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Clinicopathological correlates of out-of-hospital cardiac arrests

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Abstract

Background: Sudden cardiac arrest with or without sudden cardiac death (SCD) represents a heterogeneous spectrum of underlying etiology but is often a catastrophic event. Despite improvements in pre-hospital response and post-resuscitation care, outcomes remain grim. Thus, we aim to evaluate the predictors of survival in out-of-hospital cardiac arrests (OHCAs) and describe autopsy findings of those with the uncertain cause of death (COD).

Methods: This is a subgroup analysis of the Singapore cohort from the Pan Asian Resuscitation Outcome Study which studied 933 OHCAs admitted to two Singapore tertiary hospitals from April 2010 to May 2012.

Results: Of the patients analysed, 30.2% (n = 282) had an initial return of spontaneous circulation (ROSC) at the emergency department, 18.0% (n = 168) had sustained ROSC with subsequent admission and 3.4% (n = 32) had survival to discharge. On multivariate analysis, an initial shockable rhythm, a witnessed event, prehospital defibrillation, and shorter time to hospital predicted ROSC as well as survival to discharge. A total of 163 (17.5%) autopsies were performed of which a cardiac etiology of SCD was noted in 92.1% (n = 151). Ischemic heart disease accounted for 54.3% (n = 89) of the autopsy cohort, with acute myocardial infarction (26.9%, n = 44) and myocarditis (3.7%, n = 6) rounding out the top three causes of demise.

Conclusion: OHCA remains a clinical presentation that portends a poor prognosis. Of those with uncertain COD, cardiac etiology appears to predominate from autopsy study. Identification of prognostic factors will play an important role in improving individual-level and systemic-level variables to further optimize outcomes.

1 | INTRODUCTION

Sudden cardiac arrest (SCA) occurs when there is a sudden cessation of circulation as the heart stops beating efficiently, leading to deaths in the absence of timely interventions which is then known as sudden cardiac death (SCD).[1] This is oftentimes a catastrophic event with significant morbidity and mortality. While improvements in pre-hospital response and post-resuscitation care have led to improvements in outcomes, outcomes of SCD remain poor globally.[2,3]

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The prevalence of SCA and the relatively poor survival from those that occur out-of-hospital have spurred many efforts into better understanding the etiology for such as well as the implementation of strategies to better respond to out-of-hospital cardiac arrests (OHCAs). A key challenge faced herein is the vague definition and incomplete understanding of SCD which is contributed by the significant heterogeneity in existing classification systems. Studies based on death certificate review have tended to overestimate the incidence of SCD because of inaccuracies in stated causes of death while investigations relying on pre-hospital records often presume cardiac etiology based on the reported history.[4–6] Recognizing this gap in knowledge, a collaborative effort was made across the Asia Pacific Region to set up a common registry which culminated in the Pan Asia Resuscitation Outcome Study (PAROS).[7] There were initially seven members (Japan, South Korea, Taiwan, Thailand, United Arab Emirates [UAE]-Dubai, Singapore, and Malaysia) with later inclusions of Philippines, China, Pakistan, Vietnam, India, and UAE-Abu Dhabi. The main results were published in 2015 including 66,000 OHCA cases collated over 2.5 years. Results showed that most OHCAs occurred at home while initial response efforts were poor. Bystander cardiopulmonary resuscitation (BCPR) rates ranged from 10.5% to 40.9% and defibrillation was only administered in a very small proportion of patients (<1%). On a whole, between 0.5% and 8.5% of the patients managed eventual survival to discharge. Locally in Singapore, the eventual survival to discharge rate was only 2.5%.[8]

Following up on previous efforts in this study, we aimed to identify the predictors of ROSC and survival in patients with OHCA and to describe the autopsy findings for SCD victims who underwent an autopsy in the Singapore cohort of the PAROS clinical research network.

2 | METHODOLOGY

2.1 | Study design and setting

Singapore is a modern island city-state in South-east Asia with a multi-ethnic makeup. It has a population of 5.64 million and a land area of 719.1 square kilometers. The Singapore Civil Defense Force (SCDF) oversees the local emergency medical services (EMS) system which operates via a national universal centralized access number 995. The EMS system is staffed by a well-trained team of paramedics who operate a fleet of ambulances distributed across the island. These paramedics are competent in basic life support and defibrillation using automated external defibrillators (AEDs) and paramedics are able to administer life-saving medications. The EMS system is responsible for initial triage and will expediently transport the patient to the nearest tertiary hospital.[9]

This study analyzes a subgroup of patients collated from an international cardiac arrest registry—the Singapore cohort of the Pan Asia Resuscitation Outcome Study (PAROS). PAROS is a prospective multi-center OHCA registry for which the details have been previously published.[7] In brief, the Singapore cohort of PAROS included all OHCA patients who presented directly at tertiary hospital emergency departments or were conveyed by the EMS via the access number 995 who met the inclusion criteria of confirmed absence of pulse, unresponsiveness, and apnea. Patients who were immediately pronounced dead on-site or for whom resuscitation was not attempted were excluded. Data collection was systemically performed by assessing the emergency dispatch records, ambulance case notes, emergency department, and inpatient notes and discharge summary, and death certificate. Demographic data such as age, sex, and comorbidities were collected. Other data collected were in accordance with the Utstein template encompassing variables such as the initial arrest rhythm, information on whether OHCA was witnessed, presence of bystander CPR, public access defibrillation, response times, advanced life support details.

From the Singapore cohort of the PAROS registry, data from consecutive patients admitted to two major local institutions over a 2-year period from April 2010 to May 2012 was obtained for this study. Patients of age < 18 years were excluded. Cases of a drug overdose, trauma, homicide, or suicide were excluded from the study. Autopsy data for the deceased among the identified cases of SCA were requested from the Health Science Authority in Singapore. Ethics approval was obtained from the SingHealth Centralised Institutional Review Board (Reference number CIRB 2015/2094).

2.2 | Autopsy Proceedings

In Singapore, the death investigation system requires all deaths that occur suddenly without a known cause and/or are suspected to be because of unnatural causes to be reported to the state coroner.[10] A subsequent review of the case is then conducted by the forensic pathologists at the Health Sciences Authority who then convene with the state coroner for a final decision as to whether an autopsy is recommended to determine the cause of death (COD). Cases where death is adjudicated to be non-sudden and obviously because of natural disease processes, in light of an appropriate past medical history, as well as benign circumstances that surrounded the death, are exempted from an autopsy. Identified cases would then undergo a comprehensive forensic autopsy with an examination of the brain, neck structures, and thoracic, abdominal, and pelvic organs. Histology of the major organs and postmortem toxicology would be performed in all cases.

As part of the routine evaluation, the heart would be excised and weighed. The major epicardial arteries and main branches would be cut transversely and systemically examined for the presence of luminal thrombus. For the purposes of this study, we defined significant coronary artery disease (CAD) as ≥70% cross-sectional area reduction in at least one major epicardial coronary artery or 50% cross-sectional area reduction in the left main coronary artery; moderate CAD was defined as >40% but <70% cross-sectional area reduction in all coronary arteries and < 50% cross-sectional area reduction in the left main coronary artery; mild/no disease was defined as <40%

area reduction. An active coronary lesion was defined as the presence of disrupted coronary plaque, including erosion or rupture, luminal thrombus, or both.

2.3 | Statistical Analysis

Categorical variables were presented as percentages and analyzed using the Chi-square test or Fisher's exact test as appropriate. Continuous variables were presented as mean ± standard deviation and compared using a t-test. A multivariable logistic regression model was employed, and results were presented as adjusted odds ratios (adj OR) with 95% confidence intervals (CI). All statistical tests were performed using IBM SPSS version 25 (IBM Corp.). A *p*-value of <0.05 was considered statistically significant.

3 | RESULTS

A total of 933 cases of OHCAs were identified for this analysis. The clinical characteristics of the cohort stratified by eventual outcomes of return of spontaneous circulation (ROSC) and survival to discharge are shown in Table 1. The patients were predominantly male (65.4%, *n* = 610), the study group mean age was 65.8 ± 15.6 years old. Cardiovascular risk factors were reported in hypertension (56.5%, *n* = 527), hyperlipidemia (35.5%, *n* = 331), and diabetes (33.2%, *n* = 310). 38.3% (n=357) reported the presence of CAD; of which 15.0% (*n* = 140) had undergone prior coronary revascularization either via percutaneous coronary intervention or coronary artery bypass surgery. There were 65 (7.0%) patients who would have qualified for implantable cardioverter-defibrillator (ICD) for primary prevention but only 12 (1.3%) patients had a device implanted. A total of 17 patients had a history of prior antiarrhythmic use.

70.7% (*n* = 660) of the cardiac arrests occurred at home while other common sites include public and commercial buildings as well as public areas such as along the streets and in parks. 53.2% (*n* = 496) of the collapses were witnessed by a bystander but bystander CPR was initiated in only 23.0% (*n* = 215) of these cases. An average of 8 min 36 s was taken for the EMS to arrive on the scene and 31 min 27 s for the patient to reach the emergency department for further definitive care. The most commonly encountered rhythm on EMS arrival was asystole which was seen in 53.5% (*n* = 499) of the patients and only 19.3% (*n* = 180) of the patients had a shockable initial rhythm on assessment.

30.2% (*n* = 282) patients had an initial ROSC at the emergency department with 18.0% (*n* = 168) patients having sustained ROSC with subsequent inpatient admission. Overall, 3.4% (*n* = 32) of patients managed survival to discharge. Utstein survival as defined by survival to hospital discharge of those cardiac patients who had suffered a witnessed arrest and had a shockable initial rhythm was 8.3%.

On univariate analysis, the patient's comorbidities did not affect the ROSC or survival to discharge rates. On multivariate analysis, an initial shockable rhythm (OR 2.70, p <0.001), a witnessed event (OR 1.30, p = 0.043), prehospital defibrillation (OR 2.70, p = 0.01), and shorter time to hospital (OR 0.99, p <0.001) were predictors for ROSC. Similarly, initial shockable rhythm (OR 8.35, p <0.001), a witnessed event (OR 2.98, p = 0.034), prehospital defibrillation (OR 5.52, p = 0.001), and shorter time to hospital (OR 0.98, p <0.001) were also significant predictors for survival to discharge. See Table 2.

3.1 | Autopsy Analysis

24.5% (*n* = 229) of the cases were deemed to have an unclear COD and were referred to the coroner for further evaluation, of which 17.5% (*n* = 164) underwent full autopsies

The causes of death based on autopsy findings for those cases which underwent a full autopsy are shown in Table 3. Among those that underwent autopsy, the majority (92.1%, *n* = 151) had an underlying cardiac etiology. Ischemic heart disease (IHD) (54.3%, *n* = 89) and acute myocardial infarction (AMI) (26.9%, *n* = 44) were the most common causes of death identified. 80.4% (*n* = 131) subjects also had significant coronary artery disease, defined as a minimum of 70% stenosis in at least one or more major epicardial coronary arteries and/or a minimum of 50% stenosis in the left main coronary artery. Of those with significant CAD, 16.7% (*n* = 27) of subjects had no known prior significant cardiovascular risk factors or history of IHD. Critical left main and/or significant triple vessel disease was also noticed in 44.2% (*n* = 72) of the autopsied population and double vessel disease in 19.6% (*n* = 32) patients. In 13.5% (*n* = 22) cases, there was evidence of plaque rupture with thrombus within the atherosclerotic vessel. See Figure 1.

Other cardiac causes of death identified include myocarditis (3.7%, *n* = 6), valvular heart disease (2.4%, *n* = 4), dilated cardiomyopathy (1.8%, *n* = 3), and hypertrophic cardiomyopathy (0.6%, *n* = 1). 7.9% (*n* = 13) of the cases had non-cardiac etiologies identified such as pulmonary embolism, pneumonia, and rupture of abdominal aortic aneurysms. Chemical and toxicology analysis during autopsy did not reveal evidence of poisoning or drug overdose in any case.

For the overall cohort, a cardiac etiology was similarly the most common cause of demise (82.7%, *n* = 745). Ischemic heart disease and acute myocardial infarction represented the majority of the causes of death (67.4%, *n* = 607). Among the non-cardiac causes of death, pneumonia was the most common COD (6.0%, *n* = 54). See Table 4.

4 | DISCUSSION

In this Singapore sub-study of the PAROS clinical network, 30.2% (*n* = 282) OHCA patients achieved the return of spontaneous circulation (ROSC) at the emergency department; of which 18.0% (*n* = 168) with sustained ROSC were admitted to the hospital. 3.4% (*n* = 32) OHCA patients achieved survival to discharge. Utstein survival as defined by survival to hospital discharge of those cardiac patients

TABLE 1 Clinical characteristics of ROSC and survival to discharge in OHCA

	Total	No ROSC	ROSC			Demise	Survival to discharge		
	n = 933	*n* = 765	*n* = 168	OR (CI)	*p* value	*n* = 901	*n* = 32	OR (CI)	*p* value
Gender (Male)	610 (65.4%)	509 (66.5%)	101 (60.1%)	0.76 (0.54–1.07)	0.128	589 (65.4%)	21 (65.6%)	1.01 (0.48–2.12)	0.570
Age	65.8 ± 15.6	66.2 ± 15.7	63.9 ± 14.4	0.99 (0.98–1.01)	0.065	66.1 ± 15.4	58.8 ± 16.8	**0.96 (0.95–0.99)**	**0.010**
Smoker	187 (20.0%)	142 (18.6%)	45 (26.8%)	1.44 (1.08–1.93)	0.019	178 (19.8%)	9 (28.1%)	1.43 (0.81–2.52)	0.261
Race					0.788				0.158
Chinese	621 (66.6%)	504 (65.9%)	117 (69.6%)			596 (66.1%)	25 (78.1%)		
Malay	145 (15.5%)	122 (15.9%)	23 (13.7%)			143 (15.9%)	2 (6.3%)		
Indian	96 (10.3%)	79 (10.3%)	17 (10.1%)			95 (10.5%)	1 (3.1%)		
Others	71 (7.6%)	60 (7.8%)	11 (6.5%)			67 (7.4%)	4 (12.5%)		
Comorbidities									
None	133 (14.3%)	115 (15.0%)	18 (10.7%)	0.68 (0.40–1.15)	0.180	29 (3.6%)	3 (9.4%)	1.06 (0.94–1.19)	0.607
Hypertension	527 (56.5%)	428 (55.9%)	99 (58.9%)	0.89 (0.63–1.24)	0.493	508 (56.4%)	19 (59.4%)	1.05 (0.79–1.41)	0.857
Diabetes	310 (33.2%)	251 (32.8%)	59 (35.1%)	1.07 (0.85–1.34)	0.312	298 (33.1%)	12 (37.5%)	1.13 (0.72–1.79)	0.574
Hyperlipidemia	331 (35.5%)	261 (34.1%)	70 (41.7%)	1.22 (0.98–1.50)	0.075	311 (34.5%)	12 (37.5%)	1.03 (0.58–1.51)	0.674
Underlying CAD	357 (38.3%)	285 (37.3%)	72 (42.9%)	1.15 (0.94–1.40)	0.189	340 (37.7%)	15 (53.1%)	1.31 (0.88–1.97)	0.095
Heart failure	91 (9.8%)	71 (9.3%)	20 (11.9%)	1.28 (0.80–2.04)	0.315	90 (10.0%)	1 (3.1%)	0.32 (0.05–2.18)	0.356
CKD	87 (9.3%)	71 (9.3%)	16 (9.6%)	1.03 (0.61–1.72)	0.884	84 (9.3%)	3 (9.4%)	1.01 (0.34–3.01)	0.588
PVD	30 (3.2%)	26 (3.4%)	4 (2.4%)	0.70 (0.25–1.98)	0.633	29 (3.2%)	1 (3.1%)	1.00 (0.94–1.07)	0.725
COPD	136 (14.6%)	104 (13.6%)	32 (19.0%)	1.40 (0.98–2.01)	0.090	132 (14.7%)	4 (12.5%)	0.85 (0.34–2.17)	0.735
Stroke	135 (14.5%)	104 (13.6%)	31 (18.5%)	1.36 (0.94–196)	0.115	129 (14.3%)	6 (18.8%)	1.31 (0.63–2.74)	0.312
Implanted device	12 (1.3%)	9 (1.2%)	3 (1.8%)	1.52 (0.42–5.55)	0.461	12 (100%)	0 (0.0%)	0.97 (0.89–1.02)	0.656
Collapse details									
Witnessed event	496 (53.2%)	394 (51.5%)	102 (60.7%)	**1.18 (1.03–1.36)**	**0.033**	471 (52.2%)	25 (78.1%)	**1.49 (1.12–1.81)**	**0.04**
Bystander CPR	215 (23.0%)	173 (22.6%)	42 (25.0%)	1.11 (0.83–1.48)	0.544	205 (22.8%)	10 (31.3%)	1.37 (0.81–2.32)	0.285
Bystander AED	25 (2.7%)	22 (2.8%)	3 (1.8%)	1.65 (0.50–5.58)	0.677	24 (2.6%)	1 (3.1%)	1.23 (0.16–9.41)	0.572
Shockable initial rhythm	180 (19.3%)	121 (15.8%)	59 (35.1%)	**2.88 (1.99–4.18)**	**<0.001**	168 (18.6%)	12 (37.5%)	**7.72 (3.70–16.1)**	**<0.001**
Prehospital defibrillation	220 (24.1%)	153 (20.0%)	67 (41.4%)	**2.75 (1.92–3.93)**	**<0.001**	200 (22.2%)	20 (69.0%)	**5.84 (2.81–12.1)**	**<0.001**
Location									
Home	660 (70.7%)	555 (72.5%)	105 (62.5%)	–	**0.036**	649 (72.0%)	11 (34.4%)	–	**<0.001**
Healthcare facility	46 (4.9%)	35 (4.6%)	11 (6.5%)			44 (4.9%)	2 (6.3%)		

(Continues)

TABLE 1 (Continued)

	Total	No ROSC	ROSC			Demise	Survival to discharge		
	n = 933	*n* = 765	*n* = 168	OR (CI)	*p* value	*n* = 901	*n* = 32	OR (CI)	*p* value
Public/Commercial building	148 (15.9%)	118 (15.4%)	30 (17.9%)			139 (15.4%)	9 (28.1%)		
Public areas (e.g. Roads/Streets/Parks)	41 (4.4%)	30 (3.9%)	11 (6.6%)			35 (3.9%)	6 (18.8%)		
Others	38 (4.1%)	27 (3.5%)	11 (6.6%)			34 (3.8%)	4 (12.5%)		
Time to scene	8 min 36 s ± 3 min 25 s	8 min 45 s ± 3 min 30s	7 min 54 s ± 2 min 54 s	**0.99 (0.99–1.00)**	**0.005**	8 min 38 s ± 3 min 25 s	7 min 40s ± 3 min 11 s	1.00 (0.99–1.01)	0.150
Time to accident & emergency	31 min 27 s ± 6 min 23 s	29 min 20s ± 6 min 12 s	31 min 54 s ± 6 min ± 12 s	**0.99 (0.98–0.99)**	**<0.001**	31 min 32 s ± 6 min 23 s	28 min 52 s ± 5 min 26 s	**0.99 (0.98–0.99)**	**<0.001**

who had suffered a witnessed arrest and had a shockable initial rhythm was 8.3%. OHCA continued to portend a guarded prognosis for patients that witnessed events, initial shockable rhythm, prehospital defibrillation, and a shorter time to hospital predicted for survival and discharge from hospital.

In this series, approximately one in three had initial ROSC with sustained ROSC to admission seen in 18% and survival to discharge rate of 3.4%. In a recent meta-analysis of 141 OHCA studies, Yan et. al reported a pooled incidence of ROSC of 29.7% (95% CI: 27.6%–31.7%), rate of survival to the admission of 22.0% (95% CI 20.7%–23.4%), and a rate of survival to hospital discharge of 8.8% (95% CI 8.2%–9.4%). Yan et al also noted in Asian countries, that rates of ROSC, survival to admission, and survival to discharge were lower as compared to the European countries.[3,11] Such geographical differences in OHCA outcomes likely represent special cause variation and can potentially be attributed to differences in the incidence of shockable first rhythm, witnessed collapse, bystander CPR, and early defibrillation. The Utstein survival rate in this sub-study was 8.3%, fairly similar to the Utstein survival rate of 11% reported nationally in Singapore from 2011–2012. In other international registries, this rate varies from 5.1% to 57.9%.[12–16] Our data reflect current real-world outcomes of patients with OHCA in a developed city-state in south-east Asia.

The noted predictors of ROSC in this study of the witnessed event, shockable initial rhythm, prehospital defibrillation, and earlier time to hospital reinforce the well-accepted paradigm of the chain of survival where key tenets of good resuscitation are early recognition, early CPR, rapid defibrillation with prompt evacuation to higher echelons of care.[17,18] In the absence of robust prehospital care, subsequent resuscitation as per advanced cardiac life support guidelines are less likely to be successful. One potential explanation is that a collapse at home is less likely to be witnessed and correspondingly response and evacuation are more likely to be delayed, leading to worse outcomes. Similar trends have been observed in other local studies where living alone without a nuclear family confers a poorer prognosis and higher risk of OHCA.[19]

Recognizing this gap, there have been concerted efforts in Singapore over recent years to improve pre-hospital care. These measures included but were not limited to attempts to expose larger groups of the population to CPR and AED training, widespread dissemination of AEDs as well as the introduction of dispatch-associated CPR to improve the quality as well as the frequency of bystander response to a collapse.[20] The fruits of this labor are reflected in the improved outcomes in studies that extend beyond 2012 that have reported improved outcomes for OHCAs as compared to that described herein.[12] These measures have been recognized as fundamental measures in improving outcomes for SCA patients in the recently published 2020 APHRS/HRS Expert Consensus Statement which accorded a Class I recommendation for the wide implementation of targeted cardiopulmonary resuscitation training as well as ensuring the availability of appropriately maintained AEDs with appropriate training for users.[21]

TABLE 2 Multivariate predictors of ROSC and survival to discharge in OHCA

	ROSC ($n = 168$)		Survival to discharge ($n = 32$)	
	OR (CI)	*p* value	OR (CI)	*p* value
Age	0.99 (0.99–1.01)	0.717	0.98 (0.95–1.01)	0.162
Witnessed event	1.30 (1.03–1.87)	0.043	2.98 (1.09–2.81)	0.034
Shockable initial rhythm	2.70 (1.81–4.04)	<0.001	8.35 (3.5–19.9)	<0.001
Prehospital defibrillation	2.15 (1.92–3.93)	0.01	5.52 (2.81–12.1)	0.003
Time to accident & emergency	0.99 (0.98–0.99)	<0.001	0.98 (0.97–0.99)	<0.001

TABLE 3 Causes of deaths based on autopsy findings

Cardiac causes of death	No (%)	Non-cardiac causes of death	No (%)
Ischemic heart disease	89 (54.3)	Pulmonary embolism	5 (3.0)
Acute myocardial infarction	44 (26.9)	Ruptured abdominal aortic aneurysm	5 (3.0)
Myocarditis	6 (3.7)	Pneumonia	3 (1.8)
Valvular heart disease	4 (2.4)		
Hypertensive heart disease	4 (2.4)		
Dilated cardiomyopathy	3 (1.8)		
Hypertrophic cardiomyopathy	1 (0.6)		
Cardiac causes of death	151 (92.1)	Non-cardiac causes of death	13 (7.9)

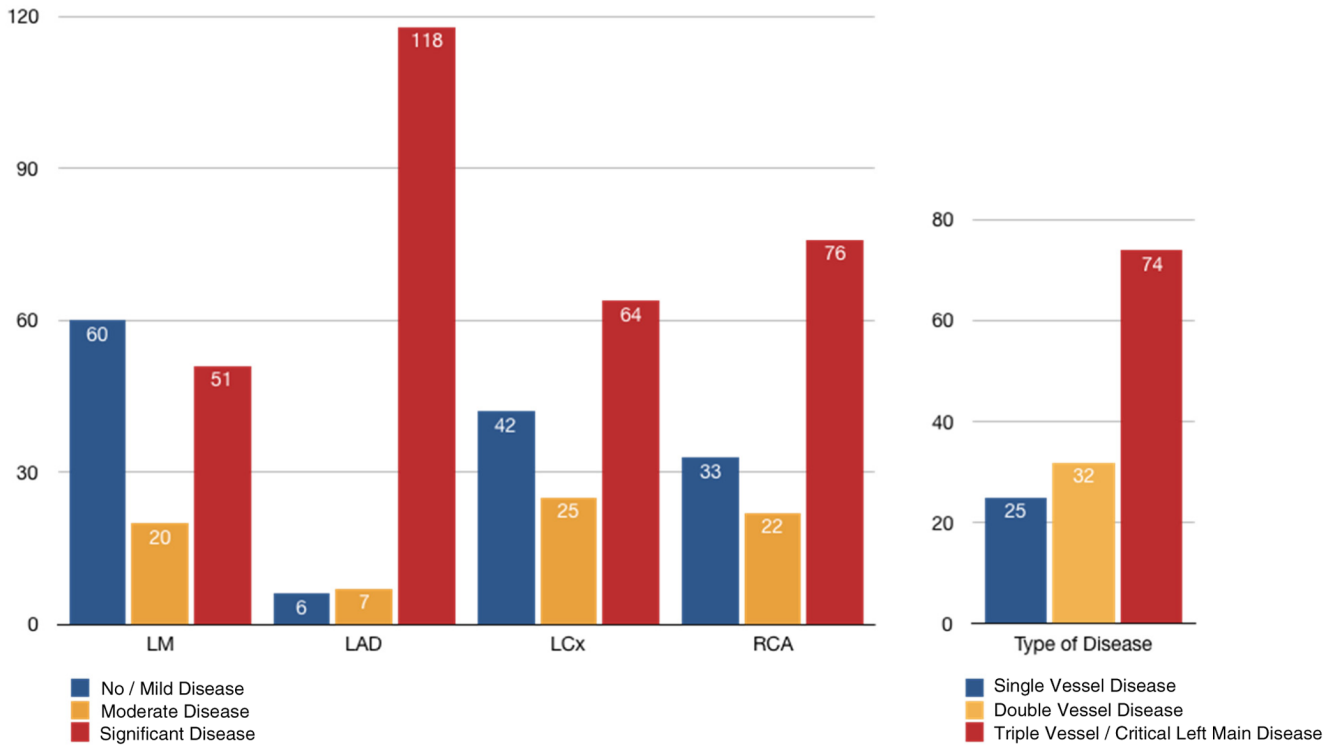

FIGURE 1 Degree of coronary artery disease based on autopsy findings

From the autopsies performed, ischemic heart disease remains the top COD in patients who have suffered an SCA with an uncertain COD. This is in keeping with previous autopsy studies which report that up to 80% of SCAs can be attributed to coronary artery disease.[22] In an earlier autopsy study by Health Sciences Authority conducted from 2009 to 2010, cardiac pathologies similarly account for a large proportion (64.6%) of all deaths ($n = 3560$) which were authorized for an autopsy by the coroner in Singapore

TABLE 4 Causes of deaths based on autopsy findings and death certificate findings

Causes of death (*n*, %)	Overall (*n* = 901)	Autopsy cases (*n* = 164)	Non-autopsy cases (*n* = 737)
Cardiac causes of death	745 (82.7%)	151 (92.1%)	594 (80.6%)
Ischemic heart disease/Acute myocardial infarction	607 (67.4%)	133 (81.1%)	474 (64.3%)
Myocarditis	6 (0.7%)	6 (3.7%)	0 (0.0%)
Valvular heart disease	10 (1.1%)	4 (2.4%)	6 (0.8%)
Hypertensive heart disease	115 (12.7%)	4 (2.4%)	111 (15.0%)
Dilated cardiomyopathy	5 (0.6%)	3 (1.8%)	2 (0.3%)
Hypertrophic cardiomyopathy	2 (0.2%)	1 (0.6%)	1 (0.1%)
Non cardiac causes of death	156 (17.3%)	13 (7.9%)	143 (19.4%)
Pneumonia	54 (6.0%)	3 (1.8%)	51 (6.9%)
Pulmonary embolism	5 (0.5%)	5 (3.0%)	0 (0.0%)
Asthma/COPD	23 (2.6%)	0 (0.0%)	23 (3.1%)
Stroke	19 (2.1%)	0 (0.0%)	19 (2.6%)
End stage kidney disease	10 (1.1%)	0 (0.0%)	10 (1.4%)
Malignancy	17 (1.9%)	0 (0.0%)	17 (2.3%)
Ruptured aneurysm	8 (0.9%)	5 (3.0%)	3 (0.4%)
Others (e.g., Urinary tract infection, colitis, soft tissue infection, other sources of infection)	20 (2.2%)	0 (0.0%)	20 (2.7%)

irrespective of presentation.[19] Notably, despite the strong preponderance toward underlying cardiac disease and ischemic heart disease as the COD from the autopsy studies, a significant proportion of patients in the cohort had no prior cardiac history or even cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, or smoking. This points to the importance of effective cardiovascular health screening and primary prevention in the general population to identify at-risk individuals who might be harboring undiagnosed ischemic heart disease and whose first presentation might be fatal.

Non-ischemic heart disease could also present a substrate for malignant arrhythmias and SCA. Previous studies have shown that roughly 10–15% of such cardiac collapses can be attributed to myocardial diseases such as hypertrophic cardiomyopathy (HCM), idiopathic dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), or other infiltrative myocardial disease or primary ion channelopathies.[23–25] While left ventricular hypertrophy was identified in a large proportion of our autopsies, only 1 case fulfilled the criteria for HCM. The most common non-ischemic cause of cardiac arrests turned out to be myocarditis. There were also no negative autopsies among this cohort. This is in keeping with the epidemiology of our study population which is more elderly with the exclusion of pediatric cases. Previous studies have shown that CAD remains the most common cause of SCA in individuals above 35 years old while cardiomyopathies and channelopathies tend to be more prevalent in those below 35 years old.[26] With an average age of 65 years old, it is not unexpected that underlying CAD is the predominant COD identified after autopsy evaluation in our study.

A toxicological examination was also notably negative in our cohort. This stands in contrast to both American and European studies where substance abuse such as the use of illicit and recreational drugs notably cocaine and amphetamines are well known to be associated with SCA.[27,28] According to the Cardiac Arrest Registry to Enhance Survival (CARES) report in 2019, drug overdose contributed to 5.7% of all OHCAs.[29] This reflects the effectiveness of the zero-tolerance attitude that Singapore has toward substance abuse with punitive laws that extend to capital punishment.[30] As such, the rate of substance abuse in Singapore is remarkably low and correspondingly, substance abuse is also an exceedingly rare cause of SCA in Singapore.[31]

While only a small proportion (7.0%, *n* = 65) of patients in this series were eligible for a primary prevention ICD, even fewer (*n* = 12, 1.2% of the whole series and 18.5% of those eligible) actually had one implanted. This low rate of ICD implantation is consistent both locally and internationally. The Swedish Heart Failure Registry found that only 10% of eligible patients received an ICD while a study of the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) Registry similarly showed a low ICD implantation rate of 12%.[32,33] Numerous studies have shown that ICD implantation can contribute greatly toward the prevention of SCD in those eligible, but there are many reasons why a patient does not receive an ICD. A common reason is poor patient knowledge where misconstrued notions about heart failure and ICDs lead a patient to under-estimate their risk of SCD and therefore turn down a device.[34] Financial considerations are another major concern where the financial burden associated with ICD therapy is an important deterrent to device uptake.[33] Another important reason is the personal considerations of living with a

long-term permanent device. Improving the uptake of ICDs in those eligible may help reduce the risk of OHCA in this subset. More can be done to educate these patients about the potentially life-saving benefit that an ICD can offer. Steps should also be made to make reduce the barrier to uptake for ICDs by improving reimbursement and subsidy coverage to make it more accessible to the average patient.

5 | LIMITATIONS

First, the study was limited to two centers from the Singapore cohort of the PAROS registry. Second, the study cohort was from 2010 to 2012 and overall OHCA outcomes have since improved further with improvements in chain-of-survival.[12,35] Third, the rate of post mortem evaluation in this study was only 17.4% as autopsies in Singapore are performed on a case-by-case basis as deemed necessary by the coroner and this may lead to a selection bias. In addition to this, there is also an element of selection bias with the managing physician deciding on whether to submit the case to the coroner versus determining a reasonable COD based on clinical grounds and assessment. Overall, the 17.4% autopsy rate in our study is similar to that reported for out-of-hospital natural deaths in the United States and European nations which ranges from 10% to 23%.[36–38] Furthermore, no genetic analysis to identify inheritable causes of SCA were performed. Reports have shown that in negative autopsy cases, molecular testing may play a role in identifying the underlying cause of SCA[39] for diseases such as cardiac channelopathies. The baseline ECGs were also not available for analysis.

Lastly, Perkins et al. have elegantly summarized the sources of special cause variation in cardiac arrests that are likely to influence survival rates.[40] One of the greatest variations arises from inconsistencies in data collection, i.e., case identification methods for patients with OHCA. Most, if not all OHCA registries are unfortunately prone to variability in case selection definition given the nuanced healthcare landscape and these must be considered when comparing outcomes across OHCA registries.

6 | CONCLUSION

OHCAs continue to portend significant morbidity and mortality; only 3.4% of OHCA patients (n = 933) achieved survival to discharge. In a subsequent series that underwent autopsies, cardiac etiology of SCD was identified in 92.1% of cases. IHD with or without AMI was identified in 81.2% of cases. Identification of prognostic factors will play an important role in improving individual-level and systemic-level intervention to further enhance survival in patients with OHCA.

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CONFLICT OF INTEREST

MEH Ong reports funding from the Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices; grants from the Laerdal Foundation, Laerdal Medical, and Ramsey Social Justice Foundation for funding of the Pan-Asian Resuscitation Outcomes Study; an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices; and funding from Laerdal Medical on an observation program to their Community CPR Training Centre Research Program in Norway. MEH Ong has a licensing agreement and a patent filed (Application no: 13/047,348) with ZOLL Medical Corporation for a study titled "Method of predicting acute cardiopulmonary events and survivability of a patient." All other authors have no conflict of interest to disclose.

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