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Clinical paper

Effects of withdrawal of life-sustaining therapy on long-term neurological outcome after cardiac arrest – A multicentre matched cohort study

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Abstract

Purpose: To assess the risk of self-fulfilling prophecy from withdrawal of life-sustaining therapy (WLST) in comatose cardiac arrest patients undergoing neuroprognostication.

Methods: Post-hoc multicentre study matching adults resuscitated from out-of-hospital cardiac arrests, in WLST-permitting cohorts (TTM and TTM2), and non-WLST-permitting cohorts (KORHN and ProNeCA). We matched patients in a 1:1 ratio based on a propensity score, assessing the risk of WLST due to a presumed poor neurological prognosis and criteria predictive of poor neurological outcome, as outlined in the 2021 European Resuscitation Council/European Society of Intensive Care Medicine (ERC/ESICM) guidelines. Functional outcome was compared at six months.

Results: We included 1717 patients, of whom 497 (29 %) had WLST due to neurological criteria at a median of 143 h (IQR 108–177). 303 (61 %) patients with WLST retrospectively fulfilled $\geq$ 2 ERC/ESICM criteria predictive of poor outcome. No patients with $\geq$ 2 ERC/ESICM criteria had good functional outcome at six months, neither in the WLST cohort nor among the matched controls. One patient (0.3 %) with an indeterminate prognosis ($\leq$1 ERC/ESICM criteria) had a good functional outcome in the WLST cohort versus 18–26 % of the matched controls. In exploratory weighted estimates, up to 18 % of patients with indeterminate prognosis may have survived with a good functional outcome, if WLST had not occurred.

Conclusion: In patients with at least 2 ERC/ESICM criteria predictive of poor outcome, the risk of self-fulfilling prophecy from WLST was negligible. However, in patients with an indeterminate prognosis, the practice of WLST was associated with a lower likelihood of good functional outcome.

Keywords: Withdrawal of Life-Support, Cardiac Arrest, Neurological Prognostication, Coma, Prognosis

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Introduction

For most patients who remain unconscious during intensive care treatment after cardiac arrest, death is preceded by a decision to withdraw life-sustaining therapies (WLST).[1–4] WLST based on neurological criteria is typically carried out when devastating brain injury is expected, and continued therapy is deemed futile. WLST aims to avoid further harm and prioritise finite medical resources when good outcomes are unobtainable. In certain contexts, where the use of WLST is minimal, such as South Korea and some communities in Italy, more patients survive with severe neurological deficits, including unresponsive wakefulness syndrome, compared to countries where WLST is routinely performed.[5–8]

The European Resuscitation Council and European Society of Intensive Care Medicine (ERC/ESICM) guidelines recommend postponing neurological prognostication until 72 h post-arrest.[4] Previous studies have shown that WLST is often performed within the first 72 h post-arrest, and that early WLST is associated with fewer patients surviving with a good outcome compared to matched controls.[9–13] However, no prior study has evaluated the potential effects on long-term functional outcome of WLST performed in accordance with the ERC/ESICM recommendations.[14,15]

In this post-hoc international multicentre matched cohort study, we aimed to evaluate the risk of self-fulfilling prophecy associated with WLST, based on compliance with the current ERC/ESICM criteria for neuroprognostication, for all patients who remain unconscious after 72 h post-arrest.

Materials and methods

Study design

We performed a post-hoc multicentre matched cohort study based on exposure to WLST after cardiac arrest. Eligible patients were adults with an out-of-hospital cardiac arrest and available functional outcome recruited from four different multicentre studies, including two WLST-permitting cohorts: the Target Temperature Management after out-of-hospital cardiac arrest trial (TTM) and the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2) as well as two cohorts with no or minimal use of WLST: the Korean Hypothermia Network Prospective Registry 1.0 (KORHN) and Prognostication of Neurological outcome after Cardiac Arrest (ProNeCA).[5,7,16,17] An overview of the differences in the previously published study designs is presented in eTable 1.[5,7,16,17] Importantly, TTM and TTM2 were randomised controlled trials of predominantly presumed cardiac cause to cardiac arrests, whereas KORHN and ProNeCA were observational studies of all-cause cardiac arrests.

Ethical consent was obtained in all participating countries, including the Regional Ethics Board at Lund University (TTM), the Swedish Ethical Review Authority (TTM2), the Institutional review board (IRB) of Seoul St. Mary's Hospital (KORHN) and the Regional Ethics Committee of Tuscany (ProNeCA).

Study cohort

We included patients who underwent WLST based on neurological criteria during the TTM or TTM2 trials. Neurological WLST was defined as a WLST decision solely or partly based on a presumed poor neurological prognosis. WLST based on ethical reasons or multi-organ failure, along with patients diagnosed as brain death, were not included in the current analysis. We also excluded all patients with WLST performed before the guideline-recommended time of 72 h post-arrest. We included control patients from the KORHN or ProNeCA studies without exposure to WLST. Patients with missing data on clinical variables included in the propensity score were excluded.

Neuroprognostication and WLST in the TTM/TTM2 trials

In the TTM/TTM2 trials, neurological prognostication was performed by an experienced physician, blinded to the treatment allocation. Full intensive care was mandated until the time of neurological prognostication, except for TTM patients with status myoclonus within 24 h post-arrest and bilaterally absent N20 somatosensory evoked potentials (SSEP), or for TTM2 patients when further treatment was considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons (eTable 1).[18] WLST was permitted after neurological prognostication when poor outcome was likely according to trial protocol criteria at 96 (TTM2) or 108 (TTM) hours post-arrest, respectively. The differences between the two protocols and the 2021 ERC/ESCIM guidelines are presented in eTable 2. Decisions on WLST were made at the treating physician's discretion.[18,19]

Outcome

The primary outcome was functional outcome, dichotomised into good or poor (i.e. independent or dependent in basic activities of daily living, respectively), and evaluated by blinded assessors at six months according to structured assessments including the modified Rankin Scale (mRS), Cerebral Performance Categories (CPC) scale or Glasgow Outcome Scale (GOS).[20–22] Good functional outcome was categorised as mRS 0-3/CPC 1-2/GOS 4-5 (no symptoms to moderate disability), while mRS 4-6/CPC 3-5/GOS 1-3 (moderate-severe or severe disability to death) were considered a poor outcome.[20–22] When a structured assessment was not available an overall binary assessment of good or poor functional outcome was allowed based on all available information e.g. medical records or telephone interviews.[6,7,18] We performed a sensitivity analysis including moderate-severe/severe disability (mRS 4, CPC 3, GOS 3) as good functional outcome.

Propensity score

We constructed a propensity score to assess a patient's risk of WLST based on a multivariable regression model. Candidate variables associated with WLST were selected based on previous research and clinical judgment.[4,9,10,13] These variables included patient characteristics, cardiac arrest characteristics, and the 2021 unfavourable ERC/ESICM criteria (with the modification of considering all CT scans within the first week as eligible).[4,23–26] Variables showing significant differences across the study cohorts were also added to the propensity score to ensure proper matching.

Due to differences in the availability of clinical data used to generate the propensity score, KORHN and ProNeCA were treated as separate and independent cohorts in the analyses. For the KORHN analysis, we used an 11-variable propensity score including age, sex, comorbidity, previous neurological deficit, time to ROSC, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), shockable rhythm, cardiac cause of arrest, number of unfavourable ERC/ESICM criteria and an interaction variable for witnessed arrest and bystander CPR. In the ProNeCA analysis, we eliminated

bystander CPR, previous neurological deficits, comorbidity and the interaction variable from the propensity score due to a lack of available data.

Matching

We matched patients from the two cohorts based on their propensity score in a ratio of 1:1 with the nearest-neighbour method, calliper width of 0.1 and exact matching in the number of unfavourable ERC/ESICM criteria. No replacements were allowed. To verify the model, we evaluated the propensity score configuration in histograms before and after matching and assessed the standardised mean difference of each included variable in forest plots.

Bias

To evaluate the robustness of our results, several sensitivity analyses were performed by varying the variables included in the propensity score and the method of matching.[27,28] Additional analyses on all included patients re-weighted by their risk distribution were performed to avoid biased conclusions due to selection bias in matching. Details on these analyses are described in supplementary methods. To evaluate the robustness of our model, we also conducted a sensitivity analysis using augmented inverse probability of treatment weighting (AIPW) on the matched cohorts to evaluate overall differences in the likelihood of a favourable outcome.

Statistical analysis

The statistical analysis plan is presented in eTable 3. First an overview of all eligible patients and crude matched analyses were presented. As primary analysis we evaluated patients with $\geq$ 2 unfavourable ERC/ESICM criteria. As secondary analysis, we evaluated all included patients as potential matches, including those with indeterminate prognosis according to the ERC/ESICM neuroprognostic guidelines. We then conducted a subgroup analysis based on the timing of WLST, dividing patients into three groups: (1) eligible but non-included patients with early neurological WLST $\leq$ 72 h, (2) an early group, with WLST performed before the median time, and (3) a late group, with WLST performed after the median time. Functional outcome was compared between the two cohorts within deciles of the propensity score. Overall differences in outcome between the two matched cohorts were evaluated using McNemar's paired test. Matching was performed using the MatchIt-package. Analyses were performed using R version 2024.04.2+764.

Results

The four cohorts comprised a total of 4415 eligible patients, of whom 2768 (63 %) patients were enrolled in WLST-allowing cohorts and 1647 (37 %) were enrolled in control cohorts (Fig. 1). Differences between the cohorts (WLST vs control) were found, including frequency in good outcome (47 % vs 31 %), poor outcome survival (4 % vs 12 %), mean age (64 vs 59) and presumed cardiac cause to arrest (91 % vs 65 %) (Fig. 1, eTable 4). In all cohorts, the functional outcome correlated to the presence of unfavourable ERC/ESICM criteria (eTable 5). A comparison of outcomes between all eligible patients from WLST-allowing and control cohorts, using both the 11- and 7-variable propensity score for matching, showed that no patients with $\geq$ 2 unfavourable ERC/ESICM criteria had good outcome, while poor outcome survival was lower in the WLST-allowing cohort (2–3 % vs 11–13 %) (eTable 6). When evaluating all matched eligible patients, regardless of ERC/ESICM criteria, good outcome rates were similar between the cohorts (31–32 % vs 31–32 %), and poor outcome survival remained lower in the WLST-allowing cohort (4 % vs 10–12 %) (eTable 6).

Included patients who were screened as potential matches

We included 497 patients with WLST performed at a median of 143 h (IQR 108–177), excluding those with WLST performed within 72 h (N = 39) and missing time to WLST (N = 2) (Fig. 1, eTable 7). One patient with WLST lacked data on bystander CPR and comorbidity and was subsequently excluded from the KORHN analyses (N = 496) (Table 1B, eTable 3). We included 1220 controls (975 from KORHN and 245 from ProNeCA), excluding those with no neurological examinations performed (N = 246) and missing clinical variables in the propensity score (N = 169) (eFig. 1). Patients excluded due to missing clinical variables are characterised in eTable 8. The mean age of all included patients (N = 1717) was 61 (SD 15) years, 73 % had a presumed cardiac cause of arrest and the median time to ROSC was 28 min (IQR 18–40) (eTable 7). Differences in baseline characteristics separated by the original study are reported in eTable 9.

Analyses on patients with $\geq$ 2 unfavourable ERC/ESICM criteria

Of the 497 patients who underwent WLST, 303 (61 %) had $\geq$ 2 unfavourable ERC/ESICM criteria registered (Table 1A). When evaluating these patients, matched controls were found for 133/303 (44 %) and 69/303 (23 %) patients from KORHN and ProNeCA cohorts, respectively (Table 2A). No patients with $\geq$ 2 unfavourable ERC/ESICM criteria had a good outcome at six months, neither in the WLST cohort nor among the matched controls (Table 2A). All matched patients with $\geq$ 2 unfavourable ERC/ESICM criteria died in the WLST-allowing cohort, while 20/133 (15 %) matched KOHRN patients and 17/69 (25 %) matched ProNeCA patients survived, all with severe neurological disability (p < 0.0001, Table 2A). When the observed outcomes of all included patients with $\geq$ 2 unfavourable ERC/ESICM criteria were re-weighted according to the risk distribution within the WLST cohort, we found that 69/303 (23 %) of patients were anticipated to have survived with a poor outcome if WLST not been performed (Table 2A, eTables 10-11). Quality measures for reliable matching are illustrated in eFigs. 1A-D (histograms of propensity score), Table 1A (patient characteristics) and eFigs. 2A-B (standardised mean difference). A sensitivity analysis using AIPW revealed no significant differences in the probability of a good functional outcome across cohorts (eTable 12).

Analyses on all patients irrespective of ERC/ESICM criteria

When evaluating all patients who underwent WLST, irrespective of the number of unfavourable ERC/ESICM predictors, matches were found for 298/496 (60 %) and 166/497 (33 %) patients from KORHN and ProNeCA cohorts, respectively (Table 2B). At most one (1/298, 0.3 %) matched patient in the WLST cohort survived with a good outcome at six months (Table 2B). However, among the matched controls, 55/298 (18 %) from the KORHN and 43/166 (26 %) from the ProNeCA cohort had a good outcome at six months (p < 0.0001, Table 2B). Detailed neurodiagnostic exam results of alive matches are presented in eTable 13. Survival with a severe neurological disability occurred in 1 % (4/297, 2/165) of all matched patients subjected to WLST compared to 41/298 (14 %) of the matched KORHN patients and 37/166 (22 %) of the matched ProNeCA

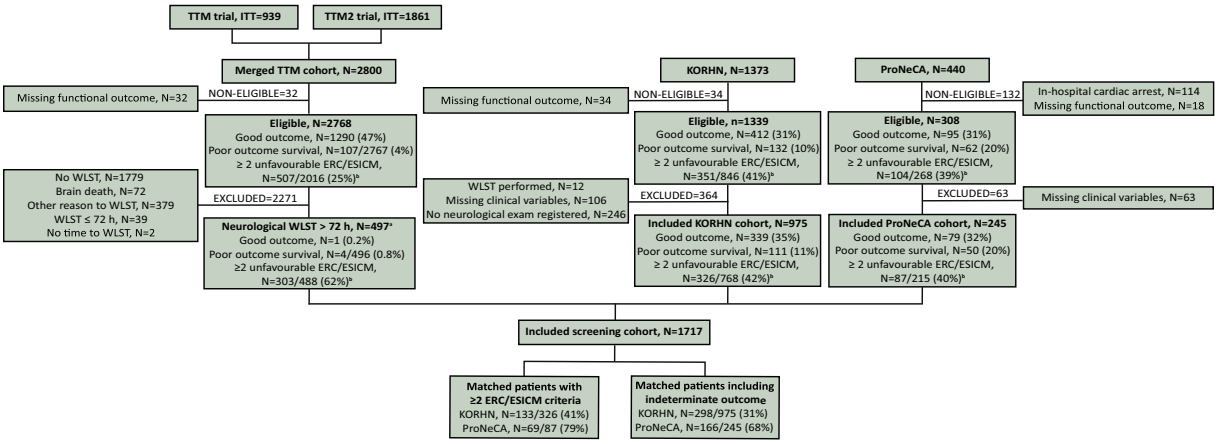

Fig. 1 – Flowchart of eligible and included patients. All patients with out-of-hospital cardiac arrest and available functional outcome at six months were eligible. We included patients with neurological WLST > 72 h from the TTM and TTM2 cohorts. Patients with early WLST ≤ 72 h (N = 39), missing time to WLST (N = 2), no WLST performed (including brain deaths) (N = 1851) or other cause to WLST (N = 379) were excluded. We also included control patients from the KORHN and ProNeCA cohorts without exposure to WLST and who had available clinical variables of the propensity score, including age, sex, minutes to ROSC, witnessed arrest, shockable rhythm, cardiac cause of arrest and ERC/ESICM criteria. For the KORHN analysis, the propensity score additionally considered previous neurological disability, previous medical conditions, bystander CPR and an interaction term for bystander CPR and witnessed arrested. ERC/ESICM = European Resuscitation Council/European Society of Intensive Care Medicine, WLST = withdrawal of life-sustaining therapy. [a] One patient was excluded from the KORHN analysis because of missing data on bystander CPR and comorbidity, N = 496, see eTable 9 for detailed patient's characteristics. [b] Patients with less than two neurological exams performed were excluded from the analysis and is presented as missing.

Table 1A – Patients' characteristics before and after matching, including patients with ≥ 2 unfavourable ERC/ESICM criteria.

	Before matching			After matching			
	N = 303	*N* = 326	*N* = 87	*N* = 133		*N* = 69	
	WLST	**KORHN**	**ProNeCA**	**WLST**	**KORHN**	**WLST**	**ProNeCA**
Age *years (SD)*	65 (11)	57 (16)	67 (13)	65 (11)	63 (13)	65 (11)	66 (13)
Male	238 (78.5)	216 (66.3)	50 (57.5)	101 (75.9)	96 (72.2)	49 (71.0)	48 (69.6)
No previous neurological deficits	250 (82.5)	284 (87.1)		112 (84.2)	113 (85.0)		
No previous medical conditions	86 (28.4)	102 (31.3)		32 (24.1)	33 (24.8)		
Minutes to ROSC *median (IQR)*	32 (24–49)	38 (28–49)	20 (15–30)	32 (24–48)	38 (24–49)	22 (16–32)	25 (15–35)
Witnessed	272 (89.8)	179 (54.9)	69 (79.3)	112 (84.2)	115 (86.5)	60 (87.0)	61 (88.4)
Bystander CPR	224 (73.9)	191 (58.6)		88 (66.2)	85 (63.9)		
Shockable first rhythm	174 (57.4)	45 (13.8)	40 (46.0)	45 (33.8)	40 (30.1)	30 (43.5)	36 (52.2)
Presumed cardiac cause	266 (87.8)	134 (41.1)	60 (69.0)	100 (75.2)	102 (76.7)	55 (79.7)	55 (79.7)
Number of ERC/ESICM criteria examined *median (IQR)*	4 (4–5)	3 (2–4)	3 (3–4)	5 (4–5)	3 (2–4)	4 (4–5)	3 (3–4)
Number of unfavourable ERC/ESICM criteria *median (IQR)*	3 (2–3)	3 (2–4)	2 (2–2)	2 (2–3)	2 (2–3)	2 (2–2)	2 (2–2)
Hours to WLST *median (IQR)*	125 (102–168)			122 (103–163)		144 (110–192)	

ROSC = return of sustained circulation, CPR = cardiopulmonary resuscitation, ERC/ESICM = European Resuscitation Council/European Society of Intensive Care Medicine, WLST = withdrawal of life-sustaining therapy.

Table 1B – Patients' characteristics before and after matching, including patients irrespective of the number of ERC/ESICM criteria met.

	Before matching			After matching			
	N = 497[a]	*N* = 975	*N* = 245	*N* = 298		*N* = 166	
	WLST	**KORHN**	**ProNeCA**	**WLST**	**KORHN**	**WLST**	**ProNeCA**
Age *years (SD)*	67 (11)	57 (16)	66 (16)	64 (11)	64 (13)	66 (11)	67 (14)
Male	391 (78.7)	692 (71.0)	157 (64.1)	226 (75.8)	225 (75.5)	122 (73.5)	123 (74.1)
No previous neurological deficits	404 (81.3)	871 (89.3)		254 (85.2)	247 (82.9)		
No previous medical conditions	137 (27.6)	320 (32.8)		91 (30.5)	72 (24.2)		
Minutes to ROSC *median (IQR)*	30 (22–45)	28 (17–41)	20 (14–30)	30 (22–44)	34 (23–45)	25 (17–36)	25 (15–35)
Witnessed	445 (89.5)	690 (70.8)	200 (81.6)	261 (87.6)	249 (83.6)	143 (86.1)	146 (88.0)
Bystander CPR	366 (73.6)	618 (63.4)		202 (67.8)	205 (68.8)		
Shockable first rhythm	306 (61.6)	385 (39.5)	125 (51.0)	154 (51.7)	138 (46.3)	85 (51.2)	91 (54.8)
Presumed cardiac cause of arrest	444 (89.3)	612 (62.8)	194 (79.2)	249 (83.6)	248 (83.2)	140 (84.3)	143 (86.1)
Number of ERC/ESICM criteria examined *median (IQR)*	4 (3–5)	2 (2–3)	3 (3–4)	4 (3–5)	2 (2–3)	4 (3–5)	3 (3–4)
Number of unfavourable ERC/ESICM criteria *median (IQR)*	2 (1–3)	1 (0–2)	1 (0–2)	2 (1–2)	2 (1–2)	1 (0–2)	1 (0–2)
At least two unfavourable ERC/ESICM criteria[b]	303/488 (62.1)	326/768 (42.4)	87/215 (40.5)	150/291 (51.5)	150/257 (58.4)	72/160 (45.0)	72/151 (47.7)
Hours to WLST *median (IQR)*	143 (108–178)			144 (114–195)		144 (115–200)	

[a] One patient was excluded from the KORHN analysis because of missing data on bystander CPR and comorbidity, *N* = 496, see eTable 9 for detailed patient's characteristics.

[b] Patients with less than two eligible neurological exams performed were excluded from the analysis and are presented as missing. ROSC = return of spontaneous circulation, CPR = cardiopulmonary resuscitation, ERC/ESICM = European Resuscitation Council/European Society of Intensive Care Medicine, WLST = withdrawal of life-sustaining therapy.

patients ($p < 0.0001$, Table 2B). When the observed outcomes of all included patients were re-weighted according to the risk distribution within the WLST cohort, we found that 88/496 (18 %) and 85/497 (17 %) of the patients were anticipated to have good outcome and 61/496 (12 %) and 95/497 (19 %) were predicted to survive with a poor outcome if WLST not been performed (Table 2B, eTables 14-15). Quality measures for reliable matching are presented in eFigs. 1E-H, Table 1B and eFigs. 2C-D. A sensitivity analysis using AIPW indicated a risk difference of 16 % (KORHN, 95 %CI 12–20) and 26 % (ProNeCA, 95 %CI 19–33) in favour of the control cohort, suggesting a higher proportion of good outcomes among the controls ($p < 0.0001$, eTable 12).

The effect of the timing to WLST

Our results were consistent across all subgroups, regardless of the WLST timing, including eligible non-included patients with WLST within 72 h (*N* = 39). WLST performed shortly after 72 h was associated with a greater proportion of patients meeting ≥ 2 unfavourable ERC/ESICM criteria (71 % vs 54 %), and their matched controls showed a trend towards lower rates of favourable outcomes compared to those with WLST after the median of 143 h (10–15 % vs 23–30 %) (eTables 16-17).

Sensitivity analyses

A series of sensitivity analyses were performed to address relevant cohort differences and evaluate the robustness of our matching. All yielded similar trends and comparable size effects in outcome differences (eTable 18). Our results were consistent even when including moderate-severe/severe neurological deficits as good outcome (eTable 19).

Discussion

Our data analysis of four multicentre clinical studies indicates that WLST can be performed in patients with two or more unfavourable ERC/ESICM criteria with a negligible risk of self-fulfilling prophecy of terminating treatment in patients who could have survived with a good outcome. In contrast, undertaking WLST in patients with an indeterminate prognosis ($\leq$ 1 unfavourable ERC/ESICM criteria), may reduce their chances of recovery. In propensity score weighted predictions, we estimated that up to 18 % of patients with an indeterminate prognosis may have survived with a good functional outcome in the absence of WLST.

Our results emphasise the two-sided ethical dilemma of WLST. On the one hand, WLST avoids further suffering and harm to patients who are likely to survive with a severe neurological disability, reduces uncertainty amongst next of kin and provides more prudent use of health care resources. Our comparison with non-WLST cohorts suggests that WLST was not associated with falsely pessimistic prediction when based on two or more unfavourable ERC/ESICM criteria. On the other hand, our study also suggests that WLST performed outside the current guideline recommendation may be potentially harmful. In our cohort, patients subjected to WLST with an indeterminate prognosis ($\leq$ 1 ERC/ESICM criteria) had lower survival with good outcome than their matched controls. Previous studies report similar findings with matched controls when WLST was performed before 72 h.[9,10] This risk of reducing good outcome survival in patients with indeterminate prognosis should be considered when evaluating patients who do not meet the ERC/ESICM criteria of a likely poor prognosis despite prolonged

Table 2A – Functional outcome for matched patients with ≥ 2 unfavourable ERC/ESICM criteria.

Deciles of propensity score	Good functional outcome (%)				Survival with poor outcome (%)			
	N = 133		*N* = 69		*N* = 133		*N* = 69	
	WLST	**KORHN**	**WLST**	**ProNeCA**	**WLST**	**KORHN**	**WLST**	**ProNeCA**
0–10%	0/2 (0)	0/3 (0)	0 (0)	0 (0)	0/2 (0)	0/3 (0)	0 (0)	0 (0)
11–20%	0/7 (0)	0/7 (0)	0 (0)	0 (0)	0/7 (0)	1/7 (14.3)	0 (0)	0 (0)
21–30%	0/14 (0)	0/16 (0)	0/3 (0)	0/3 (0)	0/14 (0)	2/16 (12.5)	0/3 (0)	2/3 (66.7)
31–40%	0/18 (0)	0/16 (0)	0/5 (0)	0/5 (0)	0/18 (0)	0/16 (0)	0/5 (0)	1/5 (20.0)
41–50%	0/16 (0)	0/15 (0)	0/6 (0)	0/5 (0)	0/16 (0)	2/15 (13.3)	0/6 (0)	2/5 (40.0)
51–60%	0/13 (0)	0/16 (0)	0/14 (0)	0/13 (0)	0/13 (0)	3/16 (18.8)	0/14 (0)	4/13 (30.8)
61–70%	0/19 (0)	0/21 (0)	0/10 (0)	0/15 (0)	0/19 (0)	4/21 (19.0)	0/10 (0)	4/15 (26.7)
71–80%	0/22 (0)	0/23 (0)	0/14 (0)	0/12 (0)	0/22 (0)	1/23 (4.3)	0/14 (0)	2/12 (16.7)
81–90%	0/19 (0)	0/13 (0)	0/10 (0)	0/9 (0)	0/19 (0)	7/13 (53.8)	0/10 (0)	0/9 (0)
90–100%	0/3 (0)	0/3 (0)	0/7 (0)	0/7 (0)	0/3 (0)	0/3 (0)	0/7 (0)	2/7 (28.6)
Outcome in matched cohort	0/133 (0)	0/133 (0)	0/69 (0)	0/69 (0)	0/133 (0)	20/133 (15.0)	0/69 (0)	17/69 (24.6)
Observed outcome in full included cohort[a]	0/303 (0)	0/326 (0)	0/303 (0)	0/87 (0)	0/303 (0)	35/326 (10.7)	0/303 (0)	23/87 (26.4)
Anticipated outcome in absence of WLST[b]	0/303 (0)		0/303 (0)		69/303 (22.7)		69/303 (22.8)	

Functional outcome separated by deciles of risk for WLST (propensity score). No significant difference in propensity score was found between the WLST-allowing and control cohorts, WLST 0.56 (0.34–0.74) vs KORHN 0.54 (0.34–0.72), $p = 0.57$ and WLST 0.66 (0.56–0.79) vs ProNeCA 0.64 (0.55–0.79), $p = 0.73$ (Mann Whitney). No patients with ≥ 2 unfavourable ERC/ESICM criteria survived with good outcome, neither in the WLST cohort nor among the matched controls. Survival with poor functional outcome was observed in 15–25 % more patients in the control cohorts compared to the WLST cohort at six months (McNemar's test, p-value < 0.0001). When outcomes were re-weighted according to risk, 23 % patients were anticipated to have poor outcome survival, had WLST not been performed.

[a] For detailed outcome see eTables 10 A-B.

[b] Calculated outcome, using the observed outcome of the control cohort reweighted according to the risk of WLST within the WLST cohort. For detailed calculations see eTables 11 A-B. ERC/ESICM = European Resuscitation Council/European Society of Intensive Care Medicine, WLST = withdrawal of life-sustaining therapy.

coma.[9–11,14,29,30] Although WLST is sometimes pursued for non-neurological reasons, including co-morbidities, ethical reasons or advance care directives, our results suggest that better adherence to the conservative approach of the ERC/ESICM guidelines is needed to avoid inappropriate WLST.[4]

A known limitation of current guidelines is that they leave many patients with an indeterminate prognosis after neuroprognostication.[8,31,32] In these cases, the ERC/ESICM recommendations suggest observing and re-evaluating the patient.[4] The lack of further guidance may lead to heterogeneous medical assessments and treatment decisions. A recent study, in which an international panel of 38 experts in neuroprognostication reviewed the clinical history of 1431 cardiac arrest patients who died following WLST, found that experts often disagreed on the patient's potential for recovery.[33] Moreover, in one-third of the cases, the panel agreed there was more than 1 % chance of recovery with a good outcome.[33] Reducing the number of patients with an indeterminate prognosis following neuroprognostication is a desirable goal of future guidelines to reduce the risk of a potentially inappropriate WLST.

Our analysis is based on the European guidelines for neuroprognostication; however, it is expected to align well with other multimodal approaches, including those of the American Heart Association and the Canadian guidelines.[34,35] Several aspects were considered to improve the generalisability of our results. Although propensity score matching is associated with a risk of bias, it entails fewer ethical concerns than a randomised trial for studying WLST.[36,37] We minimised differences in the matched variables in our analyses, however, bias from unidentified confounders cannot be ruled out. Additionally, propensity scores assume additive proportional risks, potentially equating multiple low-risk factors with a single high-risk one – an assumption that may not reflect clinical reality and could affect matching quality. To emphasise the importance of neuroprognostication in the matching process, we used exact matching on the number of unfavourable ERC/ESICM criteria.

Strengths of this study include prospectively gathered data from four multicentre studies, including two cohorts with no or minimal WLST. Sensitivity analyses found similar trends and effect sizes. Limitations include cohort differences, including variations in available data on neurological exams and baseline characteristics. Our analysis may be influenced by treatment differences, as the WLST cohort was derived from two randomised trials, while the control cohort originated from two observational studies. Most matched controls were found in the intermediate range of the propensity score, thus only representing a part of the entire cohort. Few individuals among the controls had upper range propensity scores. This imbalance may lead to statistical fragility, as few observations may have had a large impact on the estimated outcome in the WLST cohort. No analysis of the cause of death was performed, limiting the conclusion. Additional limitations included differences in follow-up routines on outcome assessment.

Table 2B – Functional outcome for all matched patients, irrespective of the number of ERC/ESICM criteria met.

Deciles of propensity score	Good functional outcome (%)				Survival with poor outcome (%)			
	N = 298		*N* = 166		*N* = 298		*N* = 166	
	WLST	**KORHN**	**WLST**	**ProNeCA**	**WLST**	**KORHN**	**WLST**	**ProNeCA**
0–10%	0/18 (0)	6/18 (33.3)	0 (0)	0 (0)	0/18 (0)	1/18 (5.6)	0 (0)	0 (0)
11–20%	0/38 (0)	12/39 (30.8)	0/3 (0)	2/3 (66.7)	1/38 (2.6)	4/39 (10.3)	1/3 (33.3)	1/3 (33.3)
21–30%	0/32 (0)	9/33 (27.3)	0/8 (0)	3/8 (37.5)	0/32 (0)	6/33 (18.2)	0/8 (0)	1/8 (12.5)
31–40%	0/46 (0)	12/50 (24.0)	0/16 (0)	9/17 (50.0)	1/46 (2.2)	8/50 (16.0)	0/16 (0)	3/17 (17.6)
41–50%	0/51 (0)	7/48 (14.6)	0/23 (0)	9/24 (37.5)	1/51 (2.0)	4/48 (8.3)	0/23 (0)	6/24 (25.0)
51–60%	1/36 (2.8)	6/37 (16.2)	0/33 (0)	9/34 (26.5)	1/35 (2.6)[c]	4/37 (10.8)	0/32 (0)[c]	7/34 (20.6)
61–70%	0/33 (0)	2/35 (5.7)	0/30 (0)	5/29 (17.2)	0/33 (0)	5/35 (14.3)	0/30 (0)	9/29 (31.0)
71–80%	0/29 (0)	1/26 (3.8)	0/24 (0)	5/24 (20.8)	0/29 (0)	8/26 (30.8)	1/24 (4.2)	5/24 (20.8)
81–90%	0/14 (0)	0/12 (0)	0/15 (0)	0/18 (0)	0/14 (0)	1/12 (8.3)	0/15 (0)	4/18 (22.2)
90–100%	0/1 (0)	0/0 (0)	0/14 (0)	1/9 (11.1)	0/1 (0)	0/0 (0)	0/14 (0)	1/9 (11.1)
Overall matched cohort	1/298 (0.3)	55/298 (18.5)	0/166 (0)	43/166 (25.9)	4/297 (1.3)[c]	41/298 (13.8)	2/165 (1.2)[c]	37/166 (22.3)
Observed outcome in full included cohort[a]	1/496 (0.2)	339/975 (34.8)	1/497 (0.2)	79/245 (32.2)	4/495 (0.8)[c]	111/975 (11.4)	4/496 (0.8) [c]	50/245 (20.4)
Anticipated outcome in absence of WLST[b]	88/496 (17.8)		85/497 (17.0)		61/496 (12.2)		95/497 (19.1)	

Functional outcome separated by deciles of risk for WLST (propensity score). There was no significant difference in propensity score between the WLST-allowing cohort and the control cohorts, WLST 0.43 (0.26–0.61) vs KORHN 0.42 (0.25–0.58), $p = 0.61$ and WLST 0.60 (0.47–0.74) vs ProNeCA 0.59 (0.46–0.73), $p = 0.62$ (Mann Whitney). A good functional outcome occurred in 18–26 % more patients from the matched controls compared to the WLST cohort (McNemar's test, p-value < 0.0001). When outcome was re-weighted according to risk, 17–18 % patients from the WLST cohort were anticipated to survive with good outcome, had WLST not been performed.

[a] For detailed outcome see eTables 14 A-B.

[b] Calculated outcome, using the observed outcome of the control cohort reweighted according to the risk of WLST within the WLST cohort. For detailed calculations see eTables 15 A-B.

[c] One patient had missing data on survival, complete cases presented. ERC/ESICM = European Resuscitation Council/European Society of Intensive Care Medicine, WLST = withdrawal of life-sustaining therapy, EEG = electroencephalogram.

Conclusion

Our study showed that the risk of self-fulfilling prophecy of WLST was negligible when performed in patients with two or more unfavourable predictors, as recommended by the 2021 ERC/ESICM guidelines. WLST reduced the risk of surviving with severe neurological disability. Propensity score matching between the WLST and control cohorts showed a lower rate of good outcome survival associated with WLST in patients with indeterminate prognosis who did not fulfil the ERC/ESICM poor outcome criteria. Adherence to the ERC/ESICM recommendations of observing and re-evaluating these patients may result in increased chances of survival with a good functional outcome after cardiac arrest.

CRediT authorship contribution statement

Alice Lagebrant: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Byung Kook Lee:** Writing – review & editing, Supervision, Resources. **Chun Song Youn:** Writing – review & editing, Supervision, Resources. **Claudio Sandroni:** Writing – review & editing, Writing – original draft, Supervision, Resources. **Jan Bělohlávek:** Writing – review & editing, Resources. **Alain Cariou:** Writing – review & editing, Resources. **Riccardo Carrai:** Writing – review & editing, Resources. **Josef Dankiewicz:** Writing – review & editing, Resources. **Hans Friberg:** Writing – review & editing, Resources, Funding acquisition. **Anders M. Grejs:** Writing – review & editing, Resources. **Antonello Grippo:** Writing – review & editing, Supervision, Resources. **Christian Hassager:** Writing – review & editing, Resources. **Janneke Horn:** Writing – review & editing, Resources, Conceptualization. **Matthias Haenggi:** Writing – review & editing, Resources. **Janus C. Jakobsen:** Writing – review & editing, Resources. **Thomas R. Keeble:** Writing – review & editing, Resources. **Hans Kirkegaard:** Writing – review & editing, Resources. **Jesper Kjaergaard:** Writing – review & editing, Resources. **Michael A. Kuiper:** Writing – review & editing,

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BKL: Received an honorarium from BD for a lecture. CH: Research funding from The Danish Heart Association, received honorarium from BD for lectures and vice president of ESC. CRo: Fees as speaker from BD. FST: Lecture fees from ZOLL and BD. JK: Research funding from NovoNordisk Foundation outside the submitted work. MPW: Served on advisory boards for DRW diagnostics and Clinical Expert NICE Advice Service. TP: Fees as speaker from BD. No other conflicts of interests were reported.

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Appendix A. Supplementary material

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