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Early and late withdrawal of life-sustaining treatment after out-of-hospital cardiac arrest in the United Kingdom: Institutional variation and association with hospital mortality

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Abstract

Aim: Frequency and timing of Withdrawal of Life-Sustaining Treatment (WLST) after Out-of-Hospital Cardiac Arrest (OHCA) vary across Intensive Care Units (ICUs) in the United Kingdom (UK) and may be a marker of lower healthcare quality if instituted too frequently or too early. We aimed to describe WLST practice, quantify its variability across UK ICUs, and assess the effect of institutional deviation from average practice on patients' risk-adjusted hospital mortality.

Methods: We conducted a retrospective multi-centre cohort study including all adult patients admitted after OHCA to UK ICUs between 2010 and 2017. We identified patient and ICU characteristics associated with early (within 72 h) and late (>72 h) WLST and quantified the between-ICU variation. We used the ICU-level observed-to-expected (O/E) ratios of early and late-WLST frequency as separate metrics of institutional deviation from average practice and calculated their association with patients' hospital mortality.

Results: We included 28,438 patients across 204 ICUs. 10,775 (37.9%) had WLST and 6397 (59.4%) of them had early-WLST. Both WLST types were strongly associated with patient-level demographics and pre-existing conditions but weakly with ICU-level characteristics. After adjustment, we found unexplained between-ICU variation for both early-WLST (Median Odds Ratio 1.59, 95%CrI 1.49–1.71) and late-WLST (MOR 1.39, 95%CrI 1.31–1.50). Importantly, patients' hospital mortality was higher in ICUs with higher O/E ratio of early-WLST (OR 1.29, 95%CI 1.21–1.38, $p < 0.001$) or late-WLST (OR 1.39, 95%CI 1.31–1.48, $p < 0.001$).

Conclusions: Significant variability exists between UK ICUs in WLST frequency and timing. This matters because unexplained higher-than-expected WLST frequency is associated with higher hospital mortality independently of timing, potentially signalling prognostic pessimism and lower healthcare quality.

Keywords: Cardiac arrest, Variability, Withdrawal of life-sustaining treatment, Mortality, Intensive care unit

Introduction

Each year in the United Kingdom (UK) approximately 30,000 patients are admitted to the Intensive Care Unit (ICU) after sustaining an Out-of-Hospital Cardiac Arrest (OHCA).[1] Only one in three patients survive to hospital discharge and many die in ICU after withdrawal of life-sustaining treatments such as mechanical ventilation (WLST).[2,3] WLST decisions are informed by a process which integrates patient/-surrogate preferences with results of neuro-prognostication tests and provider assessments but are time consuming, physician-dependent, and sometimes imperfect, especially early after ICU admission.[4–7] Therefore, WLST in the first 72 hours (early) may be premature if not driven by untreatable organ failure, due to insufficient time for

Abbreviations: WLST, withdrawal of life-sustaining treatment, ICNARC, Intensive Care Unit Intensive Care National Audit & Research Centre, CMP, Case Mix Programme, IMD, Index of Multiple Deprivation, ADLs, Activities of Daily Life, APACHE II score, Acute Physiology and Chronic Health Evaluation score version II, IRAS, Integrated Research and Application System, CPR, cardiopulmonary resuscitation, CI, Confidence Interval, CrI, Credible Interval

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thorough prognostication, while WLST after 72 h (late) may be appropriate, if aligned with patients' wishes and values.[4]

In the UK, both early and late-WLST are common: 48.9% of all OHCA patients undergo WLST, at a median of approximately 72 hours.[2,3] At the patient level, early treatment limitations after OHCA are associated with worse outcomes due to decreased time available for treatment, prognostication, and recovery.[8–11] Previous studies, however, have used variable types of treatment limitations and time frames, complicating comparisons within the literature and between healthcare systems. At the ICU level, frequency and timing of treatment limitations vary between units.[11–13] Higher ICU frequency of earlier limitations is linked to poor guideline adherence[4,14–16] and may signal a culture of prognostic pessimism,[14,17] whereas routinely delaying WLST appears beneficial.[10,16] "Optimal" ICU WLST practice, however, is difficult to define and the association between institutional practice deviation and healthcare quality remains unclear. A better understanding of WLST practice variability between ICUs and its effect on patient outcomes would inform efforts around standardisation of post-OHCA care in the UK and provide a target for quality improvement.[2]

We hypothesized that WLST decisions reflect institutional prognostication culture and that their frequency in patients with OHCA are associated with higher mortality. To assess this, we first explored the epidemiology, variability, and risk factors for early and late WLST. With this information and a clearer understanding of confounding variables at the patient and ICU level we explored the independent effect of the observed-to-expected ICU frequency of early and late WLST on patients' risk-adjusted hospital mortality.

Materials and methods

Study design, setting, and data sources

We conducted a retrospective multi-centre cohort study in patients who were admitted after OHCA to ICUs participating in the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme (CMP), between January 1st, 2010, and December 31st, 2017. The CMP is a national clinical audit of patient outcomes that prospectively collects data from all adult general ICUs in England, Wales and Northern Ireland. CMP collection and storage of identifiable data without patient consent is supported by Health Research Authority Confidentiality Advisory Group approval number PIAG 2–10(f)/2005, under section 251 of the National Health Service (NHS) Act 2006 and the requirement for Research Ethics Committee review for this study was waived (IRAS Project ID 26559/19-Apr-2019).

Participants

We included patients over 16 years and only the first ICU admission after OHCA. Patients who were not mechanically ventilated in the first 24 hours, those transferred from other institutions, or those admitted to ICUs with fewer than 5 cases per year were excluded.[11,18]

Variables

We used the observed-to-expected (O/E) ratio of early and late WLST at the ICU level as exposures since they represent the ICU's deviation from average practice.[19] We initially defined early and late-WLST as withdrawal of all active treatments within and after 72 h from ICU admission, respectively[4]; this was subjected to a range of sensitivity analyses. The primary outcome was patient-level hospital mortality.

We used the following patient-level data, as recorded in the CMP: demographic characteristics, including Index of Multiple Deprivation (IMD)[20]; prior residence and level of dependency; comorbidities (cardiac, respiratory, hepatic, renal or haematological disease, immunocompromise, metastatic cancer); ICU admission in previous 12 months; APACHE II score; ICNARC Physiology score (excluding temperature)[21]; maximum temperature (first 24 hours); sepsis diagnosis (Sepsis-3 criteria)[22]; duration and type of sedation and organ support; time and type of treatment limitations (withholding, withdrawal); time of admission, discharge, or death. Outcome was recorded as survival status at ICU and hospital discharge. Ethnicity was included to capture unmeasurable cultural and religious characteristics associated with end-of-life decision-making. We also used the following ICU-level characteristics: size (on year of admission); university affiliation; status as neurosurgical and major trauma centre, to capture the availability of neurophysiology services and halo effects[23]; median annual volume of all ICU admissions and OHCA admissions and median ICNARC physiology score, as proxies for ICU strain[24–28]; ICU IMD percentile as proxy for catchment area deprivation.[29] Details regarding variable definitions are available in the Appendix.

The study was conducted in accordance with the NHS Research Governance Framework and principles of the Declaration of Helsinki.[30] Our report is based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[31]

Statistical analysis

We used summary statistics to describe patient and ICU characteristics and explored their association with early-WLST using a mixed effects hierarchical logistic regression model with two random-intercepts, assuming that patients are nested within years within ICUs. This model allowed us to evaluate patients' risk factors for early-WLST while controlling for clustering and within-ICU variation over time, and to quantify the between-ICU variability in early-WLST by calculating the Median Odds Ratio (MOR). We also used it to predict the *expected* annual early-WLST frequency for each ICU and subsequently calculate ICU-level *observed-to-expected* frequency ratios. These formed the exposure in a separate three-level mixed effects hierarchical logistic regression model to investigate their association with patients' hospital mortality. The same process was repeated for late-WLST.

We performed several sensitivity and fragility analyses, separately for each objective and early/late WLST. First, we extended the time threshold for early-WLST to include treatment withdrawal within 96 or 120 hours,[32] assuming that a true association with mortality would be accentuated by a longer time frame for the definition of "early". Second, we broadened the WLST definition by including withholding of treatments (other than cardiopulmonary resuscitation-CPR), which also implies prognostic pessimism[33] but does not always lead to death, and assumed an unchanged or enhanced effect if pessimism is a major driver of outcome. Third, we used ICU mortality as the study outcome to investigate the dependence of primary results on deaths which happen after ICU discharge and assumed the findings would remain unchanged. Fourth, we conducted two fragility analyses: first we excluded patients with APACHE II and ICNARC Physiology scores above the cohort mean to ensure that the observed associations are not driven by patients with multi-organ failure,[34] and second we excluded patients with WLST in the first 8 hours after admission, since they may represent cases of multi-organ failure and inappropriate or unwanted resuscitation. Finally, we calculated the corresponding E-values to assess the potential impact of unmeasured confounding.[35]

Analyses were performed using Stata/MP version 17 (StataCorp LLC) and we considered a two-sided α-level of 0.05 as statistically significant. No missing data were imputed. More details regarding the statical methodology are available in the Appendix.

Results

During the 7-year study period, we recorded 1,037,673 patients and 1,179,941 ICU admissions across 234 general ICUs. Among them, 33,505 patients (3.3%) were admitted after OHCA and we included 28,438 patients (84.9%) across 204 ICUs. 10,775 (37.9%) of them had WLST, 6,397 (59.4%) within 72 hours of ICU admission (Fig. S2, Appendix). The median overall proportion of patients receiving early-WLST (23.6%, IQR 17.3–28.6%) and late-WLST (14.6%, IQR 11.0–18.2%) varied significantly between ICUs (Fig. 1) but less so over time (Fig. S3, Appendix).

Characteristics of patients who did and did not have WLST and unadjusted univariate comparisons between those with early and late WLST are shown in Table 1. Patients with early-WLST were older, more frequently female with respiratory, liver, or metastatic disease, immunocompromised, and less likely to live independently at home. Despite worse physiologic derangement with higher APACHE II and ICNARC Physiology scores, they were overall less likely to receive sedation and cardiovascular or renal support. Length of organ support and ICU stay were shorter and unadjusted ICU and hospital mortality were higher in the early-WLST group.

Table 2 shows the characteristics of patients treated in ICUs classified by tertiles of early-WLST frequency. Patients in ICUs with higher frequency were often older, female, and white but less socioeconomically deprived and less likely to live independently at home.

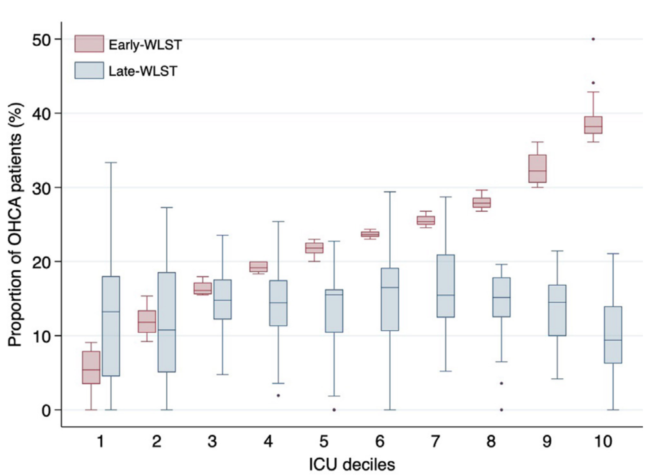

Fig. 1 – Box plot of the proportion of patients with early (within 72 h) or late (after 72 h) withdrawal of life-sustaining treatments (WSLT) across deciles of 204 included Intensive Care Units (ICUs). ICUs were ranked by increasing early-WLST frequency.

They had higher APACHE and ICNARC scores but received different sedation/paralysis patterns and overall shorter and less intensive organ support. Finally, higher early-WLST frequency was associated with shorter ICU stays and higher unadjusted ICU and hospital mortality. Characteristics of included ICUs are shown in Table 3. There is very weak association between higher early-WLST frequency and smaller ICU size, lower admissions volume, and lack of university affiliation. The corresponding tables for late-WLST are available in the Appendix (Tables S1–S2).

After adjustment for clustering and differences in patient and ICU characteristics, the following factors were associated with higher odds for early-WLST: older age, female sex, nursing home residence, some or total assistance with ADLs, history of respiratory, liver, or metastatic disease, more severe physiologic derangement, and previous ICU admission. Lower odds for early-WLST were associated with: Black, Asian or Mixed/Other ethnicity, lower area deprivation, history of severe cardiovascular disease, sepsis diagnosis, cardiovascular or renal support, larger ICU size, and higher median ICU ICNARC Physiology score. Similarly, no fixed abode, total dependence on ADLs, renal replacement therapy, and median ICU IMD percentile were associated with higher odds for late-WLST while Black ethnicity, lower area deprivation, and either sedation with paralysis or no sedation/paralysis were associated with lower odds. These associations persisted across all sensitivity and fragility analyses (Tables S3 and S4, Appendix).

WLST practice and outcomes differed significantly between ICUs (Figs. S4–S6, Appendix). After adjustment we identified a 59% median difference in odds of early-WLST between similar patients who were treated in the same year in two different, randomly chosen ICUs (MOR 1.59, 95% Credible Interval 1.49–1.71) and a 39% median difference in odds of late-WLST (MOR 1.39, 95%CrI 1.31–1.50), with correspondingly wide variation in O/E frequency ratios. We also found a 30% unexplained median difference for the odds of hospital death between similar patients treated in the same year in randomly different ICUs (MOR 1.30, 95%CrI 1.25–1.38).

Importantly, patients treated in ICUs with higher O/E ratio of early-WLST had significantly higher odds of hospital death (OR 1.29, 95%CI 1.21–1.38, $p < 0.001$), as did patients treated in ICUs with higher O/E ratios of late-WLST (OR 1.39, 95%CI 1.31–1.48, $p < 0.001$). These associations are shown in Fig. 2 for the range of observed values of O/E ratios and persisted across all sensitivity and fragility analyses (Tables S5–S6, Appendix). The result of these analyses is summarised in Fig. S7 (Appendix). Larger, academic, high case-volume ICUs had lower O/E ratios (Table S7 and Fig. S8). The E-values were 1.53 for early and 1.64 for late-WLST, implying that, to fully attribute the association to unmeasured confounding, a confounder would have to be associated with both the respective ICU-level O/E ratio and individual patients' hospital mortality with an OR at least as high as the E-value (Figs. S9-S10, Appendix).

Discussion

Our study found that WLST frequency and timing after OHCA vary significantly between UK ICUs and identified patient and ICU-level risk factors for early and late-WLST. It also found that similar patients had a higher chance of hospital death when treated in ICUs with a higher observed-to-expected ratio of early or late-WLST after adjusting for the impact of case mix, unit characteristics, and clustering.

Table 1 – Patient characteristics in the study population and in those who sustained withdrawal of life-sustaining treatment (WLST), within 72 hours (early) and after 72 hours (late) from ICU admission. Data are reported as Median (Interquartile Range-IQR) or Number (%), as appropriate.

	Study population N = 28438		WLST population N = 10775		Late-WLST N = 4378		Early-WLST N = 6397		p-value [a]
	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	
Age (years) [b]	64	50–74	67	55–77	65	53–74	70	57–78	<0.001
16–39	3634	(12.8)	921	(8.5)	397	(9.1)	524	(8.2)	
40–59	8174	(28.7)	2531	(23.5)	1234	(28.2)	1297	(20.3)	
60–79	13,022	(45.8)	5488	(50.9)	2271	(51.9)	3217	(50.3)	
≥80	3606	(12.7)	1834	(17.0)	476	(10.9)	1358	(21.2)	
Female sex	9176	(32.3)	3708	(34.4)	1388	(31.7)	2320	(36.3)	<0.001
Ethnicity [c]									
White	25,132	(88.4)	9745	(90.4)	3926	(89.7)	5819	(91.0)	0.030
Black	512	(1.8)	132	(1.2)	57	(1.3)	75	(1.2)	
Asian	1123	(3.9)	386	(3.6)	161	(3.7)	225	(3.5)	
Mixed/other	602	(2.1)	148	(1.4)	77	(1.8)	71	(1.1)	
IMD rank quintile [d]									
1 (most deprived)	6989	(24.6)	2674	(24.8)	1110	(25.4)	1564	(24.4)	0.044
2	5960	(21.0)	2303	(21.4)	924	(21.1)	1379	(21.6)	
3	5459	(19.2)	2065	(19.2)	779	(17.8)	1286	(20.1)	
4	5039	(17.7)	1897	(17.6)	769	(17.6)	1128	(17.6)	
5 (least deprived)	4456	(15.7)	1669	(15.5)	704	(16.1)	965	(15.1)	
Prior residence									<0.001
Home	27,373	(96.3)	10,300	(95.6)	4204	(96.0)	6096	(95.3)	
Nursing home or equivalent	444	(1.6)	257	(2.4)	63	(1.4)	194	(3.0)	
Other setting/no fixed abode	621	(2.2)	218	(2.0)	111	(2.5)	107	(1.7)	
Prior dependency (assistance with ADLs) [e]									<0.001
No assistance	22,216	(78.1)	7708	(71.5)	3409	(77.9)	4299	(67.2)	
Some assistance	5534	(19.5)	2782	(25.8)	883	(20.2)	1899	(29.7)	
Total assistance	241	(0.8)	133	(1.2)	35	(0.8)	98	(1.5)	
Medical history [f]									
Severe cardiovascular disease	809	(2.8)	368	(3.4)	132	(3.0)	236	(3.7)	0.053
Severe respiratory disease [g]	772	(2.7)	451	(4.2)	118	(2.7)	333	(5.2)	<0.001
End-stage renal disease	306	(1.1)	148	(1.4)	59	(1.3)	89	(1.4)	0.829
Severe liver disease	270	(0.9)	127	(1.2)	37	(0.8)	90	(1.4)	0.007
Haematological malignancy	154	(0.5)	77	(0.7)	29	(0.7)	48	(0.8)	0.582
Immunocompromise	564	(2.0)	257	(2.4)	81	(1.9)	176	(2.8)	0.002
Metastatic disease	225	(0.8)	113	(1.0)	27	(0.6)	86	(1.3)	<0.001
Previous ICU admission (within 12 months)	955	(3.4)	438	(4.1)	166	(3.8)	272	(4.3)	0.235
APACHE-II score [h]	18	14–24	20	16–26	18	14–22	23	18–29	<0.001
ICNARC Physiology score [i]	24	19–30	27	22–33	24	20–28	29	23–36	<0.001
Sepsis (SEPSIS-3 criteria)	2371	(8.3)	957	(8.9)	403	(9.2)	554	(8.7)	0.329
Sedation/paralysis (first 24 h) [j]									<0.001
Sedated for all 24 h	17,755	(62.4)	6991	(64.9)	3325	(75.9)	3666	(57.3)	
Sedated & paralysed for all 24 h	8583	(30.2)	2966	(27.5)	967	(22.1)	1999	(31.2)	
Not sedated or paralysed	2035	(7.2)	805	(7.5)	83	(1.9)	722	(11.3)	
Fever [k]	8826	(31.0)	3228	(30.0)	1384	(31.6)	1844	(28.8)	0.002
Organ support [m]									
Cardiovascular	28,308	(99.5)	10,719	(99.5)	4376	(100.0)	6343	(99.2)	<0.001
Respiratory	28,437	(100.0)	10,775	(100.0)	4378	(100.0)	6397	(100.0)	-
Renal	2541	(8.9)	1088	(10.1)	578	(13.2)	510	(8.0)	<0.001
Organ support time (days) [m]									
Cardiovascular	4	2–6	3	2–5	6	5–8	2	2–3	<0.001
Respiratory	3	2–6	3	2–5	6	5–8	2	2–3	<0.001
Renal	3	2–5	3	2–4	4	3–6	2	1–2	<0.001
Time to WLST (hours)	57.9	22.4–104.5	57.9	22.4–104.5	116.8	92.1	27.6	13.3	<0.001

Table 1 (continued)

	Study population N = 28438		WLST population N = 10775		Late-WLST N = 4378		Early-WLST N = 6397		p-value [a]
	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	
ICU length of stay (days) [n]	4	2–8	5	3–7	6	5–8	3	2–3	<0.001
Deceased on ICU discharge	15,949	(56.1)	9813	(91.1)	3725	(85.1)	6088	(95.2)	<0.001
Deceased on hospital discharge	18,144	(63.8)	10,683	(99.1)	4312	(98.5)	6371	(99.6)	<0.001

Abbreviations: WLST, withdrawal of life-sustaining treatment; ICU, Intensive Care Unit; IMD, Index of Multiple Deprivation; ADLs, Activities of Daily Life; APACHE II score, Acute Physiology and Chronic Health Evaluation score version II.

[a] Comparisons were made between early and late-WLST groups using Mann-Whitney U test tests or chi-squared tests, as appropriate.

[b] Age was missing for 2 (<1%) patients.

[c] Ethnicity was missing or not stated for 1069 (3.8%) patients.

[d] IMD rank quintiles were calculated separately for England, Wales, Scotland, Northern Ireland, the Channel Islands, and the Isle of Man. IMD rank was missing for 535 (1.9%) patients.

[e] Prior dependency was missing for 385 (1.5%) patients.

[f] Comorbidities were missing for 444 (1.6%) patients.

[g] Includes home ventilation.

[h] APACHE II was missing in 1853 (6.5%) of patients.

[i] ICNARC Physiology score was missing in 311 (1.1%) of patients; it was calculated without the temperature component to account for the implementation of TTM.

[j] Sedation type were missing for 65 (<1%) patients.

[k] Defined as highest temperature above 37.7 degrees Celsius in the first 24 h of ICU admission.

[m] Data were missing for 1 (<1%) patient.

[n] Applies only to 12,489 patients who were discharged from ICU alive. Length of stay data were missing for 527 (4.2%) of them.

More than one third of included patients had WLST. The incidence of early limitations of treatment in other countries is 15.7–22.1%,[9–10,38] but previous data other than median timing[3] are not available for the UK. Literature comparisons are also complicated by significant variability in both the definition of treatment limitations, which have included elements of treatment withholding and withdrawal, and the exact threshold between "early" and "late", which ranges from 24 to 72 h.[9–11] In our study, treatment limitations occurrence, type, and timing were prospectively and uniformly recorded, and our findings were not altered by including withholding of treatments or by using different time thresholds.

The identified associations between early or late-WLST and specific patient characteristics are known and explainable for age, comorbidity burden, and severity of acute illness,[9–11] known but difficult to explain for ethnicity and sex,[9–11] and novel in the case of area deprivation. Deprivation has been linked to higher OHCA incidence[39] and poorer prehospital management[40–42] and survival after OHCA,[18,29,43] but also with more frequent WLST, particularly in the absence of universal healthcare.[44–45] Our study indicates that this may be also true for the universally accessible, publicly funded National Health Service, even after controlling for ICU catchment area deprivation. The complicated interaction between socioeconomic factors and WLST decision-making warrants further research and validation.

As previously reported,[11,26] observable ICU characteristics (size, volume, academic status etc) had a limited role in explaining early or late-WLST occurrence among individual patients in our study, although case volume was independently associated with hospital mortality. This may be because such characteristics are often collinear and it is challenging to isolate their effect on patient-level decisions,[46–47] or because the main driver of WLST decision-making is poorly approximated by classic markers of institutional performance.[5,6,48,49]

OHCA patients often require significant time prior to awakening[36] and the self-reported quality of life of survivors is good.[37] In this context, variation in timing and frequency of WLST may contribute to worse outcomes. ICU WLST practice variation in our study remained large after adjustment. Allowing for differences in definitions and confounders, Elmer et al. found a similar MOR of 1.58[10] for early-WLST, while smaller studies reported much larger variation (MORs 1.97–3.16)[8,26]; no comparison data exist for late-WLST. Our calculated effect of between-institution variability often exceeded the effect of important patient-level covariates in explaining the occurrence of WLST, indicating that this practice variation matters.

Four previous studies which explored the effect of early treatment limitations after OHCA found an association with worse outcomes, attributed to prognostic pessimism and self-fulfilling prophecy.[8–11] In all four of these studies, the exposure was defined at the patient level, only one used treatment withdrawal[10] and none explored late-WLST. This is presumably because, unlike early-WLST, WLST later during the admission is considered to reflect a mature process which, by combining neuro-prognostication with exploration of patient preferences over sufficient time, succeeds at affecting predominantly patients who are already very likely to have a poor outcome.[4,50] We focused on the ICU level instead and assumed that, after adjustment for case mix and unit characteristics, WLST practice variation reflects differences in institutional prognostication culture which translate into patient outcomes irrespectively of early or late timing. We used each ICU's deviation from average "expected" practice (O/E ratio) as a metric for such differences and showed that higher-than-expected frequency of WLST at any time during ICU admission is indeed associated with higher patient mortality. This aligns with previous work in the general ICU population[51] and supports the hypothesis that excessive WLST may somehow signal poorer healthcare quality. Although the mechanism behind this requires elucidation, an exploratory analysis of the distribution of O/E ratios for early and late WLST across ICUs showed that larger, academic, high-volume ICUs had O/E ratios closer to one ("conformist") while smaller units varied considerably in their ratios ("mar-

Table 2 – Characteristics of patients treated in Intensive Care Units (ICUs) classified by tertiles of unadjusted ICU frequency (% of OHCA patients) of early (within 72 h) withdrawal of life-sustaining treatment (WLST). Data are reported as Median (Interquartile Range-IQR) or Number (%), as appropriate.

			Frequency of Early-WLST (Median)						
	Study population N = 28438		Low (13.8%) N = 9406		Medium (23.6%) N = 11468		High (31.3%) N = 7564		p-value[a]
	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	
Age (years) [b]	64	50–74	62	49–73	64	50–74	65	51–75	<0.001
16–39	3634	(12.8)	1309	(13.9)	1408	(12.3)	917	(12.1)	
40–59	8174	(28.7)	2878	(30.6)	3309	(28.9)	1987	(26.3)	
60–79	13,022	(45.8)	4099	(43.6)	5370	(46.8)	3553	(47.0)	
≥80	3606	(12.7)	1120	(11.9)	1379	(12.0)	1107	(14.6)	
Female sex	9176	(32.3)	2986	(31.7)	3600	(31.4)	2590	(34.2)	<0.001
Ethnicity [c]									<0.001
White	25,132	(88.4)	7910	(84.1)	10,088	(88.0)	7134	(94.3)	
Black	512	(1.8)	319	(3.4)	144	(1.3)	49	(0.6)	
Asian	1123	(3.9)	486	(5.2)	494	(4.3)	143	(1.9)	
Mixed/other	602	(2.1)	342	(3.6)	189	(1.6)	71	(0.9)	
IMD rank quintile [d]									<0.001
1 (most deprived)	6989	(24.6)	2536	(27.0)	2807	(24.5)	1646	(21.8)	
2	5960	(21.0)	1978	(21.0)	2308	(20.1)	1674	(22.1)	
3	5459	(19.2)	1749	(18.6)	2202	(19.2)	1508	(19.9)	
4	5039	(17.7)	1538	(16.4)	2081	(18.1)	1420	(18.8)	
5 (least deprived)	4456	(15.7)	1290	(13.7)	1932	(16.8)	1234	(16.3)	
Prior residence									0.003
Home	27,373	(96.3)	9069	(96.4)	11,055	(96.4)	7249	(95.8)	
Nursing home or equivalent	444	(1.6)	125	(1.3)	165	(1.4)	154	(2.0)	
Other setting/no fixed abode	621	(2.2)	212	(2.3)	248	(2.2)	161	(2.1)	
Prior dependency (assistance with ADLs) [e]									<0.001
No assistance	22,216	(78.1)	7291	(77.5)	9161	(79.9)	5764	(76.2)	
Some assistance	5534	(19.5)	1867	(19.8)	2020	(17.6)	1647	(21.8)	
Total assistance	241	(0.8)	89	(0.9)	90	(0.8)	62	(0.8)	
Medical history [f]									
Severe cardiovascular disease	809	(2.8)	309	(3.3)	293	(2.6)	207	(2.7)	0.005
Severe respiratory disease [g]	772	(2.7)	247	(2.6)	313	(2.7)	212	(2.8)	0.800
End-stage renal disease	306	(1.1)	137	(1.5)	97	(0.8)	72	(1.0)	<0.001
Severe liver disease	270	(0.9)	97	(1.0)	107	(0.9)	66	(0.9)	0.539
Haematological malignancy	154	(0.5)	51	(0.5)	51	(0.4)	52	(0.7)	0.088
Immunocompromise	564	(2.0)	183	(1.9)	209	(1.8)	172	(2.3)	0.099
Metastatic disease	225	(0.8)	87	(0.9)	71	(0.6)	67	(0.9)	0.027
Previous ICU admission (within 12 months)	955	(3.4)	291	(3.1)	379	(3.3)	285	(3.8)	0.049
APACHE-II score [h]	18	14–24	18	13–24	17	13–23	19	14–25	<0.001
ICNARC Physiology score [i]	24	19–30	24	19–31	23	18–29	25	19–31	<0.001
Sepsis (SEPSIS-3 criteria)	2371	(8.3)	773	(8.2)	915	(8.0)	683	(9.0)	0.033
Sedation/paralysis (first 24 h) [j]									0.001
Sedated for all 24 h	17,755	(62.4)	5690	(60.5)	7579	(66.1)	4486	(59.3)	
Sedated & paralysed for all 24 h	8583	(30.2)	2979	(31.7)	3161	(27.6)	2443	(32.3)	
Not sedated or paralysed	2035	(7.2)	697	(7.4)	717	(6.3)	621	(8.2)	
Fever (first 24 h) [k]	8826	(31.0)	3263	(34.7)	3379	(29.5)	2184	(28.9)	<0.001
Organ support [m]									
Cardiovascular	28,308	(99.5)	9375	(99.7)	11,419	(99.6)	7514	(99.3)	0.008
Respiratory	28,437	(100.0)	9406	(100.0)	11,468	(100.0)	7563	(100.0)	-
Renal	2541	(8.9)	1145	(12.2)	848	(7.4)	548	(7.2)	<0.001
Organ support time (days) [m]									
Cardiovascular	4	2–6	4	2–7	4	2–6	3	2–5	<0.001
Respiratory	3	2–6	4	2–7	4	2–6	3	2–5	<0.001
Renal	3	2–5	3	2–5	3	2–4	3	2–4	<0.001
ICU length of stay (days) [n]	4	2–8	5	3–11	4	2–8	4	2–7	<0.001
Time to WLST (hours)	57.9	22.4–104.5	75.2	29.2–134.6	58.9	21.8–101.8	46.8	19.9–86.0	<0.001

Table 2 (continued)

	Study population N = 28438		Frequency of Early-WLST (Median) Low (13.8%) N = 9406		Medium (23.6%) N = 11468		High (31.3%) N = 7564		p-value[a]
	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	
Death by neurological criteria	1787	(6.3)	640	(6.8)	678	(5.9)	469	(6.2)	0.006
Deceased on ICU discharge	15,949	(56.1)	5251	(55.8)	6081	(53.0)	4617	(61.0)	<0.001
Deceased on hospital discharge	18,144	(63.8)	5869	(62.4)	7029	(61.3)	5246	(69.4)	<0.001

Abbreviations: WLST, withdrawal of life-sustaining treatment; ICU, Intensive Care Unit; IMD, Index of Multiple Deprivation; ADLs, Activities of Daily Life; APACHE II score, Acute Physiology and Chronic Health Evaluation score version II; ICNARC, Intensive Care National Audit & Research Centre.

[a] Kruskal-Wallis test or chi-squared test, as appropriate.

[b] Age was missing for 2 (<1%) patients.

[c] Ethnicity was missing or not stated for 1069 (3.8%) patients.

[d] IMD rank quintiles were calculated separately for England, Wales, Scotland, Northern Ireland, the Channel Islands, and the Isle of Man. IMD rank was missing for 535 (1.9%) patients.

[e] Prior dependency was missing for 385 (1.5%) patients.

[f] Comorbidities were missing for 444 (1.6%) patients.

[g] Includes home ventilation.

[h] APACHE 2 was missing in 1853 (6.5%) of patients.

[i] ICNARC Physiology score was missing in 311 (1.1%) of patients; it was calculated without the temperature component to account for the implementation of targeted temperature management.

[j] Sedation type was missing for 65 (<1%) patients.

[k] Defined as highest temperature above 37.7 degrees Celsius in the first 24 h of ICU admission.

[m] Data were missing for 1 (<1%) patient.

[n] Applies only to 12,489 patients who were discharged from ICU alive. Length of stay data were missing for 527 (4.2%) of them.

ginal”). Since transferred patients were excluded, these preliminary results cannot be attributed to selective referral patterns and, if true, may point to differences in one or more unobservable institutional quality elements of healthcare delivery such as expertise, shared decision-making, or caregiver attitudes towards prognostic uncertainty,[5,6,17,48,49,52–54] thus providing further support for centralised OHCA care.[55]

The aim of this study was not to assess individual WLST decision-making choices or to prescribe “optimal” institutional practice, but to explore, at the institutional level, whether systematic and unexplained differences in WLST practice signal differences in healthcare quality after OHCA. In that context, institutional O/E WLST ratios could serve, similarly to the Standardised Mortality Ratio, as a crude benchmark tool and prompt more targeted institutional review when necessary. At an individual level, however, WLST decisions remain deeply personal and value-laden for all involved stakeholders; hospital mortality is a suboptimal outcome metric in that regard since survival after OHCA is not always beneficial, but it remains one of few that are available at large scale. Inclusion of long-term functional outcomes in administrative healthcare registries and modification of the current Utstein registry template to include standardised information regarding WLST decision-making (type, timing, aetiology) as a core element would facilitate benchmarking and drive future research.[56]

Our study has several strengths. First, it is the largest study to date to explore early and late WLST after OHCA and hence covers the entire spectrum of post-OHCA care provided in the UK. Second, it is based on a national, prospective, validated dataset with precise timing of WLST and few missing data, limiting misclassification. Third, the results are based on a clear conceptual model, account for the effect of time, and are robust to a range of sensitivity and fragility analyses. The study, however, is not without limitations. First, due to the organisational characteristics of the NHS, findings may not be generalisable to other healthcare systems. Second, the CMP dataset does not include details regarding cardiac arrest episode characteristics (witnessed or bystander CPR status, first rhythm etc) or Emergency Medical Services characteristics and management (call time, response time etc). These factors are highly correlated with outcomes after OHCA and their omission may have led to residual confounding despite the exclusion of transferred patients and the high E-Values. Third, no information was available regarding the exact reason for WLST or the contribution of patient/surrogate preferences to that decision, but the robustness of our results to permutations in the definitions of exposure and outcome suggests that significant bias is unlikely. Additionally, the inclusion of factors known to influence end-of-life decisions such as ethnicity and level of deprivation may have somewhat attenuated unmeasured confounding in this domain. Finally, no information was available regarding long-term functional status and quality of life, which constitute more patient-centred outcome metrics than mortality but are also harder to operationalise in the context of a large registry.

Conclusion

Approximately one third of patients admitted to ICU after OHCA in the UK received WLST, but practice between ICUs varied significantly. ICUs with higher observed-to-expected frequency of early and late-WLST had higher adjusted hospital mortality, potentially signalling differences in prognostic attitudes and lower healthcare quality.

Table 3 – Intensive Care Unit (ICU) characteristics overall and by tertile of median unadjusted ICU frequency (% of OHCA patients) of early withdrawal of life-sustaining treatment (WLST). Data are reported as Median (Interquartile Range-IQR) or Number (%), as appropriate.

	Frequency of Early-WLST (Median)								
	All ICUs N = 204		Low (13.8%) N = 68		Medium (23.6%) N = 68		High (31.3%) N = 68		p-value [a]
	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	N or Median	(%) or IQR	
University affiliated	40	(19.6)	19	(27.9)	13	(19.1)	8	(11.8)	0.059
Major Trauma Centre	14	(6.9)	5	(7.4)	5	(7.4)	4	(5.9)	0.926
Neurosurgical centre	18	(8.8)	9	(13.2)	4	(5.9)	5	(7.4)	0.278
ICU size (beds) [b]	11	8–16	12	9–18	11	8–16	10	8–14	0.021
<10	79	(38.7)	21	(30.9)	26	(38.2)	32	(47.1)	
10–19	95	(46.6)	32	(47.1)	33	(48.5)	30	(44.1)	
≥20	30	(14.7)	15	(22.1)	9	(13.2)	6	(8.8)	
Annual overall admissions volume (patients) [b]	682	486–906	686	449–910	716	544–947	628	458–876	0.238
<500	55	(27.0)	21	(30.9)	14	(20.6)	20	(29.4)	
500–999	110	(53.9)	32	(47.1)	39	(57.4)	39	(57.4)	
≥1000	39	(19.1)	15	(22.1)	15	(22.1)	9	(13.2)	
Annual OHCA case volume (patients) [b]	17	12–26	17	11–30	21	13–32	15	12–21	0.051
5–14	83	(40.7)	29	(42.6)	22	(32.4)	32	(47.1)	
15–24	64	(31.4)	20	(29.4)	20	(29.4)	24	(35.3)	
≥25	56	(27.5)	19	(27.9)	25	(36.8)	12	(17.6)	
IMD rank quintile [c]									
1 (Most deprived)	11	(5.4)	4	(5.9)	5	(7.4)	2	(2.9)	0.228
2	78	(38.2)	30	(44.1)	23	(33.8)	25	(36.8)	
3	82	(40.2)	28	(41.2)	27	(39.7)	27	(39.7)	
4	29	(14.2)	4	(5.9)	11	(16.2)	14	(20.6)	
5 (Least deprived)	3	(1.5)	1	(1.5)	2	(2.9)	0 (0)	0 (0)	
ICU ICNARC Physiology score [b,c]	24	22–26	24	22–26	23	22–25	24	24–26	0.009
Time to WLST (hours) [b]	55.3	44.1–69.7	75.8	59.7–94.6	55.7	45.5–65.7	47.0	39.1–52.3	<0.001

Abbreviations: WLST, withdrawal of life-sustaining treatment; ICU, Intensive Care Unit; IMD, Index of Multiple Deprivation; ICNARC, Intensive Care National Audit & Research Centre.

[a] Kruskal-Wallis, or Chi-squared or Fisher's exact tests, as appropriate.

[b] Median value of the annual admissions to the corresponding ICU between 2010 and 2017.

[c] Calculated using only patients admitted with OHCA.

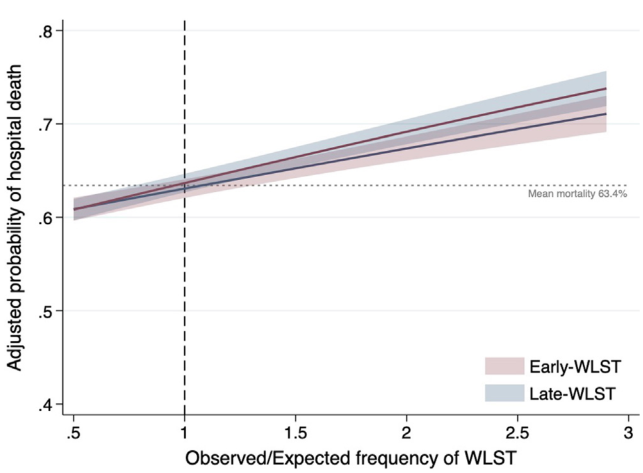

Fig. 2 – The association between the adjusted, patient-level probability of hospital death and the ICU-level ratio of observed-to-expected frequency of early (within 72 h) or late (after 72 h) withdrawal of life-sustaining treatments (WSLT). The mean cohort hospital mortality of 63.4% is displayed for reference.

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Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used no AI technologies.

CRediT authorship contribution statement

Savvas Vlachos: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Gordon Rubenfeld:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **David Menon:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **David Harrison:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Kathryn Rowan:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Ritesh Maharaj:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, 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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109956.

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