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**Title Page:** Observational study of children admitted to United Kingdom and Republic of Ireland Paediatric Intensive Care Units after out-of-hospital cardiac arrest

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**ABSTRACT (words 233/250)**

**Aims:** To estimate the prevalence of children admitted after out-of-hospital cardiac arrest (OHCA) to UK and Republic of Ireland (RoI) Paediatric Intensive Care Units (PICUs) and factors associated with mortality to inform future clinical trial feasibility.

**Method:** Observational study using a prospectively collected dataset of the Paediatric Intensive Care Audit Network (PICANet) of 33 UK and RoI PICUs (January 2003 to June 2010). Cases (0 to <16 years), with documented OHCA surviving to PICU admission and requiring mechanical ventilation were included. Main outcomes were prevalence for admission and death within PICU. Factors associated with mortality were examined with multiple logistic regression analysis.

**Results:** 827 of 111,170 admissions (0.73%; 95% CI [0.48 to 0.98%]) were identified as children admitted following OHCA. PICU mortality for OHCA was 50.5% (418/827). Recruitment into an adequately sized clinical trial would not be feasible with the current prevalence rate. Characteristics at PICU admission associated with increased risk of death included; bilateral unreactive pupils, genetically inherited condition, inter-hospital transfer to PICU, requirement for vasoactive drugs and greater base deficit. Factors associated with reduced risk of death were submersion or a respiratory aetiology and pre-existing respiratory or cardiac conditions.

**Conclusions:** Less than 120 children a year are admitted to PICUs in the UK and RoI after OHCA, limiting options for conducting UK intervention trials. The risk factors associated with mortality identified in this study will allow risk stratification in future studies.

**Key Words:** out-of-hospital cardiac arrest; paediatric; cardiopulmonary resuscitation; mortality; cohort study; paediatric intensive care.

## INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) has a high mortality rate,(1-3) accounting for one-quarter of all paediatric sudden deaths. International consensus guidelines(4), dispatcher-assisted cardiopulmonary resuscitation (CPR)(5), bystander CPR(6) and better quality CPR(7) *during* resuscitation may have improved mortality over the last ten years. However, *post* cardiac arrest therapies, including induced hypothermia, have not consistently been shown to improve survival or neurological recovery (8-12). Further epidemiological data is required to allow risk stratification of this heterogeneous population and to improve research of post-OHCA management on the paediatric intensive care unit (PICU).

The aims of this study were to quantify the prevalence of PICU admission following OHCA, quantify PICU mortality, and to examine factors associated with mortality. We consider whether the prevalence of OHCA admitted to PICUs would be adequate to enable recruitment into a UK and RoI post-OHCA intervention trial.

## METHODOLOGY

### Design

The Paediatric Intensive Care Audit Network (PICANet) dataset contains patient demographics, diagnoses, and interventions along with PICU outcomes for patients admitted to PICUs in the UK and RoI. This has been prospectively collected since 2002 (PICUs in England and Wales), 2006 (Scotland and Northern Ireland) and 2008 (RoI).(13) The data set includes severity of illness variables (Paediatric Index of Mortality (PIM)(14) (2003-2005) and PIM2 (2006 onwards) risk-adjustment models).(15) Quality control of data definitions and data collection is performed by the PICANet team.(13) PICANet has ethical approval granted by the Trent Medical Research Ethics Committee (ref 05/MRE04/17+5) and national information governance board approval by the Patient Information Advisory Group (now the NHS Health Research Authority Confidentiality Advisory Group) <http://www.hra.nhs.uk/documents/2015/04/piag-research-register.xls> to collect personally identifiable data without consent. Anonymized data was provided with the approval of the PICANet Clinical Advisory Group, and all UK and RoI PICUs.

Inclusion criteria for the study were age <16 years, admitted between January 2003 and June 2010 and after OHCA. OHCA was defined as per the Paediatric Index of Mortality 2 definition as 'documented episode of absent pulse or the requirement for external cardiac compression before hospital admission(15, 16). Cases were identified either through PICANet database coding of 'pre-hospital cardiac arrest' as a high risk category in the PIM/PIM2 score or text diagnostic discharge coding of an OHCA. An additional inclusion criterion was requirement for mechanical ventilation at PICU admission to exclude mild cases unlikely to be included in a future interventional study. **Patients who never achieved return of spontaneous circulation** or whose cardiac arrest occurred after admission to the Emergency Department or Hospital were excluded.

### **Data collection**

The following variables were recorded: age (categorized into Utstein defined age strata(17)), sex, year of admission, primary and secondary admission diagnoses, presence of chronic pre-existing conditions, inter-hospital transfer requirement to PICU, PIM (2003-2005) or PIM2 (2006 onwards) model variables and estimated probability of death using these models. PIM variables were collected within one hour of PICU admission or arrival of a specialist critical care transport team before transfer into PICU. Only one PIM score was calculated (PIM or PIM2) per patient and used in the analysis depending on year of PICU admission as PIM2 was the recalibrated score used from 2006 onwards.(15) Additional recorded variables included: interventions during PICU stay (renal replacement therapy, vasoactive drug use, intracranial pressure monitoring and extracorporeal life support (ECLS)), length of PICU stay, ventilation duration, and survival outcome to PICU discharge.

Using final discharge diagnoses recorded in the PICANet dataset, chronic pre-existing conditions were grouped into respiratory, neurologic, cardiac, prematurity, metabolic (including endocrine), genetically inherited and groups with fewer than ten cases were combined into 'other' (including liver, haematology, oncology, renal and immunodeficiency). Individual patients could be allocated into multiple chronic coding groups.

Admissions were allocated to aetiology; respiratory, sepsis, neurologic (non-trauma), cardiac, traumatic brain injury (TBI), trauma (including burns, excluding TBI), airway obstruction, hanging (including accidental strangulation), submersion, near-miss Sudden Infant Death Syndrome, other

(including toxin ingestion, non-traumatic haemorrhage, electrolyte abnormality, and anaphylaxis) or not clearly defined.

### **Statistical analysis**

Descriptive data were reported as median and interquartile range (IQR) for continuous variables and as number and percentages for categorical variables. Case mix, cause of OHCA and resource use (e.g. length of mechanical ventilation and renal replacement therapy) were compared between survivors and non-survivors. Non-parametric continuous data was analysed with the Mann Whitney U test or Kruskal-Wallis as appropriate. Categorical data were analysed using Fisher's exact test.

PICU admission numbers were extracted from the main PICANet dataset to calculate prevalence of PICU admissions with documentation of OHCA. Age specific population counts were extracted from the mid-2008 population estimates for England and Wales (Office of National Statistics).(18) This allowed calculation of age-specific incidence rates for OHCA admission to PICUs in England and Wales (Patients from Scotland and ROI were excluded in this calculation as denominator data was not available from Office of National Statistics).

Multivariate logistic regression analysis identified variables associated with mortality. Normality and linearity of continuous variables was assessed. Initially, associations with outcome were identified by univariate logistic regression analysis. Then all variables with  $p < 0.1$  for mortality were included in a multivariate logistic regression analysis model. Forward stepwise selection using F-statistic was applied to obtain the final model. The criteria for variable selection were a significance level ( $p$  value based on likelihood ratio test) to enter of 0.05 and a significance level to stay of 0.10. Hosmer-Lemeshow goodness of fit and area under the receiver operator characteristic (AUROC) curve were calculated to assess model fit.(19, 20) Missing data were not imputed. Variables with greater than 15% missing values were excluded from the model. Component variables from PIM/PIM2 were entered individually. The study model performance (sensitivity, specificity and AUROC) was compared with PIM/PIM2 estimated probability of death at PICU discharge.

Two sided  $p$  values of  $< 0.05$  are reported here. Data analysis was performed using either IBM-SPSS Statistics version 19.0 software (SPSS Inc, Chicago, USA) or Minitab 16 (USA).

## **RESULTS**

Eight hundred and twenty seven OHCA patients requiring mechanical ventilation and surviving to PICU admission were identified over the 7.5 year period (Figure 1). A mean prevalence rate of 0.73% (95% CI [0.48 to 0.98]), the denominator included all PICU admissions (Figure 2 and supplemental table 1). Data from all 33 PICUs in the UK and RoI were available from 2007 to 2009; mean number of OHCA admissions during this period was 146 [range 144-151] cases per year. Population incidence rates were calculated for OHCA patients admitted to PICUs in England and Wales (2007-2009); the denominator: all children aged 0-15 years in England and Wales. Incidence rates of OHCA, mechanically ventilated and admitted to PICU were 1.3 (95%CI [1.0-1.5]) children (0 to 15 years) per 100,000 person-years, with at least an eight-fold increase in the under-one-year-olds (8.9 (95%CI [6.9-11.3]) compared to children 1 to 4 years (1.1 [0.7-1.6]); 5 to 10 years (0.4 [0.3-0.7] and 11 to 15 years (0.7 [0.5-1.0]).

Patient characteristics are displayed in Table 1. PICU mortality was 50.5% (418/827) and remained consistent across the study period (2003: 54.9%; 2004: 50.0%; 2005: 47.4%; 2006 47.0%; 2007: 50.4%; 2008: 50.0%; 2009: 54.7%; 2010: 53.5%;  $p = 0.59$ ). 34% (144/418) of deaths occurred within 24 hours of PICU admission. There was no noteworthy difference in sex or age between survivors and non-survivors. However, 60.1% of patients with a chronic condition survived; in particular, 70.5% of patients with a chronic cardiac and 73.8% of patients with a chronic respiratory condition ( $p < 0.001$ ).

A probable cause of OHCA could be identified in 51.3% of cases (424/827) (Table 2). Increased mortality was associated with TBI or with hanging/strangulation, but a respiratory or cardiac cause was associated with reduced mortality. All patients ( $n=10$ ) admitted with a diagnosis of near-miss Sudden Infant Death syndrome died.

Continuous vasoactive infusions (inotrope or vasopressor) were used frequently (60.2%) and associated with death ( $p < 0.001$ ) (Table 3). Renal replacement therapy, intracranial pressure monitoring and the use of extracorporeal cardiopulmonary life-support (ECLS) were used infrequently in survivors and non-survivors (only 2 to 4% of cases). Survivors had significantly longer lengths of mechanical ventilation (Median [IQR] 5 [3 to 9] vs. 3 [1 to 4] days;  $p < 0.001$ ) and total length of PICU stay (7 [4 to 11] vs. 3 [2 to 5] days;  $p < 0.001$ ). Median PIM/PIM2 estimated probability of death for survivors was 24% (IQR 12-38) versus 59% (IQR 29-91) for non-survivors ( $p < 0.001$ ). Overall 22.7%

(n= 188) of patients presented to PICU with bilateral unreactive pupils and 96.3% of these cases (n=181) died in the PICU. Presence of hypoxia ( $\text{PaO}_2 < 8$  kPa or  $< 60$  mm Hg), normoxia ( $\text{PaO}_2$  8-40 kPa or 60-300 mm Hg) or hyperoxia ( $\text{PaO}_2 > 40$  kPa or  $> 300$  mm Hg) and systolic blood pressure at the time of PICU admission were not significantly associated with mortality. However, base deficit (median [IQR]) was greater in non-survivors (11.7 [6.0 to 18.0] mmol/L) compared to survivors (5.0 [1.0 to 9.8] mmol/L;  $p < 0.001$ ).

Multivariate logistic regression results are presented in Table 4. Presence of bilateral unreactive pupils (odds ratio (OR) 35.8; 95% confidence interval [14.1 to 90.4]), genetically inherited condition (OR 3.09 [1.2-8.1]), inter-transfer hospital to a PICU (OR 1.89 [1.1 to 3.2]), use of vasoactive drugs (OR 1.70 [1.1 to 2.5]) and greater base deficit (OR 1.07 [1.04 to 1.10]) were associated with increased mortality. Conversely, an OHCA secondary to submersion or a respiratory aetiology (OR 0.4 [0.2 to 0.8] and OR 0.47 [0.26 to 0.86] respectively) and pre-existing chronic respiratory or cardiac conditions (OR 0.48 [0.26 to 0.88] and OR 0.35 [0.21 to 0.59] respectively) were associated with lower risk of death. This PICU mortality estimation model (Supplemental table 2) performed with a sensitivity of 81.8% and specificity of 70.2%; area under the receiver operator characteristic (AUROC) curve: 0.844 (95%CI [0.815 to 0.872];  $p < 0.001$ ). The model performed better than PIM/PIM2 alone; sensitivity 86.8%, specificity 56.0%, AUROC 0.760 (95%CI [0.727 to 0.793];  $p < 0.001$ ).

The subgroup of patients (n=613) who required inter-hospital transfer prior to PICU admission had a significantly lower predicted probability of death (PIM/PIM2 37% [95%CI: 21-79%]) compared to children (n=214) admitted directly to a hospital with a PICU (48% [95% CI 22-91%];  $p = 0.03$ ).

Proportion of patients with bilateral unreactive pupils was also lower in the inter-hospital transfer group compared to no transfer (20 v 34%;  $p < 0.001$ ).

Using this population dataset we assessed the feasibility of a UK post cardiac arrest intervention study. Applying expected trial exclusion criteria to the dataset (excluding patients with bilateral unreactive pupils, pre-existing severe developmental delay or cardiac arrest associated with TBI) we calculated a mean of 98 patients per year.

An intervention trial powered to 80% to show a 10% absolute mortality reduction from a baseline mortality of 50% would require 388 patients in each arm. Assuming ~100 eligible patients per year and a 50% recruitment rate, a UK trial would take over 15 years to complete.

## DISCUSSION

The principal finding in this study of cases admitted to UK and Rol PICUs after OHCA and requiring on going mechanical ventilations is the estimated prevalence rate of 0.73% (95%CI [0.48 to 0.98%]) of all PICU admissions. This study did not include the population (approximately 60-80% of all OHCA cases)(3) who fail to achieve a return of spontaneous circulation. The focus was subjects in whom intensive care interventions may be applicable. Unfortunately, the low prevalence and number of potentially eligible patients would be insufficient to enable a UK comparative intervention study within a realistic timeframe. Furthermore a significant proportion of cases surviving to PICU admission died within 24 hours of admission. It is likely that many of these cases would not be considered for inclusion in a trial. Longer recruitment periods would be prohibitively expensive and are associated with additional barriers e.g. study fatigue and change in clinical equipoise.(21) **Although we identified a consistent mortality rate across the 7.5 year study period reducing the impact of study duration as a confounder.** International collaborative trial networks, potentially with multiple research funding sources, and/or alternative trial methodologies are potential solutions.

In the USA, Moler and colleagues identified 138 patients presenting to 15 paediatric centres over an 18 month period who fulfilled their criteria for entry into a post-OHCA hypothermia study (22). They used a cardiac arrest duration >1min as entry criteria and also included patients with bilateral unreactive pupils on arrival. 68% of included patients had bilateral unreactive pupils, which was associated with increased mortality whereas we only identified 23% with unreactive pupils in our study. This may reflect later pupillary assessment, with return of reactivity at PICU admission. It may also demonstrate different baseline severity of brain injury and perhaps explain our lower overall mortality rate of 50.5% compared to 62% in the USA study, Moreover, the end point in the USA study was death within hospital compared to death within PICU. Inclusion of patients with bilateral unreactive pupils in an interventions trial may increase the study population for which any intervention may not be effective and death inevitable, minimising the chances of demonstrating an effective intervention.

The national coverage of the PICANet dataset enabled the estimation of incidence rates of patients fulfilling our inclusion criteria within England and Wales (1.3 children per 100,000 person-years, with an eight fold increase in the under-one-year-olds). Previous international studies have reported incidence rates ranging from 5 to 9.8 per 100,000 person years,(1-3) with infants (less than 1 year) having a nine fold increase (72 per 100,000 person-years).(1) However, comparison is difficult owing to the differences in inclusion criteria (i.e. including all OHCA cases compared to only those reaching PICU admission) and the definition of OHCA.

The overall incidence of paediatric OHCA is low; however, nearly half of all patients have associated pre-existing chronic medical conditions and are therefore known within the health care system. In addition over half are under one year of age. Targeted health care initiatives during antenatal and postnatal care or other contact with medical professionals, teaching early identification of signs of deterioration and resuscitation training, may help prevent OHCA or improve outcome. Greater resuscitation awareness by families could have contributed to the finding of improved survival in patients with pre-existing respiratory and cardiac conditions. Another hypothesis is that their underlying condition may provide physiological resilience to a hypoxic-ischaemic insult, in the form of ischaemic pre-conditioning(23).

Non-survivors had greater base deficit on PIC admission blood gas. Severe metabolic acidosis reflects tissue hypoxia and correlates with duration of cardiac arrest in other studies.(24) However, it is unclear if aggressive correction of acidosis with sodium bicarbonate improves outcome and current clinical practice is variable.(25) Lactate has been shown to be superior to base deficit in risk stratification for critically ill children(26) and is associated with mortality after cardiac arrest(27) but unfortunately did not form part of the PICANet dataset until 2013.

Controversy exists regarding oxygen therapy in the period post-cardiac arrest. A number of experimental studies suggest that administration of 100% oxygen, which has been a standard of care for some time, may worsen neurological outcome through mechanisms that include hyperoxia induced free radical damage. Using previously described cut-off values for hypoxia (<8 kPa) and hyperoxia (> 40kPa) we did not identify any association between either hypoxia or hyperoxia with outcome, in keeping with others.(28, 29) However, we were only able to examine a single time-point (PICU admission) which may not accurately reflect the oxygenation status prior to PICU admission.

Ferguson and colleagues,(30) using continuous data from a combined OHCA and IHCA paediatric population dataset, suggested that extremes of low and high oxygen levels were associated with worse outcomes.

Approximately 75% of OHCA cases in this series were admitted to a hospital without a co-located PICU and required secondary transfer to the PICU centre. Despite transfer being undertaken by skilled PIC transport teams in most cases, and severity of illness scoring suggesting a lower severity of illness in this group, children requiring a secondary transfer had a higher mortality rate.

Contributory factors might include the time delay until full initiation of PICU care and infrequent exposure to these cases for many district general hospital emergency department resuscitation teams compared to tertiary paediatric centres. Also, PIM/PIM2 estimated probability of death for patients requiring secondary transfer may have underestimated severity compared to a similar patient directly admitted to a PICU due to lead-time bias(31). PIM/PIM2 variables are only collected after the arrival of the transport team which may be a number of hours after initial resuscitation. From the perspective of future trial design the requirement for secondary transfer should be included as a stratification criterion within randomisation balancing groups for this important prognostic variable. Data on children achieving a return of spontaneous circulation and requiring ventilation at a hospital without a PICU is not known; however, in the UK, with centralisation of pediatric critical care services, we anticipate this number to be very small.

The strength of this study, through the use of the PICANet database, is that near-complete coverage of patients admitted to PICUs in UK and RoI was possible.(21) This has enabled reliable estimates of prevalence of OHCA admissions to PICUs and incidence rates within the populations they serve and supported an exercise to explore potential trial feasibility.

This study does have a number of limitations. The PICANet database was not designed to be a cardiac arrest database or registry and therefore some Utstein resuscitation variables previously identified to be associated with outcome were not collected, for example; duration of resuscitation, temperature, blood glucose, seizure rate and partial pressure of arterial carbon dioxide. Also the end point of our study was survival to PICU discharge rather than hospital discharge which, along with neurological outcome, would be better outcome measures. Despite using two coding strategies to

identify OHCA patients it is conceivable that some cases may have been missed. We were unable to allocate location of cardiac arrest in a number of cases; potentially underestimating OHCA population size. Potential difficulties with identifying diseases and chronic conditions in electronic health records have been previously recognised with reliance on accurate data entry.(32) PICANet is enhancing ongoing data availability for OHCA patients through the PICANet Post Arrest Care in Kids 2 (NETPACK 2) study. This will include additional Utstein resuscitation variables and hopefully limit problems with missing data. Further validations of the findings presented in this study are required.

## CONCLUSION

Paediatric OHCA patients represent less than one percent of all admission to PICU in the UK with half aged less than one year. UK incidence of OHCA is too low to undertake definitive intervention studies but the importance of the condition necessitates international collaborative research or other novel trial designs. Identified multiple event characteristics (including bilateral unreactive pupils, aetiology of arrest, co-morbidities, inter-hospital transfer to PICU, requirement for vasoactive drugs and greater base deficit) associated with PICU mortality in the UK, will inform the design and allow risk stratification of future post cardiac arrest intervention studies.

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**Author Contributions:** Dr Scholefield had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Scholefield, Morris, Duncan, Gao.

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*Analysis and interpretation of data:* Scholefield, Tasker, Morris, Duncan, Gao, Parslow

*Drafting of the manuscript:* Scholefield, Morris, Gao, Tasker, Parslow

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*Study supervision:* Scholefield

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Competing interests: none

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## **FIGURES & TABLES**

Figure 1: Study inclusion flow chart

Figure 2: Chart of prevalence rates of OHCA admission requiring PICU and mechanical ventilation per 100 admissions for individual PICUs. (Data in supplemental table 1)

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## **SUPPLEMENTAL TABLES**

Supplemental table 1: Table of individual PICUs prevalence rate of OHCA admissions requiring mechanical ventilation per 100 admissions, presented in rank order.

Supplemental table 2: Logistic regression equation for predicting mortality at PICU discharge

## TABLES

Table 1 Baseline characteristics of study population

	All N=827	Survivors N= 409	Non-survivors n= 418	<i>p</i> <sup>b</sup>
Male	483 (58.4)	253 (52.4)	230 (47.6)	0.05
Age (years; median, IQR)	1.0 (0.2-7.2)	0.9 (0.2-7.1)	1.2 (0.2-7.7)	0.37
Age category (Utstein <sup>a</sup> )				0.74
0 -30 days	119 (14.4)	65 (54.6)	54 (45.4)	
31 days to <1 yr	295 (35.7)	146 (49.5)	149 (50.5)	
1yr to <4yrs	162 (19.6)	77 (47.5)	85 (52.5)	
4yrs to <12yrs	129 (15.6)	60 (46.5)	69 (53.5)	
12yrs to <16yrs	122 (14.8)	61 (50.0)	61 (50.0)	
Inter-hospital transport to a PICU	613 (74.1)	297 (48.5)	316 (51.5)	0.36
Any chronic condition	388 (46.9)	233 (60.1)	155 (39.9)	<0.001
Cardiac	156 (18.9)	110 (70.5)	46 (29.5)	<0.001
Neurological	113 (13.7)	55 (48.7)	58 (51.3)	0.94
Respiratory	107 (12.9)	79 (73.8)	28 (26.2)	<0.001
Prematurity	54 (6.5)	31 (57.4)	23 (42.6)	0.223
Genetic	28 (3.4)	14 (50.0)	14 (50.0)	0.95
Metabolic	38 (4.6)	20 (52.6)	18 (47.4)	0.69
Gastroenterological	16 (1.9)	10 (62.5)	6 (37.5)	0.29

<sup>a</sup> Utstein pre-defined age groups <sup>15</sup>. Results expressed as Median (Inter-quartile range) or number (percent). <sup>b</sup> Fisher's exact test was used for categorical variable and Mann Whitney U test for continuous variables to compare survivors and non-survivors.

Table 2 Survival outcome by cause of arrest

<b>Cause of arrest</b>	<b>All N=827</b>	<b>Survivors n=409</b>	<b>Non-survivors n=418</b>	<b>p<sup>b</sup></b>
Not Known	403 (48.7)	201 (49.9)	202 (50.1)	0.84
Respiratory	98 (11.9)	69 (70.4)	29 (29.6)	<0.001
Traumatic Brain Injury	67 (8.3)	21 (31.3)	46 (68.7)	0.005
Submersion	62 (7.5)	33 (53.3)	29 (46.8)	0.54
Sepsis	44 (5.3)	19 (43.2)	25 (56.8)	0.39
Cardiac	29 (3.5)	23 (79.3)	6 (20.7)	<0.001
Hanging or strangulation	28 (3.4)	9 (32.1)	19 (67.9)	0.06
Trauma <sup>a</sup>	27 (3.3)	14 (51.9)	13 (48.1)	0.85
Airway obstruction	23 (2.8)	11 (47.8)	12 (52.2)	0.87
Neurological (non-trauma)	18 (2.1)	2 (11.1)	16 (88.9)	0.001
Near-miss Sudden Infant death syndrome	10 (1.2)	0 (0)	10 (100)	0.002
Other	18 (2.2)	7 (38.9)	11 (61.1)	0.48

Results expressed as number (percent). <sup>a</sup>Trauma including burns, but excluding TBI, hanging or strangulation. <sup>b</sup>Fishers exact test was used for categorical variable to compare survivors and non-survivors. 'Other' including, toxin ingestion, electrolyte derangement & anaphylaxis,

Table 3 Physiological variables at PICU admission and interventions received on PICU by outcome

Physiological variables at admission	All N=827	Survivors n=409	Non-survivors n=418	$p^b$
Median PIM/PIM2 probability of death % (IQR)	40 (22-74)	24 (12-38)	59 (29-91)	<0.001
PaO <sub>2</sub> (kPa) median (IQR)	16.3 (9.9-29.7)	15.5 (9.5-27.6)	17.3 (10.2-31.2)	0.07
Hypoxia (PaO <sub>2</sub> <8kPa) n (%)	106 (16.4)	53 (50.0)	53 (50.0)	
Normoxia (PaO <sub>2</sub> 8-40kPa) n (%)	455 (70.4)	213 (46.8)	242 (53.2)	
Hyperoxia (PaO <sub>2</sub> >40kPa) n (%)	85 (13.2)	37 (43.5)	48 (56.5)	0.67
Systolic blood pressure (mmHg) median (IQR)	94 (74-112)	94 (76-114)	93 (73-112)	0.73
Base deficit (mmol/L) median (IQR)	8.1 (3.1 to 14.3)	5.0 (1.0 to 9.8)	11.7 (6.2 to 18.0)	<0.001
Bilateral unreactive pupils n (%)	188 (22.7)	7 (3.7)	181 (96.3)	<0.001
<b>Intervention in PICU</b>				
Vasoactive drugs	498 (60.2)	214 (43.0)	284 (57.0)	<0.001
Renal replacement therapy	28 (3.4)	19 (67.9)	9 (32.1)	0.12
ICP Device	32 (3.9)	12 (37.5)	20 (62.5)	0.37
ECLS	22 (2.7)	13 (59.1)	9 (40.9)	0.27
Length of ventilation (days)	4 (2-7)	5 (3-9)	3 (1-4)	<0.001
Length of stay in PIC (days)	4 (2-8)	7 (4-11)	3 (2-5)	<0.001

ECLS denotes extracorporeal life support, ICP intracranial pressure monitoring.

Physiological variables measured on 1<sup>st</sup> arterial blood gas within 1 hour of PICU admission. Data was missing for cases: vasoactive drugs (13), renal replacement therapy (14), ICP device use (13), ECLS use (10), length of ventilation (33), length of stay in PIC (3), PaO<sub>2</sub> value (181), systolic blood pressure (57), base deficit (106), and pupillary reactivity (26). Results expressed as number (percent) or median (IQR), missing values were excluded from calculations. <sup>b</sup>Fisher's exact test was used for categorical variable and Mann Whitney U test for continuous variables to compare survivors and non-survivors

Table 4 Multivariate logistic regression predicting mortality

<b>OHCA mortality risk factors</b>	<b>Adjusted Odds Ratio</b>	<b>95% CI</b>	<b>P</b>
Bilateral unreactive pupils	35.80	(14.1 to 90.4)	<0.001
Genetically inherited condition	3.09	(1.18 to 8.10)	0.006
Inter-hospital transport to a PICU	1.89	(1.10 to 3.20)	0.01
Vasoactive drugs on PIC	1.70	(1.10 to 2.50)	0.01
Base deficit (per 1 mmol/l)	1.07	(1.04 to 1.10)	<0.001
Chronic respiratory condition	0.48	(0.26 to 0.88)	0.01
Respiratory aetiology	0.47	(0.26 to 0.86)	0.01
Submersion aetiology	0.40	(0.20 to 0.79)	0.009
Chronic cardiac condition	0.35	(0.21 to 0.59)	<0.001

Variables entered into forward stepwise model: 1) continuous variables: Age and base deficit, 2) categorical: year of admission, sex, eight chronic condition groups, nine acute cause of arrest groups, transferred from secondary hospital (versus admitted into hospital with co-located PICU), use of extracorporeal life support, use of renal replacement therapy, use of vasoactive drugs and presence of bilateral unreactive pupils on PICU admission. PaO<sub>2</sub> excluded due to >15% missing values.

138/827 (16.7%) cases were missing. Area under the receiver operating characteristic (AUROC) Curve 0.844 (95%CI: [0.82-0.87]; p<0.001). Hosmer and Lemeshow Test: Chi-square 13.647, df 8, p=0.091.

**FIGURES**

Figure 1 – Study inclusion flow chart

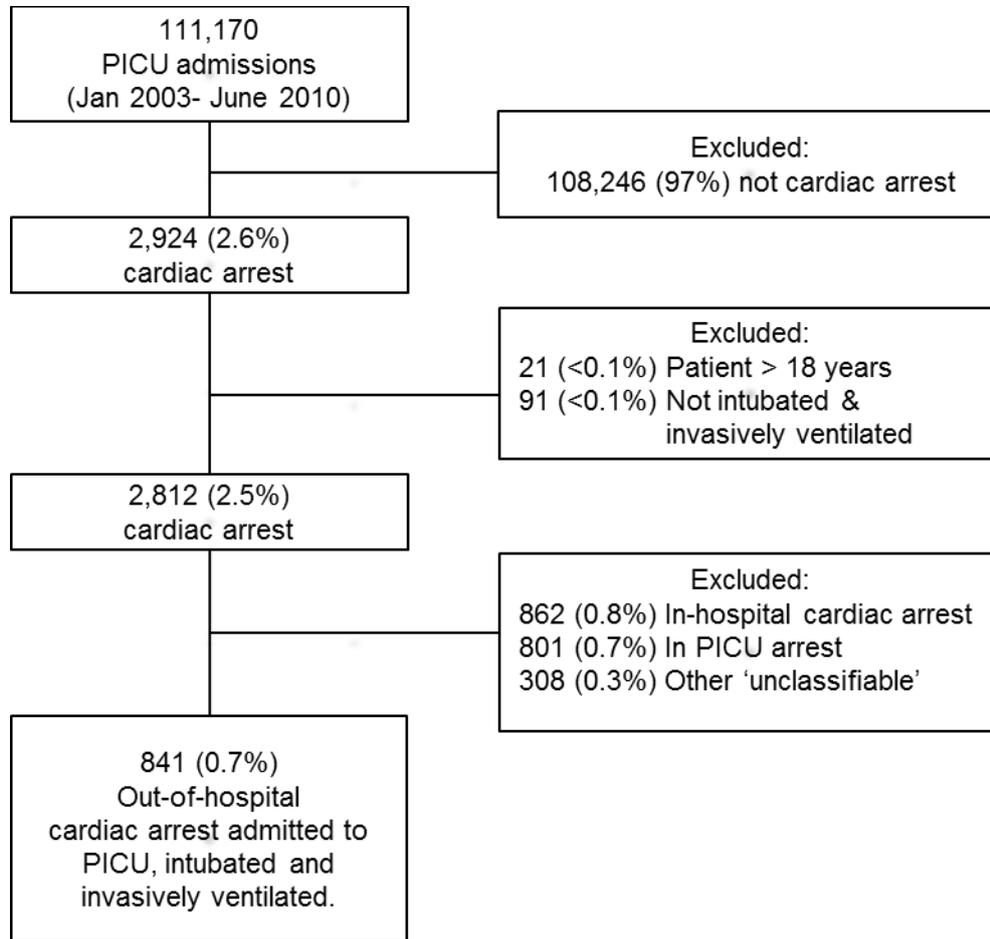
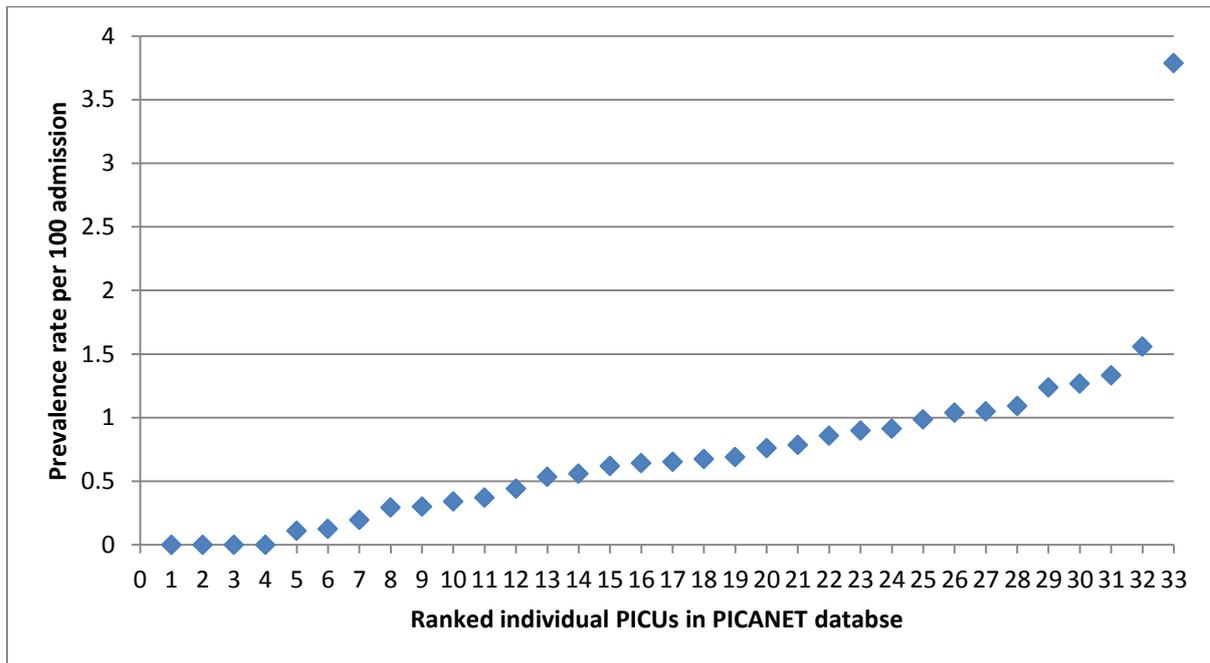


Figure 2 - Chart of prevalence rates of OHCA admission requiring PICU and mechanical ventilation per 100 admissions for individual PICUs. (Data in supplemental table 1)



Note outlier in PICU no. 33; A high proportion of OHCA cases (n=12) relative to a low number of PICU admissions (n=320).

**Supplemental files for online publication only**

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