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Clinical paper

North American validation of the Bokutoh criteria for withholding professional resuscitation in non-traumatic out-of-hospital cardiac arrest

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Abstract

Background: Certain subgroups of patients with out-of-hospital cardiac arrest (OHCA) may not benefit from treatment. Early identification of this cohort in the prehospital (EMS) setting prior to any resuscitative efforts would prevent futile medical therapy and more appropriately allocate EMS and hospital resources. We sought to validate a clinical criteria from Bokutoh, Japan that identified a subgroup of OHCAs for whom withholding resuscitation may be appropriate.

Methods: We performed a secondary analysis of the "Trial of Continuous or Interrupted Chest Compressions during CPR", which enrolled EMS-treated adult non-traumatic OHCA. We classified patients as per the Bokutoh criteria ("Bokutoh Positive": age $\geq$ 73, unwitnessed arrest, non-shockable initial rhythm) and calculated test performance for the primary outcome of favourable neurologic outcome (mRS $\leq$ 3) at hospital discharge. We calculated the number of EMS-hours and hospital days per patient with a favourable neurologic outcome.

Results: Of 26,148 patients in the parent trial, 5442 (21%) were "Bokutoh Positive", among whom 0.51% (95% CI 0.35– 0.75%) had favourable neurologic outcomes, and 1.2% (95% CI 0.92–1.5%) survived. The positive predictive value was 0.995 (95% CI 0.992–0.997). EMS and hospital-based resource utilization per favourable neurological outcome was 91 h and 199 days for in the "Bokutok Positive" group, respectively, and 5.7 h and 33 hospital days in the "Bokutok Negative" group.

Conclusion: In this validation of the Bokutoh criteria in a large North American cohort of OHCA patients, 0.51% meeting criteria had favourable neurological outcomes. This may rapidly and reliably identify the one-fifth of OHCA who are very unlikely to benefit from resuscitation.

Keywords: Cardiopulmonary resuscitation, Out-of-hospital cardiac arrest, Emergency medical services

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Introduction

Emergency medical services (EMS) attend 134 cases of out-of-hospital cardiac arrest (OHCA) per 100,000 adult citizens in the United States, with survival rates between 3–16%.[1,2] Over the past decade, with substantial investments in patient care, survival from OHCA has increased significantly.[3-5] Unfortunately, some patient subgroups may have a grim prognosis for survival in spite of full attempts at resuscitation. Reliable early identification of these patients may prevent futile ongoing resuscitative efforts and allocate EMS and hospital resources more appropriately.

Previous researchers have developed and validated prediction rules to allow prehospital termination of resuscitation after on-scene efforts, preventing futile hospital transports.[6] This concept has been carried further, as investigators from Japan sought to create a criteria which would predict non-survival at the onset of resuscitative efforts.[7] Shibahasi et al. examined a large Japanese database and reported that among patients $\geq$73 years old with an unwitnessed arrest and an initial non-shockable rhythm, 99.6% had poor 30-day neurological outcomes.[7] Using this criteria may mitigate patients with no chance of meaningful recovery from undergoing invasive treatments.

Owing to systematic differences between prehospital EMS systems in Japan and North America, including training of prehospital providers, prehospital protocols, intra-arrest transport, and protocols for termination of resuscitation,[3,7,8] we sought to externally validate the Bokutoh criteria on a North American cohort of OHCAs. We validated these criteria in the "Trial of Continuous or Interrupted Chest Compressions during CPR" (the "CCC Trial") database, which enrolled undifferentiated consecutive non-traumatic adult EMS-treated OHCAs.[9]

Methods

Study design

We performed a secondary analysis on prospectively collected data from the CCC Trial, performed by 8 sites of the Resuscitation Outcomes Consortium (ROC).[9] The ROC was a clinical research network including sites across the US and Canada with a data coordinating center at the University of Washington.[10] The data for this analysis was obtained from, and the protocol approved by, the National Institute of Health's Biological Specimen and Data Repository Information Coordinating Center.

Parent trial

The population, design, and results of the primary analysis of the CCC trial have been reported previously.[9] Briefly, patients were randomized to receive either continuous chest compressions with unsynchronized ventilations or chest compressions that were interrupted for ventilations. The trial included non–traumatic out-of-hospital cardiac arrest who received EMS-delivered chest compressions, and excluded patients if they had an EMS-witnessed arrest, a written advance directive to not resuscitate, a traumatic or asphyxial arrest, uncontrolled bleeding or exsanguination, known pregnancy, pre-existing tracheostomy, were known to be prisoners, were treated with a mechanical chest-compression device, had advanced airway management before ROC EMS agency arrival, or previously had opted not to participate in resuscitation research. Some patients were co-enrolled in a trial of antiarrhythmic therapy for recurrent ventricular fibrillation.[11] Trained abstractors systematically collected data on all patients, including basic characteristics, bystander interventions, time-stamped EMS-delivered prehospital care, duration in hospital (and in the intensive care unit), and neurologic outcomes at hospital discharge, as previously described.[9,10]

Selection of study participants

We included patients who were enrolled in the parent trial. We excluded patients missing data required to apply the Bokutoh criteria, and those lacking outcome data at hospital discharge.

Outcomes

The primary outcome was favourable neurologic outcome at hospital discharge (defined as MRS $\leq$ 3).[12] We also reported return of spontaneous circulation (ROSC, defined as a palpable pulse for any time[12]), survival, and length of time in the prehospital and hospital phases of care.

Data analysis

We used Microsoft Excel Version 14.5.0 (Microsoft Corp, Redmond, WA, USA) and R version 3.2.4 (Foundation for Statistical Computing, Vienna, Austria) for data entry and analysis. We reported binary patient characteristics as proportions, and continuous variables as medians (with interquartile range) if not normally distributed, or otherwise as means (with standard deviation). We reported the number of patients with missing data. We applied the Bokutoh criteria to all patients, which recommends against resuscitation when the following criteria are met: age $\geq$ 73, unwitnessed arrest, and a non-shockable initial cardiac rhythm. We calculated conventional test performance characteristics (with 95% confidence intervals), including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) for the primary outcome, as well as the proportion of false positive results (using the primary outcome and survival). By convention,[7] when the Bokutoh criteria recommended against professional resuscitation ("positive test") and the participant had a unfavourable neurological outcome ("positive result"), this was considered a "true positive". We reported: (1) the number of EMS management hours, defined as the interval between first EMS vehicle on-scene arrival until either termination of resuscitation or arrival at hospital; and (2) the number of hospital management days, defined as the interval from patient arrival at the hospital emergency department until the time of discharge or declaration of death. Finally, we calculated the total number of EMS hours and hospital days in both groups, and then calculated the resource utilization per survivor with favourable neurological outcome in each group. For the calculation of total resource allocation: for those with missing data required to calculate EMS or hospital-based management intervals, we imputed the median value (from those with available data) from the following groups (depending on the status of the patient with missing data): (a) declared dead in the prehospital setting, (b) declared dead in the emergency department, (c) died after being admitted to hospital, or (d) survived to hospital discharge.

Results

Patient characteristics

There were 26,148 patients enrolled in the CCC dataset; the median age was 68 (IQR 56–81), 46% achieved ROSC, and 7.3% had

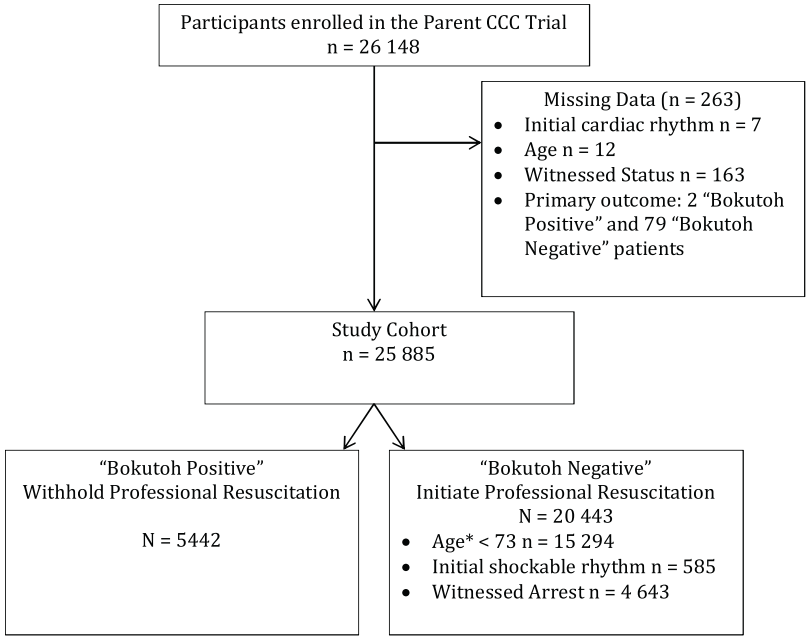

Fig. 1 – Study flow.
*** Characteristics applied sequentially.**

favourable neurological outcomes. After excluding patients with missing data (Fig. 1), 5442 patients (21%) met Bokutoh criteria for withholding professional resuscitation ("Bokutoh Positive"). Table 1 shows patient characteristics of these two groups.

Main results

For the 5442 "Bokutoh Positive" patients, 64 (1.2%, 95% CI 0.92–1.5%) survived to hospital discharge and 28 (0.51%, 95% CI 0.35–0.75%) had a favourable neurological outcome (Table 2). Among the 20 422 "Bokutoh Negative" patients 2343 (11%, 95% CI 11–12%) survived to hospital discharge, and 1963 (9.6%, 95% CI 9.2–10%) had a favourable neurological outcomes. Sensitivity and specificity of the criteria were 0.227 (95% CI 0.221– 0.232) and 0.986 (95% CI 0.979–0.990), respectively. The positive predictive value was 0.995 (95% CI 0.992– 0.997) and negative predictive value 0.0960 (95% CI 0.0920–0.100). Patient characteristics of "Bokutoh Positive" with favourable neurological outcomes can be seen in Table 3.

Resource utilization

Prehospital and hospital based-management intervals are shown in Table 4. For those In the "Bokutoh Positive" group, EMS provided a total of 2543 care hours, and patients spent a total 3333 days in hospital. This corresponds to 91 h of EMS time and 119 hospital days per survivor with favourable neurological outcome. For patients in the "Bokutoh Negative" group, EMS and hospital-based teams provided a total of 11,132 h and 65,230 days of medical management, respectively. This corresponds to 5.7 h of EMS time and 33 hospital days per survivor with favourable neurological outcome.

Table 1 – Patient characteristics, dichotomized by recommendation of Bokutoh criteria.

	"Bokutoh Positive" (n = 5442) withhold professional resuscitation		"Bokutoh Negative" (n = 20 433) perform professional resuscitation	
	n or median (% or IQR)	Missing	n or median (% or IQR)	Missing
Patients	5442		20,433	
Age (years)	83 (78–88)	0	63 (53–73)	15
Male	2928 (54)	2	13,630 (67)	4
Location public	154 (2.8)	28	3579 (18)	30
Witnessed by bystander	0	0	10,932 (55)	392
Bystander CPR	2177 (40)	0	9792 (48)	0
911 call to first EMS arrival (min)	5.6 (4.4–6.9)	74	5.5 (4.3–7.0)	376
Initial shockable rhythm	0	0	5942 (29)	19
ALS management	5205 (96)	0	19,917 (97)	0
Transported to hospital	1833 (38)	0	12,084 (59)	0

IQR, interquartile range; N, number; IQR, inter-quartile range; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ALS, advanced life support.

Table 2 – Patient Outcomes.

	"Bokutoh Positive" (n = 5442) withhold professional resuscitation		"Bokutoh Negative" (n = 20 433) initiate professional resuscitation	
	n or median (% or IQR)	Missing	n or median (% or IQR)	Missing
Return of spontaneous circulation	1131 (21)	27	8106 (40)	135
Survival to hospital admission	534 (9.8)	3	5985 (29)	40
Survival to hospital discharge	64 (1.2, 95% CI 0.92–1.5)	0	2343 (11)	0
Favourable neurological outcome	28 (0.51, 95% CI 0.35–0.75)	0	1963 (10)	0

Table 3 – Characteristics of "Bokutoh Positive" patients with favourable neurological outcomes.

	n or median (% or IQR)	Missing
Patients	28	
Age (years)	84 (78–88)[b]	0
Male	15 (54)	0
Location public	3 (11)	0
Witnessed by bystander	0	0
Bystander CPR	5 (18)	0
911 call to EMS arrival (min)	5.3 (4.0–6.9)	0
Initial shockable rhythm	0	0
ALS involvement	27 (96)	0
EMS arrival-to-ROSC	3.0 (1.2–8.7)[a]	0
Transported to hospital	28 (100)	0

N, number; IQR, inter-quartile range; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.
[a] Maximum value 32.3 min.
[b] Maximum value 89 years.

Discussion

Out-of-hospital cardiac arrest is a condition with high mortality. There are subgroups that are very unlikely to benefit from aggressive resuscitation, and if these patients can be reliably identified early, subsequent medical management, invasive therapies, and system costs can potentially be avoided. Using high-quality multijurisdictional North American data from the CCC trial, we performed a validation study of the recently published Bokutoh criteria,[7] which examined three predictors of poor neurologic outcome: unwitnessed arrest, age $\geq$ 73, and nonshockable initial cardiac rhythm. Importantly, the false negative value in our study was 0.5%, with the upper bound of the 95% confidence interval reaching only 0.75%. Despite differences between EMS delivery in North America and Japan, test performance was very similar. These data may assist both clinicians and EMS directors in rapidly and reliably identifying the approximately 20% of OHCA patients in whom any resuscitation after confirmation of these criteria is very unlikely to yield favourable results.

We extended the findings of Shibahashi et al. by identifying the substantial resources devoted to patients who have minimal meaningful chance of neurologic recovery. In the "Bokutoh Positive" group resource utilization amounted to nearly 100 h of EMS time and 17 weeks in hospital per neurologically intact survivor, mostly in critical care settings. It is unclear if patients, families, clinicians, and system administrators would view these numbers as acceptable. The 28 (0.5%) Bukotuh-postive patients had similar baseline baseline characteristics as the remainder of the cohort, and thus the early identification of these few survivors who might benefit from resuscitation is challenging. It is important to note that half of these patients achieved ROSC within 3 min, and, although our sample is small, it is possible that a short duration of resuscitation might capture these survivors. Conversely, attempting resuscitation will achieve ROSC in others as well, the vast majority of whom will have eventual poor neurological outcomes.

The Bokutoh criteria can be applied to cardiac arrest patients rapidly upon EMS arrival—the only non-historical data required is initial cardiac rhythm, which is often determined prior to EMS arrival. In contrast, previous rules guiding prehospital resuscitation have depended upon patient response to active prehospital resuscitation attempts.[13] The Universal Termination of Resuscitation Rule,

Table 4 – Patient management intervals.

	"Bokutoh Positive" (n = 5442) withhold professional resuscitation		"Bokutoh Negative" (n = 20 433) perform professional resuscitation	
	n or median (% or IQR)	Missing	n or median (% or IQR)	Missing
Prehospital intervals				
EMS arrival-to-ROSC (min)	16 (22–22)	60	14 (8.1–20)	711
EMS arrival-to-prehospital termination[a]	24 (17–29)	93	27 (21–34)	225
EMS management of patient[b] (min)	27 (20–35)	58	31 (24 – 40)	513
Hospital Intervals				
Hospital management[c] (hours)	0.53 (0.15–25)	25	4.7 (0.23–126)	288

ROSC, return of spontaneous circulation; EMS, emergency medical service.
[a] Measured from first EMS on-scene arrival until prehospital termination of efforts.
[b] Measured from first EMS on-scene arrival until either prehospital termination of efforts or arrival at hospital.
[c] Measured from first emergency department arrival until hospital discharge or death.

supported by the American Heart Association Guidelines,[14,15] recommends termination of resuscitation without transport to hospital if all of the following three criteria are met: (1) the arrest is not witnessed by EMS, (2) there are no shocks delivered, and (3) there is no return of spontaneous circulation; otherwise transport to hospital is recommended.[6,16] The rule was validated in 1240 OHCA with a PPV of 99.5% (95% CI 98.9–99.8) for the outcome of survival.[6] A subsequent validation examining the optimal time to apply the rule showed that when applied at 13 min or later the false positive rate and 95% CI was below 1%.[17] Further study is required to determine the test characteristics of sequentially applying the Bokutoh criteria and the Universal Termination of Resuscitation Rule.

Previous studies have shown that early access to professional prehospital providers is associated with improved survival and neurological outcomes.[18,19] The early identification of "Bokutoh Positive" patients in order to withhold professional resuscitative efforts may facilitate improved EMS response times to other critically ill patients, including OHCAs with more favourable prognostic features and a higher chance of meaningful recovery. Spatiotemporal analyses,[20] testing potential overall survival improvements, may be warranted to test this hypothesis. Similarly, re-allocation of the hospital-based resources required may lead to improved outcomes in other patient groups.

It is challenging to define the complex topic of medically futile interventions, especially in the context of prehospital treatments. While any treatment with less than 1% of success may be a benchmark for futility[14] this may not be appropriate for conditions in which the overall survival is often less than 10%.[1,2] This approach may overlook nuances in patient and provider beliefs; for example, the hardships incurred to patients and families from aggressive in-hospital interventions with a minimal chance of meaningful recovery may make these treatments less desirable. Other families may want all options pursued if there is any chance of a positive outcome. Further, it is unclear whether the outcome of survival or neurological outcomes should form the most important outcome measure to assess a potentially futile intervention. Importantly, whereas we primarily evaluated neurological outcomes in this study, the false positive rate for survival surpassed 1%. Further patient-centered research is required to further elucidate these concepts and determine the optimal definition of futility.[21] While opinions may vary over what is an appropriate price to pay to achieve one survivor at hospital discharge, cost effectiveness thresholds can be set by healthcare funding agencies.[22] Given the resource implications involved in the treatment of "Bokutoh Positive" patients, the low likelihood of survival to discharge, and in view of previous data showing that among those ≥75 discharged from hospital alive the 5-year of survival is near 50%,[23] an economic analysis of this population may be warranted.

Limitations

This is a secondary analysis of rigorously collected trial data.[9] A prospective blinded study, with standardized treatment and prognostication protocols, would be the most robust evaluation of this criteria. There may be additional unmeasured patient-level factors that better predict prognosis than those identified in the Bokutoh criteria. We did not include patients with EMS-witnessed arrests (as were excluded in the CCC Trial); while these patients would have would increased the number of "Bokutoh Negative" patients, none would have been included in the "Bokutoh Positive" group. Thus, the key test characteristics of PPV and false positive proportion would not be altered, although others might be. In evaluating whether resuscitation of certain patient groups is "futile" one most recognize the important risk of prognostication bias—treating clinicians (prehospital and hospital-based) may have deemed survival in these patients to be unlikely and ceased further therapy, preventing any potential good outcome. The duration of prehospital efforts prior to termination of resuscitation in the "Bokutoh Positive" group was similar to previous cohorts,[24] suggesting a low risk of prognostication bias in the prehospital setting. However, it is unclear if this bias led to premature withdrawal of life-sustaining therapies in hospital. Emerging data demonstrates that certain patients require prolonged periods until awakening.[25] In "Bokutoh Positive" patients—who by definition have poor prognostic characteristics—premature in-hospital prognostication may have occurred, thus affecting outcomes in this group and the criteria's performance. In addition, the quality of post-admission care may have varied among hospitals. Finally, missing data, although only in a very small proportion of patients, may have altered our test performance.

Conclusion

In this validation of the Bokutoh criteria in a large North American cohort of non-traumatic OHCA patients, among those ≥73 years of age with an unwitnessed arrest and an initial nonshockable rhythm, 0.5% had a favourable neurologic outcome and 1.2% were alive at hospital discharge. This criteria may rapidly and reliably identify the one-fifth of OHCAs who are very unlikely to benefit from resuscitation. Further societal and economic input may be required to determine when a therapy should be considered "futile".

Conflicts of interest

None.

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