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Review

Diagnostic performance of the basic and advanced life support termination of resuscitation rules: A systematic review and diagnostic meta-analysis

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Abstract

Aim: To minimize termination of resuscitation (TOR) in potential survivors, the desired positive predictive value (PPV) for mortality and specificity of universal TOR-rules are ≥99%. In lack of a quantitative summary of the collective evidence, we performed a diagnostic meta-analysis to provide an overall estimate of the performance of the basic and advanced life support (BLS and ALS) termination rules.

Data sources: We searched PubMed/EMBASE/Web-of-Science/CINAHL and Cochrane (until September 2019) for studies on either or both TOR-rules in non-traumatic, adult cardiac arrest. PRISMA-DTA-guidelines were followed.

Results: There were 19 studies: 16 reported on the BLS-rule (205.073 patients, TOR-advice in 57%), 11 on the ALS-rule (161.850 patients, TOR-advice in 24%). Pooled specificities were 0.95 (0.89−0.98) and 0.98 (0.95−1.00) respectively, with a PPV of 0.99 (0.99−1.00) and 1.00 (0.99−1.00). Specificities were significantly lower in non-Western than Western regions: 0.84 (0.73−0.92) vs. 0.99 (0.97−0.99), $p < 0.001$ for the BLS rule. For the ALS-rule, specificities were 0.94 (0.87−0.97) vs. 1.00 (0.99−1.00), $p < 0.001$. For non-Western regions, 16 (BLS) or 6 (ALS) out of 100 potential survivors met the TOR-criteria. Meta-regression demonstrated decreasing performance in settings with lower rates of in-field shocks.

Conclusions: Despite an overall high PPV, this meta-analysis highlights a clinically important variation in diagnostic performance of the BLS and ALS TOR-rules. Lower specificity and PPV were seen in non-Western regions, and populations with lower rates of in-field defibrillation. Improved insight in the varying diagnostic performance is highly needed, and local validation of the rules is warranted to prevent in-field termination of potential survivors.

Keywords: Cardiopulmonary resuscitation, Termination of resuscitation, Meta-analysis, Out-of-hospital cardiac arrest

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Introduction

Over 300.000 out-of-hospital cardiac arrests (OHCA) occur annually in Europe alone, and despite improvements in treatment most patients do not survive.[1] Appreciating the risks for emergency medical services (EMS) personnel and the public, and the impact on healthcare resources, emergency transport for refractory OHCA should preferably be justified by the expected benefit for the patient.[2,3]

To reduce futile hospital transportations, current cardiopulmonary resuscitation (CPR)-guidelines reference two termination-of-resuscitation (TOR) algorithms to discriminate between non-survivors and survivors.[4,5] The basic and advanced life support (BLS and ALS) TOR-rules consist of a set of key arrest characteristics (in-field defibrillation, witnessed arrest, bystander CPR or return of spontaneous circulation [ROSC], Fig. 1).[6,7] In patients meeting ≥1 criteria, the TOR-rules are considered negative, and transport is recommended. If none of the criteria are present, the TOR-rule is considered positive and termination can be considered.

The criteria on which the recommendation to transport is based are all predictors of survival. Thus, in regions where many patients have favorable arrest characteristics, transport rates will be higher than in regions with less favorable characteristics.[8] However, the factors used in the TOR-rules do not account for all variability in outcome: other factors such as age also impact survival. Therefore, their diagnostic performance may vary according to the region of study conduction.[9,10]

In many previous studies a positive TOR-rule had a predictive value for death of >99%, indicating a <1% chance of survival when a patient fulfils the TOR-criteria.[11–14] This complies with an often referenced medical futility rate of 1%.[15,16] However, other studies found that >10% of survivors would have qualified for termination based on the TOR-rule.[17–20] Further understanding of these discrepancies is of great importance in an era where guidelines call for uniform and reliable TOR-rules.[4,5]

In this context, we performed a diagnostic meta-analysis to provide a quantitative synthesis of the overall performance of the BLS and ALS TOR-rules to identify non-survivors of OHCA. In addition, we studied factors that may explain the heterogeneity among studies through meta-regression, where we focused on the impact of study region and the individual key arrest characteristics that comprise the respective TOR-rules.

Methods

We followed the recommendations of the Cochrane Collaboration and the preferred reporting items for systematic reviews and meta-analyses of diagnostic test accuracy studies (PRISMA-DTA) statement.[21,22]

BLS and ALS TOR-rules

The BLS TOR-rule recommends transportation if a patient meets ≥1 of the following criteria: in-field ROSC, shock delivered or EMS-witnessed arrest. The ALS TOR-rule recommends transportation in case of in-field ROSC, shock delivered, witnessed arrest and/or bystander CPR (Fig. 1).[6,7]

Search strategy

A systematic search was performed using Medline via PubMed, EMBASE, Web-of-Science, CINAHL and The Cochrane Library. The

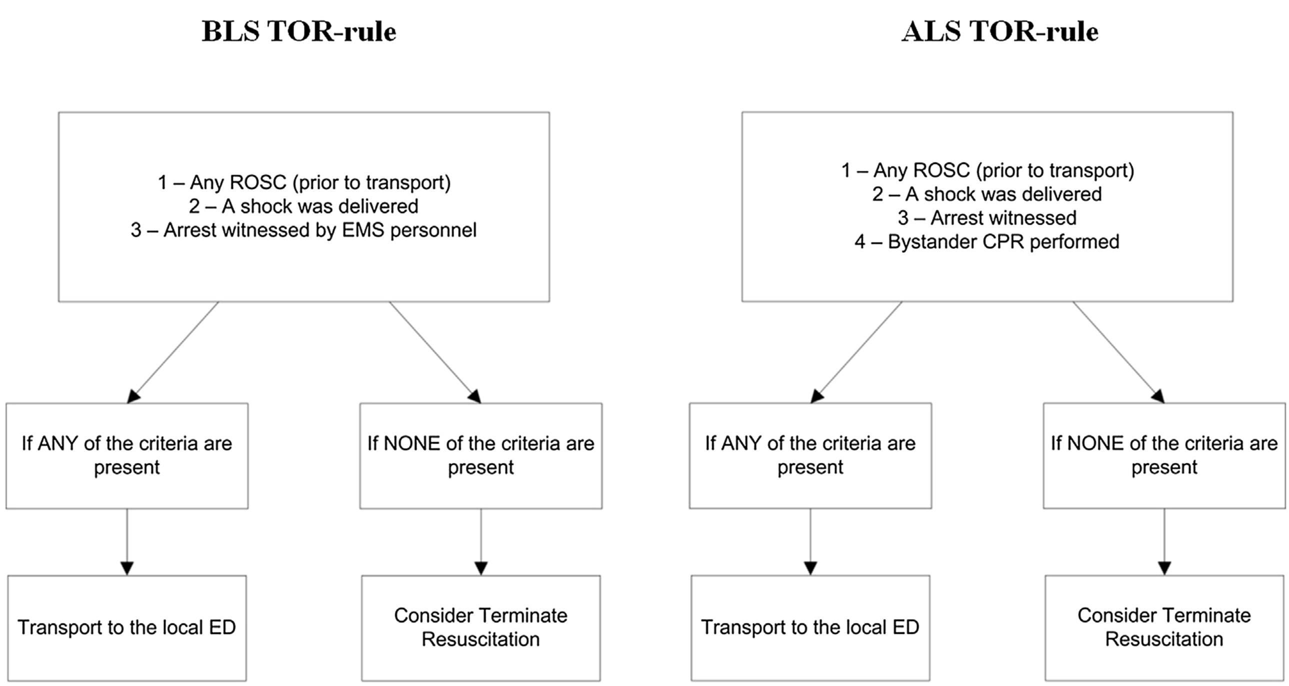

Fig. 1 – BLS and ALS TOR-rules.
Explanation of the studied TOR-rules; BLS left and ALS right. All criteria of the respective TOR-rules should be considered prior to transportation or termination of the resuscitation effort. If any of the criteria is present, the rule recommends transportation to the hospital. If none of the criteria is present, the rule recommends consideration of termination of the resuscitation effort.
BLS = basic life support, ALS = advanced life support, TOR = termination of resuscitation, ROSC = return of spontaneous circulation, EMS = emergency medical service, ED = emergency department, CPR = cardiopulmonary resuscitation.

search query combined synonyms for OHCA with synonyms for TOR. Two researchers (JN, GK) performed the searches independently. All databases were searched from inception through September 11th, 2019. References of relevant articles were searched for additional studies. The search strategy can be found in Supplemental text 1.

Study selection

We included all studies that applied the BLS and/or ALS TOR-rule to an unselected cohort of non-traumatic adult OHCA patients. We excluded studies that did not report or did not allow calculation of true positive (TP), false positive (FP), true negative (TN) or false negative (FN) rates for death and/or unfavourable neurologic outcome, as well as conference abstracts. Exact duplicates were removed. Two reviewers (JN, GK) independently assessed the eligibility of the identified articles. Discrepancies were discussed with a third reviewer (JLB) to reach consensus.

Quality assessment

Two reviewers (JN, GK) independently assessed the risk of bias and study quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, as recommended by the PRISMA-DTA group.[22,23] Four domains were scored: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing, see Supplemental Table 1. For our specific research question, in domain 4 we assessed whether or not all patients were transported to the hospital. If not, the study is prone to verification bias, as patients that are not transported to the hospital will by definition not survive to discharge.

Data extraction and synthesis

Two investigators (JN, GK) independently extracted study data using a pre-specified data collection form (Supplemental text 2). Discrepancies were discussed with a third reviewer (JLB) to reach consensus.

TP, FP, FN and TN values were summarized in 2 × 2 contingency tables to (re)calculate diagnostic test characteristics (i.e. sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and transport rates). We followed the authors' decision in which rule they would use to report the test characteristics of their population.

If the rule recommended TOR, the test was regarded positive and if the rule recommended transportation to the hospital, the test was regarded negative.[24] Consequently, death was considered "condition present". This results in the following 2 × 2 table:

TOR decision rule	Death (=condition present)	Survival (=condition absent)
Terminate (=test positive)	TP	FP
Transport (=test negative)	FN	TN

Test characteristics of interest

In theory, the ideal TOR-rule would never recommend TOR in surviving patients. Thus, specificity and PPV were regarded the test characteristics of interest. Specificity is the probability that the rule recommends transport in case the patient survives (=TN/FP + TN). The PPV is the probability of death in case the rule proposes TOR (=TP/TP + FP).

Transport rates

The observed transport rate was defined as the actual transport rate as reported in the study (disregarding the TOR-rule). The projected transport rate was defined as the transport rate in case the TOR-rule would have been followed (=FN + TN/TP + FP + FN + TN).

Outcomes measures

Primary outcomes were the PPV and specificity for death, defined as death in-hospital or at 30 days.[25] Secondary outcomes were the PPV and specificity for unfavourable neurologic outcome, defined as a cerebral performance category $\geq$3.[26]

Statistical analysis

We used the data from the 2 × 2 tables to calculate sensitivity, specificity, PPV and NPV for each study. We presented individual study results by plotting sensitivity, specificity, PPV and NPV with 95% confidence intervals in forest plots. We used a bivariate random-effects approach for the meta-analysis of the pairs of sensitivity and specificity and pairs of PPV and NPV.[27,28] We investigated heterogeneity visually by examining the forest plots and statistically by including covariates in the bivariate models and by conducting pre-specified subgroup and sensitivity analyses. The following sources of heterogeneity were assessed 1) the effect of geographic region of study conduction (i.e. non-Western vs. Western studies)[29,30]; 2) the effect of the observed transport rate (i.e. 100% vs. <100%), 3) QUADAS-2 risk of bias domains and 4) the individual components of the analysed TOR-rule (Fig. 1). We incorporated these factors as covariates in the bivariate models to examine the effect of potential sources of bias and variation across subgroups of studies. Deeks' tests and funnel plots were used to assess publication bias.[31] For analyses, we used R version 3.5.0 (R-Foundation for Statistical Computing, Vienna, Austria) with the package "mada".[32]

Results

We identified 1563 unique records after database searching. A total of 19 individual studies were included (Supplemental Fig. S1).[6–8,11–13,17–20,33–40] In total, 16 studies (205.073 patients) reported on the BLS TOR-rule and 11 studies (161.850 patients) reported on the ALS TOR-rule. Studies and patient characteristics are outlined in Table 1 and Supplemental Table S2. All studies were observational, ten of which were retrospective studies. As can be seen in Table 1 baseline characteristics varied widely among the studies (e.g. the proportion shockable initial rhythm ranged from 10% to 47%). Outcomes also varied widely, with survival ranging from 1.4% to 15.7%. There were two studies that reported test characteristics for multiple sub-populations; in these, we extracted data for which the level of care corresponds with the rule. Thus, data on BLS-treated patients for the BLS-rule and ALS-treated patients for the ALS-rule.[17,18] Twelve of the included studies had a maximum QUADAS-2 score and thus a low risk of bias (Supplemental Table S1).[6,7,12,13,17–20,36,37,39,40] Seven

Table 1 – Study characteristics.

Author (year)	Design†	Region	BLS/ ALS-rule	Outcome	*n*=	Age (yrs)	Male (%)	ROSC (%)	Shock given (%)	Initial VT or VF (%)	EMS witnessed (%)	Bystander witnessed (%)	Witnessed by someone (%)	Bystander CPR (%)	EMS response time (min)	Survival (%)
Cheong (2016)	1	Singapore	Both	Std or 30-days	2193	66	69	5	29	24	7	50	57	23		3.5
Chiang (2015)	1	Taiwan	BLS	Std (both rules)	1727	72	64	4	10				30	12	5.7	5.7
			ALS		240	71	60	29	13				35	27	6.5	9.2
Diskin (2014)	1	United States	ALS	1-month survival	322	63	59	39	33		16	48	64	34		12.1
Fukuda (2014)	1	Japan	BLS	Std (both rules)	148	68	69	4		10			25	24		4.1
			ALS		41	73	61	7		15			32	29		9.8
Grunau (2017)	3	Canada	BLS	Std	6994	67	68	49	27	25	11	40	51	47	6.5	14.9
Jordan (2017)	1	United States	BLS	Std	169	64	69	18	40		9	39	47	38	6.8	13.6
Kajino (2013)	1	Japan	BLS	1-month survival	151152	76	57	7		11	11	30	41	36	7.1	6.3
			ALS	(both rules)	137986	74	60	5		12	5	36	41	42	7.3	4.0
Kashiura (2016)	3	Japan	Both	1-month survival	6138	73	62	9	20	12	8	47	55	36	8.0	BLS: 9.1 ALS: 4.6
Kim (2015)	1	Korea	BLS	Std	4835	67	66	5	28	19	3		50	57	6.5	9.3
Lee (2019)	3	Korea	Both	Std	4608	70	65	13	26	19			59	48	7	11.7
Morrison (2006)	3	Canada	BLS	Std or 6-months*	1240	69	69	6	30		10	46	57	27	8.0	3.3
Morrison (2007)	2	Canada	Both	Std	4673	69	66	18			10					5.1
Morrison (2009)	2	United States/Canada	Both	Std	2415	69	63	19	30		9	38	47	28		5.4
Ong (2006)	2	Canada	BLS	Std	13684	69	67	11	43	37	8	45	52	17	6.7	4.7
Ong (2007)	2	Singapore	BLS	Std or 30-days	2269	61	68	2	22	19	10	55	65	21	10.0	1.4
Ruygrok (2009)	1	United States	Both	Std with CPC ≤ 2	715	65	69	31	42	30	8	41	49	25	6	5.9
Sasson (2008)	2	United States	Both	Std	5505	64	60	31		24	12	37	50	21		7.1
Verbeek (2002)	1	Canada	BLS	Std	662	72	61	5	25		13	40	52	16	6.7	2.0
Verhaert (2016)	1	The Netherlands	ALS	Std	598	66	69	47	60	47	10	63	73	54	8	15.7

Study and Patients characteristics. In case of application of the TOR-rule to multiple sub-populations in one study, we extracted the data from the sub-set of patients most comparable to the original target population of the rule (i.e. for the BLS-rule we preferably used patients resuscitated by BLS-providers, and for the ALS-rule we preferably used patients resuscitated by ALS-providers). † = Design category: 1 = Retrospective study, 2 = Retrospective analysis of prospectively collected data, 3 = Prospective study. * = Alive in-hospital at 6 months. TOR = termination of resuscitation, Std = survival to discharge, CPC = cerebral performance category, EMS = emergency medical service, ROSC = return of spontaneous circulation, VT = ventricular tachycardia, VF = ventricular fibrillation.

studies were at risk of bias in the domain “Flow and timing”, because not all patients were transported to the hospital (transport rate <100%).[8,11,14,33–35,38] No evidence of publication bias was found using Deeks' funnel plots and Deeks' test (Supplemental Fig. S2).

Diagnostic accuracy for death

BLS TOR-rule

Sixteen studies reported on a total of 205.073 patients.[6,7,11–14,17–20,35–40] Test characteristics and forest plots are shown in Fig. 2. The pooled specificity and sensitivity for all studies were 0.95 (95% CI 0.89–0.98) and 0.66 (0.61–0.70), respectively. The pooled PPV and NPV were 0.99 (0.99–1.00) and 0.14 (0.10–0.19), respectively. The mean projected transport rate was 43% and ranged from 25% to 79%, as shown in Supplemental Table 3.

ALS TOR-rule

Eleven studies reported on 161.850 patients.[7,8,11,17,18,34–37,39,40] Test characteristics and forest plots are shown in Fig. 2. The pooled specificity and sensitivity for all studies were 0.98 (0.95–1.00) and 0.26 (0.21–0.32), respectively. The pooled PPV and NPV were 1.00 (0.99–1.00) and 0.09 (0.07–0.12), respectively. The mean projected transport rate was 76% and ranged from 66% to 94% (Supplemental Table S3).

Diagnostic accuracy for unfavourable neurologic outcome

For these analyses we studied the subset of studies that reported on neurologic outcome.

BLS TOR-rule

Nine studies reported on 173.224 patients.[11,12,17,19,33,36,37,39,40] Test characteristics and forest plots are shown in Fig. 3. The pooled specificity and sensitivity for all studies were 0.96 (0.93–0.98) and 0.65 (0.56–0.74), respectively. The pooled PPV and NPV were 1.00 (1.00–1.00) and 0.11 (0.08–0.16), respectively.

ALS TOR-rule

Eight studies reported on 154.608 patients (Fig. 3).[11,17,18,33,36,37,39,40] The pooled specificity and sensitivity for all studies were 0.98 (0.96–0.99) and 0.27 (0.23–0.30), respectively. The pooled PPV and NPV were 1.00 (0.99–1.00) and 0.05 (0.03–0.08), respectively.

Subgroup and meta-regression analyses

BLS TOR-rule

For studies conducted in Western regions (n = 8) vs. studies in non-Western regions (n = 8), the pooled specificity was 0.99 (0.97–0.99) vs. 0.84 (0.73–0.92), $p < 0.001$ and PPV was 1.00 (1.00–1.00) vs. 0.99 (0.97–0.99), $p = 0.008$ (Table 2a). In studies with a transport rate of 100% (n = 12) vs. studies with a transport rate <100% (n = 4), the specificity was 0.93 (0.84–0.97) vs. 0.98 (0.93–1.00) ($p = 0.09$) and PPV was 0.99 (0.99–1.00) vs. 1.00 (0.98–1.00) ($p = 0.75$). A transport rate of <100% was the only source of bias, which has been addressed in the aforementioned analyses. Therefore, no further analyses were performed according to the QUADAS-2 score.

Meta-regression indicated that the specificity increased ($p = 0.03$) with an increasing proportion of patients that received a shock during the resuscitation. ROSC and EMS witnessed status were not significantly associated with the specificity or PPV (Supplemental Table 4a).

ALS TOR-rule

For studies conducted in Western regions (n = 5) vs. studies conducted in non-Western regions (n = 6), the specificity was 1.00 (0.99–1.00) vs. 0.94 (0.87–0.97), $p < 0.001$ and the PPV 1.00 (1.00–1.00) vs. 0.99 (0.98–0.99), $p < 0.001$ (Table 2b). In studies with a transport rate of 100% (n = 7) vs. studies with a transport rate <100% (n = 4), the pooled specificity was 0.96 (95% CI 0.90–0.98) vs. 1.00 (0.99–1.00), $p = 0.005$ and the pooled PPV 0.99 (0.98–1.00) vs. 1.00 (0.99–1.00), $p = 0.02$. A transport rate of <100% was the only source of bias, which has been addressed in

Study	Region	Transport rate	TP	FP	TN	FN	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Verbeek 2002	Western	100	425	0	13	224	0.65 [0.62,0.69]	1.00 [0.77,1.00]	1.00 [0.99,1.00]	0.05 [0.03,0.09]
Morrison 2006	Western	100	772	4	37	427	0.64 [0.62,0.67]	0.90 [0.77,0.96]	0.99 [0.99,1.00]	0.08 [0.06,0.11]
Ong 2006	Western	100	6905	3	633	6143	0.53 [0.52,0.54]	1.00 [0.99,1.00]	1.00 [1.00,1.00]	0.09 [0.09,0.10]
Morrison 2007	Western	100	2263	0	239	2171	0.51 [0.50,0.53]	1.00 [0.98,1.00]	1.00 [1.00,1.00]	0.10 [0.09,0.11]
Ong 2007	Non-Western	100	1553	6	26	684	0.69 [0.67,0.71]	0.81 [0.65,0.91]	1.00 [0.99,1.00]	0.04 [0.03,0.05]
Sasson 2008	Western	82.8	2587	5	387	2526	0.51 [0.49,0.52]	0.99 [0.97,0.99]	1.00 [1.00,1.00]	0.13 [0.12,0.15]
Morrison 2009	Western	55.4	1302	0	130	964	0.57 [0.55,0.59]	1.00 [0.97,1.00]	1.00 [1.00,1.00]	0.12 [0.10,0.14]
Kajino 2013	Non-Western	100	111980	1160	8356	29656	0.79 [0.79,0.79]	0.88 [0.87,0.88]	0.99 [0.99,0.99]	0.22 [0.22,0.22]
Fukuda 2014	Non-Western	100	100	1	5	42	0.70 [0.62,0.77]	0.83 [0.44,0.97]	0.99 [0.95,1.00]	0.11 [0.05,0.23]
Chiang 2015	Non-Western	100	1051	29	70	577	0.65 [0.62,0.67]	0.71 [0.61,0.79]	0.97 [0.96,0.98]	0.11 [0.09,0.13]
Kim 2015	Non-Western	100	3224	137	314	1160	0.74 [0.72,0.75]	0.70 [0.65,0.74]	0.96 [0.95,0.97]	0.21 [0.19,0.23]
Cheong 2016	Non-Western	100	1406	5	71	711	0.66 [0.64,0.68]	0.93 [0.86,0.97]	1.00 [0.99,1.00]	0.09 [0.07,0.11]
Kashiura 2016	Non-Western	100	2044	16	241	517	0.80 [0.78,0.81]	0.94 [0.90,0.96]	0.99 [0.99,1.00]	0.32 [0.29,0.35]
Grunau 2017	Western	51.3	4275	92	953	1674	0.72 [0.71,0.73]	0.91 [0.89,0.93]	0.98 [0.97,0.98]	0.36 [0.34,0.38]
Jordan 2017	Western	91	78	0	23	68	0.53 [0.45,0.61]	1.00 [0.86,1.00]	1.00 [0.95,1.00]	0.25 [0.17,0.35]
Lee 2019	Non-Western	100	2921	118	420	1149	0.72 [0.70,0.73]	0.78 [0.74,0.81]	0.96 [0.95,0.97]	0.27 [0.25,0.29]
Summary							**0.66 [0.61,0.70]**	**0.95 [0.89,0.98]**	**0.99 [0.99,1.00]**	**0.14 [0.10,0.19]**

Study	Region	Transport rate	TP	FP	TN	FN	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Morrison 2007	Western	100	1425	0	239	3009	0.32 [0.31,0.34]	1.00 [0.98,1.00]	1.00 [1.00,1.00]	0.07 [0.07,0.08]
Sasson 2008	Western	82.8	1192	0	392	3921	0.23 [0.22,0.24]	1.00 [0.99,1.00]	1.00 [1.00,1.00]	0.09 [0.08,0.10]
Morrison 2009	Western	55.4	743	0	130	1523	0.33 [0.31,0.35]	1.00 [0.97,1.00]	1.00 [0.99,1.00]	0.08 [0.07,0.09]
Kajino 2013	Non-Western	100	40612	418	5037	91919	0.31 [0.30,0.31]	0.92 [0.92,0.93]	0.99 [0.99,0.99]	0.05 [0.05,0.05]
Diskin 2014	Western	74	75	0	39	208	0.27 [0.22,0.32]	1.00 [0.91,1.00]	1.00 [0.95,1.00]	0.16 [0.12,0.21]
Fukuda 2014	Non-Western	100	7	0	4	30	0.19 [0.09,0.34]	1.00 [0.51,1.00]	1.00 [0.65,1.00]	0.12 [0.05,0.27]
Chiang 2015	Non-Western	100	78	4	18	140	0.36 [0.30,0.42]	0.82 [0.61,0.93]	0.95 [0.88,0.98]	0.11 [0.07,0.17]
Cheong 2016	Non-Western	100	586	1	75	1531	0.28 [0.26,0.30]	0.99 [0.93,1.00]	1.00 [0.99,1.00]	0.05 [0.04,0.06]
Kashiura 2016	Non-Western	100	947	9	144	2220	0.30 [0.28,0.32]	0.94 [0.89,0.97]	0.99 [0.98,1.00]	0.06 [0.05,0.07]
Verhaert 2016	Western	54	35	0	89	442	0.07 [0.05,0.10]	1.00 [0.96,1.00]	1.00 [0.90,1.00]	0.17 [0.14,0.20]
Lee 2019	Non-Western	100	868	17	521	3202	0.21 [0.20,0.23]	0.97 [0.95,0.98]	0.98 [0.97,0.99]	0.14 [0.13,0.15]
Summary							**0.26 [0.21,0.32]**	**0.98 [0.95,1.00]**	**1.00 [0.99,1.00]**	**0.09 [0.07,0.12]**

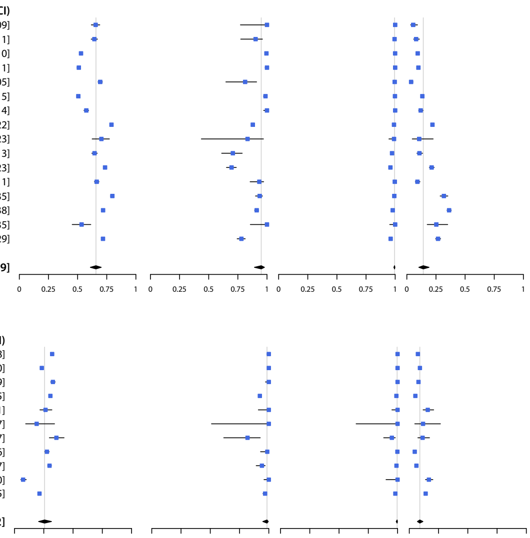

Fig. 2 – Forest plots of diagnostic accuracy for death in-hospital or at 30-days of the BLS and ALS TOR-rules. Test characteristics of the TOR-rules for the primary outcome, for individual studies and pooled values. ALS = advanced life support, TOR = termination of resuscitation, TP = True positive, FP = False positive, TN = True negative, FN = False negative, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value.

Study	Region	Transport rate	TP	FP	TN	FN	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Morrison 2006	Western	100	773	3	31	443	0.64 [0.61,0.66]	0.91 [0.77,0.97]	1.00 [0.99,1.00]	0.07 [0.05,0.09]
Sasson 2008	Western	82.8	2588	4	186	2727	0.49 [0.47,0.50]	0.98 [0.95,0.99]	1.00 [1.00,1.00]	0.06 [0.06,0.07]
Ruygrok 2009	Western	76	231	0	42	442	0.34 [0.31,0.38]	1.00 [0.92,1.00]	1.00 [0.98,1.00]	0.09 [0.06,0.12]
Kajino 2013	Non-Western	100	112947	193	5808	32204	0.78 [0.78,0.78]	0.97 [0.96,0.97]	1.00 [1.00,1.00]	0.15 [0.15,0.16]
Fukuda 2014	Non-Western	100	101	0	3	44	0.70 [0.62,0.77]	1.00 [0.44,1.00]	1.00 [0.96,1.00]	0.06 [0.02,0.17]
Kim 2015	Non-Western	100	3342	19	170	1304	0.72 [0.71,0.73]	0.90 [0.85,0.93]	0.99 [0.99,1.00]	0.12 [0.10,0.13]
Cheong 2016	Non-Western	100	1411	0	44	738	0.66 [0.64,0.68]	1.00 [0.92,1.00]	1.00 [1.00,1.00]	0.06 [0.04,0.07]
Kashiura 2016	Non-Western	100	2057	3	195	563	0.79 [0.77,0.80]	0.98 [0.96,0.99]	1.00 [1.00,1.00]	0.26 [0.23,0.29]
Lee 2019	Non-Western	100	3012	27	335	1234	0.71 [0.70,0.72]	0.93 [0.89,0.95]	0.99 [0.99,0.99]	0.21 [0.19,0.23]
Summary							**0.65 [0.56,0.74]**	**0.96 [0.93,0.98]**	**1.00 [1.00,1.00]**	**0.11 [0.08,0.16]**

Study	Region	Transport rate	TP	FP	TN	FN	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Sasson 2008	Western	82.8	1192	0	190	4123	0.22 [0.21,0.24]	1.00 [0.98,1.00]	1.00 [1.00,1.00]	0.04 [0.04,0.05]
Ruygrok 2009	Western	76	162	0	42	511	0.24 [0.21,0.27]	1.00 [0.92,1.00]	1.00 [0.98,1.00]	0.08 [0.06,0.10]
Kajino 2013	Non-Western	100	40993	37	1865	95091	0.30 [0.30,0.30]	0.98 [0.97,0.99]	1.00 [1.00,1.00]	0.02 [0.02,0.02]
Fukuda 2014	Non-Western	100	7	0	3	31	0.18 [0.09,0.33]	1.00 [0.44,1.00]	1.00 [0.65,1.00]	0.09 [0.03,0.23]
Chiang 2015	Non-Western	100	80	2	14	144	0.36 [0.30,0.42]	0.88 [0.64,0.97]	0.98 [0.92,0.99]	0.09 [0.05,0.14]
Cheong 2016	Non-Western	100	587	0	44	1562	0.27 [0.25,0.29]	1.00 [0.92,1.00]	1.00 [0.99,1.00]	0.03 [0.02,0.04]
Kashiura 2016	Non-Western	100	953	3	78	2286	0.29 [0.28,0.31]	0.96 [0.90,0.99]	1.00 [0.99,1.00]	0.03 [0.03,0.04]
Lee 2019	Non-Western	100	881	4	358	3365	0.21 [0.20,0.22]	0.99 [0.97,1.00]	1.00 [0.99,1.00]	0.10 [0.09,0.11]
Summary							**0.27 [0.23,0.30]**	**0.98 [0.96,0.99]**	**1.00 [0.99,1.00]**	**0.05 [0.03,0.08]**

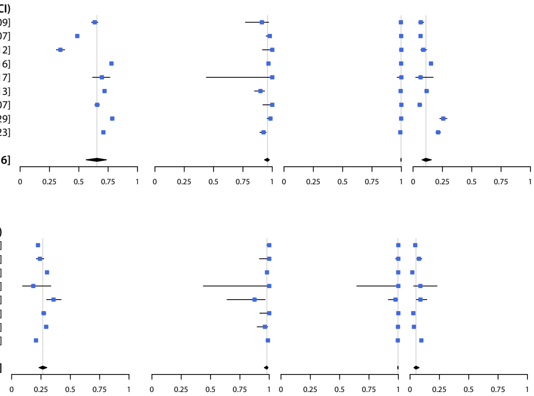

Fig. 3 – Forest plots of diagnostic accuracy for unfavourable neurologic outcome of the BLS and ALS TOR-rules. Test characteristics of the BLS and ALS TOR-rules for unfavourable neurological outcome, for individual studies and pooled values. BLS = basic life support, ALS = advanced life support, TOR = termination of resuscitation, TP = True positive, FP = False positive, TN = True negative, FN = False negative, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value.

Table 2a – Subgroup analysis BLS TOR-rule.

Studies		n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All		16	0.66 (0.61–0.70)	0.95 (0.89–0.98)	0.99 (0.99–1.00)	0.14 (0.10–0.19)
Transport rate	100% (low risk of bias)	12	0.68 (0.63–0.73)	0.93 (0.84–0.97)	0.99 (0.99–1.00)	0.12 (0.09–0.17)
	<100% (high risk of bias)	4	0.59 (0.49–0.68)	0.98 (0.93–0.99)	1.00 (0.98–1.00)	0.20 (0.11–0.33)
	p-Value		0.09	0.10	0.75	0.17
Region	Western	8	0.59 (0.54–0.64)	0.99 (0.97–0.99)	1.00 (1.00–1.00)	0.13 (0.08–0.20)
	Non-Western	8	0.72 (0.68–0.76)	0.84 (0.73–0.92)	0.99 (0.97–0.99)	0.15 (0.10–0.23)
	p-Value		<0.001	<0.001	0.008	0.67

Subgroup analysis of the BLS TOR-rule. We defined Western regions as Europe, North-America and Australia; and non-Western regions as all other countries.[29,30]

BLS = basic life support, TOR = termination of resuscitation, PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval.

Table 2b – Subgroup analysis ALS TOR-rule.

Studies		n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All		11	0.26 (0.21–0.32)	0.98 (0.95–1.00)	1.00 (0.99–1.00)	0.09 (0.07–0.12)
Transport rate	100% (low risk of bias)	7	0.29 (0.22–0.36)	0.96 (0.90–0.98)	0.99 (0.98–1.00)	0.08 (0.06–0.10)
	<100% (high risk of bias)	4	0.21 (0.15–0.29)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.12 (0.08–0.17)
	p-Value		0.15	0.005	0.02	0.10
Region	Western	5	0.23 (0.17–0.31)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	0.11 (0.07–0.15)
	Non-Western	6	0.28 (0.21–0.37)	0.94 (0.87–0.97)	0.99 (0.98–0.99)	0.08 (0.05–0.11)
	p-Value		0.32	<0.001	<0.001	0.22

Subgroup analysis of the ALS TOR-rule. We defined Western regions as Europe, North-America and Australia; and non-Western regions as all other countries.[29,30]

ALS = advanced life support, TOR = termination of resuscitation, PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval.

the aforementioned analyses. Therefore, no further analyses were performed according to the QUADAS-2 score.

Meta-regression indicated that the specificity increased with an increasing proportion of patients that received a shock (p = 0.002) or regained ROSC (p = 0.03) during the resuscitation. Witnessed status and bystander CPR were not associated with the specificity. No factors were significantly associated with the PPV (Supplemental Table S4b).

Discussion

In this in-depth diagnostic meta-analysis and systematic review on over 350.000 patients, we assessed the diagnostic performance of the two guideline-endorsed TOR-rules to identify non-survivors of OHCA. The pooled PPV of 0.99 for the BLS (95% CI 0.99–1.00) and 1.00 for the ALS TOR-rule (0.99–1.00) indicate a survival chance of ≤1% if either rule advises in-field TOR. However, we found a clinically important variation in specificity, which indicates that among survivors, there was a wide range in the proportion of patients that qualified for in-field TOR. The pooled specificity was lowest in non-Western regions, where 16 (BLS-rule) or 6 (ALS-rule) out of 100 survivors met the TOR-criteria. In addition to region, the only component of the TOR-rule associated with specificity of both rules was the proportion of patients with in-field shocks. The heterogeneity in performance of the TOR-rules calls for evaluation of the TOR-rule in the intended region before actual implementation to avoid TOR in potential survivors.

Diagnostic performance

For both TOR-rules, the cumulative available evidence indicates a pooled PPV of $\geq$0.99, for both outcome measures (death; unfavourable neurologic outcome). Fig. 2 demonstrates that there is little heterogeneity and that confidence intervals are narrow (0.99–1.00 for both rules). This indicates that overall chances of survival among patients fulfilling the TOR-criteria is $\leq$1%. This complies with a previously postulated medical futility criterion stating that further treatment may be withheld if survival chances are <1%.[15] We refer to this 1% as a reference as it is the most commonly used criterion for futility, that has also been used during the development of the TOR-rules and is referenced in guidelines.[5,6,12,16] However, it should be noted that this definition has been questioned, particularly in the field of resuscitation, and therefore remains an important topic of debate. In such discussions, ethical and religious dimensions should be taken into consideration.[4] Importantly, the PPV was high irrespective of study region and population characteristics.

However, our findings were less consistent regarding specificity, for which the pooled values were high, but confidence intervals wider and forest plots more heterogeneous. Among the included studies, specificity ranged from 70 to 100%, which indicates that up to 30% of all survivors fulfil the TOR-criteria (Fig. 2). To gain insight into this variation, we performed several pre-specified sensitivity and meta-regression analyses in which we focused on population characteristics and region.

The most striking result is the significant and clinically relevant lower specificity in non-Western regions. Notably, these are all Asian regions, in which the pooled specificity of the BLS and ALS-rule were 0.84 and 0.94, indicating that 16 and 6 out of every 100 survivors fulfil the TOR-criteria.

One major difference between Western and non-Western regions is that in several Western regions TOR is legally allowed, in contrast to non-Western regions. Consequently, all non-Western, but only half of the Western studies had a transport rate of 100%. In some Western regions, local legislation permits cessation of CPR-attempts in case of asystole despite >20 min. of full treatment.[41,42] Such cases are likely to receive a termination advice according to the ALS and BLS TOR-rules as well. This may induce a “self-fulfilling prophecy” due to verification bias. More specifically, partial verification bias, as not all patients that are subjected to the investigated test (TOR-rule) are subjected to the reference test, i.e. the “test” whether they would survive in case of transportation.[43] If all patients had been transported, it is possible that there would have been a few that would have survived.

Therefore, the reported specificity and PPV may be an overestimation of the situation as it would have been when all patients are transported. This is supported by the fact that we found a higher proportion patients with a TOR-advice among survivors in non-Western vs. Western countries (BLS and ALS-rule) and in countries with a transport rate of 100% vs. <100% (ALS-rule). However, additional study is warranted to address this issue. Furthermore, as specificities did not differ to the same extent in comparisons between studies with 100% vs. <100% transport rates and comparisons on non-Western vs. Western studies, it seems unlikely that transport rate is the sole explanation for our findings, particularly for the BLS-rule.

Several other explanations can be mentioned. First, meta-regression demonstrated that specificity is lower in studies with lower proportions of patients with in-field defibrillation attempts. The lower proportion of patients with in-field defibrillation attempts in the non-Western countries (median 20% in non-Western vs. 30% in Western regions, p = 0.001) is thus likely to have contributed to the lower specificity.[44] Second, the time between start CPR and assessment of the TOR-criteria may be an important factor. Previous studies showed that chances of falsely recommending TOR decrease with increasing time to TOR-assessment.[19,38,45] For example, patients without ROSC/defibrillation after 5 min have higher survival chances than after 20 min, and therefore early application of the rule may result in undesired termination-advice. Asian regions often apply a scoop-and-run strategy, with short in-field CPR-duration (2–4 min. in most Asian regions a recent study),[46] and possibly earlier application of the TOR-rules. Previous Asian studies indeed showed that specificity decreased with decreasing time to TOR-rule application.[19,45] However, in absence of uniform reporting of these time intervals statistical analyses on this hypothesis were not feasible.

Thirdly, patients that meet TOR-criteria may have a higher chance of being salvaged in non-Western regions, which may be due to different underlying aetiologies, more patients that have pulseless electrical activity instead of asystole, or widespread use of advanced CPR-techniques.[47,48] Finally, the lower specificity was only found for death, and not for the secondary endpoint of unfavourable neurologic outcome. The lower specificity could hypothetically be driven by patients surviving with an impaired neurologic status.[49] However, as not all studies report on neurologic outcome, these results should be interpreted with caution and the exact cause of the lower specificity remains to be elucidated.

Overall, the NPV and sensitivity were low (Fig. 2). This indicates that, even when following the TOR-rules, there would still be many transports of non-surviving patients. This is important in light of the recent proposal to use TOR-rules to identify candidates for extracorporeal CPR (eCPR).[50] If a negative TOR-rule would be used as the only criterion for eCPR, all transported patients would be eligible for eCPR, of which the a priori chance of survival is low. Therefore, the suggestion to use the TOR-rule as initial screening tool for rapid transport, followed by a secondary assessment on the emergency department to assess age, co-morbidity etc. as secondary criteria for eCPR seems sensible.[50] On the other hand, a lower threshold for early transport may also adversely affect survival chances, due to the sometimes suboptimal CPR-quality.[60] In this context, comparative trials are of utmost importance.

Our study builds on a previous meta-analysis on this topic. In contrast to the current quantitative synthesis, that study excluded studies with in-field TOR. In addition, PPV and NPV were not reported. The current analysis covers all available evidence, to specifically focus on heterogeneity in performance, as well as the related factors.[51]

Post-hoc analysis on diagnostic performance in relation to projected transport rate

Appreciating that the projected transport rate is higher in case of favourable, and lower in case of more unfavourable arrest

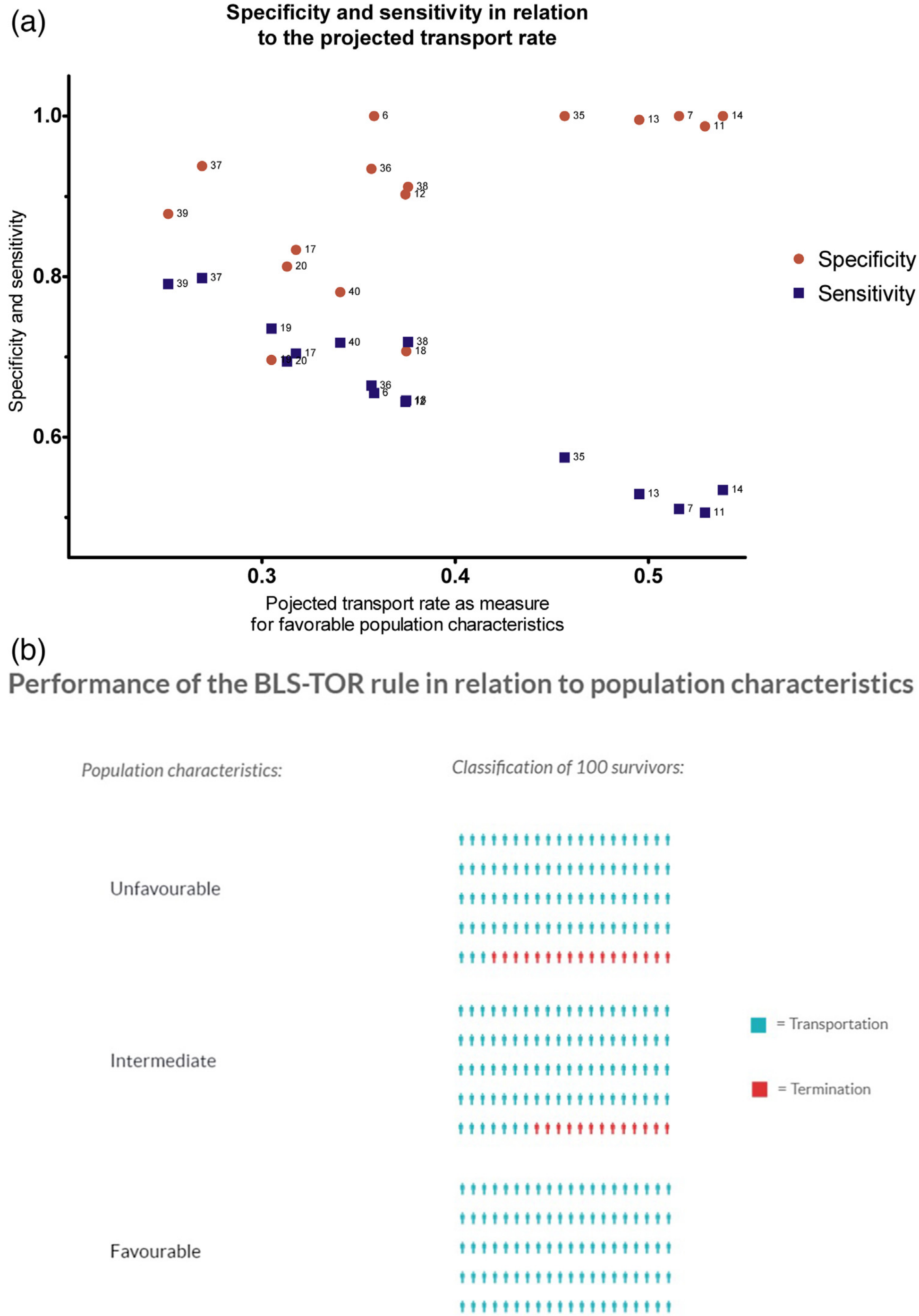

Fig. 4 – Diagnostic performance of the BLS TOR-rule in relation to population characteristics.

Figures that demonstrate that the diagnostic performance of the BLS-TOR rule is related to characteristics of the studied population. a) Specificity is the proportion transport advice among survivors; 1-specificity is thus the proportion termination advice among survivors. Sensitivity is the proportion termination advice among non-survivors. As the projected transport rate is the proportion patients that fulfil at least one criterion of the BLS TOR-rule (in-field shocks, EMS witnessed or ROSC), this can be used as a measure for general favourability of the characteristics of the studied population. b) Graphical illustration of the classification of 100 survivors in setting with favourable, intermediate and unfavourable population characteristics, defined as tertiles of the projected transport rate. The numbers are the numbers of the references. BLS = basic life support, TOR = termination of resuscitation, EMS = emergency medical services, ROSC = return of spontaneous circulation.

characteristics,[9] this rate can be considered a proxy for overall population arrest characteristics.[8] Of the individual components of the TOR-rules, mainly in-field shock was found to be associated with the specificity.

In a post-hoc analysis, we tried to gain more insight into the association between population characteristics and the diagnostic performance, by constructing Fig. 4. In this figure, sensitivity and specificity are plotted against the projected transport rate for the BLS TOR-rule, which is the proportion of patients fulfilling at least one of its criteria (ROSC, shock, EMS witnessed). This figure shows that in studies with favourable population characteristics (i.e. high projected transport rate), specificity is almost 1.00, indicating that TOR-advice among survivors is rare, whereas the sensitivity of around 0.50 indicates that about half of the unsalvageable patients should be transported when following the rule. The opposite goes for studies with less favourable characteristics (i.e. lower transport rate): TOR-advice in up to 30% of survivors due to low specificity, but markedly less futile transportations due to higher sensitivity. Similar associations were found for the ALS TOR-rule (not shown). Thus, the *overall* baseline profile of the population seems to affect its diagnostic performance.

Implications

In this most comprehensive summary of evidence to date we demonstrate a large variation in diagnostic performance of the TOR-rules. This variation should be acknowledged in practice guidelines on this topic. Furthermore, additional study on the optimal TOR-strategy is essential to further facilitate evidence-based decision making in the pre-hospital setting. This particularly applies to non-Western regions and regions with low proportions in-field defibrillation. As discussed previously, in future studies all OHCA-victims should be transported to the hospital to avoid verification bias. However, it should be noted that in such studies there is a trade-off between the optimal study setting (transporting all patients) and the purpose for which the rules are designed (reducing futile transport). Second, given the association between baseline profile, time to assessment of TOR-criteria[19,38] and diagnostic performance, these should be reported uniformly. For instance, some studies actually report the proportion of patients receiving an in-field shock, whereas others report on the proportion of patients with an initial shockable rhythm. Third, the performance of future TOR rules may be improved by incorporating other variables, such as arrest-duration, age or chest compression quality.[52–55] In addition, incorporation of clinician's judgement has been suggested as well.[56] Our findings indicate that there is room for improvement, thus optimizing existing TOR-algorithms or developing new TOR-rules remains an important topic for further research. Fourth, future studies should not only focus on PPV but also on specificity, in which we found the largest variation. This presumably relates to the low survival rates in the included studies, which is further explained in Supplemental text 3.

In Western regions the overall PPV and specificity were high. However, not all studies were performed with a 100% transportation rate, hampering the interpretability of the results. Furthermore, the landscape of cardiac arrest treatment is rapidly evolving, e.g. due to increased use of lay-person automated external defibrillators and bystander CPR, or newer technologies such as mechanical CPR and extra corporeal life support.[57–61] Probably due to these developments, survival rates are also increasing, from 2% in the derivation study to up to 15% in more recent studies.[6,8,38] Our results implicate that that the overall baseline profile might affect the diagnostic performance of the rules. Therefore, we provide an evidence-based support for the resuscitation guideline recommendation of locally evaluation of the intended TOR-rule before actual implementation.[62] This should be done in a setting that is comparable to the contemporary pre-hospital care, and ideally in a setting where all patients are transported to the hospital.

Limitations

It was inherent to the objective of this report that the included studies were of observational design and thus all limitations generally ascribed to observational research apply. Many studies were retrospective, possibly limiting the quality and uniformity of collected data (Table 1). This should be a top priority in further studies on this topic. Furthermore, although we performed several sub-analyses and meta-regression analyses, residual confounders may have affected the reported diagnostic accuracy, such as CPR-quality, quality of post-resuscitation care etc. Moreover, the quality of the included studies varied, with verification bias being a major concern, which we addressed in our sub-analyses. Not all studies reported on survival to discharge. Therefore, we used the endpoints as reported in the original studies, which was either survival to discharge or 30-day survival, which comply with the Utstein recommendations.[25] Although all analyses were prespecified, we did not formally register our study protocol. Lastly, the presented performances of the TOR-rules apply to adult non-traumatic OHCA, which precludes extrapolation to other populations.

Conclusions

In the present systematic review and diagnostic meta-analysis we found that despite an overall high PPV, there is a clinically important variation in the diagnostic performance of the BLS and ALS TOR-rules. Lower specificity and PPV were seen in non-Western regions, and populations with lower rates of in-field defibrillation. The observed regional variation calls for local validation of the TOR-rules before clinical use, and improved insight into how to reduce the risk of a termination-advice in potential cardiac arrest survivors is warranted.

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None.

Conflicts of interest

Prof. de Boer has been a member of the European advisory board on interventional cardiology of Medtronic. Dr. Wik is a member of Stryker Medical Advisor Group. Prof. van Royen received research grants from Abbott,Biotronik, AstraZeneca and Philips, and professional fees from Abbott and Medtronic. The other authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.12.016.

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