

## Predicting factors for long-term survival in patients with out-of-hospital cardiac arrest –a propensity score-matched analysis

Anna Lena Lahmann, Dario Bongiovanni, Anna Berkefeld, Maximilian Kettern, Lucas Martinez, Rainer Okrojek, Petra Hoppmann, Karl-Ludwig Laugwitz, Patrick Mayr, Salvatore Cassese, Robert Byrne, Sebastian Kufner, Erion Xhepa, Heribert Schunkert, Adnan Kastrati, Michael Joner

### Angaben zur Veröffentlichung / Publication details:

Lahmann, Anna Lena, Dario Bongiovanni, Anna Berkefeld, Maximilian Kettern, Lucas Martinez, Rainer Okrojek, Petra Hoppmann, et al. 2020. "Predicting factors for long-term survival in patients with out-of-hospital cardiac arrest –a propensity score-matched analysis." *PLoS ONE* 15 (1): e0218634. <https://doi.org/10.1371/journal.pone.0218634>.

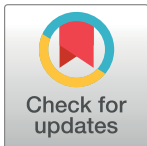
## RESEARCH ARTICLE

# Predicting factors for long-term survival in patients with out-of-hospital cardiac arrest – A propensity score-matched analysis

Anna Lena Lahmann<sup>1\*</sup>, Dario Bongiovanni<sup>2</sup>, Anna Berkefeld<sup>2</sup>, Maximilian Kettern<sup>1</sup>, Lucas Martinez<sup>1</sup>, Rainer Okrojek<sup>2</sup>, Petra Hoppmann<sup>2</sup>, Karl-Ludwig Laugwitz<sup>2,3</sup>, Patrick Mayr<sup>4</sup>, Salvatore Cassese<sup>1</sup>, Robert Byrne<sup>1</sup>, Sebastian Kufner<sup>1</sup>, Erion Xhepa<sup>1</sup>, Heribert Schunkert<sup>1,3</sup>, Adnan Kastrati<sup>1,3</sup>, Michael Joner<sup>1,3</sup>

**1** Department of Cardiology, German Heart Center Munich, Technical University Munich, Munich, Germany, **2** Department of Cardiology, Klinikum rechts der Isar, Technical University Munich, Munich, Germany, **3** DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany, **4** Department of Anesthesiology, German Heart Center Munich, Technical University Munich, Munich, Germany

\* [annalena@lahmann.at](mailto:annalena@lahmann.at)



## Abstract

### Background

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death worldwide, with acute coronary syndromes accounting for most of the cases. While the benefit of early revascularization has been clearly demonstrated in patients with ST-segment-elevation myocardial infarction (STEMI), diagnostic pathways remain unclear in the absence of STEMI. We aimed to characterize OHCA patients presenting to 2 tertiary cardiology centers and identify predicting factors associated with survival.

### Methods

We retrospectively analyzed 519 patients after OHCA from February 2003 to December 2017 at 2 centers in Munich, Germany. Patients undergoing immediate coronary angiography (CAG) were compared to those without. Multivariate regression analysis and inverse probability treatment weighting (IPTW) were performed to identify predictors for improved outcome in a matched population.

### Results

Immediate CAG was performed in 385 (74.1%) patients after OHCA with presumed cardiac cause of arrest. As a result of multivariate analysis after propensity score matching, we found that immediate CAG, return of spontaneous circulation (ROSC) at admission, witnessed arrest and former smoking were associated with improved 30-days-survival [(OR, 0.46; 95% CI, 0.26–0.84), (OR, 0.21; 95% CI, 0.10–0.45), (OR, 0.50; 95% CI, 0.26–0.97), (OR, 0.43; 95% CI, 0.23–0.81)], and 1-year-survival [(OR, 0.39; 95% CI, 0.19–0.82), (OR, 0.29; 95% CI, 0.12–0.7), (OR, 0.43; 95% CI, 0.2–1.00), (OR, 0.3; 95% CI, 0.14–0.63)].

## OPEN ACCESS

**Citation:** Lahmann AL, Bongiovanni D, Berkefeld A, Kettern M, Martinez L, Okrojek R, et al. (2020) Predicting factors for long-term survival in patients with out-of-hospital cardiac arrest – A propensity score-matched analysis. *PLoS ONE* 15(1): e0218634. <https://doi.org/10.1371/journal.pone.0218634>

**Editor:** Raffaele Bugiardini, University of Bologna, ITALY

**Received:** May 31, 2019

**Accepted:** November 25, 2019

**Published:** January 15, 2020

**Copyright:** © 2020 Lahmann et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** The authors received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusions

In our study, immediate CAG, ROSC at admission, witnessed arrest and former smoking were independent predictors of survival in cardiac arrest survivors. Improvement in prehospital management including bystander CPR and best practice post-resuscitation care with optimized triage of patients to an early invasive strategy may help ameliorate overall outcome of this critically-ill patient population.

## Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in western countries and still associated with poor prognosis despite improvement in emergency care and post-resuscitation management in recent years [1–4].

Increased rates of bystander resuscitation (CPR), and widespread availability of automated external defibrillators (AEDs) substantially contributed to improved patient outcome; in addition, it has been shown that targeted temperature management and early revascularization improve survival of patients with cardiac arrest caused by myocardial infarction [5–7].

Contemporary management of patients with ST-segment elevation recommends immediate coronary angiography (CAG) after cardiac arrest, including ad-hoc percutaneous intervention (PCI) if necessary. Current guidelines also suggest to consider immediate CAG for those patients with presumed cardiac cause of arrest in the absence of STEMI owing to the high incidence of coronary artery disease in these patients [8–9].

In this context, it remains challenging to select candidates for early CAG given the extremely heterogeneous population of cardiac arrest survivors and the difficulty to retrieve etiologic information in this specific setting [8,10].

The aim of this study was to characterize patients presenting to 2 major tertiary cardiology centers with intensive care capability after OHCA and stratification into those undergoing immediate coronary angiography or not. Furthermore, it was our goal to identify independent prognostic factors associated with survival in patients with OHCA.

## Materials and methods

We collected retrospective data of patients after out-of-hospital cardiac arrest from February 2003 to December 2017 at two centers in Munich, Germany. OHCA data were collected according to the Utstein recommendations and the ethics committee of the Technical University Munich (approval number 343/17 S) waived informed consent due to the observational nature of the study [11].

## Endpoint definitions

The primary outcome was survival at 30 days and one year, which was assessed by medical records or by telephone interview of the attending physicians; secondary outcome was functional status at discharge which was evaluated using the Cerebral Performance Category (CPC) score [12].

## Patient flow

Triage of patients to undergo immediate CAG was left to the responsible physician's discretion. When available, paramedical and early hospital information, such as ECG findings and

echocardiographic abnormalities or information derived from witnesses and former medical history aided in decision-making. An immediate coronary angiogram and subsequent PCI was performed if necessary, using standard techniques. Patients were subsequently admitted to the intensive care unit (ICU) for standard post-resuscitation care including targeted temperature management if indicated.

Immediate CAG was defined as coronary angiography performed within two hours after admission to hospital.

A coronary lesion resulting in >75% reduction of luminal diameter by visual estimation was considered significant and PCI was deemed successful when resulting in a residual stenosis of <30%.

Culprit lesion morphology was determined by angiography and defined as acute coronary occlusion, presence of thrombus, severe narrowing in the presence or absence of thrombus, and unstable-appearing lesions with high likelihood to trigger ischemia responsible for cardiac arrest.

NSTEMI, as well as the other causes of cardiac arrest, were determined by review of ECGs after return to spontaneous circulation (ROSC) and by review of patients' charts including CAG and serum parameters or CT-scan if performed. STEMI was determined by review of first ECG after ROSC.

## Statistical analysis

Continuous variables are presented as mean  $\pm$  SD. Distribution of data was checked for normality using the Shapiro-Wilk goodness-of-fit test and differences analyzed with the Wilcoxon-signed rank sum test in case of non-parametric data and student's t-test in the event of normal distribution. Categorical variables are presented as number (%) and were analyzed using the  $\chi^2$ -test. Univariate logistic regression analysis was performed to derive crude 30-days and 1-year-survival rates among patients undergoing immediate CAG or not.

To minimize selection bias of patients undergoing immediate CAG and to control for potential confounding factors, we conducted propensity score (PS) regression analysis and generated two matching cohorts of patients undergoing immediate CAG or not.

Propensity scores were estimated using binary logistic regression analysis based on variables derived from univariate analysis of baseline characteristics ( $p < 0.05$ ) available to the treating physician prior to triage of patient groups into immediate coronary angiography or conservative strategy.

The selected variables were hypercholesterolemia, smoking, daytime arrest, witnessed arrest, arrest at home, ROSC at admission and female. 1:1-propensity score matching using the nearest-neighbour method (R-package "MatchIT", version 3.0.2) with a caliper of 0.1 resulted in 119 patients assigned to undergo immediate coronary angiography and 119 patients assigned to conservative strategy.

Following the PS-matching, all available univariate factors were subsequently entered into one multivariate generalized linear regression model. Selection of covariates in the multivariate regression model was performed using the LASSO (Least Absolute Shrinkage and Selection Operator) regression method after entering all available candidates. These variables were ROSC at admission, bystander CPR, daytime presentation, witnessed arrest, arrest at home, active smoker, former smoker, diabetes, family history, female, history of prior myocardial infarction, history of coronary artery disease, arterial hypertension and immediate CAG.

Additionally, a multivariable regression model based on generalized estimation equations (GEE) and adjusted for a weighted estimation using a propensity score to be assigned to immediate CAG or not was applied (inverse probability of treatment weighting, IPTW-analysis). To

**Table 1. Baseline characteristics of patients with and without immediate CAG.**

	Entire population		p-value
	Immediate CAG n = 385	No immediate CAG n = 134	
Female	89/385 (23.1)	45/134 (33.6)	<b>0.02</b>
Age	65.1±13	66.9±16	0.11
Former smoker	143/326 (43.9)	25/83 (30.1)	<b>0.02</b>
Diabetes	79/342 (23.1)	25/87 (28.7)	0.23
Hypercholesterolemia	208/327 (63.6)	32/82 (39.0)	<b>&lt;0.001</b>
Hypertension	247/330 (74.9)	64/90 (71.1)	0.47
Family history	48/321 (15.0)	7/78 (9.0)	0.17
History of coronary artery disease	111/369 (30.0)	29/98 (29.6)	0.93
History of myocardial infarction	68/361 (18.8)	18/96 (18.8)	0.98

Data are presented as n (%) of the total cohort.

<https://doi.org/10.1371/journal.pone.0218634.t001>

confirm the benefit of immediate coronary angiography in patients excluding those presenting with STEMI, sensitivity analysis using LASSO regression was performed.

Parameters achieving p-values <0.05 were considered statistically significant and odds ratios derived with 95% confidence intervals. Analysis was performed using JMP Pro (software version 13.0, Cary, NC, USA) and R (MatchIT package, version 3.0.2 and MICE package, version 3.6.0).

## Results

We analyzed a total of 519 patients with out-of-hospital cardiac arrest between February 2003 and December 2017 that were consecutively admitted to one of two tertiary centers in Munich, Germany.

The baseline demographic characteristics are shown in (Table 1).

ECG at first contact with emergency medical service (EMS) showed ventricular fibrillation in 233/376 (62.0%) of the patients who underwent immediate CAG, and in 26/125 (20.8%) in the no immediate CAG group (Table 2) as most frequent initial rhythm.

Major causes of cardiac arrest were STEMI and NSTEMI in 111/517 (21.5%) and 141/517 (27.3%) of all patients, respectively (Table 3).

In the 385 patients undergoing immediate CAG, a culprit lesion was identified in 247/385 (64.2%) (Fig 1A and 1B).

**Table 2. Patients with and without immediate CAG according to initial ECG.**

	Entire population		p-value
	Immediate CAG n = 385	No immediate CAG n = 134	
Asystole	89/376 (23.7)	66/125 (52.8)	<b>&lt;0.001</b>
AV-Block	3/376 (0.8)	0/125 (0.0)	0.32
Bradycardia	9/376 (2.4)	1/125 (0.8)	0.27
VT	8/376 (2.1)	3/125 (2.4)	0.86
VFib	233/376 (62.0)	26/125 (20.8)	<b>&lt;0.001</b>
PEA	22/376 (5.9)	22/125 (17.6)	<b>&lt;0.001</b>
Miscellaneous	12/376 (3.2)	7/125 (5.6)	0.22

Data are presented as % of the total cohort. Abbreviations: VT, ventricular tachycardia; VFib, ventricular fibrillation; PEA, pulseless electrical activity.

<https://doi.org/10.1371/journal.pone.0218634.t002>

**Table 3. Cause of cardiac arrest in patients with and without immediate CAG.**

Entire population	Immediate CAG n = 385	No immediate CAG n = 134	p-value
STEMI	106/383 (27.7)	5/134 (3.7)	<0.001
NSTEMI	127/383 (33.2)	14/134 (10.5)	<0.001
Bradycardia	4/383 (1.0)	0/134 (0.0)	0.24
Cardiomyopathy	58/383 (15.1)	9/134 (6.7)	0.01
Hemorrhage	6/383 (1.6)	5/134 (3.7)	0.14
Metabolic disorder	5/383 (1.3)	2/134 (1.5)	0.90
Pulmonary embolism	5/383 (1.3)	12/134 (9.0)	<0.001
Respiratory failure	16/383 (4.2)	32/134 (23.9)	<0.001
Miscellaneous	56/383 (14.6)	55/134 (41.0)	<0.001

Data are presented as % of the total cohort.

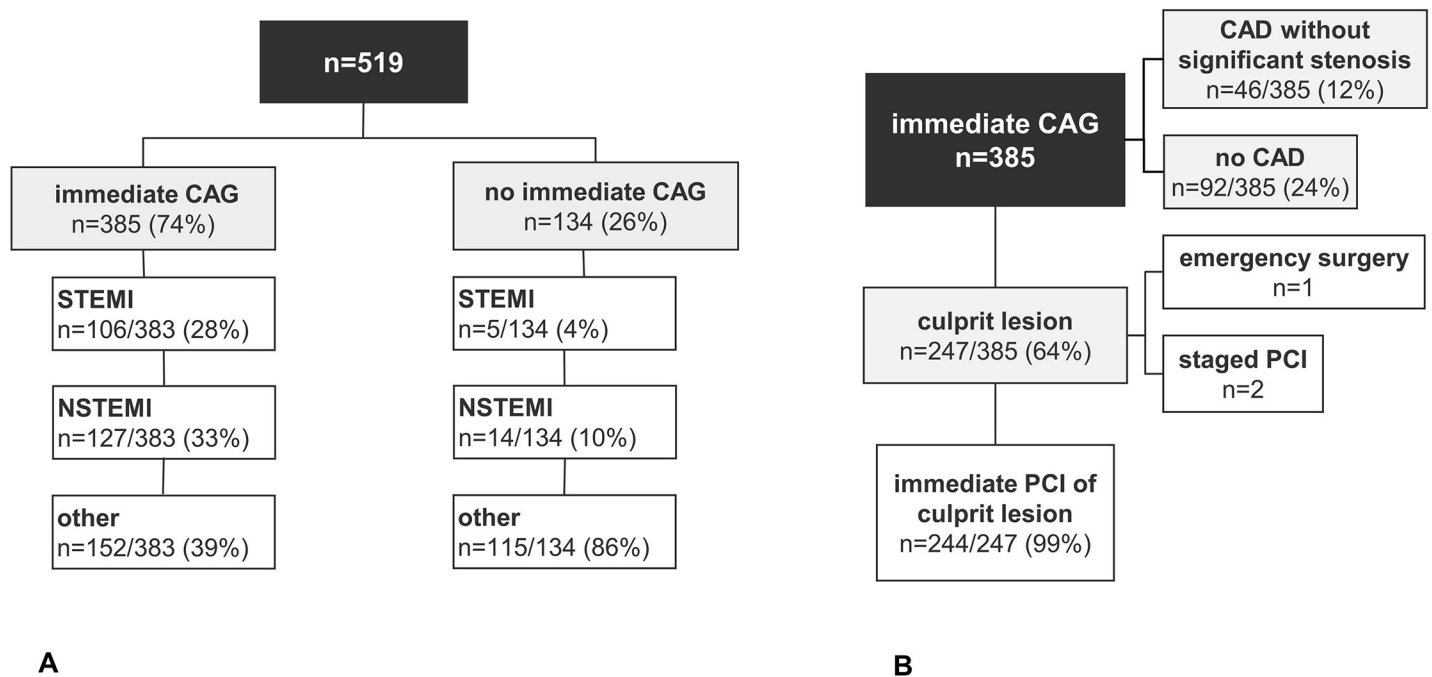
<https://doi.org/10.1371/journal.pone.0218634.t003>

With regards to pre-hospital management, 336/479 (70.1) of the patients received bystander CPR and the arrest was witnessed in 381/487 (78.2). Arrest at home was found in 298/507 (58.8) of the patients. Mean time to ROSC was  $14.4 \pm 11.3$  minutes in the immediate CAG group and  $12.9 \pm 11.6$  in patients without with no significant difference between patients undergoing immediate CAG or not (Table 4).

Coronary angiographic and intervention findings are shown in Table 5.

Patients in the immediate CAG group had significant higher pH-values and lower lactate levels in the first blood gas analysis ( $7.11 \pm 0.20$  vs.  $7.00 \pm 0.21$ ,  $p < 0.001$  and  $8.8 \pm 4.8$  mmol/l vs.  $12.4 \pm 8.2$  mmol/l,  $p < 0.001$ ).

Overall 30-days-survival of the 519 patients that were included in the study was 50.1% compared to a 1-year-survival of 37.6%. 30-days-survival as well as survival after one year was



**Fig 1. Patient flow diagrams.**

<https://doi.org/10.1371/journal.pone.0218634.g001>

**Table 4. Preclinical and hospital data of patients with and without immediate CAG.**

Entire population			
	Immediate CAG n = 385	No immediate CAG n = 134	p-value
<b>Arrest Data</b>			
Bystander CPR	259/355 (73.0)	77/124 (62.1)	<b>0.02</b>
ROSC at admission	327/384 (85.2)	86/133 (64.7)	<b>&lt;0.001</b>
Time to ROSC (min)	14.4 ± 11.3	12.9 ± 11.6	0.23
Daytime presentation	330/384 (85.9)	106/131 (80.9)	0.17
Witnessed arrest	295/364 (81.0)	86/123 (69.9)	<b>0.01</b>
Arrest at home	207/380 (54.5)	91/127 (71.7)	<b>0.01</b>
<b>Hospital data</b>			
pH-value in first BGA	7.1 ± 0.2	7.0 ± 0.2	<b>&lt;0.001</b>
pO <sub>2</sub> in first BGA (mmHg)	191.8 ± 145.2	168.0 ± 137.3	0.08
Lactate in first BGA (mmol/l)	8.8 ± 4.8	12.4 ± 8.2	<b>&lt;0.001</b>
NSE after 48 hours (ng/ml)	74.4 ± 104.3	127.9 ± 145.0	0.06

Data are presented as n (%) or as mean ± SD unless indicated otherwise. Abbreviations: CAG, coronary angiography; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; BGA, blood gas analysis; NSE, neuron-specific enolase.

<https://doi.org/10.1371/journal.pone.0218634.t004>

significantly better in the immediate CAG group [221/370 (59.7) vs. 30/131 (22.9),  $p < 0.001$ ] and [161/341 (47.2) vs. 14/124 (11.3),  $p > 0.001$ ] than in patients without.

Neurological function was evaluated at hospital discharge. In our cohort, good neurological function (CPC 1&2) was found in 164/299 patients (54.8%) at discharge (Table 6).

### Matched population

After applying PS matching to reduce confounding factors arising from differential selection of patients undergoing immediate CAG or not, two comparable cohorts were generated to identify predicting factors associated with survival after OHCA (Table 7).

By multivariate analysis, we found that immediate CAG was associated with improved 30-days-survival and 1-year-survival [(OR, 0.46; 95% CI, 0.26–0.84), (OR, 0.39; 95% CI, 0.19–

**Table 5. Coronary angiographic and intervention findings in patients with immediate CAG.**

Entire population n = 385	
Single-vessel disease	64/385 (16.6)
Double-vessel disease	81/385 (21.0)
Triple-vessel disease	148/385 (38.4)
Overall culprit lesions	247/385 (64.2)
Culprit lesion LAD	115/247 (46.6)
Culprit lesion LCx	45/247 (18.2)
Culprit lesion RCA	87/247 (35.2)
Immediate PCI of culprit lesion	244/385 (63.4)
PCI of more than culprit lesion	32/385 (8.3)
Other significant lesions not treated in the emergency setting	62/384 (16.2)

Data are presented as n (%). Abbreviations: EF, ejection fraction; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; CAD, coronary artery disease.

<https://doi.org/10.1371/journal.pone.0218634.t005>

**Table 6. Cerebral Performance Category Score 1&2 at discharge in patients with immediate and no immediate CAG.**

Entire population		
Immediate CAG n = 385	No immediate CAG n = 134	p-value
151/261 (57.9)	13/38 (34.2)	<b>0.01</b>

Data are presented as n (%). Abbreviations: CPC, cerebral performance category.

<https://doi.org/10.1371/journal.pone.0218634.t006>

0.82)]. In addition, ROSC at admission, witnessed arrest and former smoking were predictors of improved outcome after 30 days [(OR, 0.21; 95% CI, 0.10–0.45), (OR, 0.50; 95% CI, 0.26–0.97), (OR, 0.43; 95% CI, 0.23–0.81)] (Fig 2) and 1 year [(OR, 0.29; 95% CI, 0.12–0.7), (OR, 0.43; 95% CI, 0.2–1.00), (OR, 0.30; 95% CI, 0.14–0.63)] (Fig 3).

IPTW-analysis confirmed predictive modeling of variables associated with improved survival at 30 days and 1 year in the matched cohort. Immediate coronary angiography and ROSC at admission had an IPTW-adjusted probability of improved 30-days-mortality [(OR, 2.96; 95% CI, 4.98–1.77; p<0.001), (OR, 9.15; 95% CI, 4.57–18.31; p<0.001)].

To substantiate the benefit of immediate coronary angiography excluding patients presenting with STEMI, where the advantage of early revascularization is well established, we performed sensitivity analysis within the overall cohort of patients excluding patients presenting with STEMI. LASSO regression analysis revealed immediate coronary angiography to be of borderline significance with regards to its association with survival at 30 days (estimate 0.66 [-0.05–1.36], p = 0.069).

## Discussion

Although OHCA is mostly caused by acute myocardial infarction, it is unknown whether early coronary angiography is associated with improved survival in all patients after OHCA.

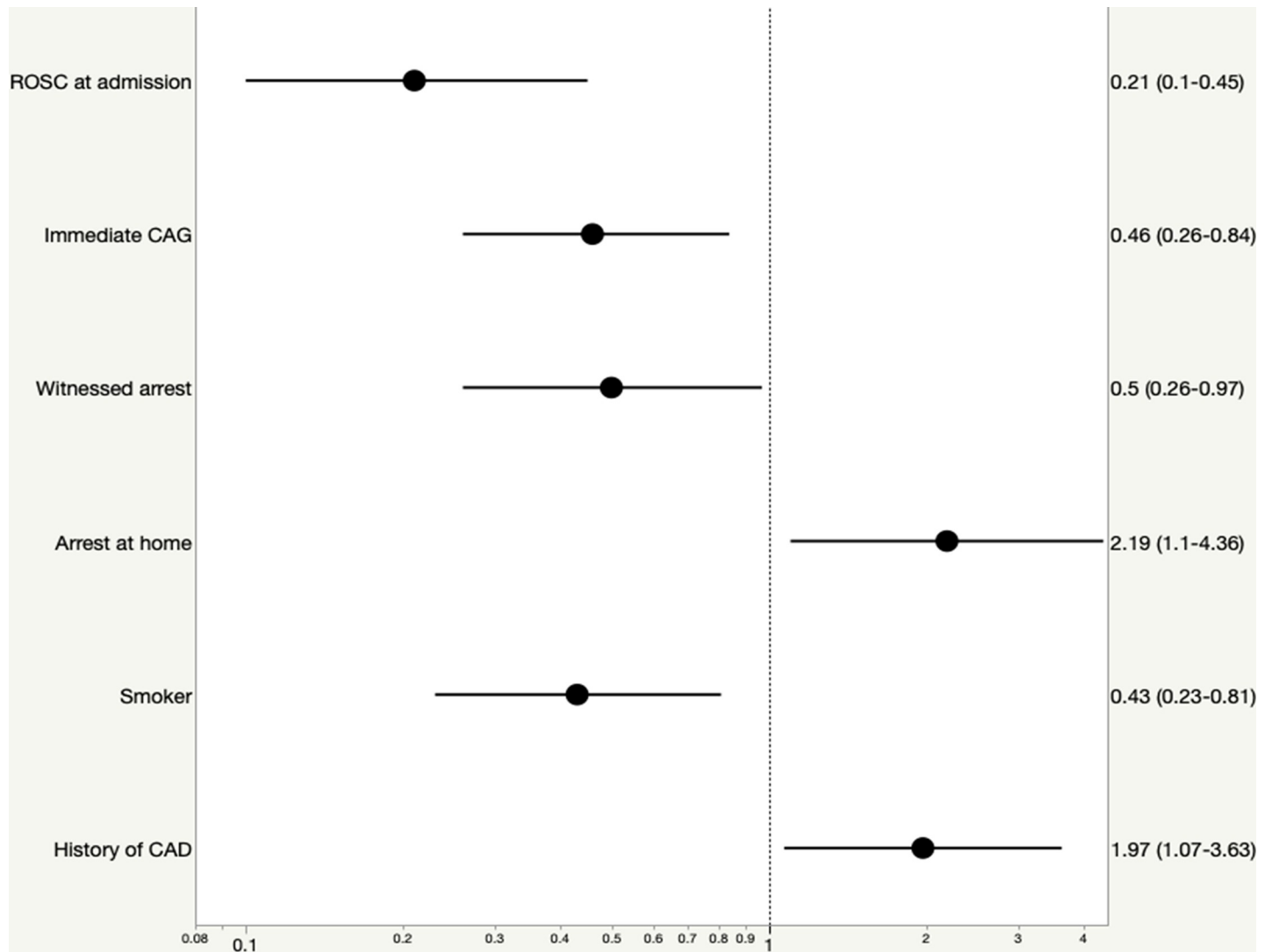
Our study represents one of the largest cohorts analyzing patients after out-of-hospital arrest with long-term survival and coronary angiographic data, collected at 2 centers specialized in coronary intervention and post-resuscitation care. It was our aim to characterize this extremely heterogeneous and critically ill population especially with regards to the impact of immediate coronary angiography. In this regard, the most salient findings can be described as follows:

**Table 7. Patients with immediate CAG and no immediate CAG according to the matching variables.**

	Entire population			Matched population		
	Immediate CAG n = 385	No immediate CAG n = 134	p-value	Immediate CAG n = 119	No immediate CAG n = 119	p-value
Female	89/385 (23.1)	45/134 (33.6)	<b>0.02</b>	26/119 (21.8)	36/119 (30.3)	0.14
Arrest at home	89/376 (23.7)	66/125 (52.8)	< <b>0.001</b>	93/119 (78.12)	86/119 (72.3)	0.29
ROSC at admission	327/384 (85.2)	86/133 (64.7)	< <b>0.001</b>	84/119 (70.6)	83/119 (69.6)	0.88
Daytime presentation	330/384 (85.9)	106/131 (80.9)	0.17	109/119 (84.9)	101/119 (84.9)	0.11
Witnessed arrest	295/364 (81.0)	86/123 (69.9)	<b>0.01</b>	83/119 (69.8)	95/119 (79.8)	0.07
Smoking	143/326 (43.9)	25/83 (30.1)	<b>0.02</b>	38/119 (31.9)	25/119 (21.0)	0.06
Hypercholesterolemia	208/327 (63.6)	32/82 (39.0)	< <b>0.001</b>	68/119 (57.1)	75/119 (63.0)	0.36

Data are presented as n (%).

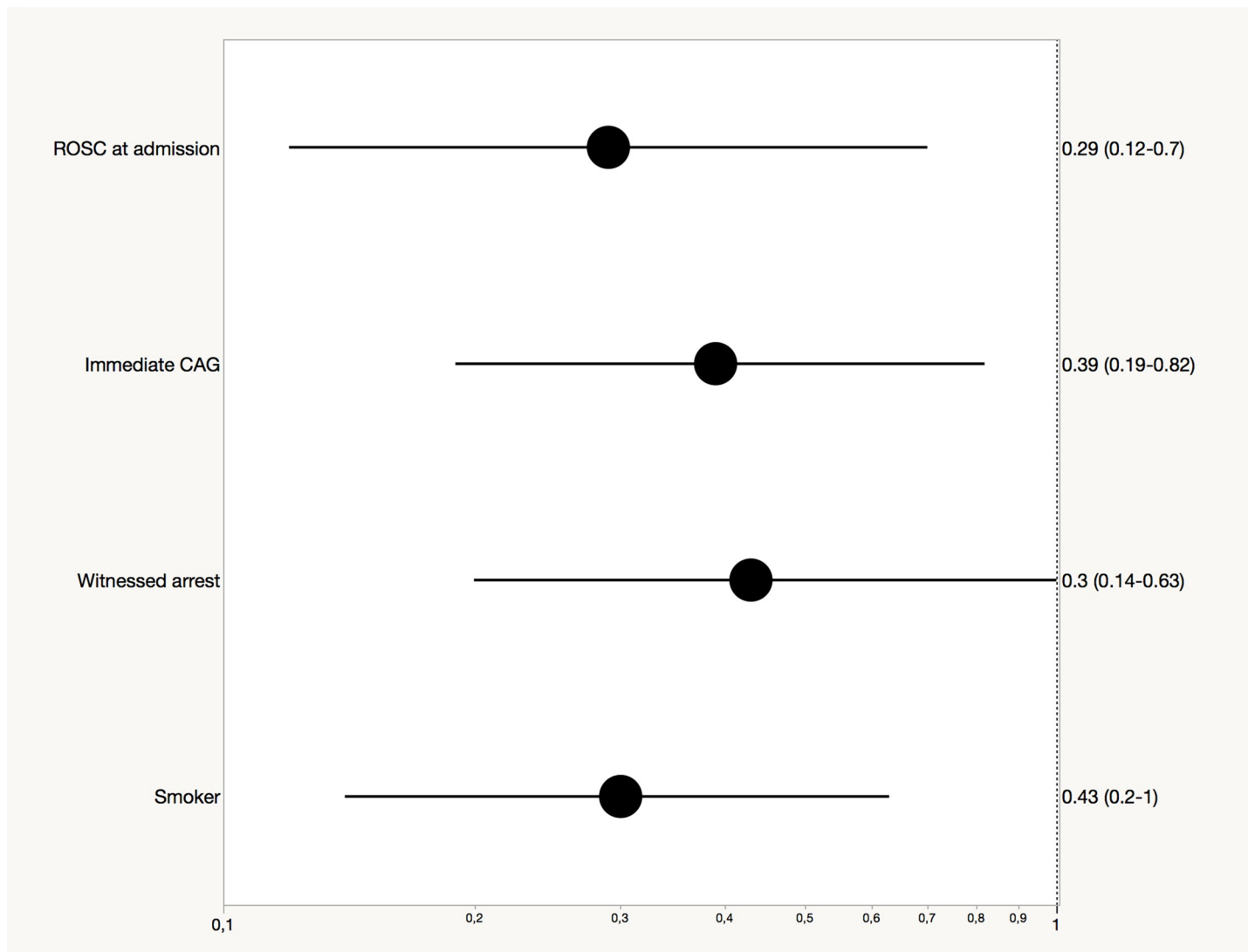
<https://doi.org/10.1371/journal.pone.0218634.t007>



**Fig 2. Forest plot with odds ratios and 95% confidence intervals of factors associated with 30-days-survival after propensity score-matched analysis.**

<https://doi.org/10.1371/journal.pone.0218634.g002>

- Of the 519 patients admitted to the 2 participating centers, 74.1% of the study population underwent emergency coronary angiography.
- 233/383 patients (60.8%) in the immediate CAG group were diagnosed with STEMI (n = 106) after first ECG following ROSC or NSTEMI (n = 127) after having completed diagnostic work-up including coronary angiography versus 19/134 patients (14.2%) in the no immediate CAG group.
- In our cohort, good neurological function at discharge, defined as CPC 1 or 2, was achieved in 164/299 (54.8%)
- 30-days-survival and survival after one year was significantly higher among patients undergoing immediate CAG compared to patients without immediate CAG [221/370 (59.7) vs. 30/131 (22.9),  $p < 0.001$ ] and [161/341 (47.2) vs. 14/124 (11.3),  $p > 0.001$ ]
- In our cohort, good neurological function at discharge, defined as CPC 1 or 2, was achieved in 164/299 (54.8%)



**Fig 3. Forest plot with odds ratios and 95% confidence intervals of factors associated with 1-year-survival after propensity score-matched analysis.**

<https://doi.org/10.1371/journal.pone.0218634.g003>

→ By multivariate analysis after PS matching, we identified ROSC at admission and immediate CAG, witnessed arrest and former smoking as independent predictive factors for 30-days-survival and 1-year-survival in patients with OHCA

### **Influence of study population and immediate coronary angiography on survival**

Our study is composed of patients presenting to 2 tertiary centers specialized in cardiac care with capability for primary PCI and post-resuscitation care after OHCA. Consequently, pre-selection of patients by on-site emergency physicians and paramedical staff is very likely to impact significantly on overall findings and survival [13]. Additional selection bias arises from early triage after patient admission, where those with ST-segment elevation and other ECG abnormalities suggestive of ischemia are likely to undergo immediate CAG. To reduce these confounding factors, we performed propensity score regression analysis, IPTW-analysis and

sensitivity analysis excluding patients with STEMI, which confirmed the survival benefit of patients undergoing immediate CAG. The partially wide confidence intervals can be interpreted as an indication for the heterogeneity of the patient population. Along these lines, the overall survival rate of 50.1% in our study further supports the previously encountered phenomenon that triage into early angiographic evaluation in dedicated cardiac care centers may help improve outcome of these critically ill patients.

Previous studies suggested a high incidence of coronary artery disease in patients without obvious extracardiac cause of arrest, proposing early coronary angiography to be performed in most patients [8,14,15]. The diagnosis of NSTEMI is oftentimes difficult to confirm in the setting of OHCA owing to prevalent ECG and laboratory abnormalities in these patients. Consequently, it is likely that patients presenting with STEMI largely benefited from early revascularization, which impacted on overall study outcome. Yet, the impact of immediate coronary angiography to rule out myocardial ischemia remains to be determined in the setting of NSTEMI and OHCA, where major randomized clinical trials to address this question are currently ongoing.

The fact that we found former smoking as predictive factor for improved 30-days and 1-year survival needs further investigation in dedicated studies and might be explained by similar mechanisms known from the well-established conundrum of the “smoker’s paradox”, which has been reported by other groups in patients after cardiopulmonary resuscitation [16,17].

Corroborated by our findings, these results emphasize the relevance of appropriate patient selection for an invasive diagnostic strategy [8,18].

### Factors impacting on neurological outcome and survival

Good neurological function (defined as CPC 1&2) at discharge was achieved in 164/299 (54.8) of the patients, comparable to previous studies [19–21], with improved neurological outcome for patients undergoing immediate CAG. While previous studies addressing this association have already suggested a favorable effect of early angiographic assessment in post-resuscitation care, most, if not all studies including ours are hampered by non-randomized and retrospective design, increasing the chance to receive immediate CAG in patients with obvious ECG abnormalities and favorable OHCA resuscitation response including those with early ROSC, bystander CPR and witnessed arrest [22,23]. These constraints especially apply to the diagnosis STEMI, which is almost exclusively based on the first ECG at admission. In accordance with the current guidelines of the European Society of Cardiology, patients with STEMI are immediately transferred to the cath lab [24]. Consequently, it is likely that patients presenting with STEMI largely benefited from early revascularization, which impacted on overall study outcome. To validate the benefit of immediate coronary angiography in the entire population, we performed sensitivity analysis excluding patients with STEMI reaching borderline significance regarding the association of immediate CAG in this setting.

Patients undergoing immediate CAG are at higher likelihood for a favorable neurological outcome compared to those patients where early triage during patient presentation is influenced by unfavorable OHCA resuscitation response and absence of ECG abnormalities.

Nevertheless, we and other authors have shown that culprit coronary lesions are detected in a large proportion of patients undergoing immediate CAG providing an opportunity to improve neurological outcome by primary PCI and by using propensity matching, we aimed to reduce the inherent selection bias of observational studies.

Patients with immediate CAG had significantly more often bystander CPR and a witnessed arrest, which is consistent with more shockable rhythms in this group leading to ROSC at

admission, which we have shown to be predictive of favorable outcome [25,26]. In line with this, our findings are congruent with those of Stiell et al. in such that bystander resuscitation is a major factor of survival and neurological outcome after cardiac arrest. In addition, the widespread availability of automated external defibrillators (AEDs) has recently been shown to be associated with favorable outcome, which highlights the importance of prehospital resuscitation quality [23,27].

In our cohort, 30-days-survival was greater among patients with immediate coronary angiography compared to those without. These results are similar to those shown in the meta-analysis by Camuglia et al. with the limitation that they only considered survival to hospital discharge [21]. However, whether immediate CAG with subsequent PCI is associated with improved outcome or whether comorbidity and yet unidentified factors prevail to determine outcome in this critically-ill patient population remains to be investigated in dedicated prospective trials.

### Limitations

In our study, we observed an overall survival rate of 50.1%, which is in agreement with a priori selection of best candidates for early CAG. Furthermore, it was performed at 2 centers, where prehospital management of OHCA is performed according to standardized protocols with great experience in the treatment of acute coronary syndrome and cardiac arrest, which might have contributed to better survival rates than elsewhere and was recently pointed out by Soholm et al [13].

Our observations are obviously limited by the retrospective design of the study. Outcomes in the heterogenous population of patients after OHCA are likely impacted by selection bias and best practice of treating physicians.

### Conclusions

Our findings support that triage for immediate coronary angiography as part of post-resuscitation care facilitated by rapid interdisciplinary decision-making is of major importance. Furthermore, we confirmed the favorable impact of optimal prehospital management with improved outcome after witnessed arrest probably resulting in ROSC at admission.

Immediate coronary angiography in cardiac arrest survivors appears to be associated with improved survival and may enable therapeutic algorithms, particularly identifying those who may benefit from acute revascularization therapy.

### Supporting information

**S1 File. Imputed data of the entire population.**  
(XLS)

**S2 File. Basic data of the matched population.**  
(XLS)

### Author Contributions

**Conceptualization:** Rainer Okrojek, Karl-Ludwig Laugwitz, Robert Byrne, Heribert Schunkert, Adnan Kastrati, Michael Joner.

**Data curation:** Anna Berkefeld, Maximilian Ketter, Lucas Martinez, Rainer Okrojek, Petra Hoppmann, Sebastian Kufner, Erion Xhepa.

**Formal analysis:** Dario Bongiovanni.

**Validation:** Salvatore Cassese.

**Writing – original draft:** Anna Lena Lahmann.

**Writing – review & editing:** Patrick Mayr.

## References

1. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation* 2005; 67:75–80. <https://doi.org/10.1016/j.resuscitation.2005.03.021> PMID: 16199289
2. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation* 2010; 81:1479–87. <https://doi.org/10.1016/j.resuscitation.2010.08.006> PMID: 20828914
3. Eisenberg MS, Mengert TJ. Cardiac resuscitation. *N Engl J Med* 2001; 344:1304–13. <https://doi.org/10.1056/NEJM200104263441707> PMID: 11320390
4. Bunch TJ, White RD, Gersh BJ, Meverden RA, Hodge DO, Ballman KV, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. *N Engl J Med* 2003; 348:2626–33. <https://doi.org/10.1056/NEJMoa023053> PMID: 12826637
5. Grubb NR, Fox KAA, Elton RA. In-hospital mortality after out-of-hospital cardiac arrest. *The Lancet* 1995; 346:417–21.
6. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–63. <https://doi.org/10.1056/NEJMoa003289> PMID: 11856794
7. Kern KB, Lotun K, Patel N, Mooney MR, Hollenbeck RD, McPherson JA, et al. Outcomes of Comatose Cardiac Arrest Survivors With and Without ST-Segment Elevation Myocardial Infarction: Importance of Coronary Angiography. *JACC Cardiovasc Interv* 2015; 8:1031–40. <https://doi.org/10.1016/j.jcin.2015.02.021> PMID: 26117462
8. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac Arrest) registry. *Circ Cardiovasc Interv* 2010; 3:200–7. <https://doi.org/10.1161/CIRCINTERVENTIONS.109.913665> PMID: 20484098
9. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33:2569–619. <https://doi.org/10.1093/eurheartj/ehs215> PMID: 22922416
10. Anyfantakis ZA, Baron G, Aubry P, Himbert D, Feldman LJ, Juliard JM, et al. Acute coronary angiographic findings in survivors of out-of-hospital cardiac arrest. *Am Heart J* 2009; 157:312–8. <https://doi.org/10.1016/j.ahj.2008.09.016> PMID: 19185639
11. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation* 2004; 63:233–49. <https://doi.org/10.1016/j.resuscitation.2004.09.008> PMID: 15582757
12. Abramson NS, Detre K, Bradley K, Kelsey SF, Ricci E, Safar P, et al. Impact evaluation in resuscitation research: discussion of clinical trials. *Crit Care Med* 1988; 16:1053–8. <https://doi.org/10.1097/00003246-198810000-00019> PMID: 3168495
13. Soholm H, Kjaergaard J, Bro-Jeppesen J, Hartvig-Thomsen J, Lippert F, Kober L, et al. Prognostic Implications of Level-of-Care at Tertiary Heart Centers Compared With Other Hospitals After Resuscitation From Out-of-Hospital Cardiac Arrest. *Circ Cardiovasc Qual Outcomes* 2015; 8:268–76. <https://doi.org/10.1161/CIRCOUTCOMES.115.001767> PMID: 25944632
14. Strote JA, Maynard C, Olsufka M, Nichol G, Copass MK, Cobb LA, et al. Comparison of Role of Early (<6 Hours) to Later (>6 Hours) or No Cardiac Catheterization Following Resuscitation From Out-of-hospital Cardiac Arrest. *The American Journal of Cardiology* 2012; 109:451–4. <https://doi.org/10.1016/j.amjcard.2011.09.036> PMID: 22100026
15. Hollenbeck RD, McPherson JA, Mooney MR, Unger BT, Patel NC, McMullan PW Jr., et al. Early cardiac catheterization is associated with improved survival in comatose survivors of cardiac arrest without

- STEMI. *Resuscitation* 2014; 85:88–95. <https://doi.org/10.1016/j.resuscitation.2013.07.027> PMID: 23927955
16. Gupta T, Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, et al. Relation of smoking status to outcomes after cardiopulmonary resuscitation for in-hospital cardiac arrest. *Am J Cardiol* 2014; 114:169–74. <https://doi.org/10.1016/j.amjcard.2014.04.021> PMID: 24878124
  17. Roberts A. Cardiac resuscitation: The 'smoker's paradox' after in-hospital cardiac arrest. *Nat Rev Cardiol* 2014; 11:374.
  18. Zanuttini D, Armellini I, Nucifora G, Carchietti E, Trillò G, Spedicato L, et al. Impact of Emergency Coronary Angiography on In-Hospital Outcome of Unconscious Survivors After Out-of-Hospital Cardiac Arrest. *The American Journal of Cardiology* 2012; 110:1723–8. <https://doi.org/10.1016/j.amjcard.2012.08.006> PMID: 22975468
  19. Wibrandt I, Norsted K, Schmidt H, Schierbeck J. Predictors for outcome among cardiac arrest patients: the importance of initial cardiac arrest rhythm versus time to return of spontaneous circulation, a retrospective cohort study. *BMC Emergency Medicine* 2015; 15:3. <https://doi.org/10.1186/s12873-015-0028-3> PMID: 25648841
  20. Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. *Resuscitation* 2011; 82:1036–40. <https://doi.org/10.1016/j.resuscitation.2011.03.034> PMID: 21524837
  21. Camuglia AC, Randhawa VK, Lavi S, Walters DL. Cardiac catheterization is associated with superior outcomes for survivors of out of hospital cardiac arrest: review and meta-analysis. *Resuscitation* 2014; 85:1533–40. <https://doi.org/10.1016/j.resuscitation.2014.08.025> PMID: 25195073
  22. Stiell IG, Wells GA, Field B, Spaite DW, Nesbitt LP, De Maio VJ, et al. Advanced Cardiac Life Support in Out-of-Hospital Cardiac Arrest. *New England Journal of Medicine* 2004; 351:647–56. <https://doi.org/10.1056/NEJMoa040325> PMID: 15306666
  23. Blom MT, Beesems SG, Homma PC, Zijlstra JA, Hulleman M, van Hoeijen DA, et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. *Circulation* 2014; 130:1868–75. <https://doi.org/10.1161/CIRCULATIONAHA.114.010905> PMID: 25399395
  24. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37:267–315. <https://doi.org/10.1093/eurheartj/ehv320> PMID: 26320110
  25. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. *Eur Heart J* 2006; 27:2840–5. <https://doi.org/10.1093/eurheartj/ehl335> PMID: 17082207
  26. Kragholm K, Wissenberg M, Mortensen RN, Hansen SM, Malta Hansen C, Thorsteinsson K, et al. Bystander Efforts and 1-Year Outcomes in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2017; 376:1737–47. <https://doi.org/10.1056/NEJMoa1601891> PMID: 28467879
  27. Stiell I, Nichol G, Wells G, De Maio V, Nesbitt L, Blackburn J, et al. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation* 2003; 108:1939–44. <https://doi.org/10.1161/01.CIR.0000095028.95929.B0> PMID: 14530198