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Experimental paper

Comparative cost-effectiveness of termination of resuscitation rules for patients transported in cardiac arrest

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Abstract

Aim: To compare the cost-effectiveness of termination-of-resuscitation (TOR) rules for patients transported in cardiac arrest.

Methods: The economic analyses evaluated cost-effectiveness of alternative TOR rules for OHCA from a National Health Service (NHS) and personal social services (PSS) perspective over a lifetime horizon. A systematic review was used to identify the different TOR rules included in the analyses. Data from the OHCAO outcomes registry, trial data and published literature were used to compare outcomes for the different rules identified. The economic analyses estimated discounted NHS and PSS costs and quality-adjusted life-years (QALYs) for each TOR rule, based on which incremental cost-effectiveness ratios (ICERs) were calculated.

Results: The systematic review identified 33 TOR rules and the economic analyses assessed the performance of 29 of these TOR rules plus current practice. The most cost-effective strategies were the European Resuscitation Council (ERC) termination of resuscitation rule (ICER of £8,111), the Korean Cardiac Arrest Research Consortium 2 (KOC 2) termination of resuscitation rule (ICER of £17,548), and the universal Basic Life Support (BLS) termination of resuscitation rule (ICER of £19,498,216). The KOC 2 TOR rule was cost-effective at the established cost-effectiveness threshold of £20,000–£30,000 per QALY.

Conclusion: The KOC 2 rule is the most cost-effective at established cost-effectiveness thresholds used to inform health care decision-making in the UK. Further research on economic implications of TOR rules is warranted to support constructive discussion on implementing TOR rules.

Keywords: Out of hospital cardiac arrest, OHCA, Termination of resuscitation, TOR, Cost-effectiveness

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health problem worldwide. It is estimated that there are over 500,000 OHCAs in the United States each year, and only about 10% of those experiencing OHCA survive to hospital discharge.[1,2] The poor survival rates after OHCA are due to a number of factors, including the underlying cause of the arrest, the time it takes for the patient to receive cardiopulmonary resuscitation (CPR) and defibrillation, and the patient's age and health status.[1,2]

Termination of resuscitation (TOR) rules have been developed to help healthcare providers make decisions about when to stop CPR and other life-saving measures in patients experiencing OHCA. TOR rules are based on factors such as the patient's age, underlying medical conditions, and the length of time they have been without a pulse.[2–4] The use of TOR rules can help to improve healthcare resource allocation and comply with ethical principles that require respecting individuals' dignity and prevent pertinent harm. However, it is important to note that TOR rules are not perfect, and they can lead to some patients who would have otherwise survived being denied life-saving treatment.[2]

Decisions about TOR, and TOR rules, also have broader economic implications related to the use of finite healthcare resources. To the best of our knowledge, only one previous economic evaluation has assessed the cost-effectiveness of TOR rules for patients

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with OHCA and this study assessed three rules only, namely the BLS-rule scenario (which involves only basic life support), the ALS-rule scenario (which involves basic and advanced life support), and the No-rule scenario (which does not involve any resuscitation efforts).[5] This study found that the use of TOR rules can lead to healthcare cost savings, but also found a small risk of denying life-saving treatment to patients who might benefit,[5] suggesting they should be used with caution. It is important to weigh potential benefits and risks, and ultimately cost-effectiveness, of TOR rules before making a decision about their implementation. The aim of this study was to evaluate the cost-effectiveness of a comprehensive set of TOR rules for patients transported in cardiac arrest.

Methods

The economic evaluation adopted a UK National Health Service (NHS) and personal social services (PSS) perspective in accordance with National Institute for Health and Care Excellence (NICE) methodological recommendations.[6] Longer term costs and quality-adjusted life-years (QALYs) were discounted at 3.5%.[6] The study is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement for health economic evaluations.[7]

Data sources

Identification of termination of resuscitation rules

A systematic review was conducted to Identify the content and structure of existing TOR rules and summarise performance characteristics of TOR rules. Further details of this systematic review are available elsewhere.[8]

OHCAO registry

The Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry data was the primary source of data used in this study around the consequences of TOR rules. The OHCAO registry collects information from all English Ambulance Services on patients who are treated by ambulance personnel for an out of hospital cardiac arrest. Further details of the OHCAO registry can be found elsewhere.[9] The analyses in this study were restricted to 60,758 cases from the OHCAO registry covering the period 2018–2019. The data was from a period pre-pandemic.

Generating outcome data for termination of resuscitation rules

A TOR rule was determined to have been met if all the criteria within the rule were available on cases within the OHCAO registry. A list of the criteria for each TOR rule and the data available from the OHCAO registry can be found in the Supplementary Material (Table S1 – Characteristics of TOR rules; Table S2 – PROTECTeD Derived Variables). The TOR rules were applied to the OHCAO registry to generate outcomes.

Resource use

Measurement of resource use

For the purpose of the analyses, participants were grouped as follows: died at scene, died at hospital (length of stay [LOS] $\leq$ 1 day), died at hospital (LOS > 1 day), and survived to hospital discharge.

The following variables and their resource implications were obtained from the OHCAO registry:

i. survived to hospital discharge.
ii. transported to hospital but did not survive.
iii. those that died and had length of stay (LOS) < 1 day
iv. those that died and LOS > 1
v. length of stay of those that did not survive to hospital discharge but stayed in hospital for more than one day.

The OHCAO does not collect information on length of stay but contains dates of the OHCA event and discharge/death and that information was used to derive estimates of length of stay. Table 1 presents the information on the above five variables for the multiple strategies assessed.

Valuation of resource use

Comparable unit cost values for the resource variables used in the analyses were not available in national compendia and therefore unit cost data were mainly obtained from the economic evaluation of the PARAMEDIC 2 trial,[10,11] which reflects a cohort of patients refractory to initial resuscitation interventions and therefore with worse outcomes than the general population. Compared with the Norwegian i.v. versus no i.v. trial,[12] patients enrolled into PARAMEDIC 2 were, on average, four years older (69 vs. 65 years) and were less likely to have a bystander-witnessed cardiac arrest (50% vs. 65%) or to have an initial shockable rhythm (19% vs. 33%). Compared with the PACA trial,[13] patients enrolled in the PARAMEDIC 2 trial were also, on average, four years older and were as likely to have a bystander-witnessed arrest, but were less likely to have an initially shockable rhythm (45% in the PACA trial).[13]

PARAMEDIC 2 was a pragmatic, randomised, allocation-concealed, placebo-controlled, parallel-group superiority trial and concurrent economic evaluation. The objectives were to evaluate the effects of adrenaline on survival and neurological outcomes, and to assess the cost-effectiveness of adrenaline use.[11]

The trial data were re-analysed, and patients categorised into groups based on survival status. The costs were considered from the UK National Health Service and Personal Social Services (NHS/PSS) perspective. Costs included Emergency Medical Service (EMS) costs, post-mortem costs, transportation costs, and inpatient costs. All hospital costs up until discharge were based on Admitted Patient Care (Hospital Episode Statistics) data.[14] The costs associated with survival status are presented in Table 2. All costs were presented in British pounds sterling and valued in 2020–21 prices. If necessary, costs were inflated or deflated to 2020–21 prices using the Hospital and Community Health Services (HCHS) Pay and Price Inflation Index.[15] The Paramedic 2 study reported long term costs for two groups of survivors, survivors with good functional state and survivors with poor functional state.[10] These were combined to generate a total long term cost (£13,103 (2021prices)) for all survivors based on the proportions of survivors with good (0.75) and poor function (0.25).

Outcomes

Measurement and valuation of outcomes

The preferred measure of health outcome for many government agencies tasked with setting health priorities under conditions of finite resources remains the quality-adjusted life year (QALY), a

Table 1 – Resource use associated with TOR rules.

ToR Rule	Transport	Died at scene	Survivors to hospital discharge, *n*	Transported but died, *n*	Transported but died LOS < 1, *n*	Transported but died LOS > 1, *n*	LOS Transported but died LOS > 1, mean
Current practice	38,937	21,821	5,634	33,303	18,363	14,940	4.16
ALS	55,957	4,801	5,609	50,348	31,456	18,892	2.6
BLS	58,632	2,126	5,616	53,016	33,242	19,774	5.05
ERC	15,899	44,859	4,477	11,422	6,530	4,892	3.56
GLOB 1	55,027	5,731	4,477	50,550	30,640	19,910	1.85
GLOB 2	55,625	5,133	5,587	50,038	25,894	24,144	2.23
GOTO 1	57,597	3,161	5,596	52,001	33,882	18,119	1.93
GOTO 2	45,523	15,235	5,585	39,938	22,932	17,006	2.81
Haukoos 1	17,311	43,447	3,049	14,262	7,719	6,543	3.89
Haukoos 2	52,964	7,794	5,499	47,465	28,443	19,022	2.24
Haukoos 3	14,990	45,768	3,725	11,265	5,005	6,260	3.58
Helsinki	55,926	4,832	5,622	50,304	28,734	21,570	1.23
House	51,077	9,681	5,590	45,487	38,724	6,763	2.34
KOC 1	53,752	7,006	5,617	48,135	41,030	7,105	1.73
KOC 2	54,407	6,351	5,623	48,784	43,606	5,178	1.56
KOC 3	55,933	4,825	5,629	50,304	44,609	5,695	1.25
KOC 4	49,306	11,452	5,612	43,694	23,906	19,788	2.22
KOC 5	49,306	11,452	5,612	43,694	23,906	19,788	2.22
Marsden	59,242	1,516	5,629	53,613	33,970	19,643	1.14
Neuro	55,626	5,132	5,610	50,016	29,396	20,620	1.56
No ROSC	25,042	35,716	5,425	19,617	12,211	7,406	2.22
PEA	52,407	8,351	5,599	46,808	40,052	6,756	2.25
Petrie	48,839	11,919	5,535	43,304	23,127	20,177	1.91
SHIB 1	52,109	8,649	5,571	46,538	27,874	18,664	2.55
SHIB 2	41,403	19,355	5,337	36,066	19,689	16,377	3.39
SOS Kanto 1	36,292	24,466	4,997	31,295	18,214	13,081	3.63
SOS Kanto 2	36,292	24,466	4,997	31,295	18,214	13,081	3.63
SOS Kanto 3	44,833	15,925	5,488	39,345	20,960	18,385	2.99
Traumatic CPA	59,645	1,113	5,619	54,026	27,013	27,013	2.29
uTOR	52,132	8,626	5,606	46,526	40,333	6,193	2.23

Table 2 – The costs associated with survival status.

Survival status	Emergency Medical services costs, mean (SD)	Hospital costs, mean (SD)	Longer term costs, mean (SD)	Total costs, mean (SD)	Source
Died at scene	£1,793.89 (1,056.61)	NA	NA	£1,793.89 (1,056.61)	Paramedic Trial
Died at hospital, Los ≤ 1	£1,507.69 (562.56)	£682.44 (1,515.93)	NA	£2,190.13 (1,616.95)	Paramedic Trial
Died at hospital, Los > 1	£1,678.90 (675.80)	£15,231.15 (16,424.81)	NA	£16,910.05 (16,438.71)	Paramedic Trial
Survived to hospital discharge	£1,502.15 (509.49)	£34,619.53 (36,613.82)	£13,110.39 (12,686.57)	£49,232.07 (38,752.81)	Paramedic 1 & 2 Trial

preference-based measure of health that combines length of life and health-related quality of life (HRQoL) in a single metric.[6] It was not possible to calculate QALYs directly as there was no information available on the quality of survival in the OHCAO data. Therefore, a stepwise approach was taken to estimate QALYs.

Firstly, the number of survivors to hospital discharge was taken from the results generated from the OHCAO registry. In addition to the number of survivors to hospital discharge, the length of stay of those that did not survive to hospital discharge but stayed in hospital for more than one day was also used. The next step converted the survival into life years using a value of mean survival of 5.4 years taken from a systematic review and meta-analysis of long term survival after out of hospital cardiac arrest.[16] The Paramedic 1 study reported mean utility values for two groups of survivors, those with good function and those with poor function.[17,18] These were combined to generate a mean utility of 0.678 per survivor, based on the proportions of survivors with good (0.75) and poor function (0.25), and multiplied by their expected life expectancies to obtain QALY values. Paramedic 1 was a pragmatic, cluster-randomised trial including adults with non-traumatic, out-of-hospital cardiac arrest, evaluating the effectiveness and cost-effectiveness of the Lund University Cardiopulmonary Assistance System-2 (LUCAS-2) device as a routine ambulance service treatment for out of hospital cardiac arrest.[17]

Cost-effectiveness analysis methods

Cost-effectiveness outcomes were generated for each TOR rule on the basis of the patient pathways shown in Fig. 1. Cost-effectiveness analysis (CEA) is a method used to compare the costs and benefits of different health interventions. The incremental cost-effectiveness ratio (ICER) has been routinely used to summarise the results of economic evaluations of health interventions.[6,19–22] The ICER is a 'pairwise' measure that must be calculated between any two strategies, regardless of the total number of strategies evaluated. It is expressed as a ratio, and an external cost-effectiveness threshold is required to interpret it.

Calculating ICERs in evaluations of more than two strategies requires numerous steps (Fig. 2). There are generally multiple ICERs to calculate, and there may be additional considerations to take into account such as dominance and extended dominance.[22] A treatment option that is both more expensive and results in poorer health outcomes is said to be 'dominated'. The principle of extended dominance is applied in incremental cost-effectiveness analysis to eliminate from consideration strategies whose costs and benefits are improved by a mixed strategy of two other alternatives.

Identifying the most cost-effective strategy using ICERs in evaluations of more than two strategies usually requires specification of a cost-effectiveness threshold. A threshold of £20,000–£30,000 per QALY was used as the benchmark, as this represented the threshold NICE uses in practice.[6] The most cost-effective strategy is that with the highest ICER less than or equal to the threshold. Only strategies that are not dominated or extendedly dominated can be the most cost-effective.[22]

A visual consideration of ICERs was made by plotting the efficiency frontier on the cost-effectiveness plane. The efficiency frontier comprises a number of straight lines connecting each of the strategies that remain after all dominated and extendedly dominated strategies have been ruled out. Each straight line connects two neighbouring non-dominated strategies, with the slope of each line reflecting the ICER of the more expensive strategy compared to the less expensive strategy. All other strategies lie above the efficiency frontier. At any specific value of the threshold, the most cost-effective strategy lies somewhere on the efficiency frontier.

Sensitivity analysis

A probabilistic sensitivity analysis was conducted to explore the impact of parameter uncertainty on cost-effectiveness outcomes. A scenario analysis was also performed to assess the impact of including the additional costs and benefits relating to organ donation. The proportion of eligible donors (0.025), incremental costs (£10,733.20) and incremental QALYs (2.335 QALY) were calculated using PARAMEDIC 2 data.[10] This information was used in conjunction with the number of people that did not survive to hospital discharge but stayed in hospital for more than one day.

Analyses were conducted using Microsoft Excel and R v4.2.3.

Results

Identification of TOR rules and generating outcome data for the TOR rules

The systematic review identified 33 TOR rules (Supplementary Table 1). There were some ToR rules that could not be determined because the information required to generate them was not available from the OHCAO registry. It was not possible to generate the results of applying the Harford, Haukoos 4, Jabre, and NAEMSP TOR rules, and they were therefore excluded from the analyses. The generated results of applying the TOR rules are presented in Supplementary Table 3. It contains information on the TOR rule, recommendation (transport or terminate), TOR Rule accuracy (ROSC at hospital), and TOR Rule accuracy (Survival to discharge).

Resource use

The analyses were based on 60,758 cases from the OHCAO registry (65.1% men; median age, 71 years). The overall number of survivors until hospital discharge for the OHCAO population was 5,634 (9.3%) and the mean length of stay for those who died after surviving for more than 1 day was 4.16 days. Table 1 lists the resource use values for the multiple strategies. The number of survivors to hospital discharge ranged from 3,049 for Haukoos 1 to 5,634 for current practice. The number of people transported to hospital ranged from

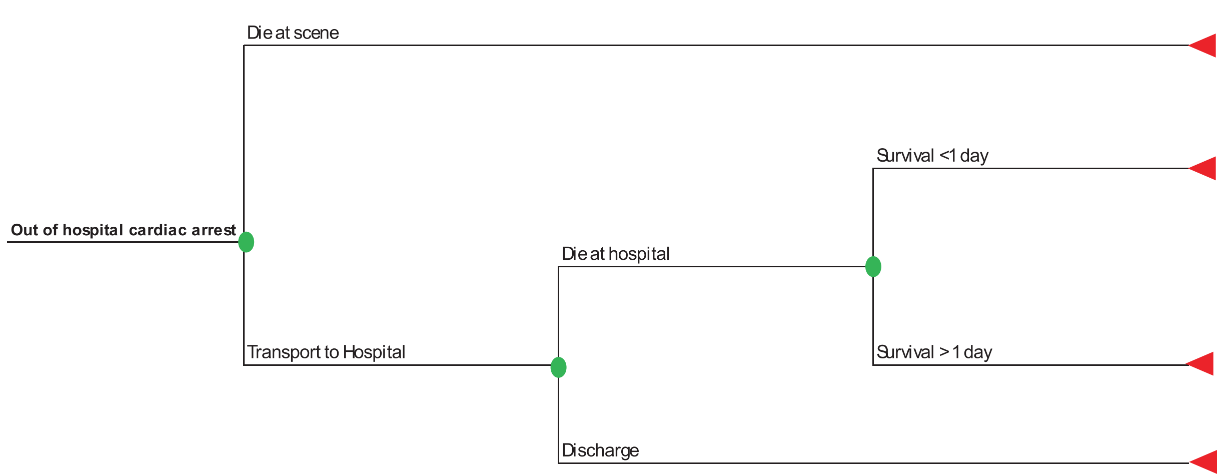

Fig. 1 – Analytical model.

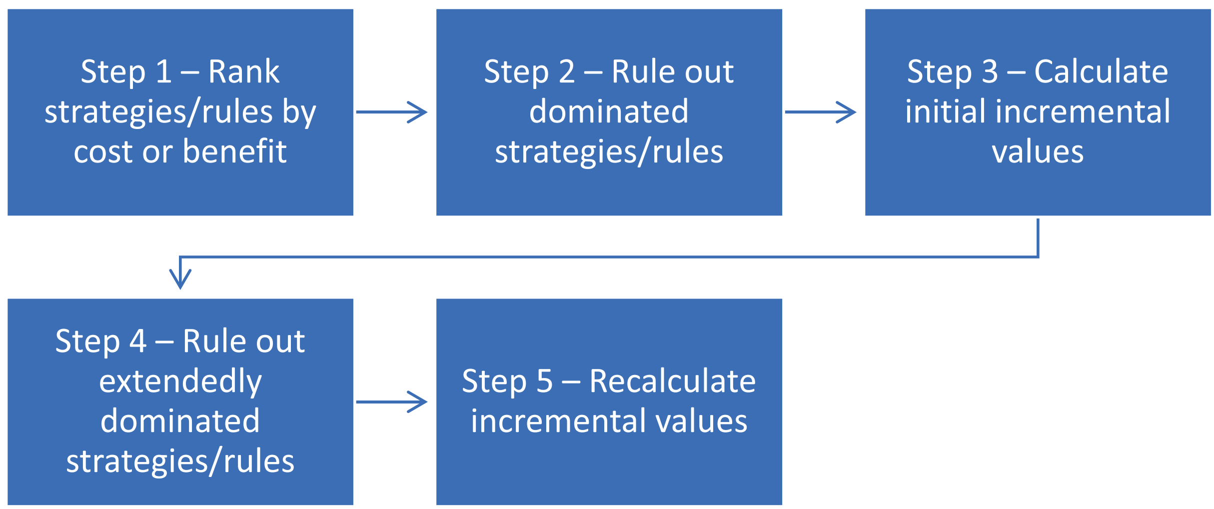

Fig. 2 – Process of calculating Incremental Cost Effectiveness Ratios (ICERs).

11,265 (Haukoos 3) to 54,026 (Traumatic CPA). Of those transported to hospital, the number of people dying within one day ranged from 5,005 (Haukoos 3) to 44,609 (KOC 3), whilst the number of people not surviving to discharge but having a stay in hospital of at least one day ranged from 4892 (ERC) to 27,013 (Traumatic CPA). The mean length of stay of people admitted for >1 day but not surviving to discharge ranged from 1.14 days for Marsden to 5.05 days for BLS.

Table 3 – Incremental Cost-Effectiveness Ratios (ICERs)-Step 1 Rank strategies by cost and Step 2 Rule out dominated strategies.

ToR Rule	Total cost	Total QALY
Haukoos 1	£355,570,988	11,216
Haukoos 3	£382,280,107	13,687
ERC	£397,881,840	16,433
KOC 2	£471,244,111	20,613
KOC 3	£479,741,982	20,634
No ROSC	**£483,092,175**	**19,904**
uTOR	**£484,480,384**	**20,562**
House	**£491,700,686**	**20,507**
PEA	**£492,559,027**	**20,539**
KOC 1	**£499,068,520**	**20,599**
SOS Kanto 1	**£550,959,512**	**18,394**
SOS Kanto 2	**£550,959,512**	**18,394**
Current practice	£609,337,377	20,754
SHIB 2	**£617,484,680**	**19,654**
GLOB 1	**£634,450,650**	**16,469**
GOTO 2	**£640,044,619**	**20,548**
SOS Kanto 3	**£655,514,047**	**20,206**
GOTO 1	**£661,729,799**	**20,565**
SHIB 1	**£666,407,196**	**20,496**
Haukoos 2	**£668,629,875**	**20,223**
ALS	**£673,075,870**	**20,638**
KOC 4	**£683,766,304**	**20,640**
KOC 5	**£683,766,304**	**20,640**
Petrie	**£685,684,545**	**20,347**
Marsden	**£686,374,506**	**20,662**
BLS	£687,448,402	20,758
Neuro	**£698,421,195**	**20,611**
Helsinki	**£713,091,477**	**20,644**
GLOB 2	**£749,214,749**	**20,566**
Traumatic CPA	**£794,544,787**	**20,699**

All dominated strategies are bolded.

Cost-effectiveness analysis results

Table 3 displays the results for ranking the TOR rules by cost and ruling out dominated ones. Haukoos 1 had the lowest total cost (£355,570,988) and is the top rule in the table and Traumatic CPA had the highest total cost (£794,544,787) and is the bottom rule in the table. All dominated strategies are shaded in Table 3. For example, the No ROSC rule is dominated by the KOC 3 rule. No ROSC had higher total costs £483,092175 compared with £479,741,982 for KOC 3 but generated fewer total QALYs (19,904 compared with 20,634).

Table 4 displays the results of calculating initial estimates of incremental values and ruling out extendedly dominated strategies. Haukoos 3 had a higher ICER of £10,810 per QALY than ERC (£5,683 per QALY). It follows that Haukoos 3 is extendedly dominated and must be ruled out.

Table 5 presents the summary final incremental values after identifying and ruling out dominated and extendedly dominated strategies for the analyses based on survivors. The cost-effective rules were Haukoos 1, ERC, KOC 2, KOC 3, current practice and BLS. Haukoos 1 is the least expensive, so no ICER is reported; ERC has an ICER of £8,111 per QALY compared to Haukoos1; KOC 2 has an ICER of £17,548 per survivor compared to ERC; KOC 3 has an ICER of £421,242 per survivor compared to KOC 2; current practice has an ICER of £1,073,416 per QALY compared with KOC 3; and BLS has an ICER of £19,498,216 per QALY compared with current practice.

In the UK, the cost-effectiveness threshold is £20,000-£30,000 per QALY as this represents the threshold NICE uses in practice.[6] KOC 2 is cost-effective, as it has the highest ICER (£17,548 per QALY) less than or equal to the threshold.

Fig. 3 displays an efficiency frontier on the cost-effectiveness plane for the analysis based on survivors. Each straight line connects two strategies, with its slope representing the incremental cost-effectiveness ratio of the more expensive compared to the less

Table 4 – Incremental Cost-Effectiveness Ratios (ICERs) – step 3 Calculate initial incremental values and step 4 Rule out extendedly dominated strategies.

ToR Rule	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Haukoos 1	£355,570,988	11,216	N/A	N/A	N/A
Haukoos 3	**£382,280,107**	**13,687**	**£26,709,120**	**2471**	**£10,810**
ERC	£397,881,840	16,433	£15,601,733	2746	£5,683
KOC 2	£471,244,111	20,613	£73,362,270	4181	£17,548
KOC 3	£479,741,982	20,634	£8,497,872	20	£421,242
Current practice	£609,337,377	20,754	£129,595,395	121	£1,073,416
BLS	£687,448,402	20,758	£78,111,025	4	£19,498,216

All extendedly dominated strategies are bolded.

Table 5 – Incremental Cost-Effectiveness Ratios (ICERs), Final incremental values.

ToR Rule	Total cost	Total QALYs	Incremental cost	Incremental QALY	ICER	Comparison
Haukoos 1	£355,570,988	11,216	N/A	N/A	N/A	N/A
ERC	£397,881,840	16,433	£42,310,853	5,216	£8,111	ERC vs haukoos1
KOC 2	£471,244,111	20,613	£73,362,270	4,181	£17,548	KOC2 vs ERC
KOC 3	£479,741,982	20,634	£8,497,872	20	£421,242	KOC3 vs KOC2
Current practice	£609,337,377	20,754	£129,595,395	121	£1,073,416	Current practice vs KOC3
BLS	£687,448,402	20,758	£78,111,025	4	£19,498,216	BLS vs Current practice

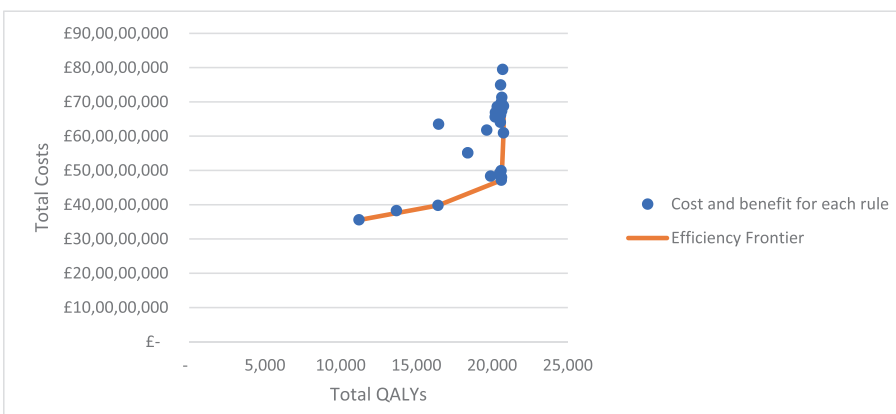

Fig. 3 – Efficiency frontier on the cost-effectiveness plane.

expensive of these strategies. Strategies plotted above the efficiency frontier are dominated or extendedly dominated.

Sensitivity analysis

Supplementary Table 4 lists the parameters used in the probabilistic sensitivity analysis. The results of the probabilistic sensitivity analysis mirrored the baseline results except for the fact that the BLS rule was no longer included in the list of potentially cost-effective rules; rather, it was replaced by the Traumatic CPA (Supplementary Table 5). Supplementary Fig. 1 displays the probability of cost-effectiveness of these rules at different cost-effectiveness threshold values (based on 1000 simulations). When the additional costs and benefits relating to organ donation were included, the cost-effective rules were Haukoos 1, ERC (£8,225 per QALY), KOC 2 (£13,149 per QALY), KOC 3 (£82,661 per QALY), and BLS (£742,118 per QALY). KOC 2 remained the cost-effective TOR, as it had the highest ICER less than or equal to the cost-effectiveness threshold of £20,000-£30,000 per QALY. The difference is that this time current practice is no longer among the cost-effective rules.

Discussion

This study evaluated the comparative cost-effectiveness of multiple TOR rules in patients transported in cardiac arrest. KOC 2 was found to be the most cost-effective, as it had the highest ICER (£17,548 per QALY) which is less than or equal to the NICE cost-effectiveness threshold of £20,000-£30,000 per QALY. KOC 3 had an ICER of

£421,242 per QALY compared to KOC 2; current practice had an ICER of £1,073,416 per QALY compared with KOC 3; and BLS had an ICER of £19,498,216 compared with current practice.

A recent study found that the BLS-rule scenario (which involves only basic life support) was cost-effective in 100% of simulations at the cost-effectiveness threshold in Japan (5 million JPY = 45,455 USD).[5] The ALS-rule scenario (which involves basic and advanced life support) was likely to be cost-effective at a cost-effectiveness threshold between 80,000 and 204,000 USD, whereas the No-rule scenario (which does not involve any resuscitation efforts) was likely to be cost-effective, but at a threshold higher than 204,000 USD.[5] The results of this study suggest that BLS-rule scenarios are the most cost-effective TOR rules, followed by ALS-rule scenarios, whereas the No-rule scenario was not cost-effective at any cost-effectiveness threshold.

There are controversial ethical issues surrounding the TOR decision. Mentzelopoulos et al. (2021) have specifically pointed out that balancing costs versus perceptions of which life is worth living can be ethically problematic,[23] and cost-effectiveness considerations are merely one of several components of debate over TOR rules and their implementation. Nevertheless, evidence of cost-effectiveness profiles of scenarios with and without TOR rules should help evaluate potential trade-offs against other desirable social investments. Further research on the economic consequences of TOR rules is warranted to support constructive discussion on whether and how TOR rules should be implemented. Moreover, this was the first study on the cost-effectiveness of TOR rules in a UK setting, with a previous study set in Japan[5]; thus, the results need to be validated in different settings.

The main strength of this study is that it examined the cost-effectiveness of 29 TOR rules along with current practice. This study had several limitations. We have no insight into the number of missed survivors under the current ROLE guideline. To the best of our knowledge there are no published data that report compliance with the existing ROLE guideline. Although it would be ideal to model performance and cost-effectiveness of alternative TOR rules in the entire cardiac arrest population, we cannot be certain of the true outcome in all patients. Second, all relevant costs and health-related quality of life outcomes were not measured in the OHCAO registry; thus, published data were used to proxy several effects, some of which were drawn from a cohort of patients with worse outcomes than the general population (PARAMEDIC2).[10,11] Third, costs and treatment effectiveness for patients with OHCA depend on demographic characteristics and emergency care systems. These differences should be considered when applying this study's results to other organisational or clinical contexts.

For future research, we recommend the inclusion of variables in the OHCA registries to facilitate the direct calculation of resource use, costs, health-related quality of life outcomes and health utilities. Further research on economic aspects of TOR rules is warranted to support constructive discussion on implementing TOR rules.

In conclusion, this study evaluated the comparative cost-effectiveness of multiple TOR rules. KOC 2 was found to be the most cost-effective. Further research is needed to confirm these findings. Additionally, the cost-effectiveness of TOR rules may vary depending on the specific organisational and clinical contexts in which they are implemented.

CRediT authorship contribution statement

Kamran Ahmad Khan: Writing – original draft, Methodology, Formal analysis. **Stavros Petrou:** Writing – review & editing, Supervision, Conceptualization. **Michael Smyth:** Writing – review & editing, Funding acquisition, Conceptualization. **Gavin D. Perkins:** Writing – review & editing, Funding acquisition, Conceptualization. **Anne-Marie Slowther:** Writing – review & editing, Funding acquisition, Conceptualization. **Terry Brown:** Writing – review & editing, Data curation. **Jason J. Madan:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: "Gavin Perkins reports financial support was provided by National Institute for Health and Care Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper".

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Appendix A. Supplementary material

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