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Clinical paper

Reduced in-hospital survival rates of out-of-hospital cardiac arrest victims with obstructive pulmonary disease☆

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ABSTRACT

Aim: Out-of-hospital cardiac arrest (OHCA) due to sustained ventricular tachycardia/fibrillation (VT/VF) is common and often lethal. Patient's co-morbidities may determine survival after OHCA, and be instrumental in post-resuscitation care, but are poorly studied. We aimed to study whether patients with obstructive pulmonary disease (OPD) have a lower survival rate after OHCA than non-OPD patients.
Methods: We performed a community-based cohort study of 1172 patients with non-traumatic OHCA with ECG-documented VT/VF between 2005 and 2008. We compared survival to Emergency Room (ER), to hospital admission, to hospital discharge, and at 30 days after OHCA, of OPD-patients and non-OPD patients, using logistic regression analysis. We also compared 30-day survival of patients who were admitted to hospital, using multivariate logistic regression analysis.
Results: OPD patients ($n = 178$) and non-OPD patients ($n = 994$) had comparable survival to ER (75% vs. 78%, OR 0.9 [95% CI: 0.6–1.3]) and to hospital admission (56% vs. 57%, OR 1.0 [0.7–1.4]). However, survival to hospital discharge was significantly lower among OPD patients (21% vs. 33%, OR 0.6 [0.4–0.9]). Multivariate regression analysis among patients who were admitted to hospital (OPD: $n = 100$, no OPD: $n = 561$) revealed that OPD was an independent determinant of reduced 30-day survival rate (39% vs. 59%, adjusted OR 0.6 [0.4–1.0, $p = 0.035$]).
Conclusion: OPD-patients had lower survival rates after OHCA than non-OPD patients. Survival to ER and to hospital admission was not different between both groups. However, among OHCA victims who survived to hospital admission, OPD was an independent determinant of reduced 30-day survival rate.
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1. Introduction

Out-of-hospital cardiac arrest (OHCA) due to ventricular tachycardia/fibrillation (VT/VF) is common and often lethal in both affluent and developing countries.[1,2] Despite much effort, survival after OHCA remains poor, even when cardiopulmonary resuscitation (CPR) by emergency medical services (EMS) personnel is attempted. Survival rate to hospital discharge is generally low and varies greatly, ranging from 3 to 40%.[3,4] This variability is largely attributable to differences in the chain of survival: location of OHCA, presence of a witness, use of automated external defibrillator (AED), and time of onset of CPR, defibrillation, and advanced care.[5–7] However, these factors do not entirely explain the variability in survival after OHCA. Rea et al. showed that these links in the prehospital chain of care (termed the Utstein measures) collectively predicted 72% of survival variability among all OHCAs, and 40% among bystander-witnessed OHCA with VF.[6] This indicates that patient characteristics may also play an important role. Clearly, recognizing the role of these characteristics can have important implications for therapy strategies for OHCA. Yet, reports on the effects of patient characteristics are scarce (on comorbidities[8,9]) and contradicting (on age[10,11] and sex[12,13]).

It is conceivable that obstructive pulmonary disease (OPD; i.e., asthma and/or chronic obstructive pulmonary disease [COPD]) may affect survival rate from OHCA. Adverse effects of ventilation and endotracheal intubation during the resuscitation efforts, and increased hypoxaemia in OPD patients may negatively impact the patient's chance on survival. Also, concomitant (yet often

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unrecognised) cardiac disease in OPD patients may play a role.[14] Yet, systematic studies on the relation between OPD and survival rates from OHCA are lacking. The primary aim of our study was to assess whether OPD patients have a lower survival rate after OHCA than non-OPD patients. We studied in detail at which point in the course of post-resuscitation care survival rates between both groups diverge by comparing survival to emergency room (ER), survival to hospital admission, survival to hospital discharge, and 30-day survival. Secondly, we aimed to compare the duration of hospital care and the quality of outcome (neurologic outcome) between OPD patients and non-OPD patients who were discharged from hospital alive.

2. Methods

2.1. Setting and study region

The AmsteRdam REsuscitation STudy (ARREST) research group prospectively collects data of all OHCA since June 2005 in the North Holland province of the Netherlands. This region covers 2404 km^2 (urban and rural communities) and had a population of 2 426 097 in 2007.[15] In case of a medical emergency, people dial the national emergency number. Calls are transferred to the regional EMS dispatch centre. When suspecting a cardiac arrest, the EMS dispatcher sends out 2 ambulances from a single tier.[16] Further details of the EMS system were described elsewhere.[17]

2.2. Study design

Data of all resuscitations during the study period, from arrival of EMS personnel until hospital discharge or death, were collected according to Utstein recommendations.[18] To determine the survival of OHCA victims with or without OPD, a prospective cohort study was performed. This study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants who survived OHCA. The Ethics Committee of the Academic Medical Center Amsterdam approved the study, including the use of data from patients who did not survive OHCA.

2.3. Patient selection

Of each patient in whom a resuscitation attempt was undertaken by EMS personnel, the ECG from the ambulance or AED was retrieved and analysed. Patients were included for the present study if they had OHCA with ECG-documented VT/VF from presumed cardiac causes. All OHCAs were considered to be from cardiac causes unless an unequivocal non-cardiac cause was documented (i.e., drowning or trauma). This was verified by reviewing all case files. We excluded EMS-witnessed OHCAs, since emergency call – response intervals and immediate resuscitation by EMS personnel have enormous impact on survival chances,[6] and excluded aborted resuscitation efforts in individuals with a "do not resuscitate" status. As we aimed to perform a complete case analysis, we excluded patients of whom the medication history of the year before OHCA could not be retrieved, and those of whom data on the chain of resuscitation care were missing.

2.4. Definitions and covariates

OHCA was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation,[18] occurring out-of-hospital. Patients were considered to have OPD if they had at least two prescriptions of any medication with Anatomical Therapeutic Chemical classification system (ATC) code R03 (drugs for obstructive airway diseases) in the year before OHCA. Data of medication use at the time of OHCA, and in the year before OHCA, were obtained from the patient's community pharmacy.

Survival was assessed at different time points: survival to emergency room (ER), survival to hospital admission, survival to hospital discharge (information retrieved from hospital records), and 30-day survival (retrieved from the civic registry). Duration of hospital care (in days) was retrieved from hospital records. Two researchers (JB and AB) classified neurologic outcome on the Cerebral Performance Category (CPC) scale by reviewing hospital charts of patients who survived until hospital discharge. Category 1 represents good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death.[19] Neurologically intact survival was defined as CPC category 1 or 2.[18]

The following prognostic factors were considered to be potential confounding factors: older age (>65 years), sex, cardiovascular co-morbidity (defined by medication use: β-adrenoceptor blockers, calcium antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, platelet aggregation inhibitors, nitrates and/or statins within 6 months before OHCA), bystander witnessed OHCA, public location of OHCA, bystander CPR performed, use of AED, and time interval from emergency call to arrival of EMS personnel.

2.5. Data analysis

To establish the association between OPD and survival after OHCA, we first studied all OHCA patients with documented VT/VF (n = 1172, Fig. 1). As primary outcome measure in this analysis, we used 30-day survival, as this can be determined for all patients regardless of hospitalisation status. Secondary outcome measures were survival rates at succeeding stages in the chain of care: (i) survival to arrival at the ER, (ii) survival to hospital admission and (iii) survival to hospital discharge. We performed logistic regression analysis for survival at all stages, adjusting for age and sex.

Next, we determined at which stage of the chain of care survival diverged between OPD patients and non-OPD patients. We then selected all patients who survived up to that stage, and performed multivariate logistic regression analysis, using 30-day survival as outcome measure. We applied two multivariate models: (1) with adjustment for all covariates that were univariately associated with OHCA with VT/VF, and (2) with adjustment for all covariates that were univariately associated with OHCA with VT/VF and changed the point estimate of the association between OPD and outcome with at least 5%.[20] Interaction between OPD and either older age, sex or concomitant cardiovascular disease was estimated by including the cross product of the two factors as a variable in the model. Results are presented as odds ratio (OR) and 95% confidence intervals (95% CI).

To compare duration of hospital care and quality of outcome between OPD patients and non-OPD patients who were discharged from the hospital alive, we studied duration of hospital care (in days) and neurologic status at hospital discharge of the patients who were discharged from the hospital alive.

Continuous variables were described as means and standard deviations (SD), or medians and interquartile range where appropriate, and categorical variables as absolute numbers and percentages. Comparisons between groups were performed with chi-square test or analysis of variance were appropriate. All data were analysed using the statistical software package of SPSS (SPSS for Mac, version 18.0, SPSS Inc.).

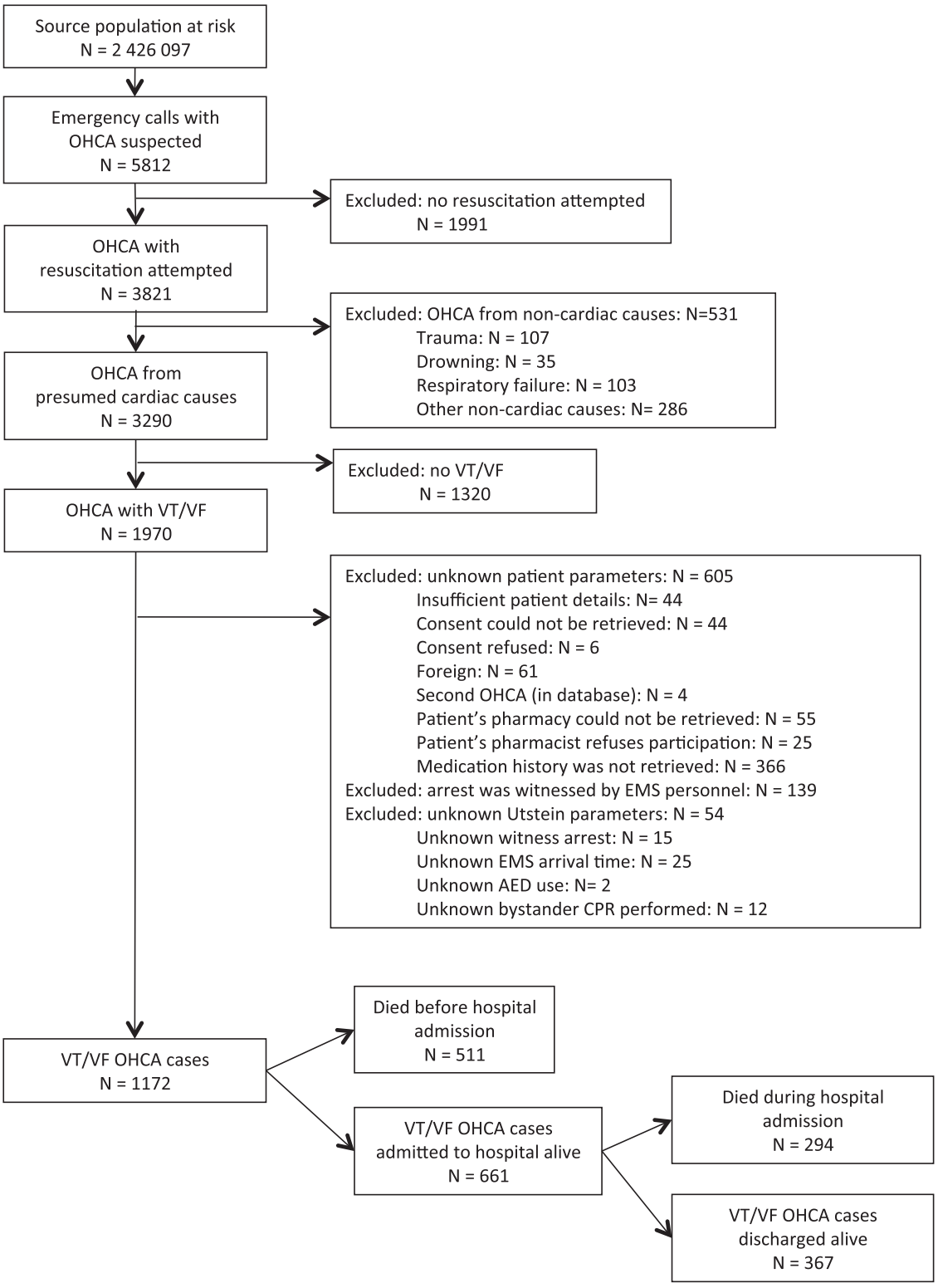


Fig. 1. Flow chart of patient inclusion.

3. Results

During the 43-month study period, there were 5812 emergency calls with EMS dispatchers suspecting OHCA. In 3821 instances, EMS personnel attempted to resuscitate. There were 3290 patients with OHCA from presumed cardiac causes, including 1970 with documented VT/VF. After exclusion of non-eligible patients (in 605 patient data unavailable, in 139 EMS-witnessed OHCA, in 54 data on circumstances of OHCA unavailable), the analysis cohort consisted of 1172 patients (Fig. 1). Age and sex of included and excluded patients were not meaningfully different: age 63.5 (14.5) vs. 65.8 (14.3) years, respectively, $p < 0.001$; male sex 78% in both groups, $p = 0.78$.

Baseline characteristics of OHCA patients with OPD ($n = 178$) and without OPD ($n = 994$) are shown in Table 1. OPD patients were older (70 [12] vs. 65 [15] years, $p < 0.001$), less often male (71 vs.

Table 1
Baseline characteristics of the study population (all patients: $n = 1172$, patients admitted to hospital alive: $n = 661$).

Baseline characteristics	All patients			Patients admitted to hospital alive		
	OPD	No OPD	*p*-Value	OPD	No OPD	*p*-value
Events, *n*	178	994		100	561	
Mean age (years, SD)	70 (12)	65 (15)	<0.001	69 (12)	64 (14)	0.006
Older age (≥65 years), *n* (%)	123 (69%)	545 (55%)	<0.001	67 (67%)	295 (53%)	0.008
Male sex	127 (71%)	785 (79%)	0.024	66 (66%)	439 (78%)	0.008
Cardiovascular disease, *n* (%)[a]	142 (80%)	668 (67%)	0.001	79 (79%)	387 (69%)	0.043
Resuscitation parameters:						
Collapse at public location, *n* (%)	50 (28%)	385 (39%)	0.007	34 (34%)	249 (44%)	0.053
Witnessed collapse, *n* (%)	152 (85%)	855 (86%)	0.826	86 (86%)	512 (91%)	0.099
Bystander CPR performed, *n* (%)	122 (69%)	734 (74%)	0.142	68 (68%)	436 (78%)	0.035
AED used, *n* (%)	31 (17%)	258 (26%)	0.015	21 (21%)	168 (30%)	0.068
EMS response time, median (Q1–Q3) (min)	10.4 (8.0–13.1)	9.6 (7.5–11.9)	0.021	9.9 (7.4–13.1)	9.0 (6.8–11.5)	0.075

AED: automated external defibrillator; CPR: cardiopulmonary resuscitation; EMS: emergency medical services; OPD: obstructive pulmonary disease; Q: quartile; SD: standard deviation. Comparisons of continuous variables were made with ANOVA; the χ^2 test was used when binary variables were compared. All statistical tests were 2 tailed.

[a] Use of β-adrenoceptor blocker, calcium antagonist, angiotensin converting enzyme inhibitor, diuretic, angiotensin-II receptor blocker, platelet aggregation inhibitors, nitrate and/or statin within 6 months prior to out-of-hospital cardiac arrest.

Table 2
Survival rates and Odds Ratio for survival at various stages, patients with and without OPD ($n = 1172$).

Outcome	Patients with OPD $n = 178$	Patients without OPD $n = 993$	OR[a] (95% CI)
30-day survival, *n* (%)	40 (23)	333 (34)	0.7 (0.5–0.97)
Survival to ER, *n* (%)	134 (75)	779 (78)	0.9 (0.6–1.3)
Survival to hospital admission, *n* (%)	100 (56)	561 (57)	1.0 (0.7–1.4)
Survival to hospital discharge, *n* (%)	38 (21)	329 (33)	0.6 (0.4–0.9)

CI: confidence interval; ER: emergency room; OPD: obstructive pulmonary disease; OR: odds ratio.

[a] ORs are corrected for age and sex.

79%, p = 0.02), and more often used (any type of) cardiovascular medication (80 vs. 67%, $p = 0.001$). In OPD patients, OHCA occurred less often at a public location (28 vs. 39%, $p = 0.007$), AED use was less common (17 vs. 26%, $p = 0.02$), and EMS response time was longer (10.4 vs. 9.6 min, $p = 0.02$). Survival rates of OPD and non-OPD patients are shown in Fig. 2 and Table 2. Thirty-day survival was lower in OPD patients than in non-OPD patients (23 vs. 34%, OR 0.7 [0.5–0.97]). However, survival to ER was comparable (75 and 78%, respectively, OR 0.9 [0.6–1.3]), as was survival to hospital admission (56 and 57%, OR 1.0 [0.7–1.4]). In contrast, survival to hospital discharge was lower in OPD patients (21 vs. 33%, OR 0.6 [0.4–0.9]).

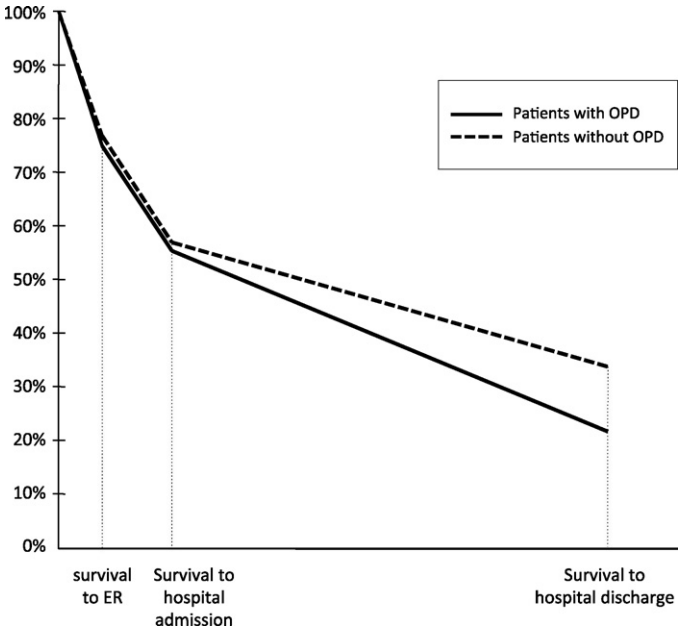


Fig. 2. Survival rates after OHCA of OPD patients and non-OPD patients, at emergency room, hospital admission and hospital discharge.

Since survival rates of OPD patients became lower than those of non-OPD patients only after admission to the hospital, we studied the cohort of patients who were admitted to the hospital alive ($n = 661$, Fig. 1, Table 1) to establish whether OPD was an independent determinant of lower survival rate. Within this cohort, OPD patients were older than non-OPD patients (69 (12) vs. 65 (14) years, $p = 0.006$), less often male (66 vs. 78%, $p = 0.008$), and more often received (any) cardiovascular medication (79 vs. 69%, $p = 0.043$). While all resuscitation parameters were less favourable for OPD patients, only the lower rate of bystander CPR reached statistical significance. Table 3 shows ORs for 30-day survival in this cohort, calculated with univariate and multivariate regression analysis (two models). OPD patients had a lower chance of survival (39% vs. 59%, $p < 0.001$; adjusted OR [first model] 0.6 [0.4–0.99], $p = 0.047$, adjusted OR [second model] 0.6 [0.4–0.95], $p = 0.035$). No significant interaction between age, sex or concomitant cardiovascular disease and OPD was observed.

Among patients who were discharged from hospital alive, duration of hospital care was not different between OPD patients and non-OPD patients (26 vs. 27 days, $p = 0.825$, Table 4). Also, CPC scores were similar (Table 4), as was the proportion of neurologically intact survival (95% and 94%, $p = 0.787$).

4. Discussion

Patients with OPD had a 40% lower chance on 30-day survival after OHCA than patients without OPD. Survival rates were similar for OPD patients and non-OPD patients at the first stages of resuscitation care (survival to ER and survival to hospital admission); it is only after admission to hospital that the survival rate of OPD patients became lower than of non-OPD patients. These findings support the idea that survival at early stages is mostly determined by pre-hospital chain of care factors, while patient characteristics play a larger role in late (eventual) survival.

Table 3
Thirty-day survival for patients with or without OPD who were admitted to the hospital alive ($n = 661$).

	30-day survival		Crude OR (95%CI)	Adjusted OR[a] (95%CI)	Adjusted OR[b] (95%CI)
	Yes ($n = 371$)	No ($n = 290$)			
OPD, *n* (%)	39 (11)	61 (21)	0.4 (0.3–0.7)	0.6 (0.4–0.99)	0.6 (0.4–0.95)
Age, mean ± SD	62 ± 14	70 ± 13	0.95 (0.94–0.97)	0.96 (0.94–0.97)	0.96 (0.95–0.97)[c]
Male sex, *n* (%)	302 (81)	203 (70)	1.9 (1.3–2.7)	1.7 (1.1–2.5)	1.6 (1.1–2.4)[d]
Cardiovascular disease,[e] *n* (%)	236 (64)	230 (79)	0.5 (0.3–0.7)	0.8 (0.5–1.2)	0.8 (0.5–1.2)
OHCA at public location, *n* (%)	191 (52)	92 (32)	2.3 (1.7–3.1)	1.7 (1.2–2.4)	1.7 (1.2–2.4)
Witnessed OHCA, *n* (%)	353 (95)	245 (85)	3.6 (2.0–6.4)	3.1 (1.7–5.8)	
Bystander CPR performed, *n* (%)	305 (82)	199 (69)	2.1 (1.5–3.0)	1.2 (0.8–1.9)	1.5 (1.0–2.2)
AED used, *n* (%)	131 (35)	58 (20)	2.2 (1.5–3.1)	1.7 (1.1–2.5)	
EMS response time in min, median (Q1–Q3)	8.4 (6.0–10.7)	10.0 (8.0–12.7)	0.93 (0.90–0.97)	0.95 (0.91–0.99)	0.94 (0.90–0.98)

AED: automated external defibrillator; CI: confidence interval; CPR: cardiopulmonary resuscitation; EMS: emergency medical services; min: minutes; *n*: number; OHCA: out-of-hospital cardiac arrest; OPD: obstructive pulmonary disease; OR: odds ratio; SD: standard deviation.

[a] Adjusted for all covariates that were univariately associated with outcome.

[b] Adjusted for all covariates that were univariately associated with outcome and that changed the beta with at least 5% (age, sex, cardiovascular medication, collapse at public location, bystander CPR performed, EMS response time).

[c] Interaction OPD and older age on a multiplicative scale: OR 0.9 (95% CI 0.3–2.4), $p = 0.832$.

[d] Interaction OPD and sex on a multiplicative scale: OR 1.0 (95% CI 0.4–2.7), $p = 0.980$.

[e] Use of β-adrenoceptor-blocker, calcium antagonist, angiotensin converting enzyme inhibitor, diuretic, angiotensin-II receptor blocker, platelet aggregation inhibitors, nitrate and/or statin within 6 months prior to out-of-hospital cardiac arrest.

In accordance with our findings, Carew et al.[8] reported that the chance of survival after OHCA declines as the number of co-morbidities (including lung disease) increases. However, co-morbidities in the study of Carew were not so well ascertained as in our study because they were collected solely from EMS reports. Moreover, their analysis included ambulance witnessed arrests, which arguably could be considered as in-hospital cardiac arrests when analysing survival. Most importantly, we discovered that reduction in survival rate of OPD patients (relative to non-OPD patients) occurs when these patients are already admitted to hospital. This finding indicates that it should be feasible to modify treatment strategies in such a way that this mortality gap can be closed (treatment strategies for pre-hospital or in-community care would be much more difficult to implement). Such efforts should be targeted at the pathophysiologic mechanisms that underlie the lower survival rates in OPD patients. While we did not study these mechanisms, various explanations may be proposed. Firstly, OPD patients have a lower potential for oxygen uptake, and may therefore have lower 'oxygen reserve', and be more vulnerable to the deleterious effects of hypoxaemia during cardiac arrest and resuscitation. Also, endotracheal intubation and ventilation during the resuscitation efforts might enhance the inflammatory response in their already affected airways. Both mechanisms may adversely influence survival. Clearly, future studies must address these issues.

Still, improved pre-hospital or in-community treatments to reduce risk of OHCA or survival from OHCA in OPD patients must also be considered. For instance, at present, β-adrenoceptor blockers are the only drugs that have shown to prevent sudden cardiac death in some patient categories, notably cardiomyopathy, heart failure, coronary artery disease, and hemodialysis.[21–23] Traditionally, β-adrenoceptor blockers have been considered contra-indicated in COPD patients, although evidence indicates that at least cardio-selective β-adrenoceptor blockers are well tolerated by COPD patients.[24] Interestingly, recent observational studies suggest that long-term treatment with β-adrenoceptor blockers may improve survival of COPD patients, including those without known cardiovascular disease.[25,26] As COPD patients have a worse prognosis after OHCA, future research must establish whether or not β-adrenoceptor blockers should be given to COPD patients with an indication for these drugs.

A major strength of our study is that ARREST was specifically designed to study the determinants and outcomes of OHCA. This ensured that OHCA diagnosis was accurate. A cardiac cause of OHCA was validated by the presence of VT/VF on the ECG. This is especially important in patients with OPD, because sudden death caused by cardiac arrest may easily be confused with sudden death caused by respiratory failure.[14] Another strength is that our findings are representative for the community at large, because we studied the general population, including both urban and rural areas, and captured ~90% of all OHCA cases.[27]

Some limitations of our study should also be discussed. Non-differential misclassification in the diagnosis of OPD could have occurred, as we defined the presence of the disease by the use of two prescriptions of respiratory drugs within 1 year before OHCA. However, these drugs are indicated exclusively for OPD, and patients with OPD who received less than two prescriptions of any respiratory drug most likely are patients with very mild disease; the misclassification therefore would result in underestimation of the effect. Similarly, our diagnosis of CVD was based on the use of β-adrenoceptor blockers, calcium antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, platelet aggregation inhibitors, nitrates and/or statins within 6 months before OHCA. Other definitions, e.g. the use of antidiabetic medication, anti-arrhythmic drugs or digitalis, may

Table 4
Neurologic outcome and duration of hospital admission for patients with and without OPD who were discharged from hospital alive ($n = 367$).

	OPD ($n = 38$)	No OPD ($n = 329$)	*p*-Value
CPC-score			0.507
Good cerebral performance (CPC = 1), *n* (%)	31 (82)	265 (81)	
Moderate cerebral disability (CPC = 2), *n* (%)	5 (13)	43 (13)	
Severe cerebral disability (CPC = 3), *n* (%)	1 (3)	19 (6)	
Coma or vegetative state (CPC = 4), *n* (%)	1 (3)	2 (1)	
Duration of hospital admission, days (SD)	26 (17)	27 (19)	0.825

CPC: cerebral performance category; OPD: obstructive pulmonary disease; SD: standard deviation.

lead to different classifications. Still, it may be assumed that patients with a recognised high cardiac risk profile will use at least one of the drugs in the categories of our definition. Furthermore, our findings may partly be explained by the possibility that some patients have been misdiagnosed as OPD, due to misinterpretation of their dyspnoea or other symptoms, while in fact they had unrecognised heart failure.[14] Finally, OPD treatment withdrawal subsequent to the resuscitation may explain part of the observed difference in survival, but was not assessed in our study. Future studies should establish whether in-hospital post-resuscitation care includes sufficient attention for OPD treatment.

In conclusion, we found that OPD patients have a 40% lower chance on 30-day survival after OHCA than non-OPD patients. Survival rates were similar in both groups at the first stages of resuscitation care (survival to ER and survival to hospital admission); it is only after admission to hospital that survival rates of OPD patients became lower than those of non-OPD patients. Our findings suggest that in-hospital post-resuscitation care of OPD patients who suffered OHCA should be adapted in order to close this mortality gap. We aim to raise awareness of the lower survival chances of OPD patients after OHCA; closer monitoring of these patients may provide insight into the pathophysiologic basis of this difference.

Conflict of interest statement

None of the authors (MTB, MJW, AB, JB, RWK, PCS, AWH, FHR, MLdB, AdB and HLT) report a personal conflict of interest.

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