Outcome differences between PARAMEDIC2 and the German Resuscitation Registry: a secondary analysis of a randomized controlled trial compared with registry data

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Background and importance   There has been much discussion of the results of the PARAMEDIC2 trial, as resuscitation outcome rates are considerably lower in this trial than in country-level registries on out-of-hospital cardiac arrest (OHCA). Here, we developed a statistical framework to investigate this gap and to examine possible sources for observed discrepancies in outcome rates.

Design   Summary data from the PARAMEDIC2 trial were used as available in the publication of this study. We developed a modelling framework based on logistic regression to compare data from this randomized controlled trial and registry data from the German Resuscitation Registry (GRR), where we considered 26 019 patients treated with epinephrine for OHCA in the GRR. To account and adjust for differences in patient characteristics and baseline variables predictive for outcomes after OHCA between the GRR cohort and the PARAMEDIC2 study sample, we included all available variables determined at the arrival of EMS personnel in the modelling framework: age, sex, initial cardiac rhythm, cause of cardiac arrest, witness of cardiac arrest, CPR performed by a bystander, and the interval between emergency call and arrival of the ambulance at the scene (baseline model). In order to find possible explanations for the discrepancies in outcome between PARAMEDIC2 and GRR, in a second (baseline plus treatment) model, we additionally included all available variables related to the interventions of the EMS personnel (type of airway management, type of vascular access, and time to administration of epinephrine).

Main results   A patient cohort with baseline variables as in the PARAMEDIC2 trial would have survived to hospital discharge in 7.7% and survived with favourable neurological outcome in 5.0% in an EMS and health care system as in Germany, compared with 3.2 and 2.2%, respectively, in the Epinephrine group of the trial. Adding treatment-related variables to our logistic regression model, the rate of survival to discharge would decrease from 7.7 (for baseline variables only) to 5.6% and the rate of survival with favourable neurological outcome from 5.0 to 3.4%.

Conclusion   Our framework helps in the medical interpretation of the PARAMEDIC2 trial and the transferability of the trial's results for other EMS systems. Significantly higher rates of survival and favourable neurological outcome than reported in this trial could be possible in other EMS and health care systems. *European Journal of Emergency Medicine* XXX: 000–000 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

Despite limited evidence, epinephrine (adrenaline) has been an integral part of international guidelines for cardiopulmonary resuscitation (CPR) for decades [1]. In 2018, Perkins *et al.* [2] published the results of their Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC2) trial, a randomized double-blind study on the safety and effectiveness of epinephrine in 8014 patients suffering from out-of-hospital cardiac arrest (OHCA). The authors reported a higher rate of survival at hospital discharge and at 30 days with the use of epinephrine than with placebo. However, although the groups were well balanced, the rate of

favourable neurological outcome at hospital discharge was almost as low in the epinephrine group (2.2%) as in the placebo group (1.9%), with no statistically significant difference and an unadjusted odds ratio (OR) of 1.18 [95% confidence interval (CI), 0.86–1.61] [2]. There has been much discussion of the reasons for the low rates of survival and the lack of good functional outcome in the PARAMEDIC2 trial when compared with data from other emergency medical service (EMS) systems around the world [3,4]. Of 11 103 patients who received epinephrine after OHCA and were enrolled in the Cardiac Arrest Registry of the Victorian Ambulance in Australia, 5.9% had a favourable neurological outcome 12 months after cardiac arrest [3]. The German Resuscitation Registry (GRR) reported that among 15 849 patients receiving epinephrine after OHCA, the rate with a favourable neurological outcome at hospital discharge was 7.2% [4]. However, differences in patient characteristics, baseline characteristics of resuscitation (e.g. rate of bystander CPR and time intervals between emergency call and ambulance arrival), as well as EMS systems (e.g. qualification and training levels, and standard procedures) make it very difficult to compare outcome parameters in different studies or registries on OHCA.

The aim of this study was first to develop a statistical methodology to be able to compare data from a randomized controlled trial (RCT) with registry data and second to use this model framework to find explanations for the discrepancies between the PARAMEDIC2 trial and GRR.

Methods

As a first step, we provided a statistical modelling framework of outcome parameters after OHCA, based on demographic, physiological, and medical predictors typically available in publications of trials on CPR in the out-of-hospital setting. This model allowed the computation of probabilities and comparison of outcomes at each step of the patient pathway after OHCA including restoration of spontaneous circulation (ROSC), survival to hospital admission/discharge, and favourable neurological outcome. Based on this modelling framework, we tried to identify factors contributing to the substantial differences in outcomes in the epinephrine group of the PARAMEDIC2 trial (which reflects the group of patients treated according to the international standards and guidelines for CPR) and the GRR.

The German Resuscitation Registry group

The GRR was started in 2007 by the German Society for Anaesthesiology and Intensive Care Medicine as an ongoing international, prospective, multicentre registry. This registry covers more than 23 million inhabitants of Germany. As of August 2021, 228 650 patients with OHCA and 137 215 patients with attempted resuscitation after OHCA have been documented. The German EMS system is based on paramedic-staffed ground ambulances and separate EMS physician vehicles, which rendezvous at the site of the emergency. For a more detailed description of the system see reference [5]. The GRR has been constructed in accordance with the Utstein style [6].

Inclusion criteria: all patients who suffered OHCA during the period 1 January 2011 to 31 December 2020 and who received treatment from an EMS in any region participating in the GRR were eligible for inclusion in the study. We excluded all patients who received no vasopressor (generally epinephrine) during CPR. This was mainly the case if ROSC was achieved or if resuscitation was withheld (e.g. due to a 'do not resuscitate' order) before the temporal sequence of the CPR algorithm according to the guidelines recommended by the administration of epinephrine. Further exclusion criteria were inhospital cardiac arrest, trauma, and age less than 18 years. In order to minimize selection bias in terms of survival and as a check for data quality, only reference EMS systems with a return rate of more than 60% for the inhospital clinical treatment dataset on an annual basis were included. This resulted in a calculated return rate of more than 87%. These reference EMS systems are known to sufficiently represent Germany as a whole. A flowchart indicating both the patient selection from the GRR as well as data availability for each logistic regression model of the resuscitation pathway is shown in Fig. 1.

In the GRR, neurological outcome is documented as a cerebral performance category (CPC) ranging from 1 (no or mild neurological deficits) to 5 (brain death), with categories 1 and 2 defined as favourable outcomes.

The PARAMEDIC2 trial

The PARAMEDIC2 trial was a randomized, double-blind trial involving a total of 8014 patients with OHCA in the UK [2]. The patients were randomly assigned to receive either parenteral epinephrine (4015 patients) or saline placebo (3999 patients), along with standard care. The primary outcome parameter was the rate of survival at 30 days. Secondary outcomes were the rate of survival until hospital admission and hospital discharge as well as hospital discharge with a favourable neurological outcome, indicated by a score of 3 or less on the modified Rankin scale (mRS), which ranges from 0 (no symptoms) to 6 (death). Due to the aim of our analysis, we only refer to the epinephrine group of the PARAMEDIC2 trial [2].

We did not have access to individual data of the PARAMEDIC2 trial.

Ethics

Since only primarily anonymised data were processed and evaluated, criteria for nonhuman subjects research were met. Therefore, the responsible institutional review board (Landesärztekammer Stuttgart) waived

Fig. 1.
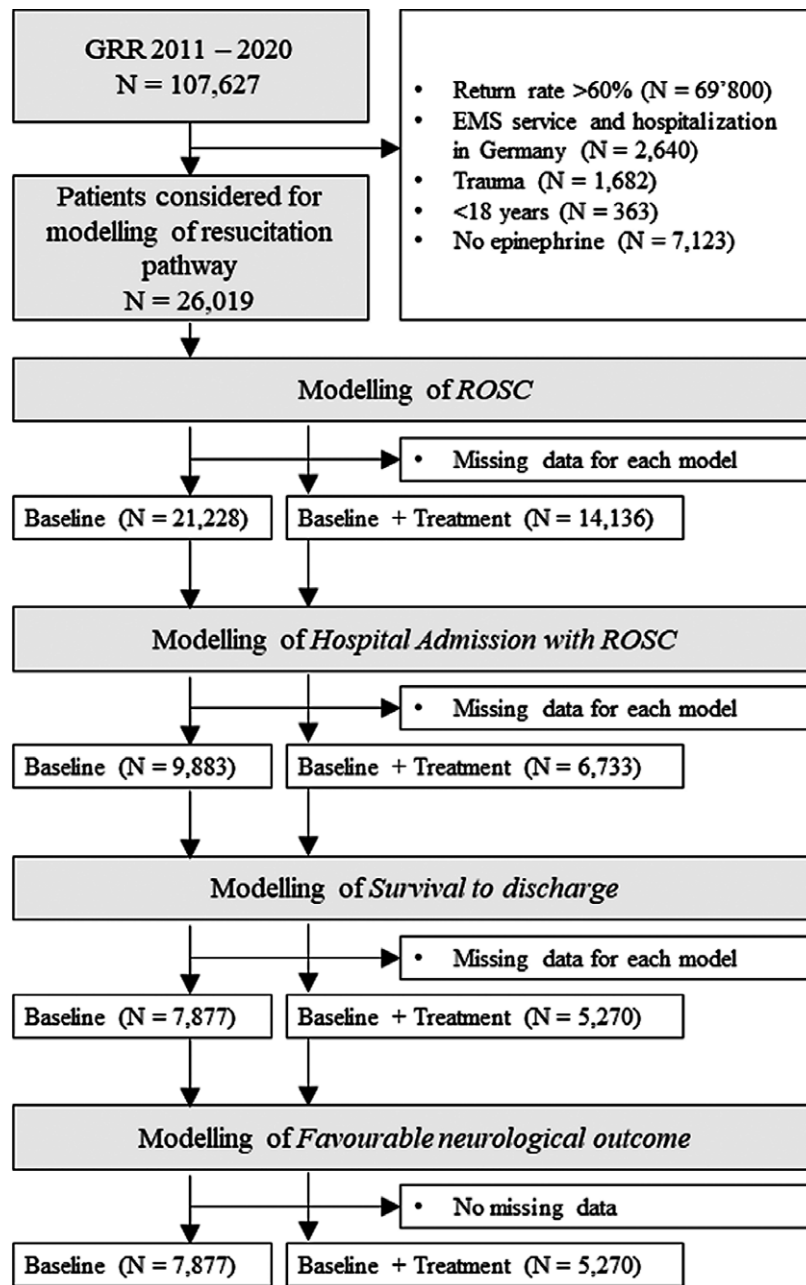
Flowchart of patient selection from the German Resuscitation Registry (GRR) for the development of the modelling framework. EMS, emergency medical service; ROSC, restoration of spontaneous circulation.

the requirement of a specific ethics vote. The study was approved by the scientific advisory council of the GRR (study identifier 2020-01).

Development of the model

In terms of patient characteristics, baseline, and treatment-related predictors of outcome after OHCA, the distribution of continuous variables was examined with Q–Q plots. Results are presented with mean and SD when normally distributed, and with median and interquartile range otherwise. Count data are presented as numbers and proportions.

We focussed on four chronologically related outcomes after CPR: ROSC, hospital admission with ROSC, survival to hospital discharge, and favourable neurological outcome at hospital discharge. For better readability, we refer to these as the 'resuscitation pathway'.

Comparison of PARAMEDIC2 with GRR

We grouped the available predictors of outcome after OHCA into two groups. The so-called baseline variables included all available predictors given before the arrival of professional EMS personnel: age, sex, initial cardiac rhythm, cause of cardiac arrest, witness of cardiac arrest, CPR performed by a bystander, and the interval between emergency call and arrival of the ambulance at the scene. The so-called baseline plus treatment variables included all previously mentioned predictors plus all available predictors of treatment-related measures influenced by the EMS team: type of vascular access (intravenous or intraosseous), devices for airway management (supraglottic airway only or tracheal tube) and the amount of time between the emergency call and the administration of epinephrine. We modelled the conditional probabilities of each outcome using a logistic regression model. We used baseline and baseline plus treatment variables as covariates to predict the success probability for each outcome during the resuscitation pathway, conditional on the previous outcome. As an example, to model the survival probability at discharge, we conditioned the GRR cohort to only those patients who were successfully admitted to the hospital (who in turn were conditioned to only those patients with a successful ROSC). We ran the models 100 times (each with n = 4015 patients) for each of the four outcomes along the resuscitation pathway.

Goodness-of-fit and discrimination ability of the models were assessed by the area under the receiver operating characteristic curve (AUROC) and Nagelkerke's pseudo R-squared statistic. Calibration plots are presented in the Supplementary Material (Supplementary Figure SM 1, Supplemental Digital Content 1, *http://links.lww.com/ EJEM/A346*).

Comparability between the two cohorts

While the PARAMEDIC2 trial used the mRS, the GRR uses CPC. However, as favourable neurological outcome is defined as mRS ≤ 3 (mRS 3: moderate disability, requiring some help, but able to walk without assistance) and CPC ≤ 2 (CPC 2: moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life, able to work in a sheltered environment), the presentation of neurological outcomes in both studies can be considered comparable. The GRR documents, the time interval from the alarm to the administration of the first vasopressor, and the PARAMEDIC2 trial report the time interval from the emergency call to administration of epinephrine. Therefore, in order for the time intervals to be comparable, we added 2 min to the time interval given in the GRR as a reliable estimate the call taker needs to alert the EMS crew [7].

Statistical software

All computations were performed using R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) (The R Foundation for Statistical Computing, Vienna, Austria) [8].

Results
Model framework
Cohort description

Patients' characteristics, baseline and treatment-related characteristics of CPR, and observed outcomes in the PARAMEDIC2 trial's epinephrine group and all 26 019 patients in the GRR group are shown in Table 1. The two cohorts display similar characteristics in their age and sex distribution, whereas differences are seen in the proportion of patients with shockable cardiac rhythm, proportion of patients with bystander CPR, type of vascular access, type of airway devices, and the time interval between emergency call and administration of epinephrine.

Model evaluation

We evaluated the goodness-of-fit and predictive performance of the logistic regression models in predicting the outcomes in the resuscitation patient pathway of the GRR. Table 2 presents the ORs and associated CIs for the logistic regression model for the short-term outcomes of ROSC and hospital admission with ROSC. The models featured moderate AUROC and Nagelkerke pseudo R-square values of 0.70 (95% CI, 0.69–0.70; pseudo-R^2, 0.15) for ROSC and 0.62 (95% CI, 0.61–0.64; pseudo-R^2, 0.05) for hospital admission with ROSC, respectively. The model fit for the outcomes 'Survival at 30 days' and 'Favourable Neurological Outcome' are shown in Table 3 with corresponding AUROC and Nagelkerke pseudo R-square values of 0.75 (95% CI, 0.74–0.77; pseudo-R^2, 0.21) and 0.77 (95% CI, 0.75–0.79; pseudo-R^2, 0.21), respectively. The calibration plots in the Supplementary Material (Supplementary Figure SM 1, Supplemental Digital Content 1, *http://links. lww.com/EJEM/A346*) indicate that the models generally slightly overestimated the success probability. In particular, the baseline plus treatment model for the patient-relevant outcomes 'Survival to discharge' and 'Favourable neurological outcome' are well-calibrated (Panels G and H in Figure SM 1, Supplemental Digital Content 1, *http:// links.lww.com/EJEM/A346*).

Modelling the resuscitation patient pathway

To assess the prediction skill of the logistic regression models, we simulated a random sample of 1000 cohorts (each with n = 4015 patients) within the GRR and compared our prediction with outcomes measured in the GRR (Fig. 2). Figure 2a illustrates the distribution of the average outcome in these 1000 cohorts. It is important to note that the success probabilities for each outcome refer to the percentage relative to the previous successful outcome. For example, the logistic regression model with baseline and treatment-related variables predicts that on average, 78.3% of those patients with an initial ROSC were admitted to hospital with a sustained ROSC. Similarly, the logistic regression

Table 1. Patients' characteristics, baseline and treatment-related characteristics, and outcomes in the Epinephrine group of the PARAMEDIC2 trial and the German Resuscitation Registry

	PARAMEDIC2 Epinephrine Group	German Resuscitation Registry (GRR)	Baseline model	Baseline plus treatment model
	$n = 4015$	$n = 26\,019$		
Baseline and treatment-related				
Age (year) [mean (SD)]	69.7 (±16.6)	72.4(±14.6)	x	x
Sex (male) (%)	65.0	66.1	x	x
Only supraglottic airway (yes) (%)	70.8	20.6		x
Intraosseous access (yes) (%)	33.4	17.0		
Intravenous access (yes) (%)	68.2	94.2		x
Tracheal tube (yes) (%)	30.0	74.2		
Interval between emergency call and ambulance arrival at scene (min) [median (IQR)]	6.7 (4.3–9.7)	8.0 (6.0–10.0)[a]	x	x
Interval between emergency call and administration of epinephrine (min)	21.5 (16.0–27.3)	16.0 (13.0–20.0)[a]		x
Initial cardiac rhythm (%)			x	x
Shockable (yes)	19.2	23.7		
Not shockable (yes)	78.4	75.0		
Asystole (yes)	53.5	53.9		
Cause of cardiac arrest (%)			x	x
Medical cause (yes)	91.1	82.6		
Asphyxia (yes)	2.9	12.7		
Drowning (yes)	0.2	0.4		
Witness of cardiac arrest (%)			x	x
Bystander (yes)	50.1	45.2		
Paramedic/EMS physician or paramedic (yes)	11.3	7.4		
CPR performed by bystander (yes) (%)	59.3	34.9	x	x
Outcomes				
ROSC (yes) (%)	36.3	46.5		
Hospital admission with ROSC (yes) (%)	23.8	36.8		
Survival at discharge (yes) (%)	3.2	9.9		
Favourable Neurologic outcome at hospital discharge (yes) (%)	2.2	6.5		

The distribution of missing data is shown in the Supplementary Material, (Supplemental Digital Content 2, *http://links.lww.com/EJEM/A347*). Further, the variables of the two types of prediction models – a baseline model and a baseline plus treatment model – are indicated as crosses.

CPR, cardiopulmonary resuscitation; EMS, emergency medical service; IQR, interquartile range; ROSC, restoration of spontaneous circulation.

[a]For comparison with the PARAMEDIC2 trial, 2 min are added to the raw values of the GRR (see Methods).

model with baseline and treatment-related variables predicted that 25.8% of all patients who were admitted to hospital with ROSC survived to hospital discharge and that 17.1% of all patients who were admitted to hospital with ROSC showed favourable neurological outcomes. The prediction agrees very well with the true underlying values of the GRR, which are portrayed as dashed lines in Fig. 2.

Figure 2b illustrates the predictions where the percentages for outcome refer to the entire cohort at the beginning of the pathway. These numbers were derived by multiplying the average outcome prediction at each step of each cohort in the 100-member ensemble with the previous outcome prediction: for example, multiplying the average predictions of two outcomes ROSC and Hospital Admission with ROSC of the logistic regression models resulted in an average prediction rate of 37.3% with successful hospital admission of the entire cohort. Similarly, multiplying the individual predictions of the outcomes ROSC, hospital admission with ROSC, and survival until discharge resulted in an average prediction of 9.6% with successful hospital admission of the entire cohort. Again, the predictions made by the logistic regression models agreed very well with the true underlying values of the GRR. Thus, the modelling framework employed in this study suggests that on a cohort level, the outcome predictions in the resuscitation pathway can be combined in a multiplicative fashion.

Comparison of PARAMEDIC2 with GRR

Using this model framework, we were able to compare two cohorts (the GRR group and the PARAMEDIC2 group) with the aim of answering the question: 'What would the outcomes in the GRR look like for patients with baseline variables of CPR comparable to those of the patients in the PARAMEDIC2 trial? And further, might the differences in the known treatment-related variables explain the discrepancies in outcome documented in the GRR and the PARAMEDIC2 trial?'

Figure 3 illustrates the modelled outcomes of patients in the GRR fitting the summary measures of patients in the Epinephrine group of the PARAMEDIC2 trial based on logistic regression modelling. Based on baseline variables only, simulation of a patient cohort as in the Epinephrine group of the PARAMEDIC2 trial resulted in an average ROSC success rate of 45.7%, average rates of hospital admissions with ROSC of 35.1%, survival to hospital discharge of 7.7%, and survival with favourable neurological outcome of 5.0%, respectively, significantly better than the

Table 2. Model coefficient and associated confidence intervals for the logistic regression model for the outcomes ROSC and Hospital Admission with ROSC

| | ROSC | | Hospital Admission with ROSC | |
| | Baseline plus treatment model[a] | | Baseline plus treatment model[b] | |
	OR (95% CI)	P-value	OR (95% CI)	P-value
Interval between emergency call and ambulance arrival at scene (min)	0.98 (0.97–0.99)	<0.001	0.99 (0.97–1.01)	0.4
Age (year)	1.00 (1.00–1.01)	0.020	0.99 (0.99–1.00)	<0.001
Sex				
Female	–		–	
Male	0.76 (0.70–0.82)	<0.001	0.91 (0.80–1.03)	0.2
Initial cardiac rhythm				
Shockable	–		–	
Nonshockable	0.31 (0.28–0.34)	<0.001	0.57 (0.49–0.65)	<0.001
Other	0.40 (0.28–0.58)	<0.001	1.95 (0.90–5.11)	0.13
Cause of cardiac arrest				
Medical	–		–	
Asphyxia	2.11 (1.90–2.34)	<0.001	2.06 (1.73–2.48)	<0.001
Other	1.43 (1.21–1.68)	<0.001	1.38 (1.04–1.84)	0.029
Witness of cardiac arrest				
Bystander	–		–	
Paramedic/Rescue-Team	1.15 (0.98–1.35)	0.087	0.65 (0.52–0.83)	<0.001
Other	0.51 (0.48–0.55)	<0.001	0.75 (0.66–0.86)	<0.001
CPR performance				
Bystander	–		–	
Not further identified	1.22 (1.13–1.32)	<0.001	1.20 (1.06–1.37)	0.005
Only supraglottic airway				
No	–		–	
Yes	0.53 (0.48–0.58)	<0.001	0.73 (0.62–0.86)	<0.001
Intravenous access				
No	–		–	
Yes	1.24 (1.03–1.48)	0.021	1.31 (0.96–1.76)	0.087
Interval between emergency call and administration of epinephrine (min)	1.00 (1.00–1.00)	>0.9	1.00 (0.99–1.01)	0.5

Coefficients are shown for the models including both baseline and treatment-related predictors (Baseline plus treatment model, Table 1). Goodness-of-fit and discrimination ability of the models are assessed by the area under the receiver operating curve (AUROC) and Nagelkerke's pseudo R-squared statistic. Numbers of patients for each logistic regression model are provided in the flowchart (Fig. 1). Note that data availability naturally decreases over the course of the resuscitation pathway as we model probabilities conditional on the previous outcome.
CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; ROSC, restoration of spontaneous circulation.
[a]AUROC: 0.70 (95% CI, 0.69–0.70), Nagelkerke's Pseudo R-square: 0.15.
[b]AUROC: 0.62 (95% CI, 0.61–0.64), Nagelkerke's Pseudo R-square: 0.05.

observed outcomes in the epinephrine group of the PARAMEDIC2 trial ($P < 0.001$ for all four outcome parameters). Simulation of patient cohorts that are comparable to the PARAMEDIC2 group in baseline plus treatment-related variables resulted in slightly lower average success rates than with baseline variables only (Fig. 3), but still significantly better than in the Epinephrine group of the PARAMEDIC2 trial ($P < 0.001$).

Discussion

We developed a method to compare outcomes of OHCA patients in the GRR with those in the PARAMEDIC2 epinephrine group. In general, comparison and calculation of (expected) outcome rates between centres according to specific prognosis factors is of great scientific interest [9–11]. Our model framework enables the comparison of outcomes published in trials with registry data in different health care systems. It is not only applicable to OHCA but to any field in medicine where comparison of registry data with RCT is desirable (e.g. national registries on sepsis, trauma care, or myocardial infarction). To

our knowledge, our study is the first one developing and using this methodology.

Simulation of a patient cohort with characteristics and baseline conditions as in the PARAMEDIC2 trial proves that outcomes would have had significantly better along the whole resuscitation pathway as observed in the trial. The reasons for this are speculative and manifold. However, as our baseline model adjusted for patient characteristics and other major predictors of outcome after OHCA before ambulance arrival (in the particular rate of bystander CPR and time interval until ambulance arrival at the scene), the answers may lie partly in treatment-related factors during out-of-hospital CPR but also after ROSC (postresuscitation care and inhospital treatment such as targeted temperature management, access to cardiac catheter lab or extracorporeal CPR, and withdrawal of care during intensive care therapy). Information from the PARAMEDIC2 group is available for only three treatment-related variables during the out-of-hospital setting: type of vascular access (intravenous/intraosseous), type of advanced airway management (supraglottic airway/

Table 3. Model coefficient and associated confidence intervals for the logistic regression model for the outcomes Survival at 30 days and favourable neurologic outcome

	Survival at 30 days		Favourable neurologic outcome	
	Baseline plus treatment model[a]		Baseline plus treatment model[b]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Interval between emergency call and ambulance arrival at scene (min)	0.97 (0.95–0.99)	0.009	0.97 (0.95–0.99)	0.017
Age (year)	0.96 (0.96–0.97)	<0.001	0.97 (0.96–0.97)	<0.001
Sex				
Female	–		–	
Male	1.20 (1.03–1.39)	0.020	1.16 (0.97–1.39)	0.10
Initial cardiac rhythm				
Shockable	–		–	
Nonshockable	0.27 (0.23–0.32)	<0.001	0.23 (0.19–0.28)	<0.001
Other	0.37 (0.19–0.69)	0.002	0.21 (0.08–0.46)	<0.001
Cause of cardiac arrest				
Medical	–		–	
Asphyxia	0.93 (0.75–1.14)	0.5	0.75 (0.57–0.97)	0.032
Other	0.71 (0.50–1.00)	0.054	0.66 (0.42–0.99)	0.054
Witness of cardiac arrest				
Bystander	–		–	
Paramedic/Rescue-Team	1.96 (1.49–2.58)	<0.001	2.90 (2.13–3.94)	<0.001
Other	0.70 (0.60–0.82)	<0.001	0.66 (0.55–0.80)	<0.001
CPR Performance				
Bystander	–		–	
Not further identified	0.97 (0.83–1.12)	0.6	0.97 (0.82–1.15)	0.7
Only supraglottic airway				
No	–		–	
Yes	0.95 (0.78–1.16)	0.6	0.90 (0.71–1.14)	0.4
Intravenous access				
No	–		–	
Yes	1.38 (0.92–2.14)	0.14	1.52 (0.92–2.67)	0.12
Interval between emergency call and administration of epinephrine (min)	1.00 (0.99–1.01)	0.6	1.00 (0.99–1.01)	0.5

Coefficients are shown for the including both demographic and therapeutic predictors (Baseline plus treatment model, Table 1). Goodness-of-fit and discrimination ability of the models are assessed by the area under the receiver operating curve (AUROC) and Nagelkerke's pseudo R-squared statistic. Full data set was available for 5270 patients for the two outcomes. Numbers of patients for each logistic regression model are provided in the flowchart (Fig. 1).
CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio.
[a]AUROC: 0.75 (95% CI, 0.74–0.77), Nagelkerke's Pseudo R-square: 0.21.
[b]AUROC: 0.77 (95% CI, 0.75–0.79), Nagelkerke's Pseudo R-square: 0.21.

tracheal tube), and time interval from emergency call to the administration of epinephrine. Adding these treatment-related variables to our logistic regression model, the rate of survival to discharge would decrease significantly from 7.7 to 5.6%, and the rate of survival with favourable neurological outcome from 5.0 to 3.4%. Therefore, comparing simulated outcomes of the baseline model with those of the baseline plus treatment model, our results suggest that patients suffering from OHCA might benefit from a higher rate of use of intravenous access, tracheal intubation, and a shorter time to administration of epinephrine. This is supported by the results from several previous studies. A secondary analysis of the ALPS trial (Resuscitation Outcomes Consortium Amiodarone, Lidocaine or Placebo Study) found that antiarrhythmic drug administration during OHCA favoured improved neurological outcome only with intravenous use [12]. A shorter time to administration of epinephrine in OHCA patients with initial nonshockable rhythms has also been shown to be associated with improved outcomes [13,14]. Also, airway management in OHCA has been an intensively investigated research area during the last years. One large RCT showed no significant difference in favourable functional outcome 30 days after OHCA

between patients ventilated by a supraglottic airway compared with a tracheal tube [15]. Wang *et al.* [16] concluded from their PART trial that a strategy of initial laryngeal tube insertion was associated with significantly greater 72-h survival compared with a strategy of initial tracheal intubation. However, this study has the significant disadvantage that the first pass success rate in patients who were tracheally intubated was only 51%. Another RCT showed inconclusive results among patients who were randomized to bag-mask ventilation or tracheal intubation during out-of-hospital CPR. However, if ROSC was achieved or in case of regurgitation of gastric contents the patients randomized to bag-mask ventilation were intubated already in the out-of-hospital setting [17]. Two other studies as well as a more recent analysis based on the GRR suggest that tracheal intubation was associated with higher short- and long-term outcome rates and better neurological recovery [18–20].

Limitations

Some limitations of our simulation study have to be discussed. Neurological outcome is defined by the CPC score in GRR and by the mRS in the PARAMEDIC2 trial. The Core Outcome Set for Cardiac Arrest statement

Fig. 2.
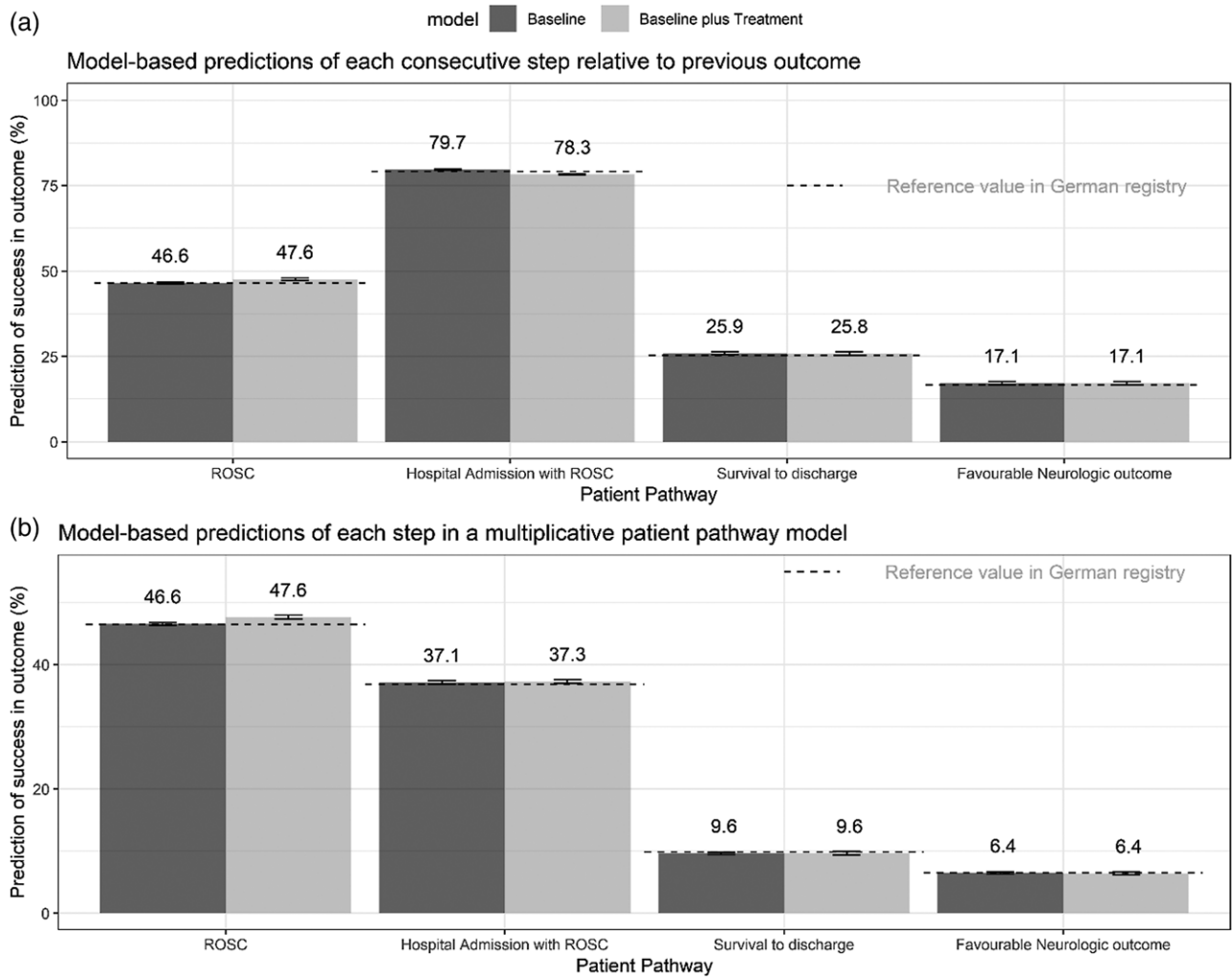
Predictions of success probability in the patients' resuscitation pathway in a random sample of 1000 cohorts (each with $n = 4015$ patients). Predictions are derived using logistic regression models with only baseline variables (blue) and using baseline plus treatment-related variables (red) fitted to the German Resuscitation Registry. (a) Prediction of individual outcomes conditional on the previous outcomes. (b) Multiplicative success predictions where the mean predicted success probabilities for each outcome for each cohort are multiplied.

considers the mRS as more reliable [21]. However, other studies have reported a good agreement between these two measures [22].

The predictive accuracy of our models is moderate, and they may have slightly overestimated the outcome probabilities. Though, particularly calibration plots for survival to discharge and survival with favourable neurological outcome for baseline plus treatment variables show very good accuracy.

We had no access to individual data of the PARAMEDIC2 trial and were only able to use the summary measures as available in the publication [2]. This was one of the major challenges of our study and, at the same time, the greatest advantage of our modelling framework. As researchers typically do not have access

to individual data from the trials of other research groups and countries, the opportunity to compare published data from randomized controlled trials to data from one's own registries is very desirable. In addition, we would like to suggest that, in the future, the raw data from randomised clinical trials be made available to interested scientists so that they can compare them with raw data from, for example, registries using simple statistical methods.

Conclusion

- We developed a framework for modelling outcomes after OHCA that enables us to achieve comparability of study results between different EMS systems worldwide.

Fig. 3.
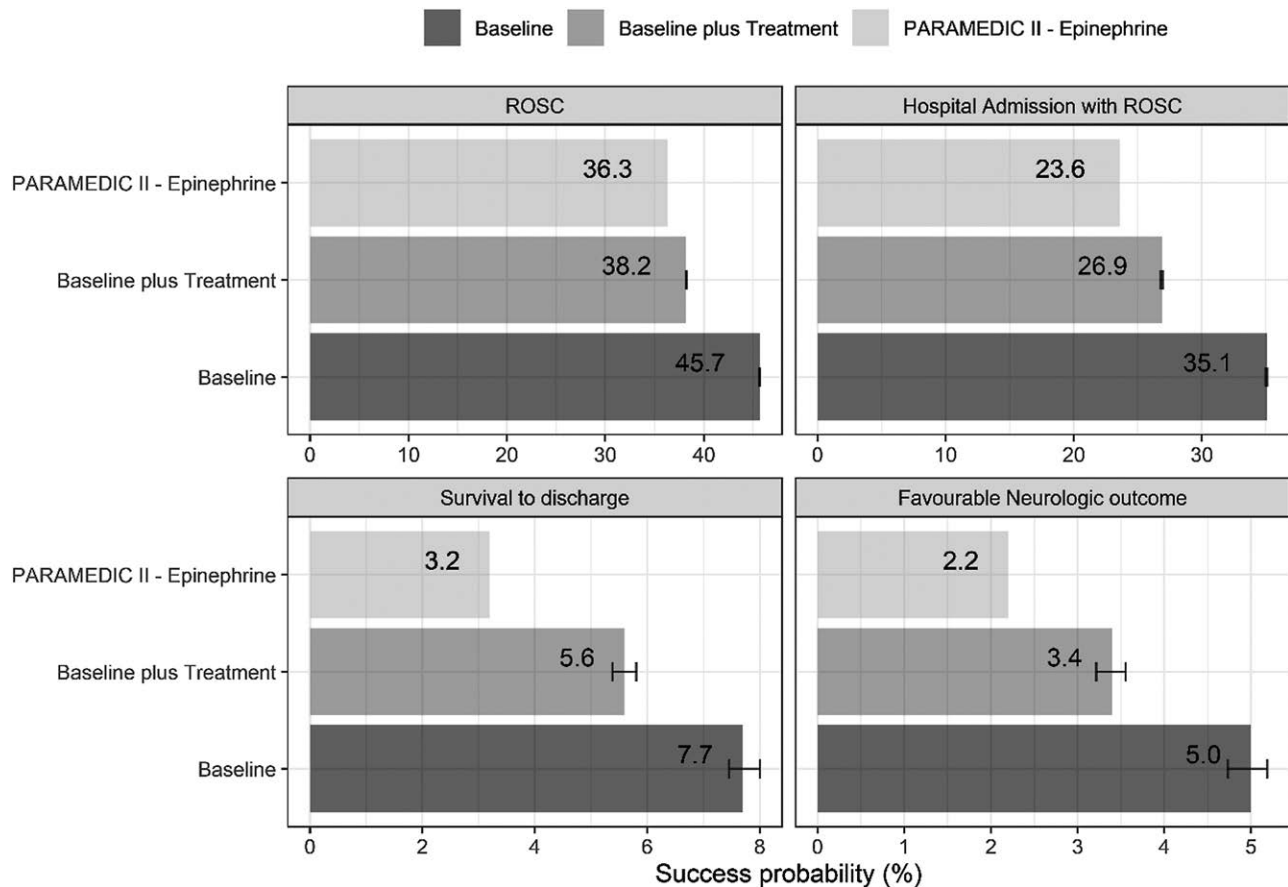
Modelled outcomes of patients in the GRR fitting the summary measures of patients in the Epinephrine group of the PARAMEDIC2 trial-based logistic regression modelling (left panels). Subcohorts with $n = 4015$ patients that match the reference cohort of the Epinephrine Group in the PARAMEDIC2 trial are repeatedly and randomly drawn from the GRR for 1000 times and the mean success probability for each outcome is computed. The figures in the table present the mean ± SD of these predicted mean success probabilities in the ensemble of random subcohorts.

- We demonstrate the multiplicative nature of the resuscitation pathway, which suggests that improvements in any part of the pathway directly propagate to successive outcomes.
- Our models comparing the outcomes reported in the PARAMEDIC2 trial with those reported in the GRR demonstrate that the ineffectiveness of epinephrine regarding survival with favourable neurological outcome after OHCA may not be easily transferred to EMS and health care systems organized differently from those in the trial.
- Our logistic regression models suggest that a higher rate of tracheal intubation, intravenous access, and a shorter time to administration of epinephrine might improve outcomes in this cohort.

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Conflicts of interest

There are no conflicts of interest.

References

1 Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, *et al*; Adult Basic and Advanced Life Support Writing Group. Part 3: adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2020; **142**:S366–S468.

2 Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, *et al*; PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2018; **379**:711–721.

3 Nehme Z, Bernard S, Smith K. Epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2019; **380**:397.

4 Wnent J, Bein B, Fischer M; German Resuscitation Registry Steering. Epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2019; **380**:396–397.

5 Neukamm J, Gräsner JT, Schewe JC, Breil M, Bahr J, Heister U, *et al*. The impact of response time reliability on CPR incidence and resuscitation success: a benchmark study from the German Resuscitation Registry. *Crit Care* 2011; **15**:R282.

6   Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, *et al*; 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 Councils of Southern Africa; ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. 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 Councils of Southern Africa). *Circulation* 2004; **110**:3385–3397.

7   SQR-BW. Quality report emergency medical service Baden-Württemberg. Reporting year 2020. 2021 https://sqrbw.de/fileadmin/SQRBW/Downloads/Qualitaetsberichte/SQRBW_Qualitaetsbericht_2020_Inhalt_web2.pdf. [Accessed 23 October 2021]

8   R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2020. https://www.R-project.org/. [Accessed 2 December 2021]. [Accessed 2 December 2021]

9   Gräsner JT, Meybohm P, Lefering R, Wnent J, Bahr J, Messelken M, *et al*; German Resuscitation Registry Study Group. ROSC after cardiac arrest– the RACA score to predict outcome after out-of-hospital cardiac arrest. *Eur Heart J* 2011; **32**:1649–1656.

10   Seewald S, Wnent J, Lefering R, Fischer M, Bohn A, Jantzen T, *et al*. CaRdiac Arrest Survival Score (CRASS) - a tool to predict good neurological outcome after out-of-hospital cardiac arrest. *Resuscitation* 2020; **146**:66–73.

11   Lefering R, Huber-Wagner S, Bouillon B, Lawrence T, Lecky F, Bouamra O. Cross-validation of two prognostic trauma scores in severely injured patients. *Eur J Trauma Emerg Surg* 2021; **47**:1837–1845.

12   Daya MR, Leroux BG, Dorian P, Rea TD, Newgard CD, Morrison LJ, *et al*; Resuscitation Outcomes Consortium Investigators. Survival after intravenous versus intraosseous amiodarone, lidocaine, or placebo in out-of-hospital shock-refractory cardiac arrest. *Circulation* 2020; **141**:188–198.

13   Khera R, Chan PS, Donnino M, Girotra S; American Heart Association's Get With The Guidelines-Resuscitation Investigators. Hospital variation in

14   Hansen M, Schmicker RH, Newgard CD, Grunau B, Scheuermeyer F, Cheskes S, *et al*; Resuscitation Outcomes Consortium Investigators. Time to epinephrine administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. *Circulation* 2018; **137**:2032–2040.

15   Benger JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, *et al*. Effect of a strategy of a supraglottic airway device vs tracheal intubation during out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 randomized clinical trial. *JAMA* 2018; **320**:779–791.

16   Wang HE, Schmicker RH, Daya MR, Stephens SW, Idris AH, Carlson JN, *et al*. Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2018; **320**:769–778.

17   Jabre P, Penaloza A, Pinero D, Duchateau FX, Borron SW, Javaudin F, *et al*. Effect of bag-mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on neurological outcome after out-of-hospital cardiorespiratory arrest: a randomized clinical trial. *JAMA* 2018; **319**:779–787.

18   Behrens NH, Fischer M, Krieger T, Monaco K, Wnent J, Seewald S, *et al*. Effect of airway management strategies during resuscitation from out-of-hospital cardiac arrest on clinical outcome: a registry-based analysis. *Resuscitation* 2020; **152**:157–164.

19   Benoit JL, Gerecht RB, Steuerwald MT, McMullan JT. Endotracheal intubation versus supraglottic airway placement in out-of-hospital cardiac arrest: a meta-analysis. *Resuscitation* 2015; **93**:20–26.

20   Sulzgruber P, Datler P, Sterz F, Poppe M, Lobmeyr E, Keferböck M, *et al*. The impact of airway strategy on the patient outcome after out-of-hospital cardiac arrest: a propensity score matched analysis. *Eur Heart J Acute Cardiovasc Care* 2018; **7**:423–431.

21   Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, *et al*; COSCA Collaborators. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the international liaison committee on resuscitation. *Resuscitation* 2018; **127**:147–163.

22   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**:1036–1040.