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Clinical paper

Sex differences in the association of comorbidity with shockable initial rhythm in out-of-hospital cardiac arrest

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Abstract

Background: Lower survival chances after out-of-hospital cardiac arrest (OHCA) in women is associated with lower odds of a shockable initial rhythm (SIR). We hypothesized that sex dierences in the prevalence of SIR are due to sex dierences in comorbidities. We aimed to establish to what extent sex dierences in the cumulative comorbidity burden, measured using the Charlson Comorbidity Index (CCI), or in individual comorbidities, account for the lower proportion of SIR in women.

Methods: The association between CCI or its constituent comorbidities, and presence of SIR was studied using data (2010–2014) from a Dutch community-based OHCA registry, and included 2510 OHCA patients aged ≥18y with presumed cardiac cause.

Results: The mean age was 67.8 ± 13.8y, 71% were men. Women were more often in high CCI categories than men. However, moderate or high disease burden was associated with lower odds of SIR compared to no disease burden only in men (OR 99 %CI 0.73 [0.53–1.00] and OR 0.54 [0.37–0.80] P-trend < 0.001), but not in women (1.00 [0.58–1.72] and 1.02 [0.57–1.84 P-trend 0.93). Adding CCI to a multivariable model did not alter the OR of sex with SIR. Of the individual comorbidities, only previous myocardial infarction was both dierently distributed between sexes (men 22.7% vs. women 13.1%, p < 0.001) and associated with odds of SIR (higher in both sexes). Adding this variable to the model changed the association of sex with initial rhythm from 0.49 (0.38–0.64) to 0.53 (0.41–0.69).

Conclusion: Sex dierences in comorbidities explained lower odds of SIR in women only modestly: dierences in previous myocardial infarction contributed little, and cumulative comorbidity not at all.

Keywords: Out-of-hospital cardiac arrest, Cumulative comorbidity, Shockable initial rhythm, Sex differences, ESCAPE-NET

Introduction

Survival rates after out-of-hospital cardiac arrest (OHCA) are generally low.[1,2] Multiple factors are associated with survival, and delineating the role of these factors and their interplay is needed to improve strategies aimed at increasing survival rates. A major predictor for survival is presence of a shockable initial rhythm (SIR).[3] A previous study from our group demonstrated lower OHCA survival rates in women as compared to men, which was partly explained by a lower proportion of SIR in women.[4] A higher prevalence of unfavourable resuscitation characteristics in women, in part, explained this lower proportion of SIR, but not completely. It was suggested that patient-related factors might also play a role.

One of those patient-related factors could be comorbidity burden, as several studies showed that a higher cumulative comorbidity burden is associated with reduced survival chances, and comorbidity burden was highest in women.[5–7] Additionally, some comorbidities

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(cardiovascular diseases [CVD], e.g. heart failure) are associated with SIR, while others are associated with non-SIR (non-CVD, e.g. respiratory disease, diabetes, cancer, cerebrovascular disease).[6,8–11] Based on these considerations, we hypothesized that the lower SIR rates and survival chances after OHCA in women may be related to a higher proportion of women in higher cumulative comorbidity burden categories, or women having more comorbidities that are associated with lower chances of SIR.

Therefore, we aimed to assess sex differences in the (relative) contribution of cumulative comorbidity burden to the presence of SIR, as well as in the distribution of comorbidities. This investigation may have clinical importance in the face of the sex difference in survival rates after OHCA, development of sex-specific comorbidity scores, and the increasing numbers of OHCA patients with combinations of CVD and/or non-CVD.[6]

Methods

Setting and study population

The Amsterdam Resuscitation Study (ARREST) is an ongoing, prospective registry of all-cause OHCA in the North-Holland province of the Netherlands. The ARREST study group collaborates with all emergency medical services in the study region. The study region covers 2404 km^2 (urban and rural communities) and has a population of 2.4 million people. Details of the design of the data collection in the ARREST study are described elsewhere.[12] The present investigation has a cross-sectional design and covered the study period 2010–2014. Patients were excluded when their OHCA had a non-cardiac cause (e.g., trauma, respiratory, drug overdose), they were under 18 years old, lived abroad, no medical history could be retrieved, or they had missing data for confounders. Written informed consent was obtained from all participants who survived the OHCA. The Medical Ethics Review Board of the Academic Medical Center, Amsterdam, approved the study, including the use of data from patients who did not survive the OHCA.

Data collection

Exposure

As a measure of cumulative comorbidity burden, the updated Charlson Comorbidity Index (CCI) was used, as it is often used to study the association of comorbidity on survival in medical situations.[13] Our patients were categorized into 3 categories of comparable size: no disease burden (CCI = 0), moderate disease burden (CCI = 1–2), and high disease burden (CCI $\geq$ 3). The comorbidities were obtained from the patients' general practitioner and treating hospital. From the general practitioner the patients' episode list and/or letters from medical specialists and a questionnaire containing a checklist of comorbidities was retrieved; from the treating hospital the letters from medical specialists were retrieved. The general practitioner information was particularly relevant, as the general practitioner in the Netherlands acts as a gatekeeper for specialist care and has a complete overview of all diagnoses made by medical specialists of the patients under his/her care.

Outcome

Initial rhythm was determined using the ECGs from either the automated external defibrillator (AED) or the manual defibrillator, whichever was the first to be connected to the patient, and defined as SIR (ventricular fibrillation, ventricular tachycardia) or non-SIR (pulseless electrical activity, asystole).

Other measurements

Resuscitation data was collected according to the Utstein recommendations. The present study included variables known to affect chance of SIR: location of OHCA (home vs. public), time to connection (time from Emergency Medical Services call to AED/manual defibrillator connection [whichever was first], in minutes), presence/absence of witness, bystander cardiopulmonary resuscitation (CPR) and AED deployment. From the medical history, in addition to comorbidities that constitute the CCI, the following CVD risk factors were derived: hypertension, obesity, hypercholesterolemia, and current smoking. Age was used as a continuous variable in our multivariable analysis, but for stratification was also categorized into 2 groups (<70 years or $\geq$ 70 years).[14]

Statistical analysis

Patient, resuscitation, and comorbidity characteristics were evaluated across men and women using ANOVA or chi-square statistics, where appropriate. The association between initial rhythm and both CCI and its constituent comorbidities (when occurring at a prevalence of >1%) was assessed in men and women with complete information on covariates using multivariable logistic regression. Model 1 adjusted for age, and model 2 additionally adjusted for resuscitation variables (location, time to AED/manual defibrillator connection, and presence/absence of a witness and bystander CPR). AED deployment was not included in the model as it is incorporated in the time to connection of AED/manual defibrillator. The P for trend was calculated by using the categorical variable as continuous variable. The relative additional contribution of CCI to a model including resuscitation characteristics and age to initial rhythm were estimated by calculating the explained variance using the Nagelkerke test.[15] A sensitivity analysis was performed in 5 imputed datasets. Multiple imputation with fully conditional specification (Markov Chain Monte Carlo) with 50 iterations and predictive mean matching for scale variables was performed. Additionally, we studied the addition of CCI and previous myocardial infarction to a model including age, sex and resuscitation characteristics in the total population to see whether CCI or previous myocardial infarction change the association between sex and SIR.

Continuous variables were described as mean ± standard deviation (SD) or median (interquartile range), and categorical variables as number (percent). All statistical analyses were performed using SPSS (SPSS, version 26.0, SPSS Inc.). To correct for multiple comparisons, $P \leq 0.01$ was considered statistically significant, and 99% confidence intervals (CI) were reported.

Results

The study population consisted of 2510 patients (eFigure 1). A missing data analysis revealed no differences in age, sex or initial rhythm between patients with complete data who were included in the study population, and patients who were excluded because of incomplete data (eTable 1). The study population was on average 67.8 years old and 71% were men. Overall, men were younger (66.8 vs. 70.1y, $p < 0.001$), were more often in a public location when OHCA struck (32.8% vs. 15.4%, $p < 0.001$), and had a shorter time to defibrillator connection (8.2 vs 8.6 min, $p = 0.003$) compared to women.

Additionally, men were less often categorized in the highest cumulative disease burden category (CCI ≥ 3: 19.2% vs. 27.1%, p < 0.001).

Overall, men were more likely to have a shockable initial rhythm as compared to women (55.1% vs. 33.7%, P < 0.001). In men, all models showed a significant trend of the association between CCI category and initial rhythm (P < 0.001, Table 2), where increasing CCI categories were associated with lower odds for SIR (CCI = 1–2 OR 0.73 [0.53–1.00]; CCI ≥ 3: OR 0.54 [0.37–0.80], Fig. 1). In women, all models showed no significant trend for an association between higher CCI category and lower odds for SIR (Table 2), with ORs of 1.00 (0.58–1.72) and 1.02 (0.57–1.84) in our fully adjusted

Table 1 – Baseline characteristics in men and women.

	Men n = 1787	Women n = 723	*P* value
Age in years, mean ± SD	66.8 ± 13.2	70.1 ± 14.7	**<0.001**
Resuscitation characteristics			
Witnessed by bystander	1303 (72.9)	502 (69.4)	0.08
Public location	586 (32.8)	111 (15.4)	**<0.001**
Bystander provided CPR	1434 (80.2)	566 (78.3)	0.27
AED connected	1042 (58.3)	391 (54.1)	0.05
Time to AED/manual defibrillator connection in min, median (IQR)	8.2 (6.3 – 10.5)	8.6 (6.8 – 11.0)	**0.003**
Charlson Comorbidity Index			**<0.001**
CCI = 0; no disease burden	922 (51.6)	205 (42.2)	
CCI 1–2; moderate disease burden	522 (29.2)	222 (30.7)	
CCI ≥ 3; high disease burden	343 (19.2)	196 (27.1)	
Charlson Comorbidity Index constituents			
Myocardial infarction	406 (22.7)	95 (13.1)	**<0.001**
Congestive heart failure	313 (17.5)	167 (23.1)	**0.001**
Peripheral vascular disease	155 (8.7)	45 (6.2)	0.04
Cerebrovascular disease	226 (12.6)	107 (14.8)	0.10
Chronic obstructive pulmonary disorder	314 (17.6)	150 (20.7)	0.06
Diabetes without chronic complications	318 (17.8)	151 (20.9)	0.07
Diabetes with chronic complications	66 (3.7)	26 (3.6)	0.91
Renal disease	216 (12.1)	95 (13.1)	0.22
Mild liver disease	60 (3.4)	19 (2.6)	0.34
Peptic ulcer disease	51 (2.9)	18 (2.5)	0.61
Any malignancy	241 (13.5)	120 (16.6)	0.04
Metastatic solid tumour	32 (1.8)	22 (3.0)	0.05
Dementia	35 (2.0)	37 (5.1)	**<0.001**
Rheumatologic and connective tissue disease	58 (3.2)	42 (5.8)	**0.003**

Results are presented as n(%) unless indicated otherwise.

Human immunodeficiency virus infection, hemiplegia/paraplegia and moderate/severe liver disease are not shown as their prevalence was <1%.

Abbreviations: AED = automated external defibrillator; CCI = Charlson Comorbidity Index; CPR = cardiopulmonary resuscitation; IQR = interquartile range; SD = standard deviation.

Table 2 – Multivariable logistic regression analysis between CCI and initial rhythm, in men and women.

	No disease burden (CCI = 0)	Moderate disease burden (CCI 1–2)	High disease burden (CCI ≥ 3)	*P* for trend
Men, n	922	522	343	
SIR, n (%)	569 (61.7)	277 (53.1)	139 (40.5)	<0.001
Crude	1.00 (ref)	0.70 (0.53–0.93)	0.42 (0.30–0.59)	<0.001
Model 1	1.00 (ref)	0.78 (0.58–1.05)	0.50 (0.35–0.71)	<0.001
Model 2	1.00 (ref)	0.73 (0.53–1.00)	0.54 (0.37–0.80)	<0.001
Women, n	305	222	196	
SIR, n (%)	117 (38.4)	72 (32.4)	55 (28.1)	0.05
Crude	1.00 (ref)	0.77 (0.48–1.24)	0.63 (0.38–1.04)	0.02
Model 1	1.00 (ref)	0.94 (0.57–1.55)	0.89 (0.51–1.53)	0.56
Model 2	1.00 (ref)	1.00 (0.58–1.72)	1.02 (0.57–1.84)	0.93

Results are shown as OR (99% CI).

Model 1 adjusted for age. Model 2 adjusted for model 1 and resuscitation characteristics (location of out-of-hospital cardiac arrest, time to connection of automated external or manual defibrillator, and presence/absence of witness or bystander cardiopulmonary resuscitation).

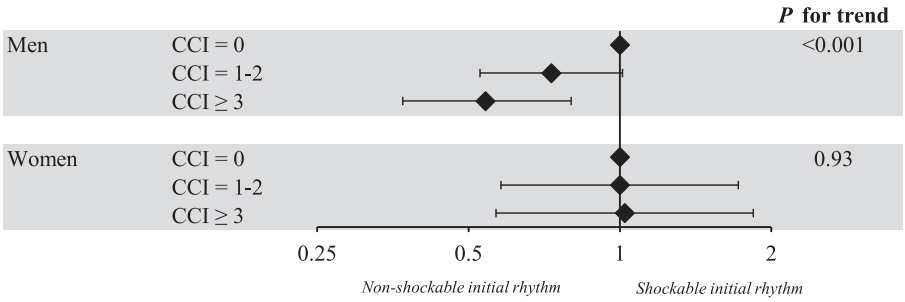

Fig. 1 – Association between Charlson Comorbidity Index and initial rhythm stratified by sex. Odds ratios (ORs) are adjusted for age (continuous) and resuscitation factors (location of out-of-hospital cardiac arrest, time to connection of automated external or manual defibrillator, and presence or absence of witness and bystander cardiopulmonary resuscitation), and presented with 99% confidence intervals (CI).

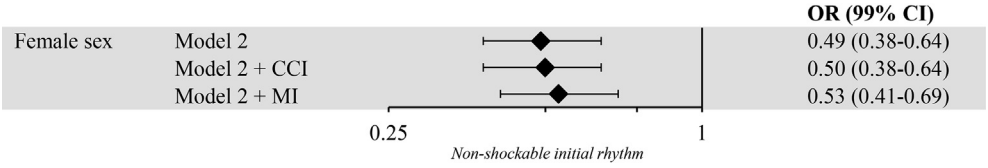

Fig. 2 – Contribution of Charlson Comorbidity Index and myocardial infarction to the association between sex and initial rhythm. Odds ratios (ORs) are adjusted for age (continuous) and resuscitation factors (location of out-of-hospital cardiac arrest, time to connection of automated external or manual defibrillator, and presence or absence of witness and bystander cardiopulmonary resuscitation), and presented with 99% confidence intervals (CI).

model for CCI = 1–2 and CCI ≥ 3, respectively (Table 2/Fig. 1). In the imputed datasets, the results were similar (eTable 2).

Accordingly, the addition of CCI to a model including age and resuscitation characteristics showed little increase in explained variance. In a model without CCI the explained variance was 25.5% (R2 = 0.255) for men and 23.5% (R2 = 0.235) in women. After including CCI to the model, the explained variance was 26.5% (R2 = 0.265, 1.1% increase) in men and 23.5% (R2 = 0.235, 0% increase) in women. Additionally, by adding CCI to a model adjusting for sex, age, and resuscitation characteristics in the total population, the association between sex and initial rhythm changed from 0.49 (0.38–0.64) to 0.50 (0.38–0.64), indicating CCI has virtually no effect on the association between sex and initial rhythm (Fig. 2).

When studying the individual comorbidities, we found that, compared to women, men had more often previous myocardial infarction (22.7% vs 13.1%, p < 0.001), which remained after comparing men and women in the CCI 1–2 and ≥ 3 3 categories (eTable 3). Moreover, men had less often congestive heart failure (17.5% 23.1%, p = 0.001), dementia (2.0% vs 5.1%, p < 0.001) and rheumatologic/-connective tissue disease (3.2% vs 5.8%, p = 0.003, Table 1). Among these comorbidities, only previous myocardial infarction had a statistically significantly improved the likelihood of SIR in either sex in a multivariable adjusted analysis (Fig. 3). However, by adding previous myocardial infarction to the model (adjusting for sex, age, and resuscitation characteristics) in the total population, the association of sex with initial rhythm changed only from 0.49 (0.38–0.64) to 0.53 (0.41–0.69), indicating previous myocardial infarction has a small effect on the association between sex and initial rhythm (Fig. 2).

Discussion

Sex differences in comorbidities accounted only little to the lower odds of SIR in women. Cumulative disease burden expressed in CCI, while higher in women, was only associated with lower odds of SIR in men, but not in women, and the relative contribution of CCI in the explanation of the observed variance was minimal in both sexes. Of the individual comorbidities that were differently distributed between men and women, only previous myocardial infarction (more prevalent in men) had significantly increased the likelihood of SIR. However, the effect of previous myocardial infarction on the association between sex and initial rhythm was small.

In a previous study on clinical predictors of initial rhythm, non-CVD was found to be associated with non-SIR while CVD was associated with SIR.[8] The results of this study are generally consistent with our results, although we found that a history of congestive heart failure or peripheral vascular disease was not associated with the presence of SIR. Moreover, previous research has suggested that sex differences in OHCA might be explained by biological differences.[4] In our study, the distribution of comorbidities in men and women was different: men were more likely to have a myocardial infarction in their medical history, while women were more likely to have congestive heart failure, rheumatologic and connective tissue disease, and dementia. However, in our multivariable adjusted models, only myocardial infarction had a significant association with odds of SIR in both sexes, but it contributed only little to the association between sex and initial rhythm. In general, less than 30% of the variance in initial rhythm observed could be explained by our full model, suggesting that other factors are important in the prediction of the ini-

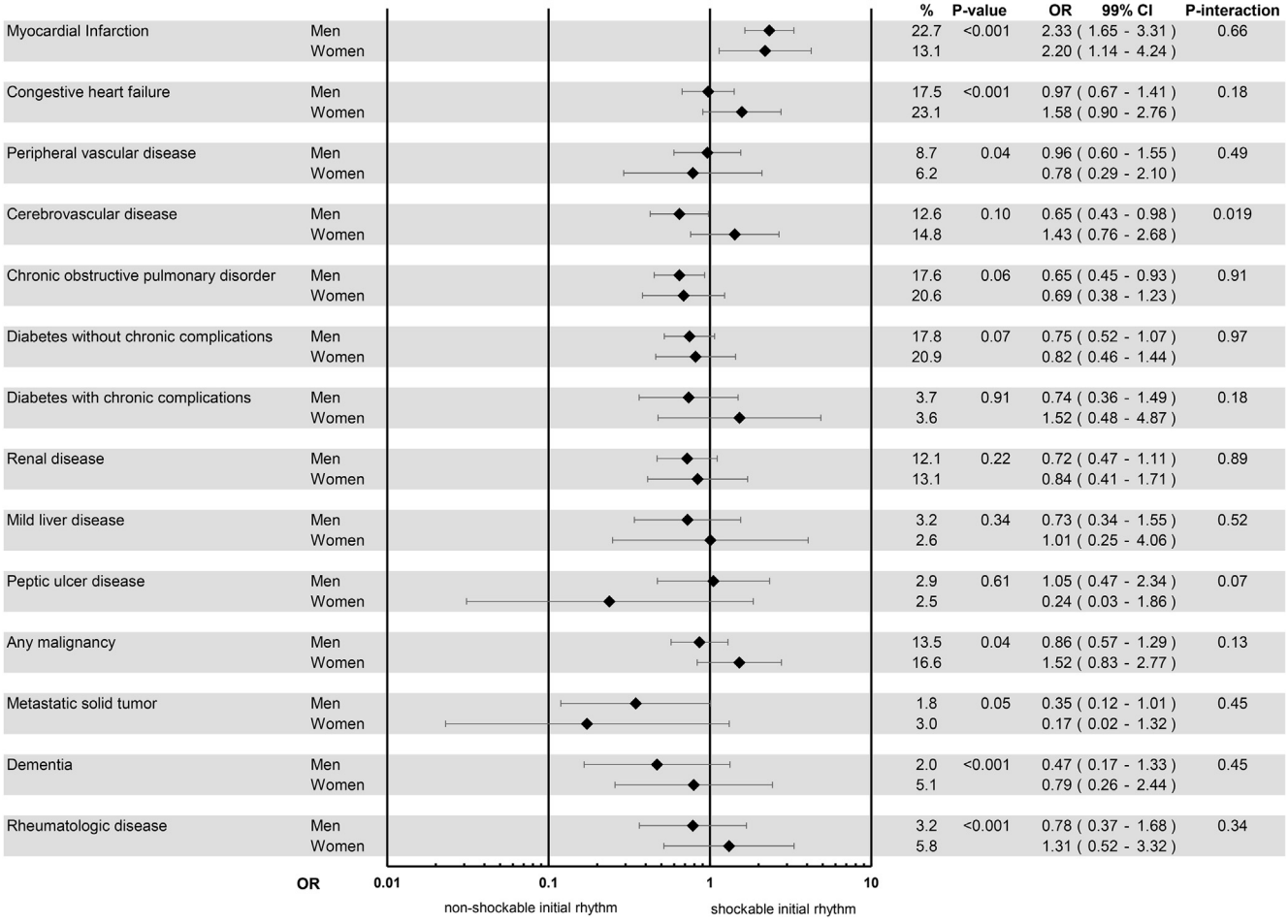

Fig. 3 – Association between Charlson Comorbidity Index constituents and initial rhythm stratified by sex. Odds ratios (ORs) are adjusted for age (continuous) and resuscitation factors (location of out-of-hospital cardiac arrest, time to connection of automated external or manual defibrillator, and presence or absence of witness and bystander cardiopulmonary resuscitation), and presented with 99% confidence intervals (CI). P for interaction shows the p for the interaction term between the Charlson Comorbidity Index constituent and sex in a multivariable model.

tial rhythm in OHCA. Possible factors to take into account might be genetics and metabolomics.[16,17] Nevertheless, sex differences in SIR might be attributable to other unmeasured characteristics, such as the recognition of OHCA[4,18] due to demographic (life-expectancy) or biological differences (symptom recognition) between men and women. Additionally, a different approach to capture cumulative comorbidities, relevant in the occurrence of OHCA and the chances to survive OHCA, might be needed as the CCI was developed for an in-hospital population to predict 1-year mortality and not specifically to predict health outcomes related to OHCA, e.g. sex-specific approach. Nevertheless, sex differences should be taken into account when researching OHCA outcomes.

Strengths and limitations

A strength of the present study is that data was collected on resuscitation parameters and medical history from the general practitioner of patients who survived to hospital admission, but also of patients who died on the scene. Additionally, the ARREST registry was specifically designed to study determinants and outcomes of OHCA. This ensured an accurate analysis of initial rhythm from ECGs of AED and/or manual defibrillator.

This study has some limitations to consider. Firstly, comorbidity data may have been less complete in patients who did not survive to hospital admission, and therefore lacked hospital record information. However, the proportion of patients for whom the CCI score was adjusted according to hospital information, was only small (<5%). Secondly, the CCI itself is based on an in-hospital population, while it has not been validated in an OHCA-population. This might have caused misrepresentation of total disease burden relevant for OHCA. Still, we decided to use the CCI in order to be able to compare our results with previous investigations. Finally, residual confounding may still exist despite our attempts to control for possible confounding factors, and the nature of this study cannot infer causality.

Conclusion

Cumulative disease burden is associated with a lower likelihood of shockable initial rhythm in OHCA in men, but not in women.

However, differences in cumulative disease burden provided no explanation for sex differences in the presence of SIR in OHCA, whereas sex differences in the prevalence of previous myocardial infarction provided only a small contribution.

CRediT authorship contribution statement

Laura H. van Dongen: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Iris Oving:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Pauline W. Dijkema:** Investigation, Writing – review & editing. **Stefanie G. Beesems:** Conceptualization, Supervision, Writing – review & editing. **Marieke T. Blom:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Hanno L. Tan:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material. The data cannot be shared publicly for privacy of individuals that participated in the study as data cannot be provided completely anonymous according to the Medical Ethics Committee and the Data Protection Officer of our institution (MEC: mecamc@amc.nl, DPO: fg@amc.nl).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.08.034.

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