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ORIGINAL RESEARCH

Comorbidity and bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest

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ABSTRACT

Objective Cardiopulmonary resuscitation (CPR) performed before the arrival of emergency medical services (EMS) is associated with increased survival after out-of-hospital cardiac arrest (OHCA). The aim of this study was to determine whether patients who receive bystander CPR have a different comorbidity compared with patients who do not, and to determine the association between bystander CPR and 30-day survival when adjusting for such a possible difference.

Methods Patients with witnessed OHCA in the Swedish Registry for Cardiopulmonary Resuscitation between 2011 and 2015 were included, and merged with the National Patient Registry. The Charlson Comorbidity Index (CCI) was used to measure comorbidity. Multiple logistic regression was used to examine the effect of CCI on the association between bystander CPR and outcome.

Results In total, 11 955 patients with OHCA were included, 71% of whom received bystander CPR. Patients who received bystander CPR had somewhat lower comorbidity (CCI) than those who did not (mean±SD: 2.2±2.3 vs 2.5±2.4; $p<0.0001$). However, this difference in comorbidity had no influence on the association between bystander CPR and 30-day survival in a multivariable model including other possible confounders (OR 2.34 (95% CI 2.01 to 2.74) without adjustment for CCI and OR 2.32 (95% CI 1.98 to 2.71) with adjustment for CCI).

Conclusion Patients who undergo CPR before the arrival of EMS have a somewhat lower degree of comorbidity than those who do not. Taking this difference into account, bystander CPR is still associated with a marked increase in 30-day survival after OHCA.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) affects more than 350 000 people in Europe annually, and people who suffer from OHCA have a low chance of survival.^{1 2} Survival from OHCA depends on the effectiveness of the chain of survival, where each link in the chain is important.³ Studies have shown that when cardiopulmonary resuscitation (CPR) is started before the arrival of emergency medical services (EMS), the chance of survival increases.^{4–7} The survival effect of bystander CPR may be to prolong the duration of and thereby the shockable phase of ventricular fibrillation.^{8 9} One often neglected factor in patients who suffer from OHCA is previous comorbidities.¹⁰ In the pre-arrest phase there is often no time for the rescue team to obtain reliable information about the patient's

clinical history. This has been unfortunate, since even 25 years ago it was argued in terms like 'one could just hope that being found in asystole and not receiving bystander CPR is not explained by suffering from a terminal disease'.⁷ In theory, such a finding may influence the observed association between bystander CPR and survival. In the discussions about the association between bystander CPR and survival after OHCA, this dilemma has more or less been neglected. Studies have shown conflicting results regarding the association between comorbidity and survival.^{11 12} We recently reported that increasing comorbidity was associated with a decreased chance of 30-day survival after OHCA.¹³

In the present study, we studied patients who suffered a witnessed OHCA, in order to (1) determine whether those who receive CPR before the arrival of EMS exhibit different comorbidity features compared with patients who do not receive such treatment, and (2) determine the association between bystander CPR and 30-day survival when adjusting for such possible differences in comorbidities.

METHODS

Setting

Sweden has a population of 10 million, with a land area of more than 450 000 km².¹⁴ In cases of OHCA, all EMS systems have a two-tier response with basic life support as the first tier and advanced life support as the second tier. In addition to the ordinary EMS, some counties send out firefighters and/or police officers.

Data sources

The Swedish Registry for Cardiopulmonary Resuscitation (SRCR) is a national quality register which was initiated in 1990 and receives support from the Swedish Association of Local Authorities and Regions. More than 90% of all individuals who have suffered an OHCA in Sweden and in whom CPR was attempted by a bystander or EMS are reported to the registry. Thus, inclusion criteria for the registry are that CPR has been started either by health professionals in EMS or before the arrival of EMS by a bystander or by other dispatched units (firefighters and/or police officers). All EMS in Sweden report cases of OHCA to the registry prospectively using the Utstein-based template.¹⁵ The SRCR has been described elsewhere.¹⁶

The National Patient Registry (NPR) is run by the Swedish National Board of Health and Welfare.

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Arrhythmias and sudden death

The coverage has been nationwide since 1987. The NPR has data on diagnoses and surgical procedure codes from hospitals and specialist clinics. An evaluation of the NPR has shown that 85%–95% of all diagnoses are valid.¹⁷ Since 2001, the registry has also included outpatient visits from both private and public healthcare providers, but primary care is not covered by the NPR. All admissions (both inpatient and outpatient) are reported to the registry with International Classification of Diseases (ICD)-10 codes.¹⁷

Study design

We retrospectively analysed all cases of witnessed OHCA in patients who were ≥ 18 years of age from 2011 to 2015 in SRCR, and merged the data with comorbidity data from the NPR. Individuals with multiple OHCA during the study period were only included once (the first occasion). Patients without a personal identification number (ie, with an unknown ID or non-residents) were excluded, as were unwitnessed cases and cases that were witnessed only by the EMS crew. This research was done without patient involvement because of the registry-based design.

Definitions

We estimated comorbidity with the Charlson Comorbidity Index (CCI)¹⁸ using ICD-10 diagnoses from the NPR registered 5 years before the OHCA. The use of ICD-10 diagnosis for determination of CCI has previously been reported.¹⁹ Bystander CPR was defined as any CPR before arrival of EMS started by a witness (a bystander) or other dispatched units (firefighters and police) before the arrival of EMS.¹⁵

Outcome measures

The primary outcome was 30-day survival. The secondary outcome was any return of spontaneous circulation (ROSC) and ROSC at hospital admission.

Statistical analysis

Baseline characteristics are presented as number (percentage) for proportions and median (10th, 90th percentiles) for continuous variables. Due to the large number of subjects in our study, we used the (absolute) standardised difference to assess the balance of baseline characteristics between the two groups (table 1).²⁰ This measure is, in contrast to p values and hypothesis testing, independent of sample size and thus avoids detecting differences that are clinically meaningless. Values of at least 0.10 were considered to indicate a clinically relevant difference.

For the comorbid conditions constituting the CCI, as well as the CCI itself, though, we also presented—in addition to the standardised difference—p values, since one of the aims of the study was to compare comorbidity between the two groups. Fisher's exact test and Mann-Whitney U test were used for these comparisons.

Fisher's exact test was also used for the unadjusted comparison of outcomes.

For calculation of ORs with corresponding CIs regarding outcomes, both in univariable (unadjusted) and multivariable (adjusted) analyses, logistic regression was used. Baseline factors used as covariates in the adjusted analysis were age, sex, location and aetiology of the cardiac arrest and time from call for EMS to arrival of EMS at the scene(). We did not primarily adjust for initial rhythm since this is believed to be an effect of bystander CPR (ie, prolonged time in shockable

Table 1 Baseline characteristics of the patients in relation to whether bystander CPR was performed before the arrival of EMS or not.

	Bystander CPR			Standardised difference
	All patients (n=11 955)	Yes (n=8510)	No (n=3445)	
Year of OHCA				0.01
2011	2287–19.1	1620–19.0	667–19.4	
2012	2263–18.9	1640–19.3	623–18.1	
2013	2432–20.3	1696–19.9	736–21.4	
2014	2391–20.0	1675–19.7	716–20.8	
2015	2582–21.6	1879–22.1	703–20.4	
OHCA during daytime 08:00 – 20:00 (643/293)*	7275–66.0	5363–68.2	1912–60.7	0.16
Age (years)	72 (52,87)	71 (50,87)	75 (55,88)	0.27
Female sex	3778–31.6	2615–30.7	1163–33.8	0.06
VF/VT as first monitored rhythm (337/91)	3456–30.0	2784–34.1	672–20.0	0.32
OHCA at home (5/2)	8430–70.6	5637–66.3	2793–81.1	0.34
Mechanical chest compression (581/293)	4188–37.8	2993–37.7	1195–37.9	0.00
Cardiac aetiology (408/142)	8070–70.8	5759–71.1	2311–70.0	0.02
Treatment				
Adrenalin (103/39)	9813–83.1	6862–81.6	2951–86.6	0.14
Intubation (70/32)	4345–36.7	3125–37.0	1220–35.7	0.03
Anti-arrhythmics (196/86)	1893–16.2	1440–17.3	453–13.5	0.11
Delay (minutes)				
Collapse to start of CPR (950/496)	4 (0,16)	2 (0,12)	10 (2,20)	1.23
Call for EMS to EMS arrival (1426/626)	10 (4,21)	10 (4,22)	8 (4,17)	0.35

Results presented as number (%) or median (10th, 90th percentile)

*Number of patients with missing information of those receiving and not receiving bystander CPR, respectively.

†Standardised difference between the two groups

CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation; VF/VT, ventricular fibrillation/ventricular tachycardia.

rhythm). However, adjustment also for initial rhythm is presented in online supplementary table 1. To assess the possible effect of comorbidity on outcomes, we compared ORs for bystander CPR (in relation to no bystander CPR) in models not involving CCI with the models where CCI was included. To analyse possible interactions between bystander CPR and CCI, the model without the interaction term was compared with the model with this term included. For descriptive purposes, we divided patients according to CCI intervals and produced interval-specific forest plots for each of the four outcome analyses.

Due to the amount of missing data regarding one or more of the adjustment factors (21% of the patients), we used multiple imputations for the multivariable analysis. Missing data were assumed to be missing at random and 50 imputed data sets were generated with the Markov chain Monte Carlo method using the expectation-maximisation algorithm. Rubin's rules were used for pooling of the results from the imputed data sets. Outcome endpoints were not imputed, and thus only patients for whom 30-day survival status and whether ROSC occurred were known were included in the respective analysis. The procedure above was repeated separately for each outcome analysis and for the subgroups of patients with ventricular fibrillation/ventricular tachycardia (VF/VT) and patients with non-shockable rhythm as the initial rhythm. For comparative purposes, we also performed a complete case analysis (ie, only using patients with no missing on the adjustment factors) (online supplementary table 2).

Tests were two sided and p values <0.05 were considered statistically significant. All analyses were performed using SAS software V.9.4 for Windows.

RESULTS

Altogether, 25 540 OHCA cases were registered in the SRCR during the study period (2011–2015). After exclusion of cases as presented in figure 1, 11 955 cases with witnessed OHCA were included in the study.

Characteristics of the patients

Bystander CPR was performed in 8510 cases (71%). Patients who received bystander CPR were younger on average, a higher proportion presented with VF/VT as first monitored rhythm, a lower proportion of their collapses had occurred at home and there was a slightly lower proportion of women.

Figure 1 Flowchart of patient selection for the study.

Table 2 Outcome in relation to whether bystander CPR was performed before the arrival of EMS or not.

		Bystander CPR		
	All patients (n=11 955)	Yes (n=8510)	No (n=3445)	p value
Survival at 30 days				
All patients	1592–13.3	1361–16.0	231–6.7	<0.0001
Patients with VF/VT as first monitored rhythm	1093–31.6	953–34.2	140–20.8	<0.0001
Patients with other initial arrhythmia	338–4.2	254–4.7	84–3.1	0.0008
ROSC anytime (210/129)*	4597–39.6	3396–40.9	1201–36.2	<0.0001
ROSC at arrival in hospital (179/74)	3676–31.4	2759–33.1	917–27.2	<0.0001

Results presented as number (%)

*Number of patients with missing information of those receiving and not receiving bystander CPR, respectively.

CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest; VF/VT, ventricular fibrillation/ventricular tachycardia.

The median time from collapse to start of CPR was substantially shorter in patients who received bystander CPR than in patients who did not (2 min vs 10 min), but a longer time elapsed between the emergency call and the arrival of EMS (10 min vs 8 min)(table 1).

The survival at 30 days was 16.0% when bystander CPR was started, as compared with 6.7% when CPR was not started before the arrival of EMS ($p<0.0001$). Patients who received bystander CPR received ROSC at any time and also on arrival at hospital more frequently than patients who did not (40.9% vs 36.2% and 33.1% vs 27.2%, respectively; $p<0.0001$ for both comparisons) (table 2).

Comorbidity of the patients

According to CCI, the degree of comorbidity was slightly lower in those who received bystander CPR (for details see table 3 and figure 2) (mean±SD: 2.2 ± 2.3 vs 2.5 ± 2.4 ; $p<0.0001$). Of those who received bystander CPR, 29.6% had a CCI value of 0 (ie, no comorbidity at all), as opposed to 24.9% for those who did not receive CPR (figure 2).

Association of bystander CPR and 30-day survival

After adjusting for age, sex, location, aetiology and time delay between the emergency call and arrival of EMS, the OR regarding 30-day survival was 2.34 (95% CI 2.01 to 2.74) for patients who received bystander CPR in relation to those who did not. Adding CCI to the model did not imply any major change in this ratio (OR 2.32, 95% CI 1.98 to 2.71) (figure 3). The degree of association between bystander CPR and 30-day survival did not change with the severity of comorbidity ($p=0.61$ for interaction between bystander CPR and CCI, for details see figure 4). Repeating these analyses including initial rhythm as an additional covariate in the model resulted in a weaker association between bystander CPR and survival, but still almost identical regardless whether adjusted for CCI or not (online supplementary file 1). When using only complete cases we found no major differences from the results above using multiple imputation (online supplementary table 2).

Table 3 Comorbidity in relation to whether bystander CPR was performed before the arrival of EMS or not.

		Bystander CPR			
	All patients (n=11 955)	Yes (n=8510)	No (n=3445)	P value	Standardised difference*
Comorbidity within 5 years before OHCA					
Myocardial infarction	2915 (24.4)	2040 (24.0)	875 (25.4)	0.10	0.03
Congestive heart failure	3441 (28.9)	2350 (27.6)	1091 (31.7)	<0.0001	0.09
Peripheral vascular disease	1356 (11.3)	925 (10.9)	431 (12.5)	0.01	0.05
Cerebrovascular disease	1713 (14.3)	1227 (14.4)	486 (14.1)	0.69	0.01
Dementia	736 (6.2)	519 (6.1)	217 (6.3)	0.67	0.01
Chronic pulmonary disease	2240 (18.7)	1495 (17.6)	745 (21.6)	<0.0001	0.10
Connective tissue disorder/rheumatic disease	650 (5.4)	455 (5.3)	195 (5.7)	0.50	0.01
Peptic ulcer disease	355 (3.0)	237 (2.8)	118 (3.4)	0.07	0.04
Mild liver disease	344 (2.9)	243 (2.9)	101 (2.9)	0.81	0.00
Diabetes without complications	2715 (22.7)	1857 (21.8)	858 (24.9)	0.0003	0.07
Diabetes with complications	1139 (9.5)	791 (9.3)	348 (10.1)	0.18	0.03
Paraplegia/hemiplegia	281 (2.4)	201 (2.4)	80 (2.3)	0.95	0.00
Renal disease	1143 (9.6)	772 (9.1)	371 (10.8)	0.005	0.06
Cancer	2065 (17.3)	1428 (16.8)	637 (18.5)	0.03	0.04
Metastatic carcinoma	525 (4.4)	352 (4.1)	173 (5.0)	0.03	0.04
Moderate or severe liver disease	71 (0.6)	37 (0.4)	34 (1.0)	0.0009	0.07
AIDS/HIV	10 (0.1)	5 (0.1)	5 (0.1)	0.16	0.03
Charlson Comorbidity Index (CCI)					
Points	2 (0, 6)	2 (0, 6)	2 (0, 6)	<0.0001	0.14
Mean±SD	2.3±2.4	2.2±2.3	2.5±2.4		

Results presented as number (%) or median (10th, 90th percentiles), unless otherwise stated.

*Standardised difference between the two groups.

CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest.

Patients with shockable or non-shockable first monitored rhythm

The adjusted OR for CPR before the arrival of EMS in relation to no bystander CPR regarding 30-day survival in patients with VF/VT as the first monitored rhythm was 1.94 (95% CI 1.55 to 2.42). When also adjusting for CCI, the OR was again almost identical (1.93, 95% CI 1.55 to 2.41). A similar absence of CCI effect was found in patients with non-shockable first monitored rhythm (although the overall association between bystander CPR and survival was weaker in this subgroup) (figure 3). The interaction between bystander CPR and CCI

regarding 30-day survival did not reach statistical significance in patients neither with non-shockable nor shockable first monitored rhythm ($p=0.052$ and $p=0.16$, respectively). (figure 4).

Association between bystander CPR and ROSC

The adjusted ORs for bystander CPR in relation to no bystander CPR regarding ROSC at any time and ROSC at hospital admission were 1.29 (95% CI 1.18 to 1.41) and 1.38 (95% CI 1.25 to 1.51), respectively. Although similar associations were found regardless of whether adjusting for CCI or not, there were significant interactions between bystander CPR and the degree of comorbidity regarding both ROSC at any time and at hospital admission, with a decreasing effect of bystander CPR with increasing degree of comorbidity (figure 4).

DISCUSSION

The major finding in this nationwide study was that the positive effect of bystander CPR on 30-day survival was not confounded by previous comorbidities. Although patients who received bystander CPR had somewhat less comorbidities than patients who did not receive such treatment, the association between bystander CPR and 30-day survival was unaffected after adjustment for the degree of comorbidity. However, with regard to ROSC at any time and ROSC at hospital admission, the effect of bystander CPR was associated with the degree of comorbidity, in that the effect of bystander CPR diminished with increasing severity of comorbidity.

Giving CPR is recommended by international guidelines on early response in cardiac arrest.²¹ A number of studies have shown an association between bystander CPR and survival after

Figure 2 Charlson comorbidity index among those who received bystander CPR before the arrival of EMS or not. Patients who received bystander CPR had somewhat lower number of total CCI points compared to those who did not.

Figure 3 Unadjusted and adjusted odds ratio regarding the three outcomes. *Age, sex, location, etiology, and time from call to EMS to EMS arrival. OR 95% CI, odds ratio and corresponding 95% confidence interval for those receiving bystander CPR in relation to those not receiving bystander CPR. CCI, Charlson comorbidity index. PEA, pulseless electrical activity. ROSC, return of spontaneous circulation.

OHCA,^{4 5 22} and the results of our study further support these findings.

The evidence for the recommendation of giving CPR before arrival of EMS is based on studies with registry data. No single trial has ever been performed whereby patients were randomised to (1) CPR before arrival of EMS or (2) no CPR before arrival of EMS. For ethical reasons, no such trial will most likely ever be performed. We therefore must analyse registry data in the most optimal way. The critical issue is to include all relevant confounders in the analysis and to be convinced that there are no hidden confounders that have not been considered, the latter being of course impossible to prove. One example of a possible confounder that has been hidden for years in most studies that have evaluated the effect of bystander CPR after OHCA is comorbidity. Our findings suggest that the degree of comorbidity is not a confounder regarding the positive association between bystander CPR and 30-day survival. However, the degree of comorbidity appears to influence the association between bystander CPR and the chance of ROSC both at any time and at hospital admission, with a stronger effect of bystander CPR in those patients with less severe comorbidity. Possible explanations as to how the degree of comorbidity appears to influence the association between bystander CPR and ROSC could be mediated through shockable rhythm. We determined in a previous study¹³ that the proportion of patients found in VF/VT decreased with increasing comorbidity.

Our results support the idea that CPR given before the arrival of EMS is effective and should be recommended regardless of

Figure 4 CCI interval specific adjusted* odds ratios regarding the three outcomes. *Adjusted for age, sex, location, etiology, and time from call to EMS to EMS arrival. # p-value for interaction between bystander CPR yes/no and CCI regarding outcome (actual CCI value used in p-value calculation). OR 95% CI: odds ratio and corresponding 95% confidence interval for those receiving bystander CPR in relation to those not receiving bystander CPR. CCI, Charlson comorbidity index. PEA, pulseless electrical activity. ROSC, return of spontaneous circulation.

comorbidity, since there was no interaction between bystander CPR and comorbidity regarding survival. Having said that, one certainly must consider other contraindications to start of CPR ('do not attempt resuscitation' issues, and so on). To our knowledge, no previous study has addressed the question of whether coexisting illnesses might affect the association between bystander CPR and survival after OHCA. We have previously reported that CPR before the arrival of EMS is performed less frequently in patients with higher degree of comorbidity.¹³ One might consider that frail patients with several comorbidities would be less likely to receive bystander CPR, as a bystander might be reluctant to initiate CPR on such a patient. Our results suggest that bystander CPR before the arrival of EMS is performed in younger and more healthier patients.

The finding that patients who collapse outside their home are more likely to receive bystander CPR is consistent with findings in other studies.^{23 24} It is more likely that those witnessing the cardiac arrest in public have had a CPR training and are therefore more likely to start CPR.

In addition, we found that patients who received bystander CPR were more frequently found in a shockable rhythm. This is in agreement with previous findings.^{4 7 25} It has been suggested that one of the mechanisms behind the association between bystander CPR and increased survival is maintenance of VF/VT due to enhanced coronary perfusion.^{8 9} Thus, the effect of bystander CPR could be in prolonging the shockable phase of

VF/VT. This is why we did not adjust for the difference in first monitored rhythm in our primary analyses.

We limited our analysis to witnessed OHCA cases only. The reason for this was to minimise the number of patients who had a very small chance of survival, and when the time of the cardiac arrest is unknown other factors become more important—such as delay in initiating treatment.

In this study, apart from the year 2015, we lacked information on the proportion of patients who had CPR started by a witness. Although we assume that the vast majority of patients who received CPR before the arrival of EMS had ‘true bystander CPR’, we know that in a number of cases CPR was started by other dispatched units (firefighters or police, during 2015 it was 2%). In this way, there is some confusion about the definition of bystander CPR, which has recently been brought to light.²⁶

In summary, we have found that patients with witnessed OHCA who underwent bystander CPR were slightly healthier than those who did not undergo bystander CPR, and that the positive effect of bystander CPR on 30-day survival was not affected by patient comorbidity. This supports previous evidence that bystander CPR is an effective and important link in the chain of survival and increases the chance of 30-day survival regardless of patient comorbidity.

Strengths and limitations

The strengths of the present study were as follows. First, we used a large nationwide SRCR registry that prospectively collects data on OHCA in Sweden, with large cohorts. Second, the data on previous comorbidities were obtained from the comprehensive NPR registry, which covers all outpatient and inpatient care since 2001. We used multiple imputation technique to handle the problem of potential bias when including only complete data.

There were also several limitations. First, we only had data on comorbidity diagnosis from 5 years before the OHCA. In the NPR, the diagnoses do not take account of the grade and duration of the disease. We were unable to adjust for that healthier patients are more likely to receive more resuscitation effort, as well as inhospital factors and treatment such as hypothermia and coronary interventions in the postresuscitation phase. The study was conducted in Sweden, and there are uncertainties whether our results can be generalised to other parts of the world, as

cultural and other psychosocial factors may play a role in the initiation of bystander CPR.

CONCLUSION

Patients who received CPR before the arrival of EMS had a somewhat lower degree of comorbidity than those who did not. When taking this difference into account, bystander CPR was still associated with a marked increase in 30-day survival after OHCA.

Contributors Each author has contributed significantly to the submitted work, in terms of design of study, data acquisition, analysis or interpretation, drafting the article or revising it and final approval of the manuscript.

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Key questions

What is already known on this subject?

- Bystander cardiopulmonary resuscitation (CPR) before the arrival of emergency medical services (EMS) is a vital link in the chain of survival and increases survival after cardiac arrest. Patients' comorbidities may have a possible influence on the effect that bystander CPR has on survival.

What might this study add?

- This study widens our knowledge regarding comorbidities in patients who have undergone CPR before the arrival of EMS.
- Our study highlights the importance of bystander CPR, and shows that the positive effect of bystander CPR on survival is not affected by the degree of comorbidity of the patient.

How might this impact on clinical practice?

- Giving bystander CPR before the arrival of EMS can have a positive effect irrespective of the severity of comorbidity. It can be beneficial in cardiac arrest.

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