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Clinical paper

In-hospital mode of death after out-of-hospital cardiac arrest

Melanie R Wittwer[a,b,*], *Thomas Armstrong*[a], *Jordan Conway*[a], *Mohammed Ishaq Ruknuddeen*[a,b], *Chris Zeitz*[a,c], *John F Beltrame*[a,c], *Margaret A Arstall*[a,b]

Abstract

Introduction: Factors associated with in-hospital mortality after out-of-hospital cardiac arrest (OHCA), such as mode of death and withdrawal of life-sustaining treatment (WLST), are not well established. This study aimed to compare clinical characteristics, timing of WLST and death, and precipitating aetiology between modes of death for OHCAs treated at hospital within a local health network.

Methods: Retrospective cohort study of adult non-traumatic OHCAs included in a hospital based OHCA registry between 2011 and 2016 and deceased at hospital discharge, excluding cases retrieved to external hospitals. Mode of death was defined as (1) cardiovascular instability, (2) non-neurological WLST, (3) neurological WLST, and (4) formal brain death. Relevant data were extracted from the registry and stratified according to mode of death and timing of death as early (within the emergency department) or late (after admission).

Results: Mode of death data was available for 69 early and 144 late deaths. Cardiovascular instability was the primary mode for 75% of early deaths, while 72% of late deaths were attributed to neurological injury (47% neurological WLST and 24% brain death, combined). Cardiovascular instability was associated with cardiac aetiology, brain death was associated with younger age and highest rates of organ donation, and neurological WLST was associated with highest rates of targeted temperature management, and longest time from arrest to death ($p < 0.05$).

Conclusions: This is the first study to compare clinical characteristics of adult patients resuscitated from OHCA according to in-hospital mode of death. A consensus on the definition of mode of death with standardised classification is needed.

Keywords: Out of hospital cardiac arrest, Mode of death, Cause of death, Aetiology, WLST, Brain death

Introduction

Out-of-hospital cardiac arrest (OHCA) remains associated with high mortality in spite of ongoing systems-based improvements.[1] Post-cardiac arrest syndrome has long been recognised as the major contributor to high mortality observed for patients who gain sustained return of spontaneous circulation (ROSC $\geq$ 20 min).[2] The four key components of post cardiac arrest syndrome include post-OHCA brain injury, post-OHCA myocardial dysfunction, systemic ischaemic-reperfusion injury, and persistent precipitating aetiology. Post-resuscitation guidelines therefore centre on addressing each of these components.[3–5] Understanding the reason for in-hospital death after OHCA and the contribution of associated factors such as post cardiac arrest syndrome, is useful for identifying organ donation candidates,[6] developing tools to aid prognostication, and ultimately for improving survival.

Previous research has identified that the mode of death for 70% of in-hospital deaths after resuscitated OHCA is neurological injury, which encompasses the spectrum of brain injury resulting in withholding or withdrawal of life-sustaining therapy (WLST) for perceived poor neurological prognosis, through to brain death. Other reported

Abbreviations: DNR, Do not resuscitate, ICU, Intensive care unit, NALHN, Northern Adelaide Local Health Network, OHCA, Out-of-hospital cardiac arrest, ROSC, Return of spontaneous circulation, SAAS, SA Ambulance Service, TTM, Targeted temperature management, WLST, Withdrawal of life sustaining treatment.

* Corresponding author at: Department of Cardiology, Lyell McEwin Hospital, Haydown Road, Elizabeth Vale, SA 5112, Australia.
E-mail address: melanie.wittwer@adelaide.edu.au (M.R Wittwer).

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modes of death include cardiovascular instability and multi-organ failure[7–14]; however, the literature on mode of death is limited. Factors associated with survival and non-survival, such as witnessed arrest and shockable initial rhythm, are established but the clinical characteristics and precipitating aetiology associated with specific modes of death have not been described in an adult population. Additionally, some evidence suggests that mode of death may differ between sexes, in part driven by higher rates of early WLST (<72 h post ROSC) in women compared with men.[7,15,16] Therefore, this study aimed to compare clinical characteristics, timing of WLST and death, and precipitating aetiology between modes of death for non-traumatic adult OHCAs with (a) early death in the emergency department (ED) and (b) late death after admission. Our secondary aim was to explore sex differences in mode of death, and timing of WLST and death.

Methods

Design

This is a retrospective observational cohort study of the Northern Adelaide Local Health Network (NALHN) OHCA registry, a hospital-based quality assurance initiative with data capture according to the Utstein style, described previously.[17,18] Briefly, potential cases are identified from existing EMS-based and hospital-based sources and eligible cases are included after full medical record review. Demographic, management, and outcome data are abstracted from the medical record into the registry. The current analysis included all adult, non-traumatic OHCAs treated at NALHN facilities and deceased at hospital discharge between 2011 and 2016. Patients retrieved to an external hospital were excluded. The Central Adelaide Local Health Network Human Research Ethics Committee approved the registry and subsequent analyses as an ongoing quality improvement activity [Q20170304].

Setting

NALHN comprises two public hospitals that service a population of 450,000 within the northern metropolitan and regional areas of Adelaide, South Australia. There is a single state-wide two-tier emergency medical service (SA Ambulance Service, SAAS) where patients are treated by paramedics on scene with transport under CPR according to local protocol. Both receiving hospitals have a resuscitation area in the ED with a multidisciplinary health team led by ED specialist physicians. The Lyell McEwin Hospital is the primary cardiac arrest centre with 24/7 PCI-capability and 13 intensive care unit (ICU) and 26 cardiac unit beds. SAAS and NALHN hospitals are guided by the ANZCOR resuscitation guidelines.[3] WLST covers both withholding and withdrawal of life-sustaining therapy including intubation, inotropes, and other life-sustaining medications.[19] Briefly, the decision for WLST is made between the physician and substitute decision maker according to known or perceived patient wishes. Timing and methods chosen for prognostication are left at the discretion of the treating physician. Following WLST, patients are palliated per local guidelines.

Measures

Primary and secondary outcome measures were extracted from the registry and analysed for patients deceased within ED and deceased after admission. Mode of death was documented in the registry according to the circumstances of death described in the medical record. Mode of death categories were based on previous studies[7–9,20] and included: (1) cardiovascular instability, including haemodynamic instability, recurrent arrest, and intractable shock; (2) WLST for non-neurological reasons are varied and may include multi-system organ failure, underlying comorbidities, advanced directive, substitute decision maker wishes etc. (non-neurological WLST); (3) WLST due to poor perceived neurological prognosis (neurological WLST); (4) formal brain death. Secondary outcome measures included sex, patient demographics, arrest characteristics, hospital management, WLST, location and timing of death, and aetiology. Clinical and multimodal methods of neurological prognostication and "Do Not Resuscitate" (DNR) orders were not consistently documented in the registry and could not be included in the current analysis.

Statistics

Continuous data is presented as median ± interquartile range and comparisons between groups made using Mann-Whitney U test or Kruskal-Wallis test. Categorical data is presented as frequency and percentage and comparisons between groups made using Fisher's exact test or Fisher-Freeman-Halton exact test with post-hoc pairwise z-tests performed as appropriate. Analyses were performed using SPSS 28 (IBM SPSS Statistics, Armonk, NY, USA).

Results

A search of the NALHN OHCA registry between 2011 and 2016 revealed 223 OHCA cases deceased at hospital discharge. Seven cases retrieved to a non-NALHN hospital were excluded, leaving a final cohort 69 cases deceased in ED and 147 cases deceased after admission, 144 with full details on mode of death (Fig. 1). Overall, the ED death rate was 18% with 32% of all deaths occurring in the ED, while the admitted death rate was 46%.

Early deaths in ED

Characteristics of patients deceased in ED stratified according to mode of death are presented in Table 1. Overall, 54% of patients were male with a median age of 72 years; 39% gained sustained ROSC $\geq$ 20 min, and median time from arrest to death was 1.5 h. Mode of death was due to cardiovascular instability in 75% of cases, non-neurological WLST in 16%, and neurological WLST in 10%. The

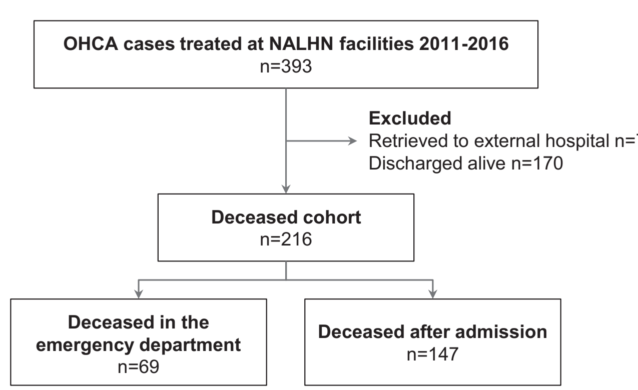

Fig. 1 – Flow-chart of included patients with early death in the emergency department and late death after admission.

Table 1 – Patient characteristics of resuscitated OHCAs with early death in the emergency department within a local health network, stratified by mode of death.

	Overall n = 69	Cardiovascular instability n = 52	WLST n = 17	p-value
Male	37 (54%)	31 (60%)	6 (35%)	0.099
Age	72 [58–84]	70 [53–80]	79 [68–86]	0.023
Arrest at home or residence	36 (52%)	25 (48%)	11 (65%)	0.27
Witnessed status				
Bystander	18 (26%)	14 (27%)	4 (24%)	>0.99
Emergency medical services	34 (49%)	29 (56%)	5 (29%)	0.093
Unwitnessed	17 (25%)	9 (17%)	8 (47%)	0.022
Bystander CPR	22/34 (65%)	14/22 (63%)	8/12 (67%)	>0.99*
Initial shockable rhythm	13 (19%)	11 (21%)	2 (12%)	0.50
Sustained ROSC $\geq$ 20mins	27 (39%)	10 (19%)	17 (100%)	<0.001
Arrest to death (h)	1.5 [0.9–2.3] (n = 68)	1.2 [0.8–1.9] (n = 51)	2.4 [1.7–4.2]	<0.001*
Aetiology				<0.01
Cardiac	57 (39%)	16 (64%)	6 (29%)	
Respiratory	42 (29%)	3 (12%)	9 (43%)	
Neurological	8 (5%)	1 (4%)	0 (0%)	
Toxicological	7 (5%)	0 (0%)	3 (14%)	
Other	15 (10%)	5 (20%)	2 (10%)	
Unknown	18 (12%)	0 (0%)	1 (5%)	
Organ donation	2 (3%)	1 (2%)	1 (6%)	–

Data presented as number (percentage), or median [interquartile range]. *P-values reflect data that excludes missing values. ROSC, return of spontaneous circulation; WLST, withdrawal of life-sustaining therapy.

Table 2 – Patient characteristics of OHCAs admitted to hospital within a local health network, stratified by mode of death.

	Overall n = 144	Cardiovascular instability n = 20	Non-neurological WLST n = 21	Neurological WLST n = 68	Brain death n = 35	p-value
Male	96 (67%)	14 (70%)	13 (62%)	45 (66%)	24 (69%)	0.96
Age	61 [47–73]	67 [48–78]	70 [53–75]	65 [52–76]	47 [33–60]	<0.001
Arrest at home or residence	115 (80%)	16 (80%)	19 (90%)	51 (75%)	29 (83%)	0.47
Witnessed						0.76
Bystander	72 (50%)	10 (50%)	11 (52%)	35 (51%)	16 (46%)	
Emergency medical services	14 (10%)	1 (5%)	4 (19%)	6 (9%)	3 (9%)	
Unwitnessed	58 (40%)	9 (45%)	6 (29%)	27 (40%)	16 (46%)	
Bystander CPR	81/130 (62%)	15/19 (79%)	12/17 (71%)	33/62 (53%)	21/32 (66%)	0.18
Initial shockable rhythm	51 (35%)	11 (55%)	7 (33%)	26 (38%)	7 (20%)	0.06
Cardiac catheterisation	55 (38%)	10 (50%)	7 (33%)	26 (38%)	12 (34%)	0.67
Cardiac intervention	19/55 (35%)	6/10 (60%)	3/7 (43%)	7/26 (27%)	3/12 (25%)	0.27
Temperature management	80 (37%)	6 (30%)	6 (29%)	50 (74%)	15 (43%)	<0.001
Neurological prognostication						
Brain Computed Tomography	71 (49%)	8 (40%)	6 (29%)	37 (54%)	20 (57%)	0.12
Brain MRI	23 (16%)	1 (5%)	1 (5%)	18 (26%)	3 (9%)	0.016
Brain perfusion scan	10 (7%)	-	-	-	10 (29%)	-
WLST <72 h after ROSC	46/86 (53%)	-	15/20 (75%)	31/66 (47%)	-	0.04*
ROSC to WLST (h)	70 [33–99] (n = 86)	-	30 [12–67] (n = 20)	74 [46–102] (n = 66)	-	<0.01*
Death in Intensive Care Unit	125 (87%)	18 (90%)	18 (86%)	54 (79%)	35 (100%)	0.012
Arrest to death (h)	57 [30–103] (n = 141)	15 [8–45]	36 [14–84] (n = 19)	85 [48–143] (n = 67)	48 [36–66]	<0.001
Organ donation	23 (16%)	1 (5%)	1 (5%)	6 (9%)	15 (43%)	<0.001

Data presented as number (percentage), or median [interquartile range]. *P-values reflect data that excludes missing values. MRI, magnetic resonance imaging; ROSC, return of spontaneous circulation; WLST, withdrawal of life-sustaining therapy.

two WLST categories were combined for analyses due to low numbers. Patients with WLST were older and more likely to have an unwitnessed arrest and longer time from arrest to death compared with patients deceased due to cardiovascular instability.

Late deaths after admission

Characteristics of patients surviving to hospital admission with sustained ROSC, stratified according to mode of death, are presented in Table 2. Overall, 67% were male with a median age of 61 years. In contrast to the ED cohort, most OHCAs occurred in the home, only 10% were EMS-witnessed, and 35% presented with an initial shockable rhythm. On arrival to the hospital 93% were comatose (Glasgow Coma Scale, GCS = 3), lactate was recorded in 58% of cases and found to be elevated > 7 mmol/L in 64%, and pH was recorded in 79% of cases and was > 7.2 in 18%. There were no differences in these prognostic indicators across modes of death ($p > 0.05$). All cases were admitted to ICU except for two cases admitted directly to the ward for poor outlook and palliation.

The primary mode of death was neurological WLST in 47% of cases, followed by brain death in 24%, non-neurological WLST in 15%, and cardiovascular instability in 14% (Table 2). Neurological injury, comprising neurological WLST and brain death, represented the primary mode of death in 72% of all admitted OHCAs. The distribution of age, but not sex, was significantly different across modes of death where brain death represented the youngest cohort with a median age of 47 years ($p < 0.01$). Rates of targeted temperature management (TTM) were highest for neurological WLST ($p < 0.05$) but did not significantly differ between other modes of death. Time from arrest to death was longest for neurological WLST ($p < 0.01$) but did not significantly differ between other modes of death (Fig. 2). Other arrest characteristics were similar across modes of death. There were no significant sex differences for rates of WLST, early WLST, and time from arrest to death (Table 3).

OHCA aetiology

Patients deceased in ED due to cardiovascular instability were more likely to have a precipitating cardiac aetiology, and less likely to have an unknown aetiology compared to deaths due to WLST ($p < 0.05$). Similar to cases deceased in ED (Table 1), the distribution of precipitating aetiology in admitted cases was 39% cardiac, 28% respiratory, 6% neurological, 5% toxicological, and 23% other/unknown. Fig. 3 presents the distribution of aetiology according to mode of death in admitted OHCAs. Cardiac aetiology was more prevalent for deaths due to cardiovascular instability when compared with confirmed brain deaths ($p < 0.05$), but not when compared to other modes of death ($p > 0.05$). There was no significant difference between modes for other aetiologies ($p > 0.05$).

Discussion

This study investigated the clinical characteristics, timing of WLST and death, and precipitating aetiology associated with mode of death in adult OHCAs transported to hospital within a local health network. The primary mode of death in 75% of ED deaths was cardiovascular instability (haemodynamic instability, recurrent arrest, and intractable shock), while in 72% of admitted deaths it was neurological injury (neurological WLST and brain death). Mode of death was significantly associated with age, timing of death, and precipitating aetiology, but not sex.

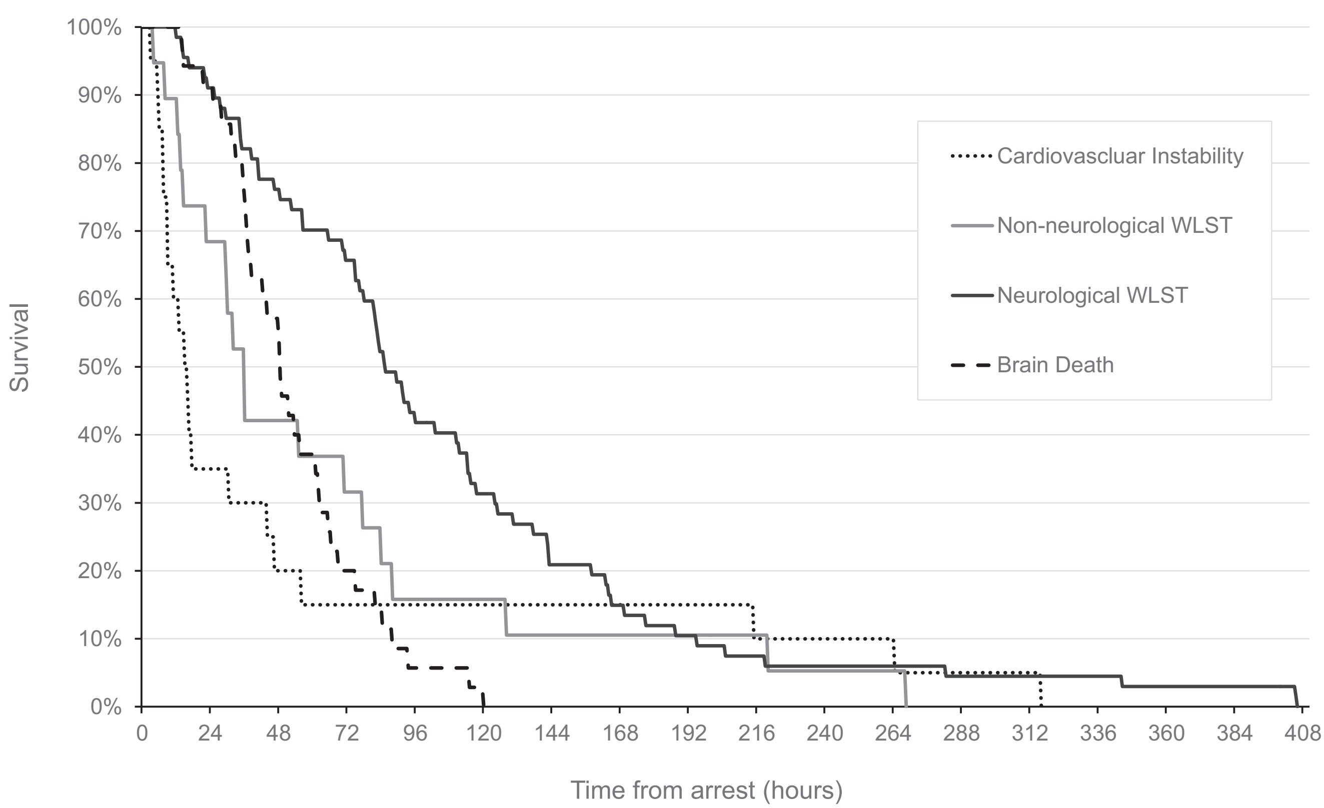

Fig. 2 – Survival percentage according to time from arrest (h) for OHCAs with sustained ROSC admitted to hospital within a local health network, stratified by mode of death (n = 144). WLST, withdrawal of life-sustaining therapy.

Table 3 – Sex differences in mode of death, timing of WLST, and location and timing of death in OHCAs with sustained ROSC admitted to hospital within a local health network (n = 147).

	Missing data	Male *n* = 98	Female *n* = 49	*p*-value
WLST		58 (59%)	31 (63%)	0.72
WLST <72 h after ROSC	3 (3%)	29 (51%)	17 (59%)	0.65
ROSC to WLST (h)	2 (2%)	71 [33–101]	67 [37–96]	0.63
Death in Intensive Care Unit	-	86 (88%)	41 (84%)	0.61
Arrest to death (h)	3 (2%)	55 [30–103]	62 [36–110]	0.48

Data presented as number (percentage) or median [interquartile range]. p-values reflect data that excludes missing values. ROSC, return of spontaneous circulation; WLST, withdrawal of life-sustaining therapy.

Early in-hospital death

The ED mortality rate was 18% and 32% of all hospital deaths occurred in ED, which is consistent with recently published Australian rates of 19% and 33%, respectively, reported over a similar period.[21] In the current study, cardiovascular instability was the primary mode of death in the ED and likely reflects a high burden of recurrent arrest. Most deaths due to cardiovascular instability occurred within the first 2 h post-OHCA and only 19% gained sustained ROSC. Extracorporeal cardiopulmonary resuscitation (ECPR) is not available within the current setting, but our results highlight the importance of such an intervention given that almost two thirds of these patients had a potentially reversible precipitating cardiac aetiology. WLST for neurological and non-neurological reasons occurred at a lower rate than reported by Kempster et al.[21] we also reported a slightly lower prevalence of cardiac aetiology and higher prevalence of respiratory aetiology in these patients, which is consistent with a high rate of respiratory OHCA in our cohort.[22]

Mode of death after admission

Consistent with previous literature, we found that neurological injury was the leading mode of death in OHCAs surviving to hospital admission, irrespective of precipitating aetiology.[8,9,11,23] Interestingly, brain death alone accounted for 24% of admitted deaths compared to previous reports in older studies of 3.7–19% in adult populations, and 47% in a paediatric population.[6,7,14,24] Only a small proportion of patients with brain death had an OHCA due to a neurological aetiology, and although this was not statistically different, the majority were of cardiac and respiratory origin, reflecting a progression of hypoxic brain injury to brain death. The higher rate of brain death observed may therefore be driven by the lower median age of this group and increased pre- and in-hospital resuscitative efforts, highlighting the importance of assessing the potential for organ donation in non-survivors.[6]

Consistent with guidelines available during the study timeframe, neurological WLST was associated with highest rates of TTM in this cohort. Neurological WLST was also associated with the longest time from arrest to death (median 3.5 days), which is similar to a report from a paediatric population.[14] Despite this finding, WLST occurred ≤72 h in 53% of cases, likely reflecting Australian cultural practice to withdraw care early rather than prolong suffering.

Deaths due to cardiovascular instability represented only 14% of admitted patients compared to other reports of 20–23 %[7,8] which may reflect differences in definitions or practice within our institutions e.g., unstable cases with poor outlook may not be transferred directly to the ICU with resulting death in the ED. Finally, rates of other established outcome predictors such as sex, arrest location, witness sta-

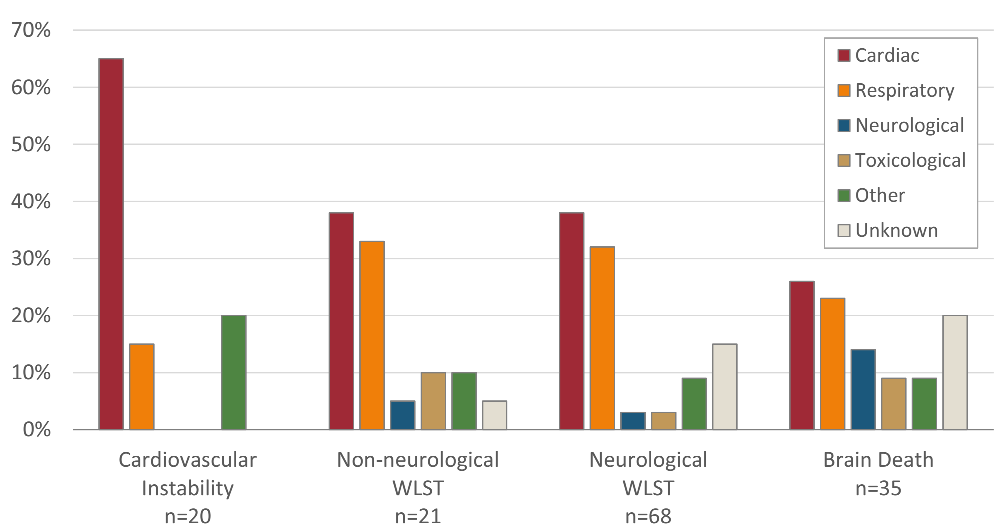

Fig. 3 – Mode of death in OHCAs deceased after admission to hospital within a local health network, stratified according to underlying aetiology as documented in hospital medical records and autopsy reports (n = 144). WLST, withdrawal of life-sustaining therapy.

tus, bystander CPR, and cardiac catheterisation were similar across modes of death. Our findings confirm previous work and continue to emphasise the need for strategies to improve neurological outcomes such avoiding fever[25] and delaying neurological prognostication for ≥72 h post-ROSC.[7,26]

No sex differences in mode of death or WLST practice

Previous research has identified that women are less likely to survive to hospital discharge after OHCA, and it has been postulated that this is due to increased withdrawal of treatment[15,27]. However, women surviving to admission in our small study had similar rates of WLST and early WLST compared to men, which is in contrast to some previous studies[7,16] but not others.[28] Similarly, we found that the distribution of sexes across the modes of death in both the ED and admitted populations was not statistically significant. Future studies in larger populations should continue to stratify according to sex, particularly considering the differences in OHCA aetiology in females compared with males.[10].

Defining Mode of Death

Few studies have explored mode of death after OHCA, and these in diverse sub-populations with varying definitions of mode of death, which limits direct comparison.[7–14] Witten et al.[11] recently proposed five clearly defined categories with good interrater agreement based on retrospective review of the medical record. This definition still requires external validation and should be expanded to include brain death.[29] A simpler categorisation may consist of *death despite full treatment, death following WLST, and brain death*, which could be supplemented with additional information on neurological prognostication, reasons for WLST, and precipitating aetiology. Consensus on the definition of mode of death with a standardised classification is needed to provide a clear distinction from cause of death defined in the Utstein template, which is likely to reflect precipitating OHCA aetiology e.g. acute myocardial infarction, rather than mode of death.[6,17].

Limitations

The findings of this small study must be interpreted in the light of the following limitations. Firstly, data variables in the registry were entered in the registry by retrospective case note abstraction and may be subject to inherent bias. The complex nature of OHCA meant it was often difficult to categorise mode of death even when the clinical documentation was adequate, as noted by others.[11] Secondly, only four categories of mode of death were defined in the registry and it was not possible to separate out deaths caused by respiratory or multiorgan failure, DNRs, or detailed reasons for WLST. A prospective study is required to address the current subjectivity associated with mode of death categorisation. Thirdly, this study was performed within a local health network in Australia and the findings may not be readily generalisable to other settings, particularly other countries with differing medical services and end-of-life culture.[30] Finally, the results should be interpreted within the context of the study period as practice changes may have occurred over the last > 5 years; we have nonetheless highlighted the consistency of our findings with other reports. The strength of this study is that it is the first to report mode of death and WLST after OHCA in patients treated at hospital in Australia, and the first to compare clinical characteristics across modes in adult patients.

Conclusions

In summary, the leading mode of death in OHCAs surviving to hospital and deceased in the ED was cardiovascular instability, while death after admission was primarily due to neurological injury. This report from within a local health network is the first to describe clinical characteristics associated with mode of death in an adult OHCA population. Mode of death was found to be associated with timing of death and precipitating aetiology, but not sex. Mode of death provides critical information for the assessment of post-cardiac arrest management but consensus regarding definition and standardised classifications are still needed.

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CRediT authorship contribution statement

Melanie R Wittwer: Conceptualization, Methodology, Investigation, Writing – original draft. **Thomas Armstrong:** Investigation, Writing – original draft. **Jordan Conway:** Investigation, Writing – original draft. **Mohammed Ishaq Ruknuddeen:** Methodology, Writing – review & editing. **Chris Zeitz:** Supervision, Writing – review & editing. **John F Beltrame:** Supervision, Writing – review & editing. **Margaret A Arstall:** Conceptualization, Supervision, Writing – review & editing.

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.

Author details

[a]Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia [b]Northern Adelaide Local Health Network, Elizabeth Vale, South Australia, Australia [c]Central Adelaide Local Health Network, Adelaide, South Australia, Australia

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