Resuscitation 124 (2018) 49–57

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Patient, health service factors and variation in mortality following resuscitated out-of-hospital cardiac arrest in acute coronary syndrome: Analysis of the Myocardial Ischaemia National Audit Project☆

Keith Couper[a,b], Peter K. Kimani[a], Chris P. Gale[c,d], Tom Quinn[e], Iain B. Squire[f], Andrea Marshall[a], John J.M. Black[g], Matthew W. Cooke[a], Bob Ewings[h], John Long[h], Gavin D. Perkins[a,b,*]

[a] Warwick Medical School, University of Warwick, Coventry, UK
[b] Academic Department of Anaesthesia, Critical Care, Pain and Resuscitation, Heart of England NHS Foundation Trust, Birmingham, UK
[c] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[d] York Teaching Hospital NHS Foundation Trust, York, UK
[e] Faculty of Health, Social Care and Education, Kingston University, London and St George's, University of London, London, UK
[f] University of Leicester and Leicester NIHR Cardiovascular Research Unit, Glenfield Hospital, Leicester, UK
[g] South Central Ambulance Service NHS Foundation Trust, Bicester, UK
[h] Patient and public involvement representative

ARTICLE INFO

Article history:
Received 7 November 2017
Received in revised form
20 December 2017
Accepted 5 January 2018

Keywords:
Out-of-hospital cardiac arrest
Acute coronary syndrome
Myocardial infarction

ABSTRACT

Aims: To determine patient and health service factors associated with variation in hospital mortality among resuscitated cases of out-of-hospital cardiac arrest (OHCA) with acute coronary syndrome (ACS).
Methods: In this cohort study, we used the Myocardial Ischaemia National Audit Project database to study outcomes in patients hospitalised with resuscitated OHCA due to ACS between 2003 and 2015 in the United Kingdom. We analysed variation in inter-hospital mortality and used hierarchical multivariable regression models to examine the association between patient and health service factors with hospital mortality.
Results: We included 17604 patients across 239 hospitals. Overall hospital mortality was 28.7%. In 94 hospitals that contributed at least 60 cases, mortality by hospital ranged from 10.7% to 66.3% (median 28.6%, IQR 23.2% to 39.1%)). Patient and health service factors explained 36.1% of this variation.

After adjustment for covariates, factors associated with higher hospital mortality included increasing serum glucose, ST-Elevation myocardial infarction (STEMI) diagnosis, and initial admission to a primary percutaneous coronary intervention (pPCI) capable hospital. Hospital OHCA volume was not associated with mortality. The key modifiable factor associated with lower mortality was early reperfusion therapy in STEMI patients.
Conclusion: There was wide variation in inter-hospital mortality following resuscitated OHCA due to ACS that was only partially explained by patient and health service factors. Hospital OHCA volume and pPCI capability were not associated with lower mortality. Early reperfusion therapy was associated with lower mortality in STEMI patients.

Introduction

Across Europe, the annual incidence of treated out-of-hospital cardiac arrest (OHCA) is 49 cases per 100,000 population [1]. Acute coronary syndrome (ACS) is a common cause of OHCA; where OHCA cause is recorded, approximately 76% of cases are attributed to cardiac aetiology [2]. Variation in OHCA mortality has been described

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at https://doi.org/10.1016/j.resuscitation.2018.01.011.

* Corresponding author at: Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK.
E-mail address: G.D.Perkins@warwick.ac.uk (G.D. Perkins).

https://doi.org/10.1016/j.resuscitation.2018.01.011

between countries, Emergency Medical Service (EMS) systems and admitting hospitals [1–3].

Regional cardiac arrest centres have been proposed as a strategy to reduce inter-hospital variation in OHCA mortality, but the quality of evidence supporting the concept is low [4,5]. Regionalised care systems are based on the premise that the benefit of immediate admission to a hospital with specialist facilities and expertise outweighs any risk associated with a potentially increased transport time. Such systems are already established in major trauma and stroke [6,7].

In OHCA, improved understanding of inter-hospital variation in mortality is essential to improve understanding of the potential value of regionalised care systems. The availability in England and Wales of the only nation-wide ACS registry (Myocardial Ischaemia National Audit Project, MINAP) provides a unique opportunity to better understand these factors. Our study objective was to identify if there was evidence of inter-hospital variation in mortality among resuscitated cases of OHCA caused by ACS in the UK, and to identify the patient and health service factors that might contribute to any variation.

Methods

Data source

MINAP is a national registry of patients admitted to hospital with acute coronary syndromes. Established in 1998, it provides a mechanism for participating hospitals to benchmark performance against national standards [8]. MINAP participation is mandatory, with all acute hospitals in England and Wales participating since 2003. Detailed care quality and clinical outcome data are collected at the hospital level, with entry validated through real-time checks and an annual hospital data validation review. This study linked MINAP to UK Office of National Statistics (ONS) data to provide information on patient social deprivation and enrich mortality data. MINAP identifies patients using their unique NHS number, which is pseudo-anonymised in the database. Patient identifiers (for example, date of birth) are encrypted prior to transfer to the central database, and are not released to researchers.

Patient eligibility

In this study, we included adult patients in the MINAP dataset where the initial cardiac arrest event occurred in the pre-hospital setting and where initial resuscitation attempts were successful leading to hospital admission. We excluded non-index (second or subsequent) cardiac arrests, events where the initial cardiac arrest event occurred in the in-hospital setting, and patients where the primary outcome was unknown.

Data definitions

For hospital-level data (volume, primary percutaneous coronary intervention (pPCI) capability, EMS distance), patients were categorised by the hospital to which they were first admitted. For hospital volume, the number of OHCA cases in each year at each hospital was calculated. Each patient was allocated to a volume category (low: 1–10 cases; medium: 11–24 cases; high: ≥25 cases) based on the hospital and year in which they were treated. We categorised patients as being treated in a pPCI capable hospital if it performed at least 100 pPCI procedures across all patients in the MINAP dataset in the year that the patient was admitted, as per UK guidance [9]. EMS distance was calculated as the Euclidian distance between the patient's home address and hospital. This assumed the OHCA event occurred at the patient's home, which is true for over 80% of UK OHCAs [2].

Reperfusion treatment was categorised as early or late. Thrombolysis was classified as early if call-to-needle time was up to 60 min, based on UK national standards [10]. PPCI was classified as early if door-to-balloon time was up to 90 min, based on the MINAP benchmark [11].

For sub-group analyses, we categorised patients, based on the MINAP variable 'ECG determining treatment,' as having STEMI (ST-elevation acute myocardial infarction or presumed new left bundle branch block (LBBB)) or NSTEACS (non-ST Elevation Acute Coronary Syndrome, which included all patients that did not meet the STEMI definition including unstable angina patients).

Outcome measures

The primary outcome was all-cause hospital mortality, as recorded in the MINAP dataset or, where this was incomplete, cross-referencing with ONS mortality data.

Sample size

Preliminary data supplied by MINAP led to a projected sample size of 14,310 eligible OHCA cases with a projected hospital mortality of 24%. Based on this, we calculated a 4% difference in mortality between categories within a predictor variable could be detected reliably with at least 90% power and a significance level of 0.05.

Statistical analysis

Multiple imputation using chained equations was used to reduce the bias associated with missing data in predictor variables (Supplementary Data Table S1), based on the approach used in previous MINAP analyses [12,13]. Case identification and sub-group allocation was undertaken prior to imputation. Twenty-five imputed datasets were generated.

After imputation, an unadjusted random effects logistic regression model was fitted to predict hospital mortality and obtain the estimate for the log of the odds ratio and the standard error for each imputed dataset. The inclusion of a random effects term for the hospital enabled variation between hospitals to be modelled. Estimates from each of the 25 imputed datasets were combined using the Rubin's rules to get an overall odds ratio estimate of mortality, 95% confidence interval and p-value [14]. We adopted a similar approach for the adjusted analysis. The model included all clinically relevant predictor variables, unless there was evidence of multi-collinearity due to two predictors being highly correlated or a variable was clearly confounded by an unmeasured variable.

Alongside data from the whole cohort, we report data from STEMI and NSTEACS sub-groups, and sensitivity analyses (complete case; admission between 2003 and 2008; admission between 2009 and 2015). This sensitivity analysis cut-off reflects the year (2009) that pPCI became the most commonly recorded reperfusion treatment in MINAP [11].

Data processing and descriptive analyses pre-imputation were performed using SPSS version 22 (IBM Corp, Armonk, NY, USA). The R statistical program (R: A language and environment for statistical computing, R development core team; R Foundation for Statistical Computing, Vienna, Austria) and associated packages (MICE and gamm4 packages) were used for multiple imputation, descriptive analysis after multiple imputation, and fitting models for hospital mortality.

Ethics/approvals

The study was undertaken in accordance with the Declaration of Helsinki. The University of Warwick Biomedical Research Ethics Committee approved the study. MINAP, as part of the National

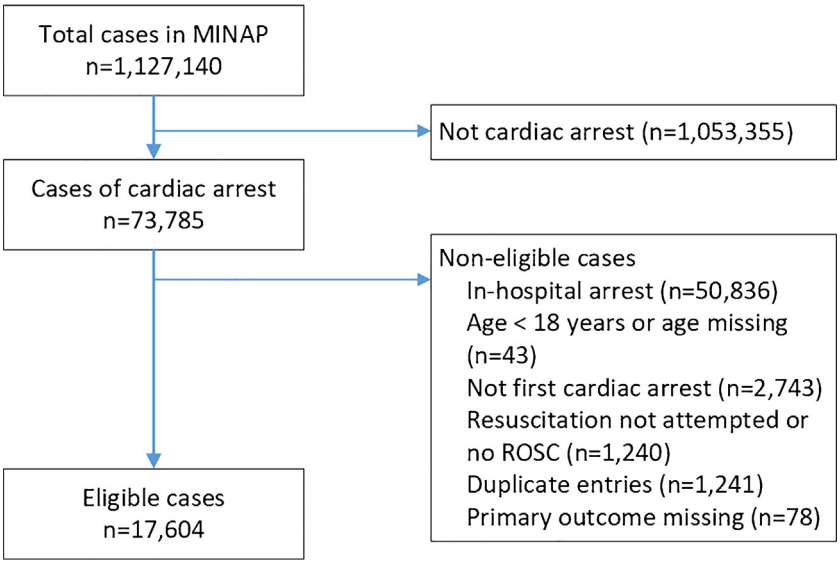

Fig. 1. Flow chart of case identification process.

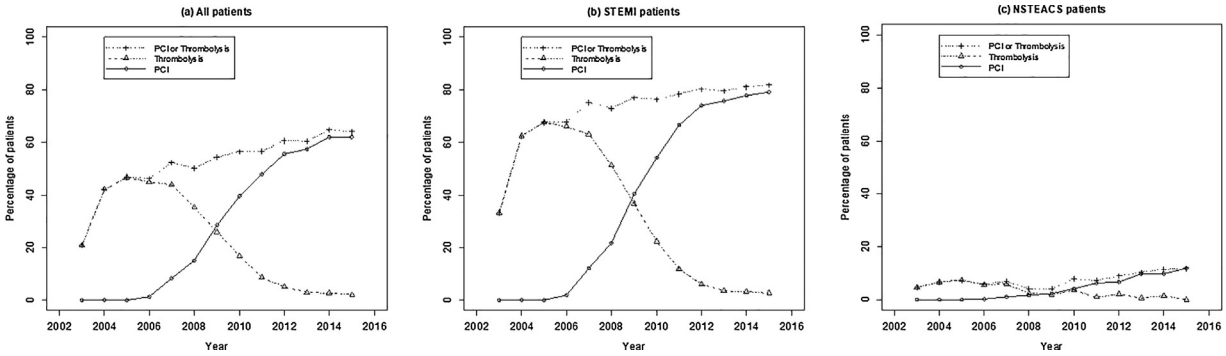

Fig. 2. Reperfusion rates by year across the whole cohort, STEMI cases, and NSTEACS cases.

Institute for Cardiovascular Outcomes Research, is approved under UK legislation to hold patient identifiable data without consent.

Results

Study population

There were 1,127,140 patient datasets collected by MINAP between January 2003 and June 2015 (Fig. 1). Of these, 73,875 (6.6%) were identified as having had a cardiac arrest. Sequential application of study exclusion criteria led to the exclusion of 56,271 patients, most of whom had sustained an in-hospital cardiac arrest (N = 50,836, 90.3%). The study sample included data from 17,604 patients across 239 hospitals. The median number of cases reported per hospital over the study period was 46 (range 1–517). Neurological outcome data were available for 15,286 patients.

The number of cases included annually increased over the study period, with a peak of 2129 cases in 2012 (Supplementary Data Fig. S1).

Patient characteristics (whole cohort)

Patients were predominantly male (n = 13,188, 75.1%) with a mean age of 65.3 years (Table 1). The most common co-morbidity was hypertension (n = 6389, 41.0%). OHCA events typically occurred prior to EMS arrival (n = 10,533, 60.1%) with a shockable presenting rhythm (n = 14,778, 89.6%). Most were classified as STEMI (n = 12,220, 71.9%), and were admitted to the coronary care (N = 8872, 51.0%) or intensive care (N = 6154, 35.4%) unit. Most patients received reperfusion therapy (n = 9540, 62.9%), of which the majority received pPCI (n = 6160, 64.6%). Reperfusion therapy use increased over time (2003: 20.8%; 2015: 64.1%), with increases in pPCI use mirrored by a decline in thrombolysis use across all patients, and in STEMI/NSTEACS sub-groups (Fig. 2). Over the study period, the percentage of patients admitted to pPCI capable hospitals increased (2003: 0%; 2014: 81%) and the percentage admitted to low-volume OHCA hospitals decreased (Fig. 3; Supplementary Data Fig. S2).

Length of stay and patient outcomes

Overall hospital mortality was 28.7% (n = 5047) and 40.9% (n = 6245) died or were discharged with neurological deficit. In non-survivors, median time to death was 2 days (IQR 1–5, range 0–96) (Supplementary Data Fig. S3). For survivors, median length of hospital stay was 7 days (IQR 3–14, range 0–372) (Supplementary Data Fig. S4).

Variation in inter-hospital mortality

In the 94 hospitals that contributed at least 60 cases over the study period, hospital mortality by hospital ranged from 10.7% to 66.3% (median 28.6%, IQR 23.2% to 39.1%) (Supplementary Data Fig. S5).

Table 1
Patient characteristics across all cases, STEMI cases and NSTEACS cases.

	All cases (n = 17,604)[a]	STEMI (n = 12,220)[a]	NSTEACS (n = 4772)[a]
Demographic variables			
Age (Years)- Mean (SD)	65.3 (13.15)	63.9 (13.06)	68.3 (12.73)
Gender (Female)- n (%)	4370 (24.9)	3034 (24.9)	1155 (24.2)
Ethnicity, n (%)			
White	14,343 (93.7)	9927 (93.4)	3904 (94.3)
Asian	531 (3.5)	386 (3.6)	135 (3.3)
Black	131 (0.9)	88 (0.8)	40 (1.0)
Other	303 (2.0)	230 (2.2)	63 (1.5)
Index of multiple deprivation score- Mean (SD)	22.31 (15.91)	22.27 (15.92)	22.42 (15.94)
Medical history variables- n (%)			
Smoking status- Ever smoked	8883 (63.5)	6510 (65.8)	2157 (57.9)
Diabetes status- Diabetic	2158 (13.7)	1283 (11.8)	795 (18.2)
Hypercholesterolaemia- Yes	3906 (25.9)	2600 (24.9)	1197 (28.4)
Heart failure- Yes	760 (5.0)	356 (3.4)	359 (8.4)
Cerebrovascular disease- Yes	1071 (7.0)	609 (5.7)	419 (9.8)
Previous MI- Yes	3092 (19.7)	1701 (15.7)	1243 (28.5)
Asthma or COPD- Yes	1814 (11.9)	1161 (11.0)	569 (13.3)
Chronic renal failure- Yes	555 (3.6)	272 (2.6)	252 (5.9)
Peripheral vascular disease- Yes	587 (3.9)	358 (3.4)	208 (4.9)
Previous Angina- Yes	2758 (17.8)	1501 (14.0)	1133 (26.3)
Previous PCI- Yes	1061 (6.9)	670 (6.3)	357 (8.3)
Previous CABG- Yes	790 (5.1)	374 (3.5)	395 (9.1)
Hypertension- Yes	6389 (41.0)	4186 (38.8)	2007 (46.3)
OHCA presenting characteristics			
Time point of cardiac arrest, n (%)			
Before ambulance arrival	10,533 (60.1)	6371 (52.3)	3747 (78.7)
After ambulance arrival	7004 (39.9)	5811 (47.7)	1013 (21.3)
Cardiac arrest rhythm, n (%)			
Asystole	885 (5.4)	422 (3.7)	388 (8.8)
PEA	837 (5.1)	444 (3.8)	353 (8.0)
VF/VT	14,778 (89.6)	10,691 (92.5)	3665 (83.2)
Serum glucose (mmol/L)- Mean (SD)	10.94 (5.00)	10.92 (4.91)	10.99 (5.23)
Creatinine (micromol/L)- Mean (SD)	108.12 (55.72)	104.12 (49.86)	117.80 (67.17)
Left Ventricular Ejection Fraction, n (%)			
Good	2783 (36.4)	1873 (34.3)	858 (41.4)
Moderate	3131 (40.9)	2347 (43.0)	744 (35.9)
Poor	1736 (22.7)	1233 (22.6)	469 (22.6)
Haemoglobin (g/dL)- Mean (SD)	13.57 (2.03)	13.69 (2.01)	13.27 (2.05)
Serum cholesterol (mmol/L)- Mean (SD)	4.80 (1.51)	4.91 (1.47)	4.46 (1.64)
Admission diagnosis, n (%)			
Definite MI – anterior infarction	3897 (27.0)	3809 (40.6)	78 (1.7)
Definite MI – other infarction site	3639 (25.2)	3463 (36.9)	159 (3.5)
Other initial diagnosis	6883 (47.7)	2105 (22.4)	4306 (94.8)
Admission systolic BP (mmHg)- Mean (SD)	125.69 (29.17)	124.95 (28.75)	127.27 (29.86)
ECG that determined treatment, n (%)			
ST elevation or LBBB	12,220 (71.9)	12,220 (100.0%)	0 (0%)
ST depression/T wave changes only	2325 (13.7)	0 (0%)	2325 (48.7%)
Other change/No acute changes	2447 (14.4)	0 (0%)	2447 (51.3%)
Admission heart rate (/minute)- Mean (SD)	89.22 (24.79)	88.55 (24.10)	90.54 (26.12)
Daytime hospital admission (8am to <8pm)- n (%)	11,741 (66.7%)	8083 (66.1%)	3272 (68.6%)
Killip Class, n (%)			
Basal crepitations and/or elevated venous pressure	796 (13.8)	517 (12.1)	269 (18.5)
Pulmonary oedema	317 (5.5)	228 (5.3)	89 (6.1)
Cardiogenic shock	1029 (17.9)	853 (20.0)	169 (11.6)
No evidence of heart failure	3612 (62.8)	2665 (62.5)	927 (63.8)
Mini-Grace score- Mean (SD)	173 (28.37)	174 (27.92)	172 (29.38)
Care pathway variables			
Hospital volume (OHCA cases per year)- n (%)			
1 to 10 cases	7984 (45.4)	4900 (40.1)	2673 (56.0)
11 to 24 cases	6516 (37.0)	4799 (39.3)	1565 (32.8)
25 to 82 cases	3104 (17.6)	2521 (20.6)	534 (11.2)
Hospital pPCI capability- n (%)			
pPCI capable	7800 (44.3)	6514 (53.3)	1205 (25.3)
pPCI incapable	9804 (55.7)	5706 (46.7)	3567 (74.7)
EMS response time (Minutes)- Mean (SD)	11.53 (11.82)	12.03 (12.42)	10.29 (10.11)
EMS travel distance (Kilometres)- Mean (SD)	11.24 (10.08)	11.96 (10.50)	9.67 (8.88)
Admitting consultant, n (%)-			
Cardiologist	10,680 (61.8)	8480 (70.6)	2008 (42.8)
Other consultant	6603 (37.5)	3534 (29.4)	2689 (57.2)
Cardiological care during admission- yes- n (%)	11,960 (90.7)	8797 (93.3)	2975 (85.0)
Admission Ward, n (%)			
CCU	8872 (51.0)	6984 (57.9)	1683 (35.4)
Cardiac ward – non CCU	500 (2.9)	366 (3.0)	123 (2.6)
Intensive therapy unit	6154 (35.4)	3666 (30.4)	2290 (48.2)

Table 1 (*Continued*)

	All cases (n = 17,604)[a]	STEMI (n = 12,220)[a]	NSTEACS (n = 4772)[a]
General medical ward or Other	1534 (8.8)	868 (7.2)	558 (11.8)
Died in Emergency Department	340 (1.9)	176 (1.5)	94 (2.0)
Place where ECG performed, n (%)			
Pre-hospital	11,053 (75.7)	8253 (79.2)	2659 (67.0)
In hospital	3551 (24.3)	2162 (20.8)	1311 (33.7)
Reperfusion treatment and timing, n (%)			
None	5633 (37.1)	2048 (18.3)	2350 (90.1)
Thrombolysis (early)	1080 (7.1)	1053 (9.4)	20 (0.5)
Thrombolysis (late)	1930 (12.7)	1832 (16.4)	85 (2.3)
Thrombolysis (time missing)	370 (2.4)	314 (2.8)	40 (1.1)
pPCI (early)	4424 (29.2)	4293 (38.5)	122 (3.3)
pPCI (late)	1063 (7.0)	994 (8.9)	65 (1.7)
pPCI (time missing)	673 (4.4)	631 (5.7)	36 (1.0)
Discharge care variables			
Discharge Diagnosis, n (%)			
Acute coronary syndrome	16,476 (95.1)	11,710 (97.5)	4232 (89.8)
Other diagnosis	843 (4.9)	304 (2.5)	483 (10.2)
Echocardiography- yes/planned- n (%)	11,140 (73.8)	7902 (75.2)	2990 (72.6)
Outcomes			
Survival to hospital discharge-n (%)	12,557 (71.3)	9049 (74.1)	3184 (66.7)
Discharged without neurological deficit- n (%)[‡]	9041 (59.1)	6736 (62.9)	2081 (51.4)

CABG- Coronary Artery Bypass Graft; CCU- Cardiac Care Unit; COPD- Chronic Obstructive Pulmonary Disease; ECG- Electrocardiogram; EMS- Emergency Medical Service; LBBB- Left Bundle Branch Block; MI- Myocardial Infraction; OHCA- Out-of-Hospital Cardiac Arrest; (p)PCI- (primary) Percutaneous Coronary Intervention; PEA- Pulseless Electrical Activity; VF- Ventricular Fibrillation; VT- Ventricular Tachycardia.

[a] The n for each variable is the total group size minus the number of missing cases (see Supplementary information). 612 cases were missing STEMI status, so not included in the sub-groups.

[‡] Neurological outcome data available for 15,286 patients.

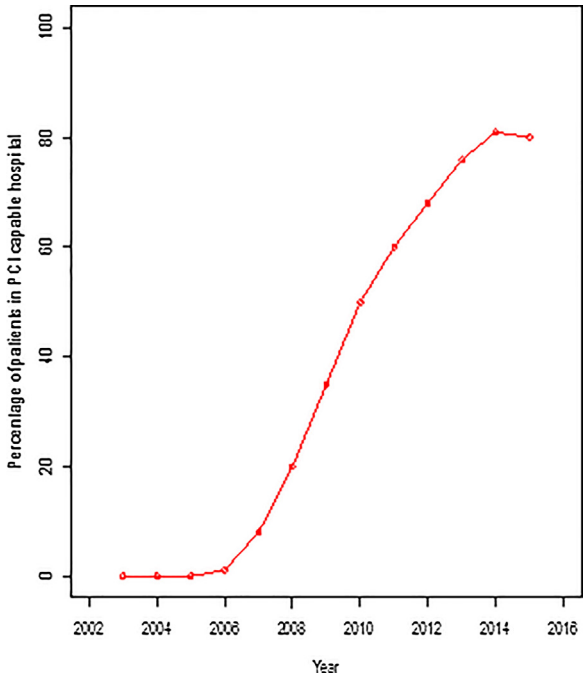

Fig. 3. Percentage of patients admitted to pPCI capable centres by year.

Demographic and medical history variables explained little variation, with age ($R^2 = 0.060$) having the highest R^2 value (Supplementary Data Table S2). A greater degree of variation was explained by some OHCA presenting characteristic and care pathway variables, such as OHCA rhythm ($R^2 = 0.104$), serum glucose ($R^2 = 0.083$), and admission ward ($R^2 = 0.178$). Little variation was explained by OHCA hospital volume ($R^2 = 0.006$), hospital pPCI capability ($R^2 = 0.003$) and reperfusion therapy ($R^2 = 0.042$). The adjusted analysis explained 36.1% ($R^2 = 0.361$) of the variation across the dataset (Table 2).

Factors influencing mortality

Across the whole cohort, after co-variate adjustment, demographic factors associated with increased mortality included increasing age and social deprivation (Table 2). Other factors associated with higher mortality included female gender, history of heart failure, increasing blood glucose, OHCA prior to EMS arrival, and STEMI or LBBB on the initial ECG. Hypertension, hypercholesterolaemia, and a shockable OHCA rhythm were associated with lower mortality.

Health service factors that did not influence mortality include time of day of admission, hospital OHCA volume, EMS response time, and first ECG location. Admission to a pPCI capable hospital was associated with higher mortality (OR 1.26, 95% CI 1.05–1.53). A supplementary analysis identified case-mix differences between patients treated in pPCI capable and non-pPCI capable hospitals. More patients initially admitted to a pPCI capable hospital presented in a shockable OHCA rhythm (92.8% v 86.9%), had a STEMI diagnosis, (84.4% v 61.5%), and were in cardiogenic shock (21.9% v 5.7%) (Supplementary Data Table S3).

Hospital admission under a cardiologist (OR 0.73, 95% CI 0.64–0.82) was associated with lower mortality. Early reperfusion treatment was the key modifiable health service factor associated with reduced mortality (early thrombolysis 0.67, 95% CI 0.52–0.86; early pPCI OR 0.70, 95% CI 0.60–0.83).

STEMI and NSTEACS cohorts

Adjusted models restricted to STEMI and NSTEACS cohorts explained a similar degree of variation as the primary analysis (STEMI: $R^2 = 0.354$; NSTEMI $R^2 = 0.365$) (Table 2). Compared to STEMI patients, NSTEACS patients were older (mean age 68.3 v 63.9 years), had more co-morbidities, and were more likely to present in a non-shockable OHCA rhythm (Table 1). NSTEACS patients were less likely to be admitted to a high-volume OHCA (11.2% v 20.6%) or pPCI capable (25.3% v 53.3%) hospital, and less likely to receive reperfusion therapy (9.9% v 81.7%).

Table 2
Multiviariate analysis across all cases, STEMI cases and NSTEACS cases.

		Odds ratio of in-hospital mortality (95% confidence intervals), p-value*		
		All cases (n = 17,604)	STEMI (n = 12,220)	NSTEACS (n = 4772)
Demographic variables				
Age (Years)**		1.046 (1.042, 1.051), <0.001	1.048 (1.043, 1.054), <0.001	1.048 (1.040, 1.056), <0.001
Gender	Male	0.877 (0.786, 0.979), 0.019	0.921 (0.806, 1.052), 0.226	0.758 (0.621, 0.925), 0.006
	Female[a]			
Ethnicity	Asian	1.022 (0.804, 1.299), 0.860	0.961 (0.725, 1.275), 0.783	1.167 (0.702, 1.939), 0.551
	Black	0.939 (0.602, 1.464), 0.780	0.833 (0.509, 1.364), 0.468	1.059 (0.511, 2.198), 0.877
	Other	0.991 (0.723, 1.358), 0.956	1.023 (0.726, 1.440), 0.898	0.871 (0.417, 1.819), 0.713
	White[a]			
Index of multiple deprivation score**		1.005 (1.002, 1.008), 0.003	1.002 (0.998, 1.006), 0.323	1.010 (1.004, 1.016), 0.002
Medical history variables[a]				
Smoking status- ever smoked		0.903 (0.812, 1.004), 0.059	0.875 (0.765, 1.000), 0.050	1.009 (0.830, 1.226), 0.927
Diabetes status- Diabetic		1.125 (0.981, 1.290), 0.092	1.162 (0.976, 1.384), 0.091	1.123 (0.890, 1.416), 0.329
Hypercholesterolaemia		0.692 (0.615, 0.779), <0.001	0.669 (0.577, 0.776), <0.001	0.684 (0.551, 0.850), 0.001
Heart failure		1.318 (1.074, 1.618), 0.008	1.584 (1.178, 2.128), 0.002	1.192 (0.874, 1.624), 0.267
Cerebrovascular disease		1.299 (1.097, 1.537), 0.002	1.075 (0.858, 1.348), 0.529	1.703 (1.294, 2.241), <0.001
Previous MI		1.028 (0.900, 1.173), 0.685	0.997 (0.836, 1.188), 0.971	1.118 (0.899, 1.39), 0.327
Asthma or COPD		1.247 (1.087, 1.431), 0.002	1.228 (1.030, 1.463), 0.022	1.246 (0.975, 1.591), 0.079
Chronic renal failure		1.065 (0.841, 1.350), 0.601	0.864 (0.613, 1.219), 0.406	1.390 (0.969, 1.995), 0.073
Peripheral vascular disease		1.517 (1.208, 1.904), <0.001	1.723 (1.286, 2.309), <0.001	1.338 (0.903, 1.981), 0.146
Previous angina		1.011 (0.885, 1.156), 0.867	1.037 (0.869, 1.239), 0.684	0.926 (0.743, 1.154), 0.494
Previous PCI		1.025 (0.840, 1.251), 0.806	1.051 (0.815, 1.356), 0.700	0.923 (0.652, 1.305), 0.649
Previous CABG		0.996 (0.811, 1.222), 0.966	1.189 (0.894, 1.583), 0.235	0.830 (0.607, 1.135), 0.244
Hypertension		0.865 (0.784, 0.955), 0.004	0.849 (0.752, 0.960), 0.009	0.866 (0.723, 1.038), 0.120
OHCA presenting characteristics				
Time point of cardiac arrest	After EMS arrive	0.492 (0.441, 0.548), <0.001	0.483 (0.425, 0.548), <0.001	0.424 (0.331, 0.544), <0.001
	Before EMS arrival[a]			
Cardiac arrest rhythm	PEA	0.847 (0.658, 1.088), 0.194	0.730 (0.507, 1.051), 0.091	0.846 (0.573, 1.248), 0.399
	VF/VT	0.217 (0.180, 0.262), <0.001	0.189 (0.145, 0.247), <0.001	0.231 (0.172, 0.310), <0.001
	Asystole[a]			
Serum glucose**		1.109 (1.096, 1.122), <0.001	1.113 (1.097, 1.130), <0.001	1.103 (1.081, 1.126), <0.001
Haemoglobin**		0.912 (0.878, 0.946), <0.001	0.920 (0.884, 0.958), <0.001	0.892 (0.842, 0.945), <0.001
Serum cholesterol**		0.956 (0.906, 1.010), 0.108	0.953 (0.892, 1.017), 0.150	0.980 (0.910, 1.056), 0.595
Admission diagnosis	Other diagnosis	0.876 (0.750, 1.024), 0.097	1.005 (0.850, 1.188), 0.956	0.586 (0.329, 1.043), 0.069
	Definite MI – other infarct site	1.022 (0.890, 1.173), 0.762	1.029 (0.898, 1.179), 0.679	1.192 (0.603, 2.358), 0.614
	Definite MI – anterior infarct[a]			
Admission systolic blood pressure	Linear term***	-42.15 (-48.35, −35.96), <0.001	-33.76 (-40.3, −27.3), <0.001	-23.45 (-29.6, −17.3), <0.001
	Quadratic term***	17.68 (11.79, 23.57), <0.001	16.96 (11.00, 22.92), <0.001	6.42 (0.46, 12.38), 0.035
ECG that determined treatment	ST elevation or LBBB	1.592 (1.364, 1.858), <0.001	Only ST elevation/LBBB patients included in this analysis	Data not included
	ST depression/T wave changes only	0.907 (0.775, 1.062), 0.227		0.859 (0.728, 1.014), 0.073
	Other change/No acute changes[a]			

Admission heart rate**		1.005 (1.004, 1.007), <0.001	1.006 (1.004, 1.008), <0.001	1.005 (1.002, 1.008), 0.004
Time of the day of admission	8pm to <8am (night)	1.091 (0.994, 1.196), 0.066	1.037 (0.926, 1.163), 0.528	1.203 (1.010, 1.433), 0.038
	8am to <8pm (day)[a]			
Admission year**	Slope (2003–2008)	0.947 (0.895, 1.002), 0.057	0.996 (0.931, 1.066), 0.916	0.885 (0.810, 0.968), 0.008
	Slope (2009–2015)	1.044 (1.009, 1.079), 0.012	1.038 (0.998, 1.081), 0.065	1.016 (0.953, 1.082), 0.632
Care pathway variables				
Hospital volume (OHCA cases per year)	0–10 cases	1.033 (0.723, 1.474), 0.860	1.229 (0.904, 1.670), 0.189	0.688 (0.386, 1.229), 0.207
	11–24 cases	1.259 (0.877, 1.808), 0.211	1.242 (0.926, 1.667), 0.148	0.948 (0.534, 1.681), 0.854
	25 to 82 cases[a]			
Hospital pPCI capability	pPCI capable pPCI incapable[a]	1.262 (1.043, 1.527), 0.017	1.584 (1.261, 1.989), <0.001	0.849 (0.605, 1.190), 0.342
EMS response time (Mins)**		0.999 (0.995, 1.004), 0.776	1.000 (0.995, 1.005), 0.996	0.997 (0.987, 1.007), 0.589
EMS travel distance (Km)**		0.994 (0.989, 0.999), 0.024	0.992 (0.986, 0.998), 0.012	0.997 (0.987, 1.008), 0.612
Admitting consultant	Cardiologist	0.725 (0.641, 0.822), <0.001	0.794 (0.680, 0.927), 0.003	0.615 (0.494, 0.766), <0.001
	Other consultant[a]			
Admission ward	Intensive therapy unit	3.741 (3.331, 4.202), <0.001	3.267 (2.852, 3.742), <0.001	5.239 (4.107, 6.685), <0.001
	Died in ED	Not estimable	Not estimable	Not estimable
	General ward or other	3.452 (2.941, 4.051), <0.001	3.549 (2.884, 4.368), <0.001	3.575 (2.642, 4.838), <0.001
	Cardiac ward – non CCU	1.212 (0.841, 1.748), 0.302	1.148 (0.728, 1.810), 0.552	1.588 (0.861, 2.929), 0.138
	CCU[a]			
Place where ECG performed	In hospital	1.125 (0.970, 1.304), 0.120	1.127 (0.956, 1.329), 0.154	1.088 (0.878, 1.348), 0.439
	Pre hospitala[a]			
Reperfusion treatment and timing	Thrombolysis (early)	0.672 (0.523, 0.863), 0.002	0.714 (0.550, 0.926), 0.011	0.501 (0.121, 2.071), 0.340
	Thrombolysis (late)	0.860 (0.723, 1.023), 0.088	0.893 (0.741, 1.075), 0.231	0.939 (0.480, 1.837), 0.854
	Thrombolysis (time missing)	0.954 (0.702, 1.298), 0.766	0.940 (0.672, 1.315), 0.717	1.248 (0.500, 3.117), 0.635
	pPCI (early)	0.704 (0.600, 0.826), <0.001	0.618 (0.518, 0.737), <0.001	0.802 (0.430, 1.498), 0.490
	pPCI (late)	0.941 (0.773, 1.145), 0.542	0.836 (0.675, 1.035), 0.100	0.967 (0.479, 1.952), 0.926
	pPCI (time missing)	0.690 (0.532, 0.893), 0.005	0.610 (0.463, 0.802), <0.001	1.496 (0.593, 3.773), 0.393
	None[a]			
Random Effects estimate (R squared, Akaike Information Criterion)		0.215[b] (0.361[b], 14134[b])	0.118[b] (0.354[b], 9471[b])	0.378[b] (0.365[b], 4133[b])

CABG- Coronary Artery Bypass Graft; CCU- Cardiac Care Unit; COPD- Chronic Obstructive Pulmonary Disease; ECG- Electrocardiogram; ED- Emergency Department; EMS- Emergency Medical Service; LBBB- Left Bundle Branch Block; MI- Myocardial Infraction; OHCA- Out-of-Hospital Cardiac Arrest; (p)PCI- (primary) Percutaneous Coronary Intervention; PEA- Pulseless Electrical Activity; VF- Ventricular Fibrillation; VT- Ventricular Tachycardia.

* Values describe odds ratio (95% confidence interval), p value unless stated.

** Per whole unit increase.

*** Estimates on the logarithmic scale.

[a] Reference category (Medical History variables compared with absence of condition).

[b] Median from 25 datasets.

Admission to pPCI hospital was associated with higher mortality in STEMI (OR 1.58, 95% CI 1.26–1.99) but not in NSTEACS (OR 0.85, 95% CI 0.61–1.19) patients. Reperfusion therapy was associated with lower mortality in STEMI patients, but not in NSTEACS patients (e.g. early pPCI STEMI OR 0.62, 95% CI 0.52–0.74; NSTEACS OR 0.80, 95% CI 0.43–1.50). Compared to daytime, overnight admission was associated with higher mortality in the NSTEACS (OR 1.20, 95% CI 1.01–1.43), but not the STEMI (OR 1.04, 95% CI 0.93–1.16) group.

Sensitivity analyses

Sensitivity analyses for the complete case (n = 2284, 13.0%), 2003–2008 (n = 6075, 34.5%), and 2009–2015 (n = 11,529, 65.5%) cohorts, explained a similar degree of variation to the primary analysis (Supplementary Data Table S4). Findings of these analyses were generally consistent with the primary analysis, albeit confidence intervals were typically wider. Point estimates for most reperfusion treatments in the complete case cohort indicated higher mortality, which may reflect a selection bias inasmuch as a complete dataset is likely easier to collect in patients that die.

Discussion

In this analysis of 17,604 OHCA patients with ACS, admitted alive to 239 UK hospitals, just under three in ten died in hospital. Across the 94 hospitals contributing at least 60 cases, we identified wide variation in inter-hospital mortality. Modelling explained approximately one third of this variation. Over the 12-year study period, we observed changes in clinical practice, including increased admission of patients to pPCI capable hospitals and high-volume OHCA hospitals, and increased use of reperfusion treatment. The key modifiable factor associated with lower hospital mortality in STEMI patients was early reperfusion treatment.

Previous studies of OHCA have been inconsistent as to the association between hospital facilities, OHCA volume and outcome, which may be partly reflect variability in how these concepts are defined across the literature [15–18]. In contrast to the findings of a recent analysis of the American Cardiac Arrest Registry to Enhance Survival dataset, we unexpectedly observed an association between admission to a pPCI capable hospital and higher mortality [19]. This finding may be partly explained by case-mix differences between patients treated in pPCI and non-pPCI capable hospitals. In particular, a higher proportion of patients in cardiogenic shock were admitted to pPCI capable hospitals, although the degree of missingness within this variable precluded its imputation and modelling.

The decisions by paramedics as to the most appropriate hospital to which to transfer a patient for ongoing treatment may be influenced by patient condition, hospital facilities, patient preference, local care pathways, and transfer time. Increased transfer time may increase the risk of clinical adverse events, but, in keeping with previous studies, we observed no harm associated with increasing transport distance [15,20].

In line with previous ACS studies, we observed an association between increasing admission blood glucose and higher mortality [21,22]. Active management of hyperglycaemia in ACS has been associated with improved outcome [23], and is recommended in international guidelines [24,25]. Our study did not analyse the medical management of hyperglycaemia, but our findings highlight a need for further research on this potentially modifiable clinical parameter.

Our findings indicate the widespread implementation of evidence-based guidelines for the immediate management of myocardial infarction following OHCA [24,25]. Most STEMI patients (81.7%) and some NSTEACS patients (9.9%) received reperfusion therapy. In keeping with clinical trial data, early reperfusion treatment was associated with lower mortality in STEMI patients [26,27].

We used the MINAP dataset to analyse outcomes in OHCA due to ACS. The key advantages to this dataset are national coverage and longevity. For the purpose of this study, its key limitation was that it does not capture key variables relevant to OHCA such as location (public v private) and bystander CPR. Future studies may consider enriching MINAP data through linkage with other relevant UK datasets, such as the OHCA outcomes project and intensive care case mix programme [2,28]. The OHCA outcomes project could provide key data on OHCA characteristics, but was established only in 2013 thereby limiting the opportunity for linkage. The intensive care case mix programme was established in the 1990s, but only approximately one in three patients in this study was admitted to the intensive care unit and the case mix programme does not directly collect provision of targeted temperature management although this may be derived from other variables [29].

Our study has the limitations inherent in all observational studies. In particular, despite its large size and use of complex statistical analyses, our findings may be affected by unmeasured residual confounders. A key challenge in analysing audit datasets such as MINAP is the management of missing data [13]. Whilst we used sophisticated techniques to impute data, the degree of missingness in some important variables, such as Killip class, precluded this approach. Finally, there is known inter-hospital variation in methods used to identify patients for reporting to MINAP, particularly in NSTEACS patients, which may lead to selection bias [11].

Conclusions

This large cohort study of patients with OHCA due to ACS found evidence of marked variation in mortality between hospitals, which was not fully explained by modelled patient and health service factors. Whilst we observed no association between cardiac arrest centre characteristics (volume, pPCI capability) and lower mortality, the early use of reperfusion treatment, which is likely to be available only in such centres, was associated with lower mortality in STEMI patients.

Funding

This project was funded by the National Institute for Health Research HS&DR programme (project number 11/2004/30).

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the National Institute for Health Research HS&DR programme, NIHR, NHS or the Department of Health. The funder had no involvement in: study design; collection, analysis, and interpretation of data; writing of the manuscript; or the decision to submit the manuscript for publication.

Conflict of interest

KC, PKK, CPG, TQ, IBS, AM, JJMB, MWC, GDP report research grants from the NIHR. KC is supported as an NIHR Post-Doctoral Research Fellow. GDP and TQ are members of the NHS England Community Resuscitation Group and contributed to the national OHCA framework. GDP is an NIHR senior investigator, director of the national OHCA registry (funded by British Heart Foundation and Resuscitation Council (UK)), is a panel member of NIHR HSDR, and is editor of Resuscitation journal. Bob Ewings and JL report personal fees from the NIHR for time spent as study PPI representatives.

Acknowledgements

We acknowledge the support of Professor John Deanfield and Dr Mark de Belder of NICOR during the course of this research. We would also like to thank Dr Marlous Hall and Dr Paul Norman of the University of Leeds for specialist advice on data analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.01.011.

References

[1]. Gräsner J-T, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, et al. EuReCa ONE—27 nations, ONE, Europe, ONE registry. Resuscitation 2016;105:188–95.
[2]. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation 2017;110:133–40.
[3]. Carr BG, Kahn JM, Merchant RM, Kramer AA, Neumar RW. Inter-hospital variability in post-cardiac arrest mortality. Resuscitation 2009;80:30–4.
[4]. Finn JC, Bhanji F, Lockey A, Monsieurs K, Frengley R, Iwami T, et al. Part 8: education, implementation, and teams: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 2015;95:e203–24.
[5]. OHCA steering group. Resuscitation to recovery: a national framework to improve care of people with out-of-hospital cardiac arrest (OHCA) in England; 2017 (Accessed 31 July 2017 at https://www.resus.org.uk/EasySiteWeb/GatewayLink.aspx?alId=20609).
[6]. Pickering A, Cooper K, Harnan S, Sutton A, Mason S, Nicholl J. Impact of prehospital transfer strategies in major trauma and head injury: systematic review, meta-analysis, and recommendations for study design. J Trauma Acute Care Surg 2015;78:164–77.
[7]. Pickering A, Harnan S, Cooper K, Sutton A, Mason S, Nicholl J. Acute ischaemic stroke patients – direct admission to a specialist centre or initial treatment in a local hospital? A systematic review. J Health Serv Res Policy 2016;21:51–60.
[8]. Birkhead JS. Responding to the requirements of the National Service Framework for coronary disease: a core data set for myocardial infarction. Heart 2000;84:116–7.
[9]. Banning AP, Baumbach A, Blackman D, Curzen N, Devadathan S, Fraser D, et al. Percutaneous coronary intervention in the UK: recommendations for good practice. Heart 2015;101:1–13.
[10]. Department of Health. National service framework for coronary heart disease. London: Department of Health; 2000.
[11]. Myocardial Ischaemia National Audit Project. Myocardial Ischaemia National Audit Project: annual public report: april 2013–march 2014; 2014 (Accessed 31 July 2017 at http://www.ucl.ac.uk/nicor/audits/minap/documents/annual_reports/minap-public-report-2014).
[12]. Buuren S. Mice: multivariate imputation by chained equations in R. J Stat Software 2011;45:1–67.
[13]. Cattle BA, Baxter PD, Greenwood DC, Gale CP, West RM. Multiple imputation for completion of a national clinical audit dataset. Stat Med 2011;30:2736–53.
[14]. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
[15]. Tranberg T, Lippert FK, Christensen EF, Stengaard C, Hjort J, Lassen JF, et al. Distance to invasive heart centre, performance of acute coronary angiography, and angioplasty and associated outcome in out-of-hospital cardiac arrest: a nationwide study. Eur Heart J 2017;38:1645–52.
[16]. Chocron R, Bougouin W, Beganton F, Juvin P, Loeb T, Adnet F, et al. Are characteristics of hospitals associated with outcome after cardiac arrest? Insights from the Great Paris registry. Resuscitation 2017;118:63–9.
[17]. Cudnik MT, Sasson C, Rea TD, Sayre MR, Zhang J, Bobrow BJ, et al. Increasing hospital volume is not associated with improved survival in out of hospital cardiac arrest of cardiac etiology. Resuscitation 2012;83:862–8.
[18]. Schober A, Sterz F, Laggner AN, Poppe M, Sulzgruber P, Lobmeyr E, 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.
[19]. Kragholm K, Malta Hansen C, Dupre ME, Xian Y, Strauss B, Tyson C, et al. Direct transport to a percutaneous cardiac intervention center and outcomes in patients with out-of-hospital cardiac arrest. Circ. Cardiovasc. Qual. Outcomes 2017;10:e003414.
[20]. Geri G, Gilgan J, Wu W, Vijendira S, Ziegler C, Drennan IR, et al. Does transport time of out-of-hospital cardiac arrest patients matter? A systematic review and meta-analysis. Resuscitation 2017;115:96–101.
[21]. Svensson A-M, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005;26:1255–61.
[22]. Squire IB, Nelson CP, Ng LL, Jones DR, Woods KL, Lambert PC. Prognostic value of admission blood glucose concentration and diabetes diagnosis on survival after acute myocardial infarction: results from 4702 index cases in routine practice. Clin Sci 2010;118:527–35.
[23]. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65.
[24]. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.
[25]. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
[26]. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17, 187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–60.
[27]. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
[28]. Harrison D, Brady A, Rowan K. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the intensive care national audit & research centre case mix programme database. Crit Care 2004;9:S1–13.
[29]. Nolan JP, Ferrando P, Soar J, Benger J, Thomas M, Harrison DA, et al. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. Crit Care 2016;20:219.