Prognostic Implications of Level-of-Care at Tertiary Heart Centers Compared With Other Hospitals After Resuscitation From Out-of-Hospital Cardiac Arrest

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Background—Studies have found higher survival rates after out-of-hospital cardiac arrest and admission to tertiary heart centers. The aim was to examine the level-of-care at tertiary centers compared with nontertiary hospitals and the association with outcome after out-of-hospital cardiac arrest.

Methods and Results—Consecutive out-of-hospital cardiac arrest patients (n=1078) without ST-segment–elevation myocardial infarction admitted to tertiary centers (54%) and nontertiary hospitals (46%) were included (2002–2011). Patient charts were reviewed focusing on level-of-care and comorbidity. Survival to discharge differed significantly with 45% versus 24% of patients discharged alive (P<0.001), and after adjustment for prognostic factors admissions to tertiary centers were still associated with lower 30-day mortality (hazard ratio, 0.78 [0.64–0.96; P=0.02]), independent of comorbidity. The adjusted odds of predefined markers of level-of-care were higher in tertiary centers: admission to intensive care unit (odds ratio [OR], 1.8 [95% confidence interval, 1.2–2.5]), temporary pacemaker (OR, 6.4 [2.2–19]), vasoactive agents (OR, 1.5 [1.1–2.1]), acute (<24 hours) and late coronary angiography (OR, 10 [5.3–22] and 3.8 [2.5–5.7]), neurophysiological examination (OR, 1.8 [1.3–2.6]), and brain computed tomography (OR, 1.9 [1.4–2.6]), whereas no difference in therapeutic hypothermia was noted. Patients at tertiary centers were more often consulted by a cardiologist (OR, 8.6 [5.0–15]), had an echocardiography (OR, 2.8 [2.1–3.7]), and survivors more often had implantable cardioverter defibrillator’s implanted (OR, 2.1 [1.2–3.6]).

Conclusions—Admissions to tertiary centers were associated with significantly higher survival after out-of-hospital cardiac arrest in patients without ST-segment–elevation myocardial infarction in the Copenhagen area even after adjustment for prognostic factors including comorbidity. Level-of-care seems higher in tertiary centers both in the early phase, during the intensive care unit admission, and in the workup before discharge. The varying level-of-care may contribute to the survival difference; however, differences in comorbidity do not seem to matter significantly. (Circ Cardiovasc Qual Outcomes. 2015;8:268-276. DOI: 10.1161/CIRCOUTCOMES.115.001767.)

Key Words: cardiac arrest ■ health care ■ outcome assessment

Out-of-hospital cardiac arrest (OHCA) is still associated with a poor prognosis despite improvement in survival in recent years.1,2 In a previous study, we found a higher survival rate after OHCA and admission to tertiary heart centers compared with admission to nontertiary hospitals.3 The difference in survival has also been found in several other studies from different countries, which has not been explained by differences in prehospital circumstances only.4,9 In the recent advanced life support guidelines, postresuscitation care has been included in the chain-of-survival emphasizing the treatment and prevention of the metabolic and hemodynamic disturbances that often develop as part of postcardiac arrest syndrome.10,11

The reasons for the difference in survival in tertiary centers versus nontertiary hospitals are largely unknown and have only been speculative. The establishment of high-volume cardiac arrest centers with implementation of postresuscitation management protocols with targeted temperature management,
WHAT IS KNOWN

• Previous observational studies have found higher survival rates after successful resuscitation from out-of-hospital cardiac arrest with postresuscitation care performed at tertiary heart centers.
• However, the reasons for the survival differences have only been speculative.

WHAT THE STUDY ADDS

• The current study finds that admission to tertiary heart centers after out-of-hospital cardiac arrest was associated with a significantly higher survival rate in patients without ST-segment–elevation myocardial infarction even after adjustment for prognostic factors including prearrest comorbidity.
• Level-of-care seems higher in tertiary centers both in the early phase, during the intensive care unit admission, and in the workup before discharge.
• The varying level-of-care may contribute to the survival difference, but further investigation is required to better define which treatment patterns are most associated with survival.

focus on early revascularization, and specialized intensive care treatment may have contributed to the improved survival seen in recent years after OHCA.1,5,8,12–14 It is well known that high patient volume is associated with better outcome in various procedures and conditions, which has also been shown for patients with OHCA treated at high- versus low-volume intensive care unit (ICU).4,15 Baseline health status likely predicts outcome after OHCA, and previous studies reported that higher comorbidity burden was associated with a higher mortality after OHCA.15,17 We have previously suggested that the higher survival rate reported at tertiary centers may be caused by referral bias with patients presenting with a worse general health status admitted more often to nontertiary hospitals, however, this has not been thoroughly examined previously.1

In this study, we sought to investigate the previously found difference in survival in OHCA patients without ST-segment–elevation myocardial infarction (STEMI) depending on admission hospital in the Copenhagen area, and whether this difference is explained by differences in level-of-care and the association with outcome and neurological status.

Methods

Patients and Study Area

Consecutive patients with OHCA (≥18 years) were included in the study from June 2002 through 2011. OHCA of all causes with return of spontaneous circulation or ongoing cardiopulmonary resuscitation at hospital admission in the greater Copenhagen area treated by the Copenhagen emergency medical services (EMS) was included. Non-Danish residents were excluded because of unavailable outcome data. Patients were admitted to the nearest located hospital either 1 of the 2 tertiary university heart centers or at 1 of the 6 nontertiary university hospitals in the Copenhagen area. All patients with STEMI were referred directly to a tertiary heart center for primary coronary angiography (CAG) and were thus excluded to avoid referral bias.3 The STEMI diagnosis was based on review of patient charts, including CAGs and biomarkers. A single investigator comprehensively reviewed all individual patient charts with focus on in-hospital postresuscitation care.

The EMS in Copenhagen, the capital of Denmark, cover the Copenhagen area of 675 km² (260 mi²), which is inhabited by a total of 1.2 million people. An emergency ambulance with basic life support equipment and a defibrillator and a response unit in a separate vehicle staffed with a paramedic and an attending physician (anesthesiologist) comprise the EMS. The EMS are dispatched to all patients with assumed OHCA with the treatment protocol adherent to the advanced life support guidelines from the European Resuscitation Council.13,14 The attending physician used an Utstein registration sheet as documentation and entered the data into the OHCA database immediately after end of case.15–21

Predefined Markers of Level-of-Care

The 2 tertiary centers have their cardiothoracic facilities organized in heart centers with dedicated anesthesiologists, cardiologists, and surgeons. Interventional cardiology and cardiac surgery were performed 24 hours a day, 7 days a week, and the patients were subsequently treated in a cardiac ICU staffed by anesthesiologists and cardiologists. Therapeutic hypothermia (TH) was implemented during the study period from 2002 to 2004. Patients could be referred from nontertiary hospitals for acute CAG, temporary pacemaker, and implantation of an implantable cardioverter defibrillator (ICD) or other interventions at any time at the tertiary centers. In the present analysis, patients referred to a tertiary heart center after primary admission to a nontertiary hospital was defined as admitted to the nontertiary hospital, whereas the opposite never occurred.

Level-of-care parameters were collected by individual chart review, and data were collected with date and whether the procedure/treatment was performed. Parameters collected were (1) in the acute phase after OHCA: withdrawal of life sustaining therapy in the emergency department, whether the patient was admitted to an ICU and number of ICU admission days, (2) during the ICU admission: placement of temporary pacemaker, treatment with vasoactive agents (dopamine, norepinephrine, epinephrine, or dobutamine), TH (in patients with Glasgow Coma Scale Score ≤8 and cardiac pathogenesis), use of prophylactic antibiotics (in patients treated with TH), acute (<24 hours) CAG, neurophysiological examination (electroencephalography/somatosensory evoked potentials), computed tomography (CT) of the brain, hemodialysis, or continuous venovenous hemodiafiltration, and (3) the general workup before hospital discharge: whether the patient was consulted by a cardiologist during the hospital admission, late CAG, percutaneous coronary intervention, or coronary artery bypass grafting, whether echocardiography was performed, and implantation of an ICD in patients surviving to hospital discharge. In patients not surviving to hospital discharge, reasons for termination of active therapy was noted as documented by the attending physician in the patient chart (>1 reason could be noted).

Comorbidity

Using the personal identification number provided to all Danish residents, the OHCA cohort was linked to The Danish National Patient Registry, where diagnoses and surgical procedures from all national admissions are registered since 2002 and onwards.19–21 Based on the obtained data from the registry and from comorbidity data in the patient charts, the Charlson Comorbidity Index (CCI) was calculated. The index is a validated weighted index that takes the severity of 22 conditions into account and is commonly used to predict short-term mortality.21,24 Inter-registry reliability analyses showed moderate agreement between the registry data and the data from the patient charts with κregistry−patient = 0.56 (95% confidence interval [CI], 0.52–0.59) for the CCI. Based on the individual diseases in the index, the kappa values ranged from 0.15 for dementia (highest in the chart review) to 0.64 for cerebrovascular disease. Validation of patient chart review was performed in 30 patients by a second investigator blinded to previous assessment. For comorbidity data (by CCI), interobserver reliability analysis showed fair agreement κregistry−patient = 0.69 (95% CI, 0.55–0.83).
Outcome
Survival to discharge and at 30 days after OHCA were the primary outcomes. Survival data were acquired from the Civil Registration Registry by the unique personal identification number, which holds vital status on all Danish citizens. Neurological outcome was assessed with the Cerebral Performance Category (CPC) scale for survivors at hospital discharge, and favorable neurological outcome was defined as CPC 1 or 2, nonfavorable as 3 to 4, and dead as CPC score 5. Validation was performed in 30 patients by a second investigator by review of patient charts and blinded to previous assessment. For neurological outcome at hospital discharge, interobserver reliability analysis showed complete agreement with \( \kappa_{\text{weighted}} = 1.0 \).

The regional ethics committee waived informed consent to the study with the reference number: H-2-2012-53, and the study was approved by the Danish Data Protection Agency.

Statistics
Continuous variables are presented as mean±SD for normally distributed data and as median and interquartile range for non-normally distributed data. Differences were analyzed with Student unpaired \( t \) test or Wilcoxon-signed rank test as appropriate. Categorical variables are presented as number (n), and percent and differences are analyzed with \( \chi^2 \) test.

Odds ratios (OR) and 95% CI were estimated by multivariable logistic estimating the odds of level-of-care parameters performed in tertiary heart centers. Mortality is presented as Kaplan–Meier curves, and differences are tested using log-rank test. Univariate and multivariable proportional hazard regression analysis (COX-regression) was performed estimating hazard ratios (HR) and 95% CI for 30-day mortality adjusting for potential confounders after checking for the underlying assumptions of proportionality and interactions. Calendar year was used to estimate the temporal trends during the study period, and differences were tested by the Mantel–Haenszel \( \chi^2 \) test (trend test). A landmark analysis was performed illustrating the survival rate in tertiary heart centers and nontertiary hospitals each day. Only patients alive on the current day were included in the analysis. All statistical analyses were performed in SAS Statistics version 9.3 (Cary, NC) with a level of significance defined as \( P<0.05 \).

Results
Patient Characteristics
A total of 1078 patients were included in the study with 54% of patients transported to a tertiary heart center and 46% to a nontertiary hospital (Figure 1). Each tertiary heart center treated 30+14 OHCA patients a year (plus the excluded STEMI with OHCA patients), whereas each nontertiary hospital treated 9+1 OHCA patients per year with no time trend in the percentage of patients admitted to tertiary heart centers compared with nontertiary hospitals (\( P_{\text{trend}}<0.8 \)). Patients admitted to tertiary centers were younger, were more frequently male, shockable rhythm, and OHCA in public were more common with no significant differences in bystander cardiopulmonary resuscitation or witnessed arrests (Table 1). Cardiac pathogenesis of the arrest was more common in patients admitted to tertiary centers, whereas no significant difference in time to return of spontaneous circulation, time to EMS arrival, or time to first defibrillation was noted. Prearrest comorbidity was significantly lower in patients admitted to tertiary centers with 35% versus 18% without any comorbidity and 28% versus 41% with a CCI≥3 compared with patients admitted to nontertiary hospitals (Table 1).

Predefined Markers of Level-of-Care
Markers of level-of-care were different in the acute phase, during the ICU admission, and in the general workup before hospital discharge (Table 2, left panel). The temporal trends in level-of-care parameters are shown in Figure in the Data Supplement. No time trends in withdrawal of active therapy in the emergency department or number of patients admitted to an ICU were found. During the ICU admission, the use of TH and vasoactive agents were found to increase during the study period in both tertiary centers from none to 55% for TH (\( P_{\text{trend}}<0.001 \)) and 40% to ≥80% for vasoactive agents (\( P_{\text{trend}}<0.001 \)), and in nontertiary hospitals from a few percent to ≥40% for TH (\( P_{\text{trend}}=0.007 \)) and from 30% to 60% for vasoactive agents (\( P_{\text{trend}}=0.001 \)). CT of the brain (from ≥30% to 50%, \( P_{\text{trend}}=0.01 \)), acute CAG (from a few percent to 24%, \( P_{\text{trend}}=0.04 \)), and neurophysiological examination (from ≥10% to 40%, \( P_{\text{trend}}=0.02 \)) were found to increase only in tertiary heart centers, whereas the number of TH patients treated with prophylactic antibiotics were found to increase

![Figure 1. Flowchart of included and excluded patients. CPR indicates cardiopulmonary resuscitation; and STEMI, ST-segment elevation myocardial infarction.](http://circoutcomes.ahajournals.org/)

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**Table 1.** Predefined Markers of Level-of-Care

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tertiary Centers</th>
<th>Nontertiary Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH</td>
<td>55%</td>
<td>40%</td>
</tr>
<tr>
<td>Vasoactive agents</td>
<td>≥80%</td>
<td>30% to 60%</td>
</tr>
<tr>
<td>CT of the brain</td>
<td>≥30% to 50%</td>
<td>24%</td>
</tr>
<tr>
<td>Acute CAG</td>
<td>&lt;10% to 40%</td>
<td>&lt;10% to 40%</td>
</tr>
<tr>
<td>Neurophysiological exam</td>
<td>&lt;10% to 40%</td>
<td>&lt;10% to 40%</td>
</tr>
</tbody>
</table>

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**Table 2.** Prearrest Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tertiary Centers</th>
<th>Nontertiary Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50%</td>
<td>≥50%</td>
</tr>
<tr>
<td>Sex: male</td>
<td>≥70%</td>
<td>&lt;70%</td>
</tr>
<tr>
<td>Shockable rhythm</td>
<td>≥80%</td>
<td>&lt;80%</td>
</tr>
<tr>
<td>OHCA in public</td>
<td>≥70%</td>
<td>&lt;70%</td>
</tr>
</tbody>
</table>

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**Figure 1.** Flowchart of included and excluded patients. CPR indicates cardiopulmonary resuscitation; and STEMI, ST-segment elevation myocardial infarction.
only in nontertiary hospitals from 60% to 90% \( (P_{\text{trend}}=0.005) \). In the general workup before hospital discharge, implantation of ICDs in patients surviving to hospital discharge was found to increase in both tertiary centers and nontertiary hospitals from 25% to 60% \( (P_{\text{trend}}=0.01) \) and from none to 30% \( (P_{\text{trend}}=0.04) \), respectively. In nontertiary hospitals, significantly more patients were consulted by a cardiologist from 50% to 80% \( (P_{\text{trend}}<0.001) \), and CAG from almost none to 2% \( (P_{\text{trend}}=0.07) \), circulatory treatment in 29% versus 12% \( (P_{\text{trend}}=0.007) \). During the ICU admission, the odds of being admitted to an ICU was 1.8 \( (95\% \text{ CI}, 1.3–2.5) \) for all patients and 1.9 \( (1.3–2.7) \) for patients with a GCS<9 at tertiary centers (Table 2). The ICU admission in patients surviving to hospital discharge was also significantly longer at tertiary heart centers 4 (interquartile range, 3–8) compared with 3 (1–6) days at nontertiary hospital \( (P=0.007) \). During the ICU admission, the odds of a temporary pacemaker (OR, 6.4 \([2.2–19]\)), treatment with vasoactive agents (OR, 1.5 \([1.1–2.1]\)), prophylactic antibiotics in patients treated with TH (OR, 5.3 \([2.7–11]\)), acute CAG (OR, 10 \([5.3–22]\)), neurophysiological examination (OR, 1.8 \([1.3–2.6]\)), and a CT of the brain (OR, 1.9 \([1.4–2.6]\)) were significantly more often performed in patients admitted to tertiary heart centers (Table 2). No differences in the odds of treatment with TH (OR, 1.1 \([0.7–1.5]\)) or hemodialysis (OR, 1.2 \([0.7–2.3]\)) were found. In the general workup before hospital discharge at tertiary centers, patients were significantly more often consulted by a cardiologist (OR, 8.6 \([5.0–15]\)), more often had a CAG (OR, 3.8 \([2.5–5.7]\)), an echocardiography (OR, 2.8 \([2.1–3.7]\)), and an ICDs were more often placed in survivors to hospital discharge (OR, 2.1 \([1.2–3.6]\)), however, no difference in the odds of a percutaneous coronary intervention or coronary artery bypass grafting was found (OR, 1.5 \([0.8–2.7]\); Table 2). The ICDs were placed 28±44 days after OHCA in patients admitted to tertiary centers compared with 23±18 days in patients admitted to nontertiary hospitals \( (P=0.5) \). In patients alive after day 5 after OHCA, similar odds ratios and significance levels were found despite in the odds of CT of the brain and electroencephalography, which is not significantly different in this subgroup of patients (Table 3).

### Survival

Survival to discharge was significantly higher in patients admitted to tertiary heart centers compared with nontertiary hospitals (45% versus 24%, \( P<0.001 \); Figure 1). A significant difference in survival was noted in the first days after OHCA depicted in the 1-week Kaplan–Meier curves (Figure 2A; \( p_{\text{trend}}<0.001 \)). Figure 2B shows the landmark analysis of survival in patients admitted to tertiary heart centers compared with nontertiary hospitals. The daily survival rate was significantly lower at nontertiary hospitals compared with tertiary heart centers during the first 5 days after OHCA, however, no difference was found on day 6 and 7 (Figure 2B). Of patients treated with TH and admitted to the ICU, 46 (16%) patients at the tertiary centers compared with 89 patients (46%) at nontertiary hospitals died during the first 96 hours (4 days; \( P<0.001 \)) with a median survival of 2 (interquartile range, 2–3) days for both groups of patients. The primary reasons for termination of active therapy in all patients not surviving to discharge were presumed anoxic brain injury (162 \([56\%]\) in tertiary centers versus 159 \([44\%]\) in nontertiary hospitals; \( P=0.002 \)), futile treatment in 88 \([29\%]\) versus 127 \([36\%]\; \( P=0.07 \)), circulatory failure in 115 \([40\%]\) versus 126 \([35\%]\; \( P=0.2 \)), and organ failure in 44 \([15\%]\) versus 28 \([8\%]\) of patients \( P=0.003 \).

Table 1. Demographic and Prehospital Data for Patients Having OHCA Admitted to Tertiary Heart Centers Versus Nontertiary Hospitals

<table>
<thead>
<tr>
<th>Tertiary Heart Centers, n=586 (54%)</th>
<th>Nontertiary Hospitals, n=492 (46%)</th>
<th>Differences (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 433 (74%)</td>
<td>303 (62%)</td>
<td>12% (7–18)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men 62±15</td>
<td>66±14</td>
<td></td>
</tr>
<tr>
<td>Women 65±16</td>
<td>71±14</td>
<td></td>
</tr>
<tr>
<td>OHCA in public</td>
<td>265 (46%)</td>
<td>23% (17–28)</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>484 (86%)</td>
<td>4% (1–7)</td>
</tr>
<tr>
<td>EMS-witnessed arrest</td>
<td>20 (5%)</td>
<td>−2% (−4, 1)</td>
</tr>
<tr>
<td>Ongoing CPR</td>
<td>307 (56%)</td>
<td>6% (1–13)</td>
</tr>
<tr>
<td>Alarm to DC, min</td>
<td>6 (4–9)</td>
<td></td>
</tr>
<tr>
<td>Time to ROSC, min</td>
<td>19 (9–22)</td>
<td></td>
</tr>
<tr>
<td>Primary rhythm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF/pVT</td>
<td>325 (55%)</td>
<td>25% (20–31)</td>
</tr>
<tr>
<td>Asystole</td>
<td>108 (18%)</td>
<td>−12% (−17, −7)</td>
</tr>
<tr>
<td>PEA</td>
<td>114 (19%)</td>
<td>−7% (−12, −1)</td>
</tr>
<tr>
<td>Other</td>
<td>39 (7%)</td>
<td>−7% (−11, −3)</td>
</tr>
<tr>
<td>Time of arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime (8 AM–4 PM)</td>
<td>281 (48%)</td>
<td>−2% (−8, 4)</td>
</tr>
<tr>
<td>Evening (4 PM–00 AM)</td>
<td>234 (40%)</td>
<td>−4% (−8, 4)</td>
</tr>
<tr>
<td>Night-time (00–8 AM)</td>
<td>71 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac pathogenesis</td>
<td>471 (81%)</td>
<td>12% (7–18)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>205 (35%)</td>
<td>17% (12–22)</td>
</tr>
<tr>
<td>1</td>
<td>122 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>95 (16%)</td>
<td>−3% (−8, 1)</td>
</tr>
<tr>
<td>≥3</td>
<td>161 (28%)</td>
<td>−13% (−19, −8)</td>
</tr>
<tr>
<td>GCS at hospital arrival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>481 (82%)</td>
<td>7% (2–12)</td>
</tr>
<tr>
<td>4–8</td>
<td>58 (10%)</td>
<td>−7% (−3, −11)</td>
</tr>
<tr>
<td>9–14</td>
<td>15 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>32 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**CPR indicates cardiopulmonary resuscitation; DC, defibrillation; EMS, emergency medical services; GCS, Glasgow Coma Scale Score; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electric activity; pVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; and VF, ventricular fibrillation.**
The number of patients with CCI≥3 increased significantly during the study period in patients admitted to tertiary centers from ∼20% to 30% (P trend=0.03) and nontertiary hospitals from ∼30% to >50% (P trend<0.001; Figure 3). The survival to discharge rate was constant during the study period at 45% in patients admitted to tertiary heart centers (P trend=0.99), whereas it was found to increase from 15% to almost 30% in patients admitted to nontertiary hospitals (P trend=0.006; Figure 3). After adjustment for known prognostic factors, including CCI, admission to a tertiary center was associated with lower 30-day mortality (HR, 0.78 [0.64–0.96]; P=0.02) independent of CCI (Table 4).

Neurological Status

Prearrest neurological function was more favorable in patients admitted to tertiary centers compared with patients admitted to nontertiary hospitals with 3% (n=18) versus 9% (n=43) of admitted patients with a nonfavorable neurological function (CPC 3 or 4) before OHCA (P<0.001). In patients surviving to discharge from tertiary centers compared with nontertiary hospitals, no difference in neurological status was found with 84% (n=218) versus 83% (n=96) being discharged with a favorable neurological outcome (P=0.5) with no difference during the study period (P trend=0.6 and P trend=1.0, respectively). Fewer patients were discharged to nursing home from a tertiary center (8% versus 16%, P<0.04), whereas no significant difference was found in the number of patients discharged to neurorehabilitation (17% versus 15%; P=0.5) or to home as final destination (88% versus 79%, P=0.06) in tertiary centers versus nontertiary hospitals.

Discussion

In this cohort study of 1078 OHCA-patients without STEMI in the Copenhagen area, a significant difference in survival depending on type of admission hospital was noted. Survival to hospital discharge was 45% in patients admitted to tertiary heart centers compared with 24% in patients admitted to nontertiary hospitals. The difference in survival was significant during the first 5 days of admission after which no difference was found. Markers of level-of-care were significantly more frequent in tertiary centers both in the acute phase after OHCA, during the ICU admission, and in the general workup before discharge. Prearrest comorbidity was significantly lower in patients admitted to tertiary centers; however, after adjustment for known prognostic factors, admissions at tertiary centers were still associated with better survival independent of the

Table 2. Level-of-Care Parameters in All Patients After OHCA Admitted to Either Tertiary Heart Centers or Nontertiary Hospitals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tertiary Centers, n=586</th>
<th>Nontertiary Hospitals, n=492</th>
<th>Multivariable* (Admission to Tertiary Centers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>OR adjusted (95% CI)</td>
</tr>
<tr>
<td>Acute phase after OHCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WLST in emergency department</td>
<td>67 (11)</td>
<td>82 (17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Admission ICU</td>
<td>478 (82)</td>
<td>334 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>During ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporary pacemaker</td>
<td>31 (5)</td>
<td>4 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasoactive agents†</td>
<td>351 (73)</td>
<td>207 (62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapeutic hypothermia‡</td>
<td>242 (64)</td>
<td>147 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prophylactic antibiotics§</td>
<td>260 (95)</td>
<td>143 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary angiography, &lt;24 h</td>
<td>115 (20)</td>
<td>8 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EEG/SSEP</td>
<td>118 (20)</td>
<td>56 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT of the brain</td>
<td>243 (41)</td>
<td>122 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVVHD/hemodialysis</td>
<td>32 (5)</td>
<td>19 (4)</td>
<td>0.2</td>
</tr>
<tr>
<td>General workup before discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consulted by a cardiologist</td>
<td>563 (97)</td>
<td>262 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>207 (35)</td>
<td>39 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>80 (12)</td>
<td>19 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiography performed</td>
<td>412 (70)</td>
<td>188 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICD (in patients surviving to discharge)</td>
<td>137 (52)</td>
<td>30 (26)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression analysis with adjustment for age, sex, public arrest, shockable rhythm, cardiac pathogenesis, Charlson Comorbidity Index, and admission to tertiary centers.
†Dopamine, norepinephrine, epinephrine, or dobutamine in patients admitted to the ICU.
‡Therapeutic hypothermia in patients with GCS ≤8 and cardiac pathogenesis (implemented during 2002–2004).
§Prophylactic antibiotics in patients admitted to the ICU and treated with therapeutic hypothermia.
difference in the comorbidity burden. The difference in survival may therefore be attributed to differences in inhospital level-of-care after OHCA, whereas differences in comorbidity do not seem to matter significantly.

Several previous studies have found a higher survival rate depending on admission hospital characteristics compared with other hospitals after admission for OHCA, however, the reasons have only been speculated. In this study, the survival rate was significantly higher in the first 5 days after OHCA in patients admitted to tertiary centers, and whether this was because of differences in patient characteristics, referral bias, differences in level-of-care, in criteria for withdrawal of active treatment, or if the treatment strategy was more aggressive at the tertiary heart centers can only be speculated. However, the difference in survival was no longer statistically significant after the fifth day of hospital admission. Active therapy was significantly more often withdrawn in tertiary hospitals, however, after adjustment for prognostic factors, no difference was found. Current guidelines recommend that prognostication in patients treated with TH are not performed until >72 hours after rewarming because of residual effects of the sedatives and the cooling. In the current study, we found that 16% versus 46% of patients treated with TH died before 72 hours after rewarming (96 hours from OHCA) from TH in tertiary centers compared with nontertiary hospitals, which may be because of a too early prognostication or resignation of therapy in the nontertiary hospitals.

Postresuscitation care was included in the chain-of-survival described in the most recent advanced life support guidelines, emphasizing the importance of optimizing vital organ perfusion and limiting organ damage by preventing the metabolic and hemodynamic disturbances that often develop as a postcardiac arrest syndrome. Implementation of standardized postresuscitation treatment protocols and establishment of high-volume cardiac arrest centers have been shown to improve survival after OHCA. Treatments, such as mild TH, focus on early revascularization, and specialized intensive care treatment, may therefore have contributed to the improved survival seen in recent years after OHCA.

In this study, the odds of admission to an ICU was almost double at tertiary centers, however, TH was after adjustment for prognostic factors applied equally in tertiary heart centers compared with nontertiary hospitals. The use of vasoactive agents, the recommended prophylactic antibiotics, and both temporary pacemakers, CT of the brain, neurophysiological prognostication, and CAGs were more often performed in tertiary centers. The workup before discharge was also significantly different.

Table 3. Level-of-Care Parameters in Patients Surviving After Day 5 After OHCA Admitted to Either Tertiary Heart Centers or Nontertiary Hospitals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tertiary Centers, n=360</th>
<th>Nontertiary Hospitals, n=174</th>
<th>PValue</th>
<th>OR adjusted (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission ICU</td>
<td>328 (91)</td>
<td>142 (82)</td>
<td>0.006</td>
<td>2.2 (1.3–4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporary pacemaker</td>
<td>23 (6)</td>
<td>4 (2)</td>
<td>0.02</td>
<td>3.2 (1.0–9.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Vasoactive agents</td>
<td>243 (74)</td>
<td>79 (56)</td>
<td>&lt;0.001</td>
<td>2.0 (1.3–3.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>187 (85)</td>
<td>73 (73)</td>
<td>0.02</td>
<td>1.1 (0.5–2.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>209 (99)</td>
<td>80 (87)</td>
<td>&lt;0.001</td>
<td>15 (3.1–74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary angiography, &lt;24 h</td>
<td>93 (26)</td>
<td>6 (3)</td>
<td>&lt;0.001</td>
<td>7.6 (3.2–18.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EEG/SSEP</td>
<td>82 (23)</td>
<td>30 (17)</td>
<td>0.1</td>
<td>1.5 (0.9–2.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>CT of the brain</td>
<td>159 (44)</td>
<td>67 (39)</td>
<td>0.2</td>
<td>1.3 (0.8–1.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>CVVHD/hemodialysis</td>
<td>20 (6)</td>
<td>12 (7)</td>
<td>0.5</td>
<td>0.8 (0.4–1.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Consulted by a cardiologist</td>
<td>353 (99)</td>
<td>125 (91)</td>
<td>0.002</td>
<td>5.7 (1.7–19)</td>
<td>0.004</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>185 (51)</td>
<td>37 (21)</td>
<td>&lt;0.001</td>
<td>2.7 (1.7–4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>70 (19)</td>
<td>19 (11)</td>
<td>0.007</td>
<td>1.2 (0.6–2.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Echocardiography performed</td>
<td>297 (83)</td>
<td>102 (59)</td>
<td>&lt;0.001</td>
<td>2.7 (1.7–4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICD (in patients surviving to discharge)</td>
<td>137 (52)</td>
<td>30 (26)</td>
<td>&lt;0.001</td>
<td>2.1 (1.2–3.6)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Multivariable analyses predicting the odds of a specific level-of-care parameter to be performed depending on admission hospital. CABG indicates coronary artery bypass grafting; CI, confidence interval; CT, computed tomography; CVVHD, continuous venovenous hemodiafiltration; EEG, electroencephalography; GCS, Glasgow Coma Scale Score; ICD, implantable cardioverter defibrillator; ICU: intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; SSEP, somatosensory evoked potentials; and WLST, withdrawal of life sustaining therapy.

*Multivariable logistic regression analysis with adjustment for age, gender, public arrest, shockable rhythm, cardiac etiology, Charlson Comorbidity Index and admission to tertiary centers.
†Dopamine, norepinephrine, epinephrine, or dobutamine in patients admitted to the ICU.
‡Therapeutic hypothermia in patients with GCS ≤ 8 and cardiac etiology (implemented during 2002–2004).
§In patients admitted to the ICU and treated with therapeutic hypothermia.
with the odds of consultation by a cardiologist of almost 9,
an echocardiography of 3, and ICD placement in survivors
to discharge of 2× the odds compared with nontertiary hospitals.
Importantly patients admitted to nontertiary hospitals
could at any time be transferred for ICU treatment or cardiac
workup in the tertiary heart centers, and during the study
period a significant increase in transfer to tertiary centers for
CAG, percutaneous coronary intervention/coronary artery
bypass grafting, and ICD placement from nontertiary hospitals
were noted (Figure in the Data Supplement). Likewise
more patients were consulted by a cardiologist, had an echo-
cardiography, were treated with TH, with vasoactive agents,
and prophylactic antibiotics at the nontertiary hospitals dur-
ing the study period. The increase in level-of-care parameters
during the study period may have contributed to the increased
survival seen at nontertiary hospitals.

High patient volume has, in various procedures and condi-
tions, been associated with better outcome including OHCA
patients treated at high-volume ICUs.4,15 In the current study,
a significant difference in the number of patients with OHCA
were treated at each tertiary centers (average 30 patients per
year) compared with each nontertiary hospitals (average 9
patients per year). In addition, the experience from inhospital
cardiac arrests and referral of STEMI patients must be added,
which has not been included in the numbers mentioned above.

The general western population is aging and more people
live with ≥1 chronic diseases, such as cardiovascular disease,
cancer, diabetes mellitus, and respiratory-, kidney-, or liver-
disease, which may be attributed to a better control of the dis-
eases in recent years.31 In this study, we likewise found an
increasing comorbidity burden during the study period with
more than a third of the OHCA patients with a high comorbid-
ity burden (CCI ≥3) in 2011. The overall survival after OHCA
was despite increasing comorbidity burden found to increase
during the study period. Admissions to tertiary heart centers
were associated with a higher survival independent of the dif-
ferences in the comorbidity burden. Interestingly, no increase
in survival at tertiary centers during the study period was
found. Importantly, the goal with cerebral, circulatory, hemody-
amic, and systemic resuscitation is to return people to a
prearrest functional level for a sustained period of time.32 In
this study, we found that >80% of patients were discharged
with a favorable neurological outcome with no difference in
patients discharged from tertiary heart centers compared with
nontertiary hospitals, despite a higher survival rate at tertiary
centers.

Whether the intensity of care with a higher level-of-care
at the tertiary centers contributes to a higher survival rate or

![Figure 2](http://circoutcomes.ahajournals.org/)

**Figure 2.** A, One-week Kaplan–Meier mortality plot in patients admitted to tertiary heart centers compared with nontertiary hospitals. B, Landmark analysis of the time-dependent mortality per day since out-of-hospital cardiac arrest and differences in mortality in tertiary heart centers compared with nontertiary hospitals.

![Figure 3](http://circoutcomes.ahajournals.org/)

**Figure 3.** Temporal trends in overall survival to discharge, and comorbidity according to Charlson Comorbidity Index ≥3 in patients admitted to tertiary heart centers and nontertiary hospitals. OHCA indicates out-of-hospital cardiac arrest.
Table 4. Univariate and Multivariable Predictors of 30-Day Mortality for Successfully Resuscitated Patients (ROSC or Ongoing CPR at Hospital Arrival) Having OHCA

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate HR (95% CI)</th>
<th>Multivariable HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary heart centers</td>
<td>0.55 (0.48–0.64)</td>
<td>0.78 (0.64–0.96)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>1.20 (0.96–1.50)</td>
<td>0.84 (0.61–1.16)</td>
</tr>
<tr>
<td>2</td>
<td>1.25 (0.99–1.59)</td>
<td>0.90 (0.65–1.26)</td>
</tr>
<tr>
<td>≥3</td>
<td>1.58 (1.30–1.93)</td>
<td>1.11 (0.84–1.47)</td>
</tr>
<tr>
<td>Age at arrest per 5 y</td>
<td>1.10 (1.07–1.23)</td>
<td>1.10 (1.06–1.14)</td>
</tr>
<tr>
<td>Sex, men</td>
<td>0.68 (0.59–0.80)</td>
<td>1.08 (0.87–1.33)</td>
</tr>
<tr>
<td>Shockable primary rhythm</td>
<td>0.42 (0.36–0.49)</td>
<td>0.41 (0.32–0.53)</td>
</tr>
<tr>
<td>Witnessed cardiac arrest</td>
<td>0.86 (0.70–1.05)</td>
<td>0.90 (0.69–1.17)</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>0.62 (0.53–0.73)</td>
<td>0.70 (0.57–0.86)</td>
</tr>
<tr>
<td>OHCA in public</td>
<td>0.50 (0.42–0.60)</td>
<td>0.70 (0.55–0.89)</td>
</tr>
<tr>
<td>Time to ROSC per 5 min</td>
<td>1.07 (1.03–1.11)</td>
<td>1.11 (1.07–1.16)</td>
</tr>
<tr>
<td>Cardiac pathogenesis</td>
<td>0.75 (0.64–0.89)</td>
<td>1.00 (0.79–1.26)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CPR, cardiopulmonary resuscitation; HR, hazard ratio; OHCA, out-of-hospital cardiac arrest; and ROSC, return of spontaneous circulation.

the higher survival rate during the first days after OHCA provides an opportunity for a greater intensity of care is unknown because the current observational study only provides association and not causalities. Further studies are needed to understand and reduce the difference in survival after OHCA and admission to hospitals with different levels of care, and whether overall survival increases if resuscitated OHCA patients are admitted to tertiary heart centers for postresuscitation care is another important research question.

This study is limited in its nonrandomized retrospective design; however, the cohort is prospectively and consecutively collected by the EMS physicians. Missing data are limited in the study with up to a maximum of only 5% in selected variables—primarily the prehospital parameters. No data were available for the patients’ socioeconomic status before OHCA, which might bias the result as some hospitals in the region may have an uneven distribution of patients with a poor socioeconomic status compared with other hospitals. However, the Danish healthcare system is public and financed through general taxes, and admission to a tertiary center or a nontertiary hospital is determined by distance only—health insurance and socioeconomic status are not involved in the referral decision. The risk of residual unknown confounding could also have influenced the results, as some factors may not currently be able to be measured.

In conclusion, admissions to tertiary heart centers was associated with a higher survival rate specifically during the first 5 days after OHCA compared with admissions to nontertiary hospitals in patients suffering from all-cause OHCA except STEMI in the Copenhagen area. Even after adjustment for known prognostic factors, including age, sex, and comorbidity survival, was significantly higher after admission to tertiary centers independent of comorbidity. Level-of-care seems significantly higher in tertiary centers both in the acute phase after OHCA, during the ICU admission, and in the general workup before discharge. The difference in survival may thus be partly attributed to differences in inhospital level-of-care after OHCA, whereas comorbidity does not seem to matter significantly.

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We would like to thank the following for contributing to data collection at the 8 admission hospitals: Thomas Mohr at Copenhagen University Hospital Gentofte, Ager Ole Bendtsen at Glostrup Hospital, Tina Waldau at Herlev Hospital, Christian Lange at Amager Hospital, and Allan Kofod Enevoldsen at Frederiksberg Hospital.

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Disclosures

None.

References


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**Supplemental Material**

**Supplementary figure:** Temporal trends in level-of-care parameters stratified in the acute phase after OHCA, during the intensive care admission, and in the general workup before hospital discharge in **A:** Patients admitted to tertiary heart centers and **B:** Patients admitted to non-tertiary hospitals.

### A: TERTIARY HEART CENTRE

**Acute phase after OHCA**

- **WLSIT in ED**
  - 2002-2005: 80%
  - 2006-2009: 70%
  - 2010-2013: 60%
  - p = 0.44

- **Admission ICU**
  - 2002-2005: 70%
  - 2006-2009: 60%
  - 2010-2013: 50%
  - p = 0.71

### B: NON-TERTIARY HOSPITAL

**Acute phase after OHCA**

- **WLSIT in ED**
  - 2002-2005: 60%
  - 2006-2009: 50%
  - 2010-2013: 40%
  - p = 0.4

- **Admission ICU**
  - 2002-2005: 50%
  - 2006-2009: 40%
  - 2010-2013: 30%
  - p = 0.05

### During ICU-admission

- **Tnt**
  - 2002-2005: 50%
  - 2006-2009: 40%
  - 2010-2013: 30%
  - p = 0.003

- **Cardiac CT**
  - 2002-2005: 40%
  - 2006-2009: 30%
  - 2010-2013: 20%
  - p = 0.003

- **Acute CAG**
  - 2002-2005: 60%
  - 2006-2009: 50%
  - 2010-2013: 40%
  - p = 0.1

- **EEG/SEP**
  - 2002-2005: 30%
  - 2006-2009: 20%
  - 2010-2013: 10%
  - p = 0.002

- **Proph. Antibiotics**
  - 2002-2005: 50%
  - 2006-2009: 40%
  - 2010-2013: 30%
  - p = 0.005

- **Nerispan**
  - 2002-2005: 40%
  - 2006-2009: 30%
  - 2010-2013: 20%
  - p = 0.001

### General workup before discharge

- **Consulted by cardiologist**
  - 2002-2005: 60%
  - 2006-2009: 50%
  - 2010-2013: 40%
  - p = 0.003

- **CAG**
  - 2002-2005: 50%
  - 2006-2009: 40%
  - 2010-2013: 30%
  - p = 0.001

- **PCI / CAG**
  - 2002-2005: 40%
  - 2006-2009: 30%
  - 2010-2013: 20%
  - p = 0.01

- **Echocardiography**
  - 2002-2005: 30%
  - 2006-2009: 20%
  - 2010-2013: 10%
  - p = 0.001

- **CJD**
  - 2002-2005: 50%
  - 2006-2009: 40%
  - 2010-2013: 30%
  - p = 0.04

**Abbreviations:**