

**- CONFIDENTIAL -**

## The effect of prehospital critical care on survival following out-of-hospital cardiac arrest: a prospective observational study

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## Abstract

**Aim** To examine the effect of prehospital critical care on survival following OHCA, compared to routine advanced life support (ALS) care.

**Methods** We undertook a prospective multi-centre cohort study including two ambulance services and six prehospital critical care services in the United Kingdom (UK), between September 2016 and October 2017. Inclusion criteria were adult patients with non-traumatic OHCA treated by either prehospital critical care teams or ALS paramedics. Patients who received prehospital critical care were matched to those receiving ALS using propensity score matching. Primary outcome was survival to hospital discharge; secondary outcome was survival to hospital admission.

**Results** The primary analysis included 658 patients with OHCA receiving prehospital critical care and 1,847 patients receiving ALS care. Rates of survival to hospital discharge (primary outcome) were 11.9% in both groups; rates of survival to hospital admission (secondary outcome) were 34.4% and 27.7% in the prehospital critical care and ALS group, respectively. The corresponding odds ratios for survival to hospital discharge and survival to hospital admission with prehospital critical care were 1.06 (95% confidence interval 0.75 – 1.49) and 1.39 (95% confidence interval 1.10 – 1.75), respectively. Results were consistent across subgroups and sensitivity analyses.

**Conclusions** Despite a positive association with the secondary outcome of survival to hospital admission, prehospital critical care was not associated with increased rates of survival to hospital discharge following OHCA.

## Introduction

Survival rates following out-of-hospital cardiac arrest (OHCA) vary considerably but remain disappointingly low in many parts of the world.<sup>1,2</sup> Some of this variation in survival following OHCA has been attributed to international differences in prehospital care.<sup>3,4</sup> Prehospital care for OHCA is most commonly provided in the form of advanced life support (ALS).<sup>5</sup> More recently, prehospital critical care teams have been developed in some countries and provide additional care to the most critically ill or injured patients.<sup>6,7</sup> It has been hypothesised that the additional training, experience, and interventional capability of prehospital critical care providers result in better outcomes, including for patients with OHCA.<sup>7,8</sup> However, reliable evidence for this hypothesis is lacking. A recent systematic review demonstrated a potential small to moderate benefit from prehospital critical care for OHCA, when compared to ALS care.<sup>9</sup> However, the review also highlighted concerns about confounding by indication which systematically favoured good outcomes in patients receiving prehospital critical care.<sup>9</sup> In addition, it remained unclear which additional interventions prehospital critical care providers actually delivered, when compared to their ALS-trained colleagues. Given the likely additional costs of providing prehospital critical care for OHCA, this prospective, multicentre observational study examines the additional effect of prehospital critical care on survival following OHCA, when compared to prehospital ALS care alone.

## Methods

Due to the ethical and logistical challenges of randomising the intervention of prehospital critical care,<sup>10</sup> we chose a prospective observational research design. We used propensity score matching to adjust for confounding, including a number of sensitivity analyses. The research protocol has been published<sup>11</sup> and the research was prospectively registered with the ISRCTN registry (ISRCTN18375201).

### Setting

The study took place in two neighbouring ambulance services in England, covering a geographically varied area of over 25,000 square miles with a total population of approximately 11.2 million people in urban, suburban and rural zones. In each ambulance service, the response to emergency calls consisted of a combination of community first responders, basic life support (BLS)-trained emergency medical technicians (EMTs), or emergency care assistants (ECAs), and ALS-trained paramedics. In addition, six prehospital critical care services operated in the area covered by the ambulance services. Four of the prehospital critical care services provided teams using helicopters or rapid response vehicles (RRVs). The other two services provided a critical care team on an RRV and a single prehospital

critical care doctor on an RRV, respectively. These prehospital critical care teams were activated through the corresponding ambulance service's emergency call and triage system.

### **Advanced Life Support**

Prehospital care for patients with OHCA was provided by paramedics trained in ALS, supported by EMTs and/or ECAs. Data from one ambulance service showed that care on scene was provided by a mean of 2.4 core resources (paramedic-staffed double-crewed ambulances and/or rapid response vehicles) during the study period. ALS was provided according to current guidelines.<sup>12</sup> Advanced airway management included placement of a supraglottic airway or tracheal intubation; intravenous drugs were adrenaline, amiodarone, crystalloid fluids, or glucose.<sup>13</sup> During cardiac arrest, ALS paramedics could use clinical judgement whether to provide all available care at scene or whether to continue resuscitation en route to hospital. There were standard guidelines in place to support the commencement, continuation, and cessation of resuscitation when criteria indicating futility were fulfilled.<sup>13</sup>

### **Prehospital critical care**

Prehospital critical care was provided by a combination of specialist paramedics in critical care (SPCCs) and prehospital doctors. SPCCs were paramedics who undertook additional postgraduate university education as well as theoretic and practical training in the management of critically ill patients, resulting in additional clinical competencies. Prehospital doctors were senior doctors in emergency medicine, anaesthesia, and/or intensive care medicine who underwent local training in prehospital care. A sub-speciality of prehospital emergency medicine was approved shortly before the study period and provided a national training framework for prehospital critical care doctors.<sup>14</sup> A detailed analysis of the competencies of ALS paramedics, SPCCs and prehospital critical care doctors has been published previously.<sup>6</sup> In regards to prehospital critical care for OHCA, Box 1 provides a comprehensive list of diagnostic or therapeutic options available to prehospital critical care providers in this study which exceeded those of their ALS paramedic colleagues.

**Box 1.** Potential prehospital critical care interventions for out-of-hospital cardiac arrest

**During cardiac arrest**

- Ultrasound
- Surgical airway
- Central venous access
- Mechanical chest compression
- Atropine IV
- Magnesium IV
- Calcium IV
- Sodium bicarbonate IV
- Thrombolysis
- Thoracostomy
- Peri-mortem hysterectomy
- Blood transfusion
- Recognition of Life Extinct (ROLE) outside of ambulance service guidelines

**After return of spontaneous circulation**

- Rapid sequence induction of anaesthesia
- Sedation and / or paralysis
- Central venous access
- Inotropes or vasopressors IV
- Amiodarone IV
- Magnesium IV
- Sodium bicarbonate IV
- Calcium IV
- Synchronised cardioversion
- Ultrasound
- Blood transfusion
- Air transfer
- Bypass of nearest hospital for cardiac centre

*IV: intravenous*

**Inclusion and exclusion criteria**

Patients were included if they were aged 18 years or older, suffered a non-traumatic OHCA, and were treated by prehospital providers of the participating ambulance services. Exclusion criteria were cases of OHCA due to trauma, drowning, electrocution, or traumatic asphyxia, as well as OHCA occurring in children aged less than 18 years.

**Selection of patients to prehospital critical care or ALS**

For all patients with confirmed or suspected OHCA, the ambulance services would mobilise the closest resource as soon as possible during the emergency call, often based on limited information. In addition, a prehospital critical care team could be dispatched, depending on a number of factors such as current availability of the team, geographical location, weather, and an assessment of the likelihood of benefit for the individual patient from prehospital critical care. This resulted in a natural experiment in which one group of patients with OHCA received routine ALS prehospital care, while the other group received prehospital critical care in addition to routine ALS care.

**Outcomes**

The primary outcome was survival to hospital discharge, with a secondary outcome of survival to hospital admission.

## **Data collection**

Data were collected prospectively by the national Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry<sup>15</sup> and included primary and secondary outcomes as well as the core Utstein criteria predicting survival following OHCA.<sup>16</sup> Six participating prehospital critical care services provided data on the presence of a prehospital critical care team at scene and the prehospital critical interventions delivered. Data were collected between September 2016 and October 2017.

## **Statistical analysis**

We used propensity score matching to adjust for the expected imbalance in prognostic factors between patients with OHCA receiving standard ALS care only, and those receiving both prehospital critical and ALS care. The propensity score was calculated through a multiple logistic regression model which included factors associated with the attendance of a prehospital critical care team and/or survival to hospital discharge. The model was optimised through a backwards stepwise deletion process. We used nearest neighbour matching with calliper (0.2 \* the standard deviation of the propensity score) and a greedy algorithm without replacement.<sup>17</sup> To optimise the balance between power and matching performance, we trialled matching ratios between one-to-one and one-to-four, with a ratio of one prehospital critical care case to up to three ALS cases resulting in the best balance between power and matching precision. We used standardised differences between the prognostic factors to assess whether balance between the ALS and prehospital critical care group was achieved for each prognostic factor, with a standardised difference of less than 10% considered to be adequately balanced.<sup>18</sup> To adjust for any residual imbalance and to calculate 95% confidence intervals, we undertook a conditional logistic regression of the matched groups. Descriptive analysis of unmatched data included the Wilcoxon Rank Sum test for non-normally distributed data and Pearson's chi-square test for categorical data. All statistical analyses were undertaken in Stata SE 14 (StataCorp).

## **Primary, subgroup and sensitivity analyses**

A priori, we had defined the primary analysis to be an as-treated analysis (prehospital critical care team provides care at scene) of cases with complete data.<sup>11</sup> We also planned a subgroup analysis (defined a priori) of bystander-witnessed OHCA due to ventricular fibrillation (VF), known as the Utstein comparator group.<sup>16</sup> In addition, we undertook three ad-hoc sensitivity analyses to address potential confounding by indication, to reduce bias from missing data, and to maximise sample size, respectively. During the data collection period, it became clear that the decision to dispatch or not dispatch prehospital critical care during the initial emergency call was frequently reversed once more information was available from the scene. Such secondary activations and "stand-downs" of prehospital critical care teams can introduce considerable confounding by indication.<sup>9</sup> We therefore

added a sensitivity analysis which excluded all cases with secondary activations or “stand-downs” of prehospital critical care services. Within this subgroup, we also analysed the effects of physician-led prehospital critical care (excluding cases where prehospital critical care was provided by critical care paramedics). The need for a further sensitivity analysis, using multiple imputation, arose due to the fact that variables were not missing completely at random in the dataset.<sup>19</sup> We performed ten imputations of missing variables, using a multiple logistic regression model based on the non-missing fraction of the dataset. Propensity score matching as described above was performed for each of the imputed datasets, the resulting odds ratios and confidence intervals were combined using Rubin’s Rule.<sup>20</sup> In addition, we obtained further data from two more ambulance trusts and two corresponding prehospital critical care services for latter parts of the study period. As these additional data did not include the core Utstein variables of EMS response times or location of OHCA, we did not include them in the primary analysis. However, we undertook a third sensitivity analysis without these two variables, using the expanded dataset from all four ambulance services (see Appendix 1). Primary and secondary outcomes are reported for each analysis.

### **Sample size estimation**

We aimed to recruit at least 600 cases of prehospital critical care for OHCA, which would have involved approximately 6,000 cases of OHCA overall.<sup>11</sup> This would allow us to detect an absolute improvement in the primary outcome of survival to hospital discharge from 7.5% to 11.5% (4% absolute difference) with a power of 0.8 and alpha 0.05, assuming one-to-three matching. The absolute treatment effect of 4% was based on the minimal clinically and economically important difference for survival to hospital discharge after OHCA, identified in a recent stakeholder survey<sup>21</sup> and economic analysis (manuscript in submission).

### **Ethics and consent**

The research was reviewed and approved by the Sheffield National Research Ethics Committee, York and Humber on 29 July 2016, reference number 16/YH/0300. The need for patient consent was waived by the committee as there was no change in treatment and no identifiable patient data were accessed by the research team. The OHCAO registry was approved to share non-identifiable patient data for authorised research projects by South Central and Oxford Research Ethics Committee, reference number 13/SC/0361.

## **Results**

Between September 2016 and October 2017, resuscitation was commenced in 8,512 cases of adult OHCA. After application of exclusion criteria, 8,015 cases of OHCA remained for analysis, with an overall survival to hospital discharge of 9.1%. Fig. 1 gives an overview of exclusion criteria, first presenting cardiac rhythm during OHCA, missing data rates, and outcomes.

During the study period, a prehospital critical care team was activated 969 times for OHCA and provided treatment at scene in 866 cases (103 “stand-downs”). Of the 866 OHCA treated at scene, dispatch of the prehospital critical care team was primary (based on information from the emergency call only) in 616 (71.1%) cases and secondary (requested by ALS paramedics on scene) in 238 (27.5%) cases (no information was available for 12 cases). Each prehospital critical care service attended a mean of 10 OHCA per month (range 3-23). Dispatch to scene was by helicopter in 71% of cases, the overall median critical care team response time was 28min from the time of the emergency call. A prehospital doctor was present in 68% of cases. Table 1 gives an overview of important characteristics of patients with OHCA who received routine ALS care only and those who received both routine ALS care and additional prehospital critical care.

### **Unadjusted outcomes**

The unadjusted rates of survival to hospital after OHCA were 26.8% and 36.4% for the ALS group and the prehospital critical care group, respectively ( $p < 0.001$ ). Rates for the primary outcome of survival to hospital discharge were 8.7% and 12.8% in the ALS and prehospital critical care group ( $p < 0.001$ ). Rates of missing data were 0.1% and 0% for survival to hospital admission and 3.2% and 2.2% for survival to hospital discharge for the ALS group and prehospital critical care group, respectively. Given the imbalance of prognostic factors demonstrated in Table 1, neither the primary nor secondary outcome should be interpreted without adjustment. ROSC occurred a median of 32min (95%CI 7min – 89min) and 31min (95%CI 11min – 93min) after EMS arrival in the ALS and prehospital critical care group, respectively ( $p = 0.09$ ).

### **Adjusted outcomes**

After excluding all cases which were missing relevant data, 5,123 OHCA patients remained for complete case analysis. Of these, 665 received prehospital critical care. Propensity score matching resulted in matched groups of 658 and 1,847 patients with OHCA receiving prehospital critical care and prehospital ALS care, respectively. Table 2 demonstrates the balance of prognostic factors achieved through the matching process and the rates of survival to hospital discharge and survival to hospital admission in the matched groups.

The absolute estimated benefit of prehospital critical care for OHCA on the treated population was 0% for the primary outcome of survival to hospital discharge and 6.7% for the secondary outcome of



survival to hospital admission. Conditional logistic regression on matched groups resulted in an odds ratio (OR) of 1.06 (95%CI 0.75 – 1.49) for survival to hospital discharge and an OR of 1.39 (95%CI 1.10 – 1.75) for survival to hospital admission (p-values 0.75 and 0.005, respectively). Fig. 2 and Fig. 3 show the ORs and 95% confidence intervals for the primary, subgroup and sensitivity analyses for primary and secondary outcome. The ORs for the subgroup analysis of primary dispatch of physician delivered prehospital critical care were 1.00 (95%CI 0.57 - 1.76) and 1.56 (95%CI 1.07 - 2.27) for primary and secondary outcome, respectively (n=881).

### **Prehospital critical care interventions**

Four prehospital critical care services provided data on the interventions performed during the care of patients with OHCA (Table 3).

Other interventions performed during OHCA, but with a frequency of less than five, were surgical airway and intravenous (IV) lidocaine (once each), IV atropine (twice), thrombolysis and central venous access (three times each), and double sequential defibrillation (four times). With the exception of one administration of IV atropine, all interventions were undertaken in non-survivors. Further interventions undertaken after ROSC were central venous access (once) and IV calcium (twice), all in non-survivors.

203 of the 520 patients (39.0%) who were still in cardiac arrest on arrival of the prehospital critical care team received no intervention beyond routine ALS care. 80 of 299 patients (26.8%) did not receive any prehospital critical care intervention after return of spontaneous circulation (ROSC).

The interventions most frequently undertaken during the cardiac arrest phase were either non-therapeutic (cessation of resuscitation), of unclear clinical benefit (ultrasound)<sup>22</sup> or proven to have no impact on survival following OHCA (mechanical CPR).<sup>23</sup>

The most common interventions provided after ROSC were prehospital anaesthesia or sedation, intravenous vasopressors or inotropes, and transfer of patients to a cardiac centre. Prehospital anaesthesia or sedation was frequently provided in the group of patients who survived to hospital discharge following OHCA. This was likely due to this group of patients displaying signs of cerebral activity, thus requiring anaesthesia/sedation but also predicting a favourable outcome.<sup>24</sup> Intravenous vasopressors or inotropes on the other hand were used most frequently in patients with ROSC who survived to hospital but then died during their in-hospital care. Overall, 74% of patients transferred to hospital by a prehospital critical care team were brought to a cardiac centre, compared to approximately 47% of patients receiving ALS prehospital care.

## **Discussion**

After adjusting for an imbalance in prognostic factors, the attendance of prehospital critical care teams at OHCA was associated with higher rates of survival to hospital admission (secondary outcome), but not survival to hospital discharge (primary outcome). These results remained stable across several subgroup and sensitivity analyses. Interventions beyond ALS care were required infrequently and seemed to have either no benefit or effected only short-term survival.

### **Comparison to previous research**

The findings of our research are in contrast to the three largest publications which address a similar question, all three of which demonstrated benefit from prehospital physicians (delivering prehospital critical care) for OHCA.<sup>25-27</sup> The authors of two of these retrospective observational studies acknowledged two independent sources of unmeasured confounding which they were unable to account for in their adjustments, both specific to the Japanese setting and both favouring outcomes in the prehospital physician groups.<sup>26,27</sup> In addition, the ALS providers in these two studies were trained to a considerably lower level of autonomy and expertise than the ALS paramedics in our research.<sup>26,27</sup> The survival benefit associated with prehospital (critical care) physicians in the third retrospective observational study seemed to be mainly due to a difference in the earlier years of data collection (2005 to 2008), with no or little difference in outcomes described in the later period from 2009 to 2011.<sup>25</sup> It is possible that increased training of the ALS providers over the data collection period resulted in findings more similar to ours, in the later period.

### **Explanations of research findings**

A possible explanation for the lack of benefit from prehospital critical care for OHCA can be found in the timing of prehospital critical care. Due to the dispatch over greater distances, by the time prehospital critical care providers arrived at scene of an OHCA (median of 20 minutes after ALS providers' arrival), most of the important early interventions would have already been established by ALS providers. Research has consistently shown that the early minutes of OHCA care have the most important effect on survival.

Nevertheless, prehospital critical care providers kept significantly more patients with ROSC alive to the point of arrival at hospital, mainly through the use of vasopressors/inotropes. A possible explanation is that the use of vasopressors/inotropes allowed prehospital critical care providers to maintain coronary perfusion pressures, avoiding re-arrest before hospital admission. Unfortunately, the severity of the underlying pathophysiology, which caused the requirement for this intervention, may indicate an irreversible injury that then results in death prior to hospital discharge.

Finally, transfer to a cardiac arrest centre is thought to improve survival following OHCA but a potential effect size has not been clearly defined.<sup>28,29</sup> In our study, bypass of the nearest hospital in favour of a cardiac centre was a relatively common prehospital critical care intervention. However, the receiving hospital for patients in the ALS group was a cardiac arrest centre in nearly half of the patients transferred, thereby diluting a potentially small to moderate effect of prehospital critical care.

### **Implications for clinicians and policy makers**

Given the lack of association between prehospital critical care and higher rates of survival to hospital discharge, prehospital critical care is very unlikely to be cost-effective, in its current configuration. Policy makers and clinicians should consider the indirect benefits of prehospital critical care services in the care for OHCA, such as their role in training and supporting ALS providers, in conducting research, or as early innovators. The dispatch of existing prehospital critical care services should focus on patients with OHCA who might require critical care interventions, patients with a high likelihood of achieving ROSC, and/or where transfer to a cardiac arrest centre is indicated but unlikely to be achievable with the means available to prehospital ALS providers. Other factors to consider are the ethical issues and social acceptability of the provision of prehospital care for patients in OHCA.<sup>10</sup>

### **Limitations**

An important limitation in the interpretation of our research is the fact that we only examined the effect of prehospital critical care in adult patients with non-traumatic OHCA. The findings of this research should not be extrapolated to other causes of OHCA, or patient populations.

Our study is the first to combine a prospective, multicentre research design with propensity score matching to examine this particular research question. As with any observational research, confounding and bias remain a possibility. While measured confounders have been successfully adjusted for in the analysis, unmeasured confounding may persist. However, it is likely that any unmeasured confounding in this research would favour prehospital critical care for OHCA.<sup>9</sup> The possibility of remaining confounding would therefore strengthen, rather than weaken, the conclusion of no benefit from prehospital critical care for OHCA. Our conclusions are further supported by consistent results in a number of sensitivity analyses.

Because our research used routinely available outcome data, we were unable to measure the more patient-focused outcomes of favourable neurological survival, functional outcome, or quality of life. It is therefore possible that prehospital critical care did not result in higher rates of survival to hospital discharge, but still conveyed a benefit through a higher proportion of patients with other measures of a good outcome. However, in all three large observational studies relevant to this research, the

proportion of patients with good neurological recovery was approximately equal in survivors in both the prehospital physician and prehospital ALS groups.<sup>25-27</sup>

Finally, due to the inherent indication bias and confounding, we did not attempt to analyse the effectiveness of individual prehospital critical care interventions. Table 3 should therefore be regarded as hypotheses-generating only.

## **Conclusions**

Prehospital critical care for adult patients with non-traumatic out of hospital cardiac arrest was associated with higher rates of short-term survival to hospital admission, but not survival to hospital discharge, when compared to routine advanced life support care provided by well-trained paramedics.

## **Conflicts of interests**

JVVF and JB work as prehospital critical care doctors with a regional air ambulance service.

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## **Data sharing statement**

Data for this analysis were provided by the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry via a data sharing agreement which excludes passing on data to third parties. We are therefore unable to make these data available to others. Please refer to the OHCAO project website for information relating to data sharing requests:

[http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/ohcao/health/data/data\\_sharing](http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/ohcao/health/data/data_sharing)

## References

1. Hawkes C, Booth S, Ji C, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation* 2017;110:133-40.
2. Girotra S, van Diepen S, Nallamothu BK, et al. Regional Variation in Out-of-Hospital Cardiac Arrest Survival in the United States. *Circulation* 2016;133:2159-68.
3. Dyson K, Bray JE, Smith K, Bernard S, Straney L, Finn J. Paramedic Exposure to Out-of-Hospital Cardiac Arrest Resuscitation Is Associated With Patient Survival. *Circ Cardiovasc Qual Outcomes* 2016;9:154-60.
4. Bottiger BW, Bernhard M, Knapp J, Nagele P. Influence of EMS-physician presence on survival after out-of-hospital cardiopulmonary resuscitation: systematic review and meta-analysis. *Crit Care* 2016;20:4.
5. Lockey D. International EMS systems. *Resuscitation* 2003;59:163-63.
6. von Vopelius-Feldt J, Bengler J. Who does what in prehospital critical care? An analysis of competencies of paramedics, critical care paramedics and prehospital physicians. *Emerg Med J* 2014;31:1009-13.
7. Mikkelsen S, Kruger AJ, Zwisler ST, Brochner AC. Outcome following physician supervised prehospital resuscitation: a retrospective study. *BMJ Open* 2015;5:e006167.
8. Christensen EF, Melchiorson H, Kilsmark J, Foldspang A, Sogaard J. Anesthesiologists in prehospital care make a difference to certain groups of patients. *Acta Anaesthesiol Scand* 2003;47:146-52.
9. von Vopelius-Feldt J, Brandling J, Bengler J. Systematic review of the effectiveness of prehospital critical care following out-of-hospital cardiac arrest. *Resuscitation* 2017;114:40-46.
10. Von Vopelius-Feldt J, Brandling J, Bengler J. Variations in stakeholders' priorities and views on randomisation and funding decisions in out-of-hospital cardiac arrest: An exploratory study. *Health Sci Rep* 2018;e78.
11. von Vopelius-Feldt J, Powell J, Morris R, Bengler J. Prehospital critical care for out-of-hospital cardiac arrest: An observational study examining survival and a stakeholder-focused cost analysis. *BMC Emerg Med* 2016;16:47.

12. Soar J, Nolan JP, Bottiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;95:100-47.
13. Brown S, Kumar D, Millins M, Mark J. UK ambulance services clinical practice guidelines 2016. Bridgewater, 2016.
14. Intercollegiate Board for Training in Pre-hospital Emergency Medicine. Sub-specialty Training in Pre-hospital Emergency Medicine. [http://www.ibtphem.org.uk/IBTPHEM/Resources\\_files/Guide.pdf](http://www.ibtphem.org.uk/IBTPHEM/Resources_files/Guide.pdf)
15. Perkins GD, Brace-McDonnell SJ. The UK Out of Hospital Cardiac Arrest Outcome (OHCAO) project. *BMJ Open* 2015;5:e008736.
16. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation* 2015;132:1286-300.
17. Guo S, Fraser MW. *Propensity Score Analysis: Statistical Methods and Applications*. Thousand Oaks: Sage Publications; 2010.
18. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107.
19. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clin Epidemiol* 2017;9:157-66.
20. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991;10:585-98.
21. Nichol G, Brown SP, Perkins GD, et al. What change in outcomes after cardiac arrest is necessary to change practice? Results of an international survey. *Resuscitation* 2016;107:115-20.
22. Blanco P, Martinez Buendia C. Point-of-care ultrasound in cardiopulmonary resuscitation: a concise review. *J Ultrasound* 2017;20:193-98.

23. Perkins GD, Lall R, Quinn T, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet* 2015;385:947-55.
24. Kaye P. Early prediction of individual outcome following cardiopulmonary resuscitation: systematic review. *Emerg Med J* 2005;22:700-5.
25. Hamilton A, Steinmetz J, Wissenberg M, et al. Association between prehospital physician involvement and survival after out-of-hospital cardiac arrest: A Danish nationwide observational study. *Resuscitation* 2016;108:95-101.
26. Yasunaga H, Horiguchi H, Tanabe S, et al. Collaborative effects of bystander-initiated cardiopulmonary resuscitation and prehospital advanced cardiac life support by physicians on survival of out-of-hospital cardiac arrest: a nationwide population-based observational study. *Crit Care* 2010;14:R199.
27. Goto Y, Funada A. Impact of prehospital physician-led cardiopulmonary resuscitation on neurologically intact survival after out-of-hospital cardiac arrest: a nationwide population-based observational study. *Resuscitation* 2018;136:36-46.
28. Couper K, Kimani PK, Gale CP, et al. Variation in outcome of hospitalised patients with out-of-hospital cardiac arrest from acute coronary syndrome: a cohort study. *Health Services and Delivery Research* 2018. <https://www.ncbi.nlm.nih.gov/books/NBK488090/>
29. Schober A, Sterz F, Laggner AN, et al. Admission of out-of-hospital cardiac arrest victims to a high volume cardiac arrest center is linked to improved outcome. *Resuscitation* 2016;106:42-8.



**Table 1** Patient demographics and prognostic factors in patients with out-of-hospital cardiac arrest who received routine advanced life support (ALS) care only, or who received both routine ALS care and additional prehospital critical care

	ALS care (n=7,149)	Critical care (n=866)	Statistical significance*
<b>Age</b> (median, IQR)	74 (62 – 84)	67 (54 – 76)	p<0.001
<i>Missing data</i>	58 (0.8%)	13 (1.5%)	
<b>Gender</b> (male)	4,549 (63.9%)	611 (70.6%)	p<0.001
<i>Missing data</i>	24 (0.3%)	1 (0.1%)	
<b>Location of OHCA</b>			
Public area	758 (10.6%)	225 (26.0%)	p<0.001
Private residence	3,754 (52.5%)	536 (61.9%)	
Assisted living	274 (3.8%)	12 (1.4%)	
Other	324 (4.5%)	22 (2.5%)	
<i>Missing data</i>	2,039 (28.5%)	71 (8.2%)	
<b>Aetiology</b>			
Presumed cardiac	6,486 (90.7%)	821 (94.8%)	p<0.001
Drug overdose	122 (1.7%)	22 (2.5%)	
Exsanguination	4 (0.1%)	0 (0%)	
Other	435 (6.1%)	8 (0.9%)	
<i>Missing data</i>	102 (1.4%)	15 (1.7%)	
<b>Event witnessed</b>			
Bystander	3,506 (49.0%)	540 (62.4%)	p<0.001
EMS	1,225 (17.1%)	68 (7.9%)	
Not witnessed	2,390 (33.4%)	251 (29.0%)	
<i>Missing data</i>	28 (0.4%)	7 (0.8%)	
<b>Cardiac rhythm</b>			
Shockable	1,531 (21.4%)	305 (35.2%)	p<0.001
PEA	1,539 (21.5%)	130 (15.0%)	
Asystole	3,542 (49.6%)	339 (39.2%)	
<i>Missing data</i>	537 (7.5%)	92 (10.6%)	
<b>Bystander CPR**</b>			
Yes	3,986 (67.3%)	620 (77.7%)	p<0.001
No	1,925 (32.5%)	169 (21.2%)	
<i>Missing data</i>	13 (0.2%)	9 (1.0%)	
<b>AED used</b>			
AED used	233 (3.3%)	54 (6.2%)	p<0.001
<i>Missing data</i>	-	-	
<b>EMS response time</b>			
(median, IQR)	7.2min (4.8 – 11.0)	8.8min (5.8 – 13.7)	p<0.001
<i>Missing data</i>	8 (0.1%)	-	

ALS: Advanced Life Support, IQR: Interquartile range, OHCA: Out-of-hospital cardiac arrest, EMS: Emergency Medical Services, PEA: Pulseless electrical activity, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator

\*Wilcoxon Rank Sum test for non-normally distributed data. Pearson's chi-square test for categorical data

\*\* Excludes EMS-witnessed OHCA's

**Table 2** Patient demographics and prognostic factors after one-to-three propensity score matching (complete case analysis)

	ALS care (n=1,847)	Critical care (n=658)	Standardised difference*
<b>Age</b> (median, IQR)	69 (57 – 77)	68 (55 – 77)	9.1%
<b>Gender</b> (male)	1,302 (70.5%)	457 (69.5%)	2.3%
<b>Location of OHCA</b>			
Public area	392 (21.2%)	162 (24.6%)	12.0%
Private residence	1,379 (74.6%)	464 (70.5%)	
Assisted living	16 (0.9%)	12 (1.8%)	
Other	60 (3.3%)	20 (3.0%)	
<b>Aetiology</b>			
Presumed cardiac	1,802 (97.6%)	639 (97.1%)	2.8%
Drug overdose	45 (2.4%)	19 (2.9%)	
Exsanguination	-	-	
Other	-	-	
<b>Event witnessed</b>			
Bystander	1,106 (59.9%)	414 (62.9%)	7.1%
EMS	185 (10.0%)	55 (8.4%)	
Not witnessed	556 (30.1%)	189 (28.7%)	
<b>Cardiac rhythm</b>			
Shockable	668 (36.2%)	254 (38.6%)	5.1%
PEA	310 (16.8%)	108 (16.4%)	
Asystole	869 (47.1%)	296 (45.0%)	
<b>Bystander CPR**</b>			
Yes	1,282 (77.1%)	466 (77.3%)	0.5%
No	380 (22.9%)	137 (22.7%)	
<b>AED used</b>	48 (2.6%)	22 (3.3%)	4.3%
<b>EMS response time</b> (median, IQR)	8.1min (5.3 – 13.0)	8.8min (5.7 – 13.7)	9.2%
<b>Survival to hospital admission</b>	<b>511 (27.7%)</b>	<b>226 (34.4%)</b>	
<b>Survival to hospital discharge</b>	<b>220 (11.9%)</b>	<b>78 (11.9%)</b>	

ALS: Advanced Life Support, IQR: Interquartile range, OHCA: Out-of-hospital cardiac arrest, EMS: Emergency Medical Services, PEA: Pulseless electrical activity, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator

\* Values of 10% or less are considered to indicate a good balance for a given variable <sup>18</sup>

\*\* Excludes EMS-witnessed OHCA

**Table 3** Prehospital critical interventions delivered during out-of-hospital cardiac arrest and after return of spontaneous circulation, stratified by patient outcomes

<b>Interventions during OHCA*</b>				
	<b>Prehospital death (n=411)</b>	<b>Hospital death (n=89)</b>	<b>Survivors (n=20)</b>	<b>Overall (n=520)</b>
Mechanical CPR	155 (38%)	42 (47%)	7 (35%)	204 (39%)
ROLE outside of fixed guideline criteria	124 (30%)	N/A	N/A	124 (24%)
Ultrasound	89 (22%)	7 (8%)	1 (5%)	97 (19%)
IV Magnesium	22 (5%)	7 (8%)	2 (10%)	31 (6%)
IV Sodium Bicarbonate	22 (5%)	5 (6%)	0 (0%)	27 (5%)
IV Calcium Chloride	14 (3%)	1 (1%)	0 (0%)	15 (3%)
Sedation and/or neuromuscular blocker	7 (2%)	1 (1%)	3 (15%)	11 (2%)
Thoracostomy	4 (1%)	1 (1%)	0 (0%)	5 (1%)
<b>Interventions after ROSC*</b>				
	<b>Prehospital death (n=43)</b>	<b>Hospital death (n=164)</b>	<b>Survivors (n=92)</b>	<b>Overall (n=299)</b>
Rapid sequence induction of anaesthesia (RSI)	1 (2%)	45 (27%)	48 (52%)	94 (31%)
IV inotropes or vasopressors	14 (33%)	71 (43%)	9 (10%)	94 (31%)
Sedation and/or paralysis (excludes RSI)	9 (21%)	45 (27%)	10 (11%)	64 (21%)
Ultrasound	1 (2%)	8 (5%)	4 (4%)	13 (4%)
IV amiodarone	2 (5%)	5 (3%)	2 (2%)	9 (3%)
IV magnesium	1 (2%)	6 (4%)	0 (0%)	7 (2%)
IV sodium bicarbonate	1 (2%)	3 (2%)	1 (1%)	5 (2%)
Electrical cardioversion	1 (2%)	3 (2%)	1 (1%)	5 (2%)
Bypass of nearest hospital for OHCA centre	N/A	38 (23%)	27 (30%)	65 of 256** (25%)

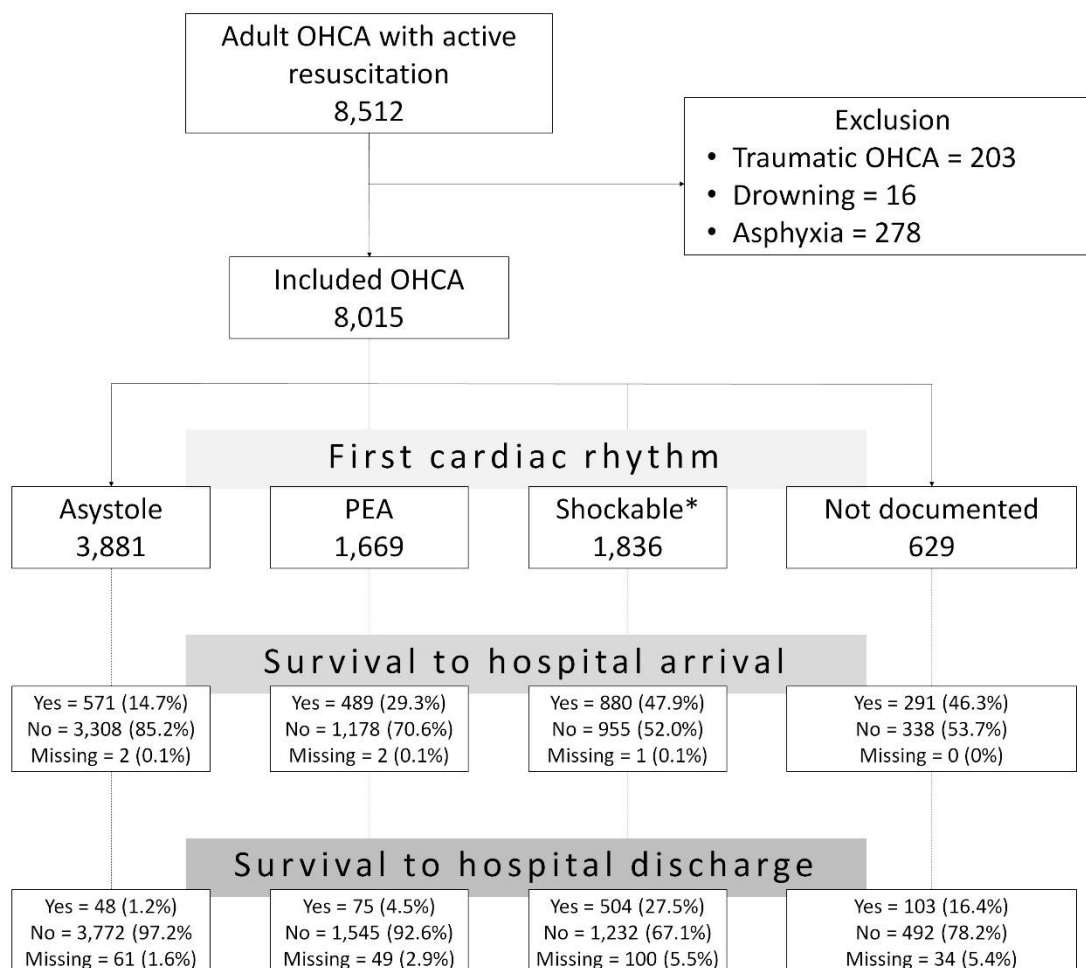
\* Multiple interventions per individual patient were possible

\*\* Excluding cases of prehospital death

OHCA: Out-of-hospital cardiac arrest, IV: Intravenous, ROLE: Recognition of life extinct, N/A: Not applicable, CPR: Cardiopulmonary resuscitation

## Figure legends and footnotes

**Figure 1** Flowchart showing the out-of-hospital cardiac arrest patients included in the analysis

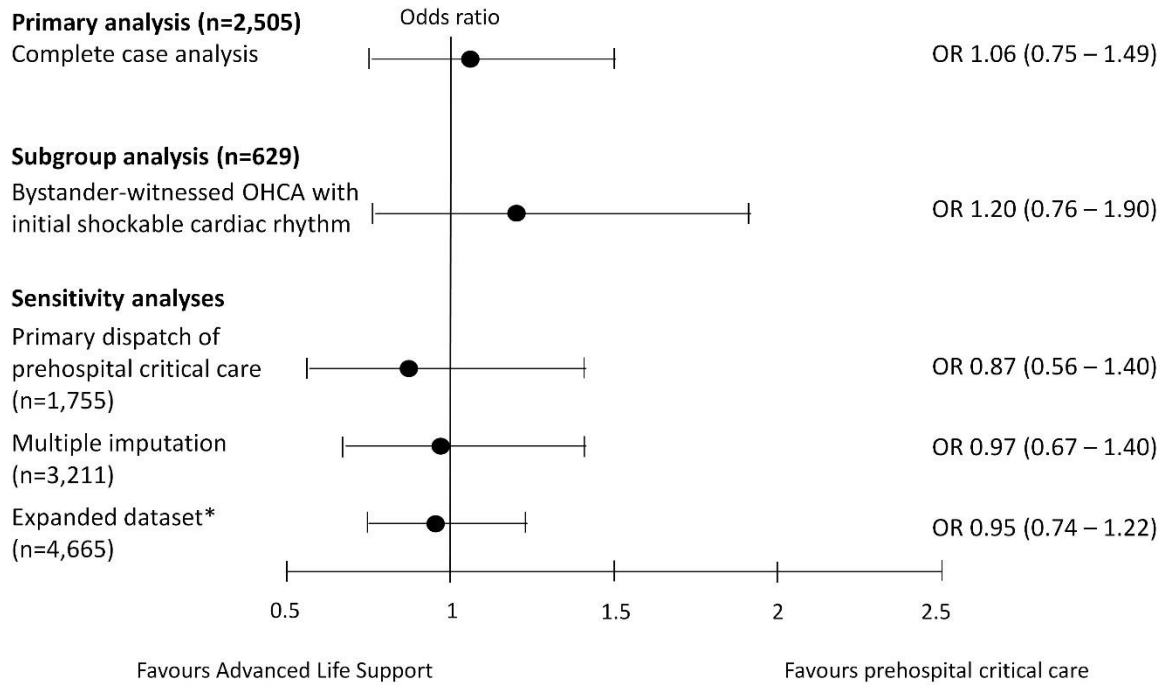


\* Ventricular fibrillation or pulseless ventricular tachycardia

OHCA: Out-of-hospital cardiac arrest, PEA: Pulseless electrical activity

**Figure 2** Odds ratios and 95% confidence intervals for the primary, subgroup and sensitivity analyses for the primary outcome of survival to hospital discharge, after propensity score matching

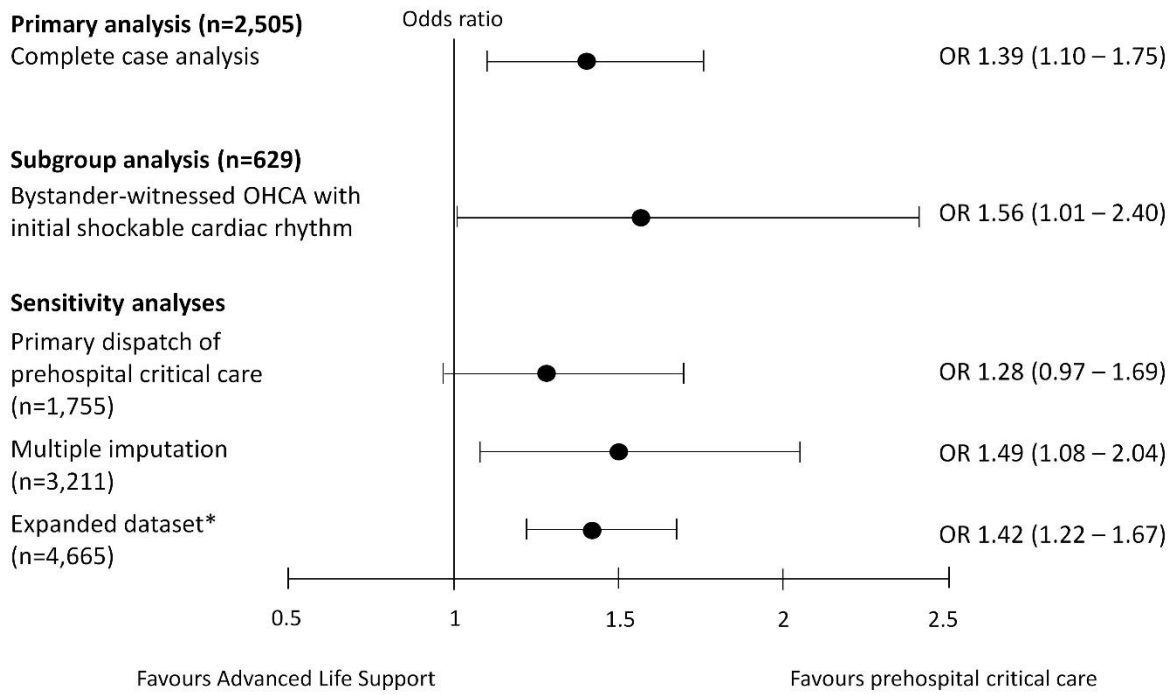
Primary outcome – survival to hospital discharge



\*Propensity score matching did not include location of OHCA or EMS response times

**Figure 3** Odds ratios and 95% confidence intervals for the primary, subgroup and sensitivity analyses for the secondary outcome of survival to hospital admission, after propensity score matching

Secondary outcome – survival to hospital arrival



\*Propensity score matching did not include location of OHCA or EMS response times

