Early withdrawal of life support after resuscitation from cardiac arrest is common and may result in additional deaths.

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Clinical paper

Early withdrawal of life support after resuscitation from cardiac arrest is common and may result in additional deaths

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Abstract

Aim: "Early" withdrawal of life support therapies (eWLST) within the first 3 calendar days after resuscitation from cardiac arrest (CA) is discouraged. We evaluated a prospective multicenter registry of patients admitted to hospitals after resuscitation from CA to determine predictors of eWLST and estimate its impact on outcomes.

Methods: CA survivors enrolled from 2012–2017 in the International Cardiac Arrest Registry (INTCAR) were included. We developed a propensity score for eWLST and matched a cohort with similar probabilities of eWLST who received ongoing care. The incidence of good outcome (Cerebral Performance Category of 1 or 2) was measured across deciles of eWLST in the matched cohort.

Results: 2688 patients from 24 hospitals were included. Median ischemic time was 20 (IQR 11, 30) minutes, and 1148 (43%) had an initial shockable rhythm. Withdrawal of life support occurred in 1162 (43%) cases, with 459 (17%) classified as eWLST. Older age, initial non-shockable rhythm, increased ischemic time, shock on admission, out-of-hospital arrest, and admission in the United States were each independently associated with eWLST. All patients with eWLST died, while the matched cohort, good outcome occurred in 21% of patients. 19% of patients within the eWLST group were predicted to have a good outcome, had eWLST not occurred.

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Conclusions: Early withdrawal of life support occurs frequently after cardiac arrest. Although the mortality of patients matched to those with eWLST was high, these data showed excess mortality with eWLST.
Keywords: Arrest, Withdrawal, Support, WLST, Palliative, End-of-life, Prognostication

Introduction

Withdrawal of life support therapies (WLST) is common in patients with hypoxic-ischemic brain injury following cardiac arrest (CA) and may have a substantial impact on mortality.[1,2] The decision to withdraw life sustaining therapies may be influenced by a patient's prior stated wishes or family preference, but can also be driven by the perception of the treating clinical team that the prognosis is poor. Determination of poor prognosis in the early course of the intensive care unit admission is confounded by the inaccuracy of early physical exam findings, often due to delayed metabolism of sedation in the setting of targeted temperature management (TTM) and organ dysfunction.[3–7] The effect of WLST on outcomes is important to consider. Up to 20% of long-term survivors are reported to have had delayed awakenings,[8–11] remaining comatose and intubated for >48 h after rewarming from TTM [8–12]; this rate is higher in patients that received benzodiazepines infusions for sedation, especially in the setting of renal dysfunction.[7,13,14] Since early markers of neurologic recovery are difficult to assess, current guidelines recommend delaying neurological prognostication ≥72 h after rewarming from TTM,[15,16] but practice patterns vary widely and are influenced by low quality data, local customs, and disagreements among experts in the field. Early withdraw of life support (eWLST), usually defined as life support withdrawn <72 h post-arrest[15,17] typically results in death, but a lingering concern is that some patients would have had a good functional outcome with a longer period of intensive care management. In clinical trial data, the incidence of eWLST is 25% and 16% of those patients may have a good neurologic recovery[18] but how important this factor is in an unselected registry population is unknown.

We addressed this question using data from the INTernational Cardiac Arrest Registry (INTCAR), which pools in- and out-of-hospital cardiac arrests and includes demographics, arrest-related factors, elements of post-resuscitation care, and functional outcomes. We used propensity matching to compare the outcomes of patients that underwent eWLST to similar patients that had full supportive care continued >3 calendar days after resuscitation. Our hypothesis was that due to the inaccuracy of early prognostication and other factors, there would be patients similar to those that underwent eWLST that ultimately had good outcomes. Those matched cohorts could be used to estimate the number of patients with eWLST who might have done well with ongoing care, which could facilitate estimates of the influence of eWLST in a general post-resuscitation cohort.

Methods

Data source

We included patients enrolled in INTCAR from 2012–2017. Twenty-four centers from Europe and the United States enrolled consecutive adult patients with both in-hospital and out-of-hospital cardiac arrests. Post-resuscitation care, including timing and decision of WLS, occurred at the discretion of the treating clinicians, but INTCAR centers tend to be those with an academic interest in cardiac arrest care, with protocols and standards in place. The database was maintained at Lund, Sweden and each center had approval from their own Institutional Review Board (IRB) for data collection. The analysis presented here was approved by the IRB at Maine Medical Center.

Outcome assessment

eWLST was defined as DNR (do not resuscitate) status, withdraw of life support, and death within three calendar days of cardiac arrest. The risk for a patient to have eWLST was estimated using a logistic regression model for the outcome of eWLST for the entire cohort. As INTCAR is an observational registry, there is no specific treatment protocol for the management of these patients, including prognostication or practices around WLST.

For the analysis of variables associated with eWLST, the functional outcome of interest was defined as a dichotomized Cerebral Performance Category (CPC) at hospital discharge, with good outcome being CPC of 1–2 and poor outcome CPC 3–5 (a range from severe functional impairment to death). The impact of missing data for candidate and outcome variables on the model was assessed.

Development of a propensity model for eWLST

First, a propensity score for eWLST was developed and used to estimate the probability of each patient to have eWLST. The propensity score was developed using a multivariable logistic regression process.

An *a priori* list of candidate variables associated with eWLST was selected using previously established factors and clinical judgment. We selected variables present at the time of admission for consideration, including age, sex, medical diagnosis, independent living status prior to arrest, geographic region (United States vs. European), initial shockable rhythm, ischemic time (including no-flow and low-flow time), location of arrest (in-hospital vs. out-of-hospital), witnessed event, defibrillation, bystander CPR, and shock on admission (defined as systolic blood pressure <90 mmHg for 30 min or the need for supportive measures needed to maintain a systolic blood pressure of 90 mmHg. Continuous variables were assessed for linear associations with the (log odds) of the eWLST outcome and final model variables were assessed for collinearity. Age was transformed from continuous to decade-intervals, starting at age 18. We evaluated standardized mean differences, using an alpha of <0.1 to assess for covariate imbalance.

Identifying cardiac arrest survivors similar to eWLST patients using the propensity score

We identified patients with eWLST and used the propensity score to match those eWLST patients to patients who did not undergo eWLST in a 1:2 ratio, using the R *MatchIt* package.[19] The method of matching was 'optimal,' where the patients were matched based on the smallest average absolute distance across all the matched pairs. Matching was evaluated by visual inspection of covariates,[20] including histograms of the propensity score of matched and non-matched patients in each treatment group as well as a univariate mean distance for key covariates. Unmatched patients were excluded.

Once cohorts were matched, deciles of propensity score for eWLST were calculated and within each decile the percentage of the matched cohort without eWLST was determined. In each decile of propensity for eWLST, the incidence of good functional outcome was calculated in patients who did not experience eWLST. We then computed a weighted average of the percent with a good functional outcome based on each decile of propensity in the patients that underwent eWLST.

Results

Participants

3104 patients from 24 different hospitals were included in the registry between the selected dates. 2688 (87%) patients had complete data for candidate variables and outcomes. Mean age was 62 (±16) years, median ischemic time was 20 (IQR 11, 30) minutes, 1148 (43%) had a shockable rhythm, and 1677 (62%) received bystander CPR (Table1). Of the total 2688 patients with complete data, WLST occurred in a total of 1162 (42%) patients at any time, with 459 (17%) defined as eWLST.

Missing data

There were 416 patients with missing data. Patients with missing data had a mean age of 62 (±17) and median ischemic time of 30 (IQR 17, 53) min. A comparison of the groups of patients with and without missing data is shown in Supplement Table 1.

Propensity model eWLST

In the univariate model, all 12 factors were associated with eWLST and were included in the propensity model with the exception of bystander CPR and defibrillation, which were dropped due to association with the witnessed arrest variable. In the multivariate model, variables associated with eWLST were older age, by decade, (OR 1.2, CI 1.1–1.3), increased ischemic time, a non-shockable initial heart rhythm (OR 2.6 (1.4–2.4), out-of-hospital arrest (OR 1.7 (1.3–2.4), shock on admission (OR 1.8 (1.5–2.3), and United States region (OR 1.9 (1.3–2.3) (Supplement Table 2).

Table 1 – Patient demographics.

Variable	All patients in analysis
N	2688
Age, mean (SD)	62 (±16)
Female sex, n (%)	915 (34)
Number of medical comorbidities (median, IQR)	2 (1,3)
Prior independent living	2172 (81)
US Center n (%)	1752 (65)
Shockable Rhythm n (%)	1148 (43)
Ischemic time (median, IQR)	20 (11, 30)
Out-of-hospital arrest n (%)	1717 (77)
Witnessed n (%)	2168 (81)
Defibrillation n (%)	1639 (61)
Bystander CPR n (%)	1677 (62)
Shock on admission n (%)	1466 (55)
WLST n (%)	1162 (43)
eWLST n (%)	459 (17)

Description of patients included in risk model.
US: United States, CPR: cardiopulmonary resuscitation, WLST: withdraw of life sustaining therapies.

Matching patients with and without eWLST

Using 1:2 matching ratio, all 459 patients with eWLST were matched (without replacement) to 918 patients without eWLST. 1311 patients without eWLST were unmatched and not included in the analysis. Overlap between the probability of eWLST in the matched and unmatched groups are shown in Fig. 1. A comparison of matched and unmatched data is shown in Table 2. There were no differences in the frequency of candidate variables between the two exposure groups after propensity matching (Table 3).

Outcome by propensity of eWLST

Among matched patients grouped into deciles of probability for eWLST, survival with good functional outcome occurred between 0 and 40% of patients. The highest good outcome rate was in the lowest deciles of risk. No patients survived in the matched cohort past the 50th percentile of risk. The overall rate of good outcome in the matched group that did not receive eWLST was 21%. When outcomes of matched patients were reweighted according to risk, we found that 19% of the eWLST cohort were anticipated to have a good outcome.

Discussion

Withdrawal of life support therapies within 3 calendar days of admission was common, occurring in 17% of all patients in this registry cohort. Twenty one percent of patients matched to those who received eWLST had a good outcome. Risk factors for eWLST were older age, female gender, medical comorbidities, non-independent living prior to arrest, non-shockable initial heart rhythm, longer ischemic time, unwitnessed arrest, out-of-hospital arrest, shock on admission, and admission in the United States.

This study complements work done by Elmer et al. who showed in an adjusted propensity analysis that in a clinical trial population, subjects exposed to eWLST were expected to have 26% survival and 16% good functional outcome with ongoing intensive care.[18] Extrapolated nationally, they reported that eWLST may lead to approximately 2300 excess deaths in the United States each year of whom nearly 1500 (64%) might have had good functional recovery.[18] Our findings show a similar rate of eWLST as the above study and a higher rate of good functional outcomes in survivors compared to the cohort described above.

Strengths of this study include data from a large number of (mostly) academic centers, and the use of a propensity matched model to compare patients with and without eWLST. This is also the first assessment of this type outside of a clinical trial setting, a "real-world" cohort of patients which may be comparable to those seen in general clinical practice. There are also several important study limitations to consider. As sequential registry enrollments could not be verified, selection bias is possible. Since patients with short hospital course would more likely be excluded, this bias would cause underestimation of eWLST. Additionally, the reasons for eWLST were not recorded in the data set, and therefore the

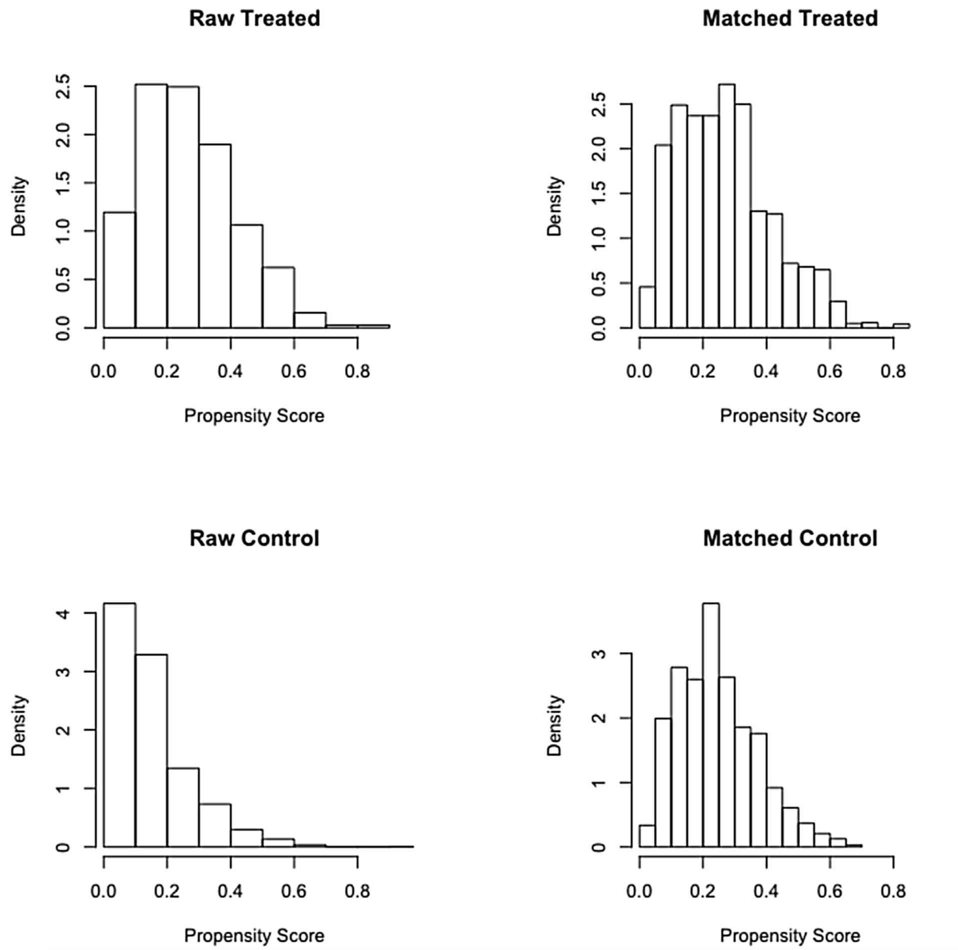

Fig. 1 – Distribution of risk for eWLST for all patients with eWLST (A), all patients (C), and matched patients without eWLST (D).

Table 2 – Patient characteristics by eWLST status.

Variable	All patients without eWLST	Matched patients without eWLST	Patients with eWLST
N	2229	918	459
Age, mean (SD)	61 (±16)	65 (±15)	66 (±15)
Female sex, n (%)	721 (32)	368 (40)	194 (42)
Number of medical comorbidities (median, IQR)	2 (1,3)	2 (1,3)	2 (1,3)
US Center n (%)	1399 (63)	638 (70)	353 (77)
Shockable Rhythm n (%)	1037 (47)	190 (23)	111 (24)
Ischemic time (median, IQR)	20 (10, 30)	35 (15, 40)	26 (17,41)
Out-of-hospital arrest n (%)	1684 (76)	767 (84)	388 (85)
Witnessed n (%)	1825 (82)	694 (76)	343 (75)
Shock on admission n (%)	941 (44)	546 (61)	281 (63)
WLST n (%)	703 (32)	0 (0)	459 (100)
Hospital CPC 1-2 n (%)	862 (39)	396 (43)	0 (0)

US: United States, WLST: Withdraw of life sustaining therapies, eWLST: early withdraw of life sustaining therapies, CPC: cerebral performance category.

reasons for eWLST (whether due to a patient's previously stated wishes, family wishes or to presumed medically futility) cannot be established. Another limitation is that the model cannot account for registered covariates, including severity of shock, early seizures or center resources for more aggressive treatment. With the data available, however, these patients were well-matched by propensity score, as our matched cohort was extremely similar to the eWLST group. Next, since the exact time of admission is unavailable in INTCAR, we were unable to use a precise 72 h time frame to define eWLST. Instead, we chose to define eWLST as being within three calendar days. This may have resulted in exclusion of some patients that died after WLST on hospital day 4 but within 72 h, thus possibly underestimating the true incidence of eWLST. Lastly, we included a CPC of 3 in the poor outcome group

Table 3 – Rate of outcome in eWLST and matched non-eWLST by decile of risk.

Likelihood of eWLST:	eWLST (459)	Non eWLST (matched) (918)	% of non-eWLST with GOOD OUTCOME
<10%	55 (12)	110 (12)	44 (40)
10–20%	127 (28)	255 (28)	74 (29)
20–30%	109 (24)	288 (31)	47 (16)
30–40%	71 (15)	162 (18)	19 (12)
40–50%	53 (12)	69 (8)	4 (6)
50–60%	28 (6)	18 (2)	0 (0)
60–70%	16 (3)	16 (2)	0 (0)
All	100%	100%	
% non eWLST with good outcome			21%
Reweighted to match eWLST group, estimate of % matched patients that may have had a good outcome			19%

which some patients and families would not consider equivalent to coma or death; this would also underestimate the true incidence of good outcome after eWLST.

Previously reported reasons for early withdrawal include family-team communication difficulties[2] and documentation of 'probable' poor outcome by the primary team, even despite patients receiving sedation during clinical exams.[21] Age and gender were not predictive of early vs. delayed awakening in some reports[12,21] but were predictive in others. Overall, very little data exist on patient selection for eWLST. In the Targeted Temperature Management Trial, reasons for WLST before prognostication included failing circulation, multi-organ failure, ethical reasons, medical co-morbidities, and brain death.[22] The difference between United States and European Centers has been previously described, suggesting a patient or physician cultural difference, with US centers having a higher propensity for eWLST in patients with otherwise similar prognostic factors.

Although some patients may undergo eWLST for entirely appropriate reasons, such as the determination of a prior existing "do not attempt resuscitation" order that was not honored, or impending circulatory collapse, it is likely that in some patients eWLST may have been performed due to mistaken prognosis. Addressing this aspect of cardiac arrest care in appropriate patients has the potential to influence the timing of neurologic prognostication, the content of family communications, and even the overall outcomes of patients resuscitated from cardiac arrest internationally– especially in the United States where eWLST occurs more often. As most patients who had a good outcome had a low propensity for early withdrawal, and because our propensity score was composed of variables that are well known to be highly prognostic for poor outcomes, this suggests that formal application of a futility instrument may be able to prevent some inappropriate withdrawal of therapy due to inaccurate prognostication. Given that eWLST may be largely based on often inaccurate perceptions of poor outcome, more work should be done to understand the potential biases affecting this decision.

Conclusions

Early withdrawal of life support after cardiac arrest occurs frequently in clinical practice, and has a profound, independent association with mortality and functional outcome after cardiac arrest. Patients matched to those with eWLST had 21% survival with favorable neurologic outcomes, when stratified across propensity deciles. These data support a strategy of delayed prognostication and delay of decisions regarding WLST in the first three days post-arrest in most cardiac arrest. Further research, focusing on the reasons for eWLST to separate clinically appropriate patient-centered decisions from prognostic error are warranted.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.031.

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