

## **Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant?**

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## Abstract

**Objective** To determine whether initial cardiac arrest rhythm remains a prognostic determinant in longer term OHCA survival.

**Methods** The St John Western Australian OHCA database was used to identify adults who survived for at least 30 days after an OHCA of presumed medical aetiology, in the Perth metropolitan area between 1998 and 2017. Associations between 8-year OHCA survival and variables of interest were analysed using a Multi-Resolution Hazard (MRH) estimator model with 1-year intervals.

**Results** Of the 871 OHCA patients who survived 30 days, 718 (82%) presented with a shockable initial arrest rhythm and 153 (18%) presented with a non-shockable rhythm. Compared to patients with initial shockable arrests, patients with non-shockable arrests experienced increased mortality in the first (HR 3.33, 95% CI 2.12-5.32), second (HR 2.58, 95% CI 1.22-5.15), third (HR 2.21, 95% CI 1.02-4.42) and fourth (HR 2.21, 95% CI 1.02-4.42) year post arrest; however, in subsequent years the initial arrest rhythm ceased to be significantly associated with survival. The overall 8-year survival estimates after adjustment for peri-arrest factors (as potential confounders) were 87% (95% CI 77-93%) for shockable arrests and 73% (95% CI 55-86%) for non-shockable arrests.

**Conclusions** Patients with non-shockable (as opposed to shockable) initial arrest rhythms experienced higher mortality in the first 4-years following their OHCA; however, after four years the initial arrest rhythm ceased to be associated with survival.

## Introduction

Initial cardiac arrest rhythm is one of the strongest predictors of short-term survival after out-of-hospital cardiac arrest (OHCA), with higher survival rates (survival to hospital discharge (STHD) / 30-day survival) among patients with an initial shockable rhythm (ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]).<sup>1,2</sup> Limited research has also shown that initial arrest rhythm is similarly important for long-term survival.<sup>3,4</sup> However, it is unclear if this association continues indefinitely or reduces over time. In this study we aim to; i) determine whether long term survival differs by initial arrest rhythm and ii) examine how mortality risk in initial OHCA survivors changes over time.

## Methods

### *Study Design*

We conducted a population-based retrospective cohort study of patients aged  $\geq 16$  years who experienced an OHCA in metropolitan Perth, Western Australia (WA), between 1<sup>st</sup> January 1998 and 31<sup>st</sup> December 2017, and were attended by St John Western Australia (SJ-WA) emergency medical services (EMS). Patients were included if i) they survived at least 30 days following arrest, ii) their primary residence was in WA and iii) they had an OHCA of presumed medical aetiology.<sup>5</sup> The exposure variable of primary interest was initial cardiac arrest rhythm, described as ‘shockable’ (i.e. ventricular fibrillation or pulseless ventricular tachycardia (VF/VT)) or ‘non-shockable’ (i.e. pulseless electrical activity (PEA) or asystole). A shockable initial arrest rhythm was recoded in cases where either the first assessed rhythm

by paramedics was VF/VT or a bystander automated external defibrillator (AED) shock was delivered prior to EMS arrival.

### *Study Setting*

Perth is the capital and largest city in the state of Western Australia (WA) and currently has a population of 2.06 million people.<sup>6</sup> The sole provider of road based emergency medical services (EMS) in Perth is SJ-WA, which operates a single-tiered advanced life support (ALS) service, staffed by nationally registered paramedics. OHCA patients are transported to one of nine hospital emergency departments within the Perth metropolitan area, unless resuscitative efforts are ceased in the field by paramedics (or not commenced), due to futility or pre-existing not-for-resuscitation orders.

### *Data Sources*

This study sourced data from the SJ-WA OHCA database which contains details for all metropolitan OHCA attended by SJ-WA EMS since 1996 (and all rural OHCA since 2014). The SJ-WA OHCA database is maintained by the Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU) at Curtin University, using data from patient care records (PCR) completed by SJ-WA paramedics, and linked to computer-aided dispatch data. The database contains patient demographics, arrest characteristics, EMS response intervals and interventions. The so-called ‘Utstein variables’<sup>5</sup> are captured in the database, including: patient age and sex, witnessed status (bystander-witnessed; EMS-witnessed; unwitnessed), bystander cardiopulmonary resuscitation (B-CPR), EMS response interval from call answer to arrival on scene, ROSC in the field, and ROSC on arrival at the Emergency Department (ED). The initial cardiac arrest rhythm is recorded on the PCR by the attending paramedic. Date of death was determined by manual look-up in the WA Death Registry.

### *Statistical Analysis*

Baseline patient characteristics are presented as frequencies and percentages, stratified by initial arrest rhythm (shockable/non-shockable); with differences tested using chi square tests. Follow-up time (in years) was calculated as the difference between the date of arrest and date of death or censoring date (31<sup>st</sup> December 2018). A Kaplan Meier survival curve, stratified by initial arrest rhythm, was produced to provide a visual representation of the cumulative 8-year survival by arrest rhythm. The relationship between initial arrest rhythm and long-term survival was examined by comparing the hazard rate of patients with shockable, versus non-shockable arrest rhythms. Unadjusted and adjusted 8-year mortality hazard rates and 95% confidence intervals (95% CI) were estimated using a Multi-Resolution Hazard (MRH) estimator with pruning.<sup>7-11</sup> The MRH estimator is a semi-parametric Bayesian statistical method that enables joint estimation of the baseline and covariate hazard rates<sup>7-11</sup> - see Appendix A Supplementary data. Importantly, unlike Cox regression,<sup>12</sup> the MRH method can accept covariates with both proportional and non-proportional hazards and provide a robust estimate of hazard rates in data that may contain long intervals with few ‘events’.<sup>7-11</sup> To optimize the fit of the MRH model we chose to use 1-year intervals across the 8-year follow-up period (interval length and follow up period are intrinsically linked in the MRH estimator methodology as described in Appendix A). Each 1-year interval (eight in total) represent the mortality risk for an OHCA survivor for that respective year post arrest. The

Utstein covariates included in the adjusted models were: age at arrest (16-39; 40-64; 65-79;  $\geq 80$  years), sex (female; male), arrest witness status (bystander-witnessed; EMS-witnessed; unwitnessed), bystander CPR (yes; no), EMS response time ( $\leq 10$  mins;  $> 10$  mins) and arrest location (public; private residence). For the multivariable models, the first category of each covariate was used as the reference value. Adjusted hazard rate curves for shockable and non-shockable initial arrest rhythms were produced using the MRH estimator to visualise differences in survival outcomes. Statistical analysis was performed using R (<https://r-project.org> - version 3.5.3) with hazard rates obtained using the R package 'MRH' (<https://CRAN.R-project.org/package=MRH>). Statistical significance for all analyses and the MRH estimator was set at  $p < 0.05$ .

### *Ethics*

This study was approved by the Human Research Ethics Committee of Curtin University as a sub-study of the Western Australian Pre-hospital Care Record Linkage Project (HR128/2013).

## **Results**

### *Study cohort*

Between the 1<sup>st</sup> of January 1998 and the 31<sup>st</sup> of December 2017 there were 27,069 cases of OHCA attended by SJ-WA in the Perth metropolitan area. After excluding cases where patients were  $< 16$  years of age, had no EMS attempted resuscitation or bystander AED defibrillation, were non-residents of WA or had a non-medical arrest aetiology, 9,328 OHCA cases remained. Of these, 871 patients survived at least 30 days following arrest (Figure 1); 718 (82%) with an initial shockable rhythm and 153 (18%) with a non-shockable rhythm (PEA=124 and Asystole=29).

### *Baseline characteristics of cohort*

Table 1 shows the baseline characteristics of patients who survived at least 30-days following OHCA, stratified by initial arrest rhythm (shockable vs non-shockable). The mean patient age at time of arrest was 60.7 years, with 79% of patients between the ages of 40 and 79 years. Patients with an initial shockable rhythm (compared to a non-shockable rhythm) were more likely to: be under 65 years of age (58.5% vs 47.7%,  $p=0.001$ ), male (79.1% vs 75.4%,  $p<0.001$ ), have arrested in a public location (44.7% vs 40.3%,  $p<0.001$ ), received bystander CPR (57.9% vs 52.4%,  $p<0.001$ ) and have a witnessed (bystander or EMS) arrest (79.5% vs 70.0%,  $p<0.001$ ). Bystanders administered an AED shock in 72 (10%) of the shockable patients. Of the 153 patients with a non-shockable initial rhythm, 15 (9.8%) subsequently converted to a shockable rhythm prior to achieving ROSC.

### *Relationship between initial arrest rhythm and 8-year OHCA survival*

#### *Unadjusted*

The Kaplan Meier estimates for 8-year OHCA survival (from time of arrest) are displayed in Figure 2 and show a statistically significant difference between OHCA patients with a

shockable versus non-shockable initial arrest rhythm (log-rank test,  $p < 0.001$ ). The unadjusted MRH model estimates for 8-year survival were similarly higher for shockable (75%, 95% CI 71-79%) than for non-shockable (47%, 95% CI 38-57%) arrest rhythms, with the effect being most pronounced in the first few years following OHCA (Figure 3a). The unadjusted 8-year MRH model detailing the mortality hazard ratios by 1-year intervals for initial shockable and non-shockable arrest rhythms are shown in Table 2. Mortality was significantly higher for non-shockable arrests (compared to shockable arrests) in each of the first four years following arrest, with the mortality hazard ratio in the first, second, third and fourth year being 4.40 (95% CI 2.62-6.37), 3.10 (95% CI 1.43-6.37), 2.56 (95% CI 1.20-5.08) and 2.56 (95% CI 1.20-5.08) respectively. However, there was no statistically significant association between initial arrest rhythm and subsequent survival for the remaining four years (i.e. years 5 to 8).

### *Adjusted*

The adjusted 8-year survival estimates were 87% (95% CI 77-93) for shockable arrests and 73% (95% CI 55-86) for non-shockable arrests. Figure 3b) shows the adjusted 8-year mortality rate curve for shockable and non-shockable arrest rhythms; while Table 2 provides the 8-year mortality hazard ratio by 1-year intervals. The 8-year mortality rate curve shows an increased mortality rate for non-shockable arrests in the initial years following OHCA, before approximating the shockable mortality rate curve (Figure 3b). The 1-year interval mortality hazards ratio estimates for patients presenting with non-shockable arrest rhythm (compared to shockable arrest rhythms) were significantly higher for the first four years following arrest, with the mortality hazard in the first, second, third and fourth years being 3.33 (95% CI 2.12-5.32), 2.58 (95% CI 1.22-5.15), 2.21 (95% CI 1.02-4.42) and 2.21 (95% CI, 1.02-4.42) respectively. There was no statistically significant association between initial arrest rhythm and subsequent survival for the remaining four years (i.e. years 5 to 8).

## **Discussion**

In this retrospective cohort study of initial 30-day OHCA survivors, we compared the long-term survival prospects of patients presenting with shockable and non-shockable arrest rhythms. We found that despite surviving 30-days, patients with non-shockable arrests continued to experience disproportionately higher mortality than patients with an initial shockable arrest. However, this increased mortality risk was time limited; with survival after four years post arrest being statistically no different for shockable and non-shockable arrest patients. The findings of this study are novel, as they not only describe the overall differences in long term survival between shockable and non-shockable arrests, but detail how the mortality risk for shockable and non-shockable arrests evolves over time. As there are limited studies describing the relationship of long term OHCA survival and peri-arrest factors, we included a range of peri-arrest factors (see methods) to adjust for any potential confounding. Of the peri-arrest factors included, only older age ( $\geq 65$  years) was found to be associated with an increased mortality risk.

The overall adjusted 8-year MRH survival estimates (from time of arrest) for our cohort of 30-day OHCA survivors was 87% for shockable arrest rhythms and 73% for non-shockable arrest rhythms. The mortality rate for shockable arrest rhythms appeared to be relatively stable over time; with little variation over the 8-year period. In contrast, the non-shockable

arrest rhythm mortality rate was more dynamic; where, despite an initial downward trend, it remained significantly elevated over the initial four years following arrest before finally stabilising. Our findings suggest that the use of 30-day survival as an outcome measurement may not reflect an accurate picture of ‘survival’ for all OHCA. Given this, we believe future revisions of the Utstein guidelines<sup>5</sup> may benefit from recommending additional, longer term survival variables which provide a more realistic measure of OHCA survival.

To the best of our knowledge no prior studies have directly examined the relationship between initial arrest rhythm mortality rate over time; although a few have examined the relationship between initial arrest rhythm and long term survival. A 2017 study<sup>4</sup> from Melbourne (Australia) reported adjusted 10-year survival for shockable arrests was 70.8% while those for non-shockable arrests were 59.8% and 63.8% for PEA and asystole, respectively. However, the authors of this study stratified their Cox PH model by arrest rhythm (due to non-PH). This meant that they were unable to describe the association between initial arrest rhythm and long term OHCA survival. A 2012 study<sup>13</sup> from the US reported five-year survival as 73% for shockable arrests and 43% for non-shockable arrests. These estimates were lower than those from our own study even though ours had a longer follow-up (8 years vs 5 years). Importantly both these studies, like our own, reported that non-shockable arrests were negatively associated with long term survival. The main point of difference however, is that we demonstrate that this reduction in survival is time-limited; with the mortality hazard rate beyond 4-years being indistinguishable for shockable and non-shockable arrests.

Patients with initial non-shockable cardiac arrest rhythms are generally considered to have poor outcomes;<sup>14</sup> and within our study cohort most (82%) of the OHCA 30-day survivors had a shockable initial arrest rhythm. The initial arrest rhythm likely reflects the underlying aetiology, with non-shockable rhythms being more common in OHCA with non-ischemic aetiologies.<sup>15</sup> However, our results do show that OHCA patients with an initial non-shockable rhythm do survive, and many are still alive several years later. Such findings will hopefully help to reduce the risk of prognostication bias; which occurs when resuscitative efforts are prematurely terminated on the basis of a perceived futility, ultimately guaranteeing a negative outcome (i.e. the ‘self-fulfilling prophecy’).<sup>16-18</sup>

The use of mortality hazard rates to model OHCA survival offers a number of unique advantages over the more traditional survival analysis techniques. Firstly, cumulative survival (or hazard) models tend to obscure temporal changes in mortality hazard.<sup>9</sup> In contrast, hazard rate functions more readily expose changes (or patterns) in mortality rate over time.<sup>19</sup> Secondly, the hazard rate function can help identify the time point/s when two competing groups (e.g. shockable and non-shockable arrests) begin to experience comparable mortality risks. This situation can be readily observed in our study where the Kaplan Meier curves (Figure 2) show a clear difference in survival at 8-years between shockable and non-shockable arrests. Therefore, examining the Kaplan Meier curves alone could lead to an erroneous conclusion; that initial arrest rhythm has a persistent effect on long term OHCA survival. However, our 8-year hazard rate curves (Figure 3) demonstrate that the increased mortality risk in non-shockable arrest victims (relative to their shockable arrest counterparts) is time-limited; with the mortality hazard rates after four years post arrest being statistically no different to that seen in shockable arrest victims. Our analysis demonstrated that peri-arrest factors, such as initial arrest rhythm, may not always demonstrate proportional hazards.

Applying a Cox PH regression model in cases where the PH assumptions are not met, or even tested, is statistically inappropriate and may produce erroneous results (see Supplementary file).<sup>20</sup>

### *Limitations*

Our study has a number of limitations. Firstly, due to the relatively small number of 30-day OHCA survivors with an initial arrest rhythm of PEA or Asystole (n=153), we grouped the initial arrest rhythm into either shockable or non-shockable which prevented us describing the effect of individual rhythms on long term OHCA survival. Although the MRH estimator (with pruning) used in this study has been shown to perform well in cases of low ‘event’ counts, we acknowledge that the estimates for the earlier survival period of our study will be more accurate than those near the end. Thirdly, our study did not describe the neurological status of our long term OHCA survivor cohort. However, a 2017 WA study<sup>21</sup> reported that a high proportion of OHCA patients who survived to hospital discharge had a good neurological outcome (93% had a Cerebral Performance Category of either one or two). Finally, we used the WA death registry records to determine the date of death. There is therefore a risk that we failed to capture out-of-state deaths; leading to increased survival estimates. To reduce the risk of this potential bias in our study, we restricted our cohort to OHCA patients who were WA residents at the time of their arrest. Moreover, previous studies have shown that incomplete ascertainment of deaths after cardiac events is very low in WA.<sup>22, 23</sup>

## **Conclusion**

Our study found that although patients with non-shockable (as opposed to shockable) arrests experience an increased initial mortality risk, this risk does not persist over time. Using the MRH estimator we found that after four years the mortality hazard rates for shockable and non-shockable arrest were not statistically different. Future studies examining factors related to OHCA survival over time should consider using this statistic over Cox proportional-hazard models.

## **Conflicts of Interest**

Professor Judith Finn receives research support from SJ-WA. A/Prof. Paul Bailey is Medical Director at SJ-WA. None of the other authors have any conflicts of interest to declare.

## **Acknowledgments**

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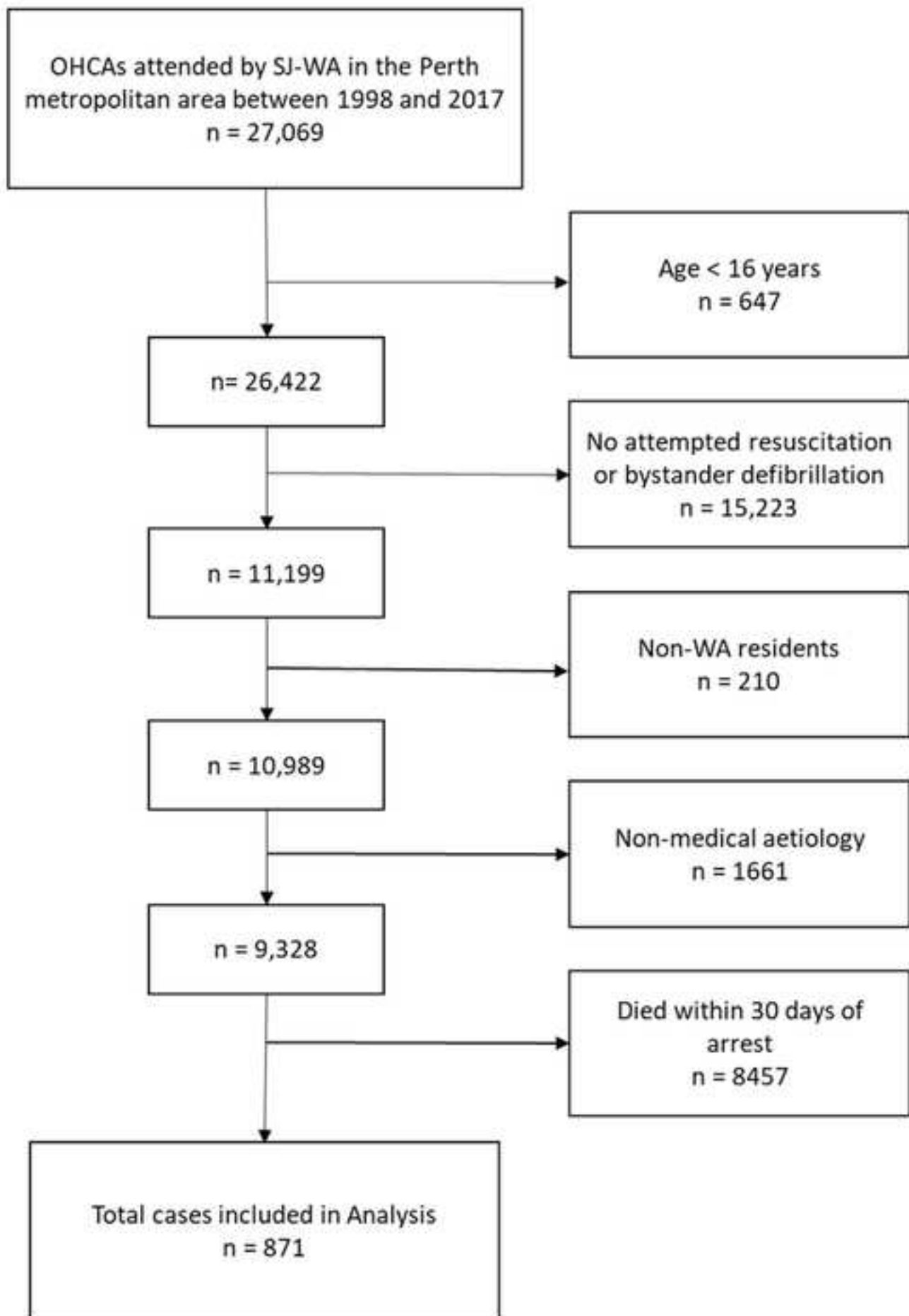
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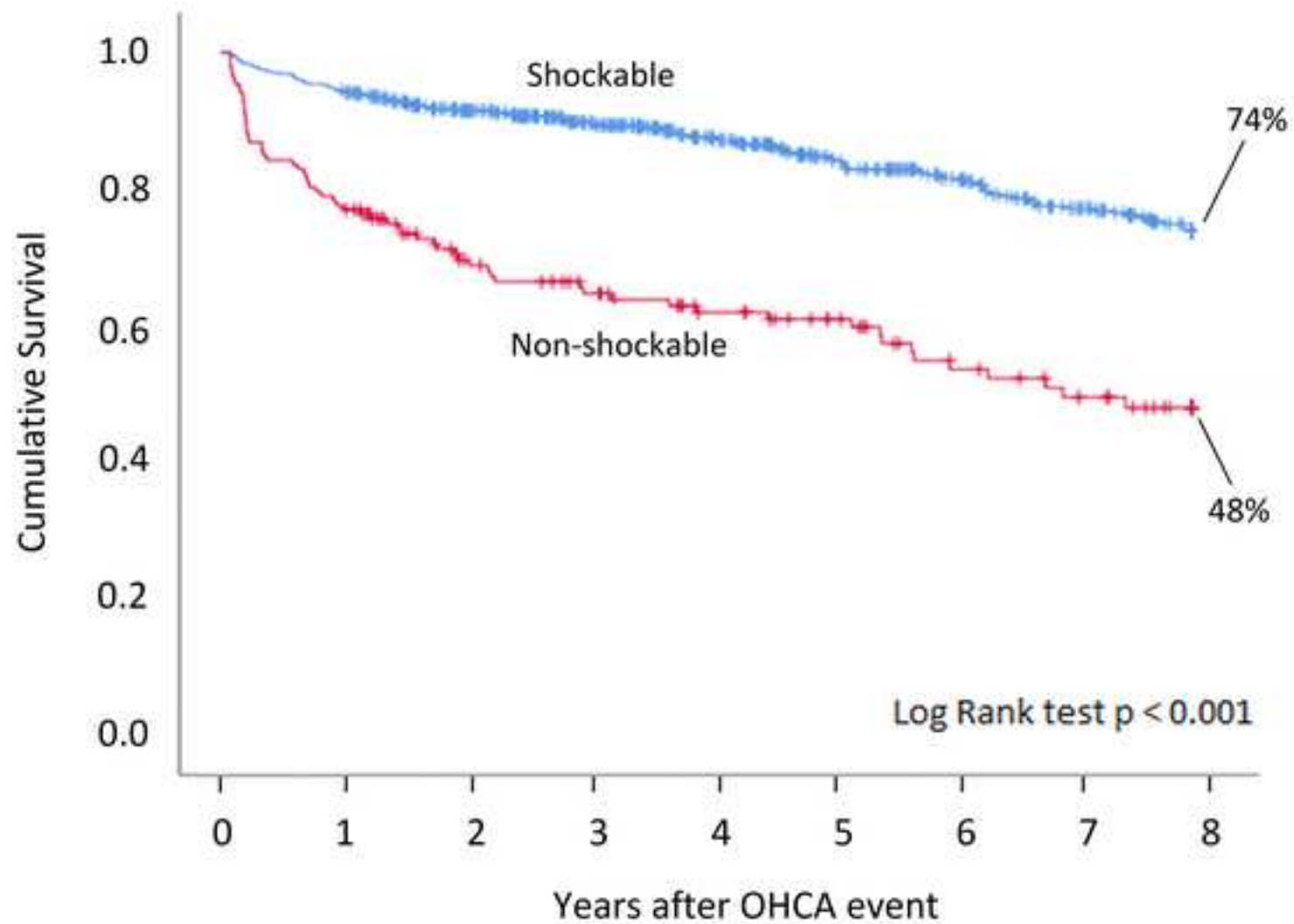
**Table 1. Baseline characteristics of OHCA patients in the study cohort stratified by initial cardiac arrest rhythm.**

	VF/VT Initial Arrest Rhythm n=718		PEA/Asystole Initial Arrest Rhythm n=153		Total		Chi-squared (degrees of freedom - <i>df</i> )	p-value
<b>Age, n (%)</b>								
16-39	70	(9.7)	17	(11.1)	87	(10.0)	15.85 (3 <i>df</i> )	0.001
40-64	351	(48.9)	56	(36.6)	407	(46.7)		
65-79	229	(31.9)	50	(32.7)	279	(32.7)		
≥80	68	(9.5)	30	(19.6)	98	(11.3)		
<b>Sex, n (%)</b>								
Male	568	(79.1)	89	(75.4)	568	(75.4)	29.84 (1 <i>df</i> )	<0.001
<b>Witness status, n (%)</b>								
Unwitnessed	154	(21.5)	46	(30.1)	200	(23.0)	21.40 (2 <i>df</i> )	<0.001
Bystander	344	(47.9)	42	(27.4)	386	(44.3)		
EMS	220	(30.6)	65	(42.5)	285	(32.7)		
<b>Arrest location, n (%)</b>								
Residence	397	(55.3)	123	(59.7)	520	(59.7)	33.03 (1 <i>df</i> )	<0.001
Public	319	(44.7)	32	(40.3)	351	(40.3)		
<b>Bystander CPR, n (%)</b>								
No	302	(42.1)	113	(47.6)	415	(47.6)	51.11 (2 <i>df</i> )	<0.001
Yes	414	(57.9)	42	(52.4)	456	(52.4)		
<b>EMS response time, n (%)</b>								
< 10 minutes	588	(81.9)	128	(83.7)	716	(82.2)	0.27 (2 <i>df</i> )	0.604
≥ 10 minutes	130	(18.1)	25	(16.3)	155	(17.8)		
<b>Arrest Decade, n (%)</b>								
1998-2007	201	(28.0)	36	(27.2)	237	(27.2)	1.27 (2 <i>df</i> )	0.260
2008-2017	517	(72.0)	117	(72.8)	634	(72.8)		

**Table 2. Unadjusted and adjusted 8-year mortality hazard rate estimates for initial 30-day OHCA survivors (n= 871)**

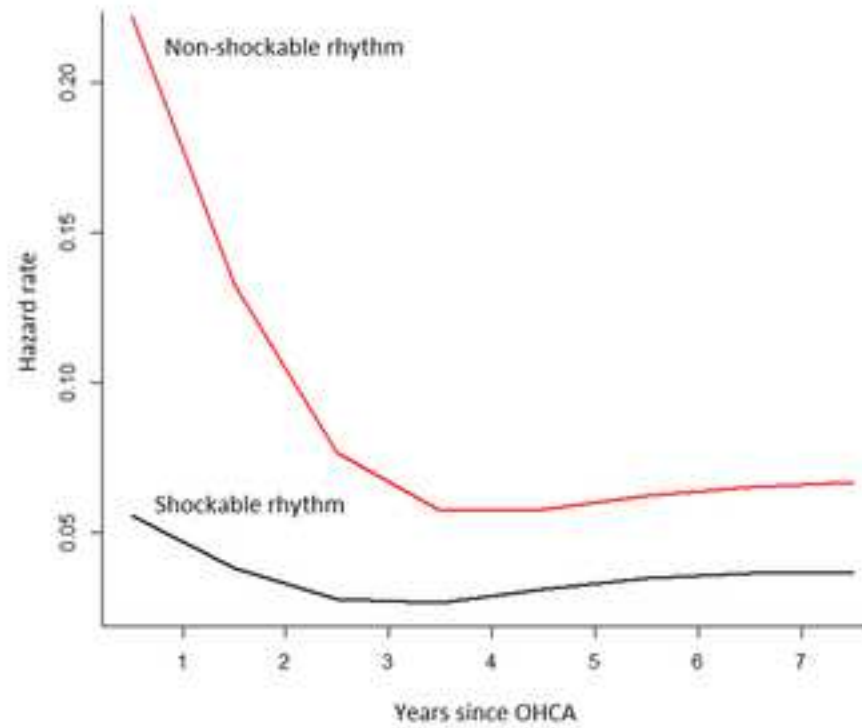
	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
<b>Age</b>				
16-39	ref		ref	
40-64	0.67	(0.37-1.26)	0.64	(0.37-1.23)
65-79	1.94	(1.11-3.55)	1.88	(1.11-3.49)
≥80	5.41	(3.02-10.07)	4.91	(2.73-9.37)
<b>Gender</b>				
Female	ref		ref	
Male	0.76	(0.56-1.04)	1.30	(0.94-1.79)
<b>Witness status</b>				
Bystander	ref		ref	
EMS	1.30	(0.90-1.91)	1.01	(0.64-1.63)
Unwitnessed	1.57	(1.15-2.14)	1.10	(0.74-1.62)
<b>Arrest location</b>				
Public	ref		ref	
Private residence	1.56	(1.16-2.13)	1.11	(0.80-1.58)
<b>Bystander CPR</b>				
Yes	ref		ref	
No	1.75	(1.32-2.34)	1.11	(0.74-1.66)
<b>EMS response time</b>				
< 10 minutes	ref		ref	
≥ 10 minutes	1.06	(0.72-1.51)	1.43	(0.95-2.13)
<b>Arrest Rhythm</b>				
VF/pVT	ref		ref	
PEA/Asystole				
Year 1	4.10	(2.62-6.37)	3.33	(2.12-5.32)
Year 2	3.10	(1.43-6.37)	2.58	(1.22-5.15)
Year 3	2.56	(1.20-5.08)	2.21	(1.02-4.42)
Year 4	2.56	(1.20-5.08)	2.21	(1.02-4.42)
Year 5	1.83	(0.98-3.08)	1.79	(0.95-3.10)
Year 6	1.83	(0.98-3.08)	1.79	(0.95-3.10)
Year 7	1.83	(0.98-3.08)	1.79	(0.95-3.10)
Year 8	1.83	(0.98-3.08)	1.79	(0.95-3.10)



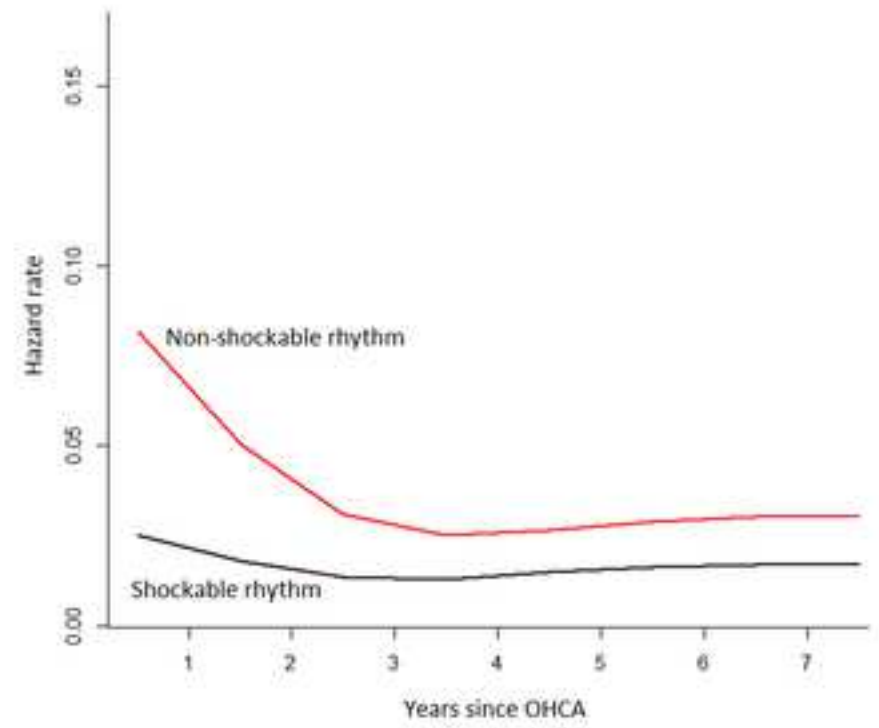


No. at Risk

Shockable:	718	678	595	516	438	365	314	264	213
Non-shockable:	153	119	89	76	64	56	44	36	27



(a)



(b)



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**Supplemental files for online publication only**  
Appendix A.docx

