clinical practice and use. In addition, we have also tapped into existing OHCA registries funded by local governments (Japan, Korea, Taiwan, and Singapore). These registries have been integrated with PAROS using a standardized data dictionary and definitions. Data are merged through an export field entry process, which autopopulates the PAROS registry.

CONCLUSIONS

The Pan-Asian Resuscitation Outcomes Study is a unique, low-cost, self-funded model of an Asia-Pacific collaborative research network and has potential to provide the long-term data needed to inform policy and interventions to improve outcomes of out-of-hospital cardiac arrest in many regions of the world. This article will serve as the reference for subsequent Pan-Asian Resuscitation Outcomes Study manuscripts and for the common data elements captured in the study.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. PAROS Taxonomy, Version 1.0, 14 June 2010.

Data Supplement S2. Pan-Asian Resuscitation Outcomes Study (PAROS).

The documents are in PDF format.

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