Impact of Cooling Method on the Outcome of Initial Shockable or Non-Shockable Out of Hospital Cardiac Arrest Patients Receiving Target Temperature Management: A Nationwide Multicentre Prospective Cohort Study

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Research

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Abstract

Background: Little is known about the effectiveness of surface cooling (SC) and endovascular cooling (EC) on the outcome of out-of-hospital cardiac arrest (OHCA) patients receiving target temperature management (TTM) according to their initial rhythm.

Methods: We retrospectively analysed data from the Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest registry, a multicentre, prospective nationwide database in Japan. For our analysis, OHCA patients aged ≥ 18 years who were treated with TTM between June 2014 and December 2017 were included. The primary outcome was 30-day survival with favourable neurological outcome defined as a Glasgow-Pittsburgh cerebral performance category score of 1 or 2. Cooling methods were divided into the following groups: SC (ice packs, fans, air blankets, and surface gel pads) and EC (endovascular catheters and any dialysis technique). We investigated the efficacy of the two categories of cooling methods in two different patient groups divided according to their initially documented rhythm at the scene (shockable or non-shockable) using multivariable logistic regression analysis and propensity score analysis with inverse probability weighting (IPW).

Results: In the final analysis, 1082 patients were included. Of these, 513 (47.4%) had an initial shockable rhythm and 569 (52.6%) had an initial non-shockable rhythm. The proportion of patients with favourable neurological outcomes in SC and EC was 59.9% vs. 58.3% (264/441 vs. 42/72), 11.8% and (58/490) vs. 21.5% (17/79) in the initial shockable patients and the initial non-shockable patients, respectively. In the multivariable logistic regression analysis, differences between the two cooling methods were not observed among the initial shockable patients (adjusted odd ratio [AOR] 1.45, 95% CI 0.81–2.60), while EC was associated with better neurological outcome among the initial non-shockable patients (AOR 2.13, 95% CI 1.10–4.13). This association was constant in propensity score analysis with IPW (OR 1.40, 95% CI 0.83–2.36; OR 1.87, 95% CI 1.01–3.47 among the initial shockable and non-shockable patients, respectively).

Conclusion: We demonstrated that the use of EC was associated with better neurological outcomes in OHCA patients with initial non-shockable rhythm, but not in those with initial shockable rhythm. A TTM implementation strategy based on initial rhythm may be important.

Trial registration: None

Background

Target temperature management (TTM) is a recommended treatment strategy to minimise the development of anoxic brain injury for out-of-hospital cardiac arrest (OHCA) patients.[1, 2] TTM can be induced and maintained with surface cooling (SC), such as ice packs, fans, cold air blankets, and SC pads or with endovascular cooling (EC), such as endovascular catheters and dialysis techniques. While SC was used in two pivotal randomised studies that established TTM efficiency for OHCA patients,[3, 4] EC was newly developed for more precise temperature management. Thus far, several studies have compared the impact of cooling methods on the outcome of OHCA patients with inconclusive results,[5–10] suggesting the presence of uninvestigated confounding factors.

It is worth mentioning that there may be a potential interaction between cooling methods and initial rhythm on the outcome of OHCA patients. The known advantages of EC over SC are rapid induction and tighter temperature control during maintenance and rewarming phase,[6, 9, 10] while the disadvantage is procedure-related complication.[11] These differences between cooling methods are largely derived from their different mechanism of heat exchange and their clinical significance may alter depend on patients' physiological status. Since initial rhythm represents not only cardiac electrophysiological status but also various pre-arrest physiological statuses such as no-flow time, obesity, rate of co-existing chronic condition, and age;[12, 13] initial rhythms may influence the impact of the cooling method on the outcome of OHCA patients. However, data on the effectiveness of the cooling method among patients with different initial rhythms are limited, and therefore requires further investigation.

The aim of this study was to investigate the efficacy of SC and EC on the outcome of OHCA patients with initial shockable and non-shockable rhythm, using the database of the Japanese Association for Acute Medicine (JAAM)-OHCA Registry, a multicentre prospective registry.

Methods

Design, setting, and patient selection

We retrospectively analysed data from the JAAM-OHCA registry. The JAAM-OHCA registry is a multicentre, prospective, nationwide database that includes pre-hospital information, in-hospital information, and outcomes among OHCA patients transported to emergency departments in Japan. The registry started in June 2014 and is ongoing without setting the end date of the registry period. Currently, the registry includes 87 institutions: 66 of the included hospitals were university hospitals and/or critical care centres; the remaining 21 institutions were community hospitals providing emergency care at each community. The registry included all OHCA patients who were transported to the participating institutions and attempted resuscitation by emergency medical services (EMS). The registry excluded OHCA patients who were not resuscitated by a physician after hospital arrival, who were transported to a participating institution from another institution and who refused to participate in our registry, either personally or by family members. The protocol was approved by the institutional review board of each participating hospital. The registry was approved by the Ethics Committee of Kyoto University, and each hospital approved the JAAM-OHCA Registry protocol as necessary.

For our analysis, OHCA patients aged ≥ 18 years who were treated with TTM from June 2014 to December 2017 were included. Patients who were treated with extracorporeal membrane oxygenation (ECMO) and whose initially documented rhythm at the scene or applied cooling method were unknown were excluded.

Data collection

Prehospital data were collected by paramedics according to the international Utstein-style.[14] In-hospital data were collected by physicians or medical staff at each institution using a standardised format in an Internet-based system. The pre- and in-hospital information were integrated by the JAAM-OHCA registry committee, as previously described.[15]

The following resuscitation-related data were used for this analysis: patient age, sex, cause of arrest (cardiac or not), presence of a bystander who witnessed the collapse of patient and who performed cardiopulmonary resuscitation (CPR), use of public accessed automated external defibrillator (AED), initially documented rhythm at the scene (shockable or non-shockable), prehospital epinephrine administration, prehospital advanced airway management, EMS response time (time from call to contact with a patient), use of ancillary cooling method (cold fluid for intravenous infusion or stomach cooling with nasogastric tube), performance of percutaneous coronary intervention (PCI), targeted temperature during TTM (targeted at 32–34°C as TTM-low or targeted at 35–36°C as TTM-high), and cooling methods (SC or EC) applied for TTM implementation. The TTM protocol was entirely entrusted to each physician or institution. The data collected as outcome measures were as follows: neurological outcome 30 days after cardiac arrest, survival 30 days after cardiac arrest, and completion of TTM. Neurological outcomes were evaluated using the Glasgow-Pittsburgh cerebral performance category (CPC) scale [16]: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death/brain death. TTM completion included those who completed all the process of TTM or recovered from coma during TTM, but excluded those who died during TTM.

Outcome

In this study, the primary outcome was 30-day survival with favourable neurological outcome, defined as a CPC score of 1 or 2. The secondary outcomes were 30-day survival and TTM completion. In addition, we investigated outcome interactions between the cooling method and the initial rhythm to explore the heterogeneity of treatment effects.

Statistical analysis

Cooling methods were divided into the following two groups: SC (ice packs, fans, air blankets, and surface gel pads) and EC (endovascular catheters and any dialysis technique). If the cooling methods were duplicated, the TTM procedure category was defined as EC. We investigated the efficacy of two categories of cooling methods in two different patient groups divided according to their initially documented rhythm at the scene (shockable or non-shockable). Baseline patient characteristics and outcomes were evaluated using the Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables. To investigate the impact of the cooling method on each outcome, crude odds ratios (ORs) or adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated by applying univariable and multivariable logistic regression analyses. Based on previous studies,[17,18] we adjusted for factors that were biologically essential and considered to be associated with clinical outcomes, including age category (aged 18–64 years or aged ≥ 65 years), sex (men or women), cause of arrest (cardiac or non-cardiac aetiology), bystander witness (yes or no), bystander CPR status (yes or no), use of public-access AEDs (yes or no), prehospital adrenaline administration (yes or no), prehospital advanced airway management (yes or no), EMS response time (from call to contact with a patient). To account for the nonrandomised selection of each cooling method, we also used propensity score methods to reduce the effects of confounding factors. The individual propensities for receipt of EC were estimated with the use of a multivariable logistic regression model that included the same covariates as mentioned above for each of the overall cohort, shockable patients, and non-shockable patients. Associations between cooling methods and neurological outcomes were then estimated using inverse probability weighting (IPW). In addition, we calculated the OR in each subgroup and investigated the interaction effect to test for heterogeneity of the relative treatment effect across the particular patient characteristics of age category, presence of bystander witness, performance of PCI, and the targeted temperature. All P values were two-sided, and the level of significance was set at 0.05. All statistical analyses were performed using R (The R Foundation for Statistical Computing, version 4.03, Saitama, Japan) and EZR (Saitama Medical Center, Jichi Medical University, version 1.54, Saitama, Japan), which is a graphical user interface for R.[19]

Results

A total of 34,754 OHCA patients were registered in the JAAM-OHCA registry between June 2014 and December 2017. After excluding 833 patients who were not resuscitated by physicians, 3065 patients whose prehospital data were not available, 655 patients aged under 18 years, 28389 patients not receiving TTM, 535 patients who received ECMO, 130 patients whose initially documented rhythm was unknown, and 65 patients whose applied cooling method was unknown, 1082 patients were eligible for our final analysis (Fig. 1). Of the 1082 patients, 513 (47.4%) had an initial shockable rhythm and 569 (52.6%) had an initial non-shockable rhythm. Of the patients treated with EC, 151 (14.0%), 72 (14.0%), and 79 (13.9%) in the overall cohort, shockable rhythm, and non-shockable rhythm, respectively. Table 1 shows the baseline characteristics of the study population according to the cooling method. Baseline patient characteristics were similar in both cooling method groups, while patients treated with EC were more likely to receive prehospital epinephrine, PCI, and TTM-low. Standardised mean differences in baseline characteristics of the study population, defined as covariates for propensity score analysis, according to the cooling method before and after adjustment for IPW are shown in Table S1. Regarding the primary outcome, the proportion of patients with favourable neurological outcomes treated with SC and EC was 34.6% (322/931) vs. 39.1% (59/151) in the overall cohort, 59.9% (264/441) vs. 58.3% (42/72) among initial shockable patients, and 11.8% (58/490) vs. 21.5% (17/79) among initial non-shockable patients (Table 2). In the multivariable logistic regression analysis, treatment with EC was associated with significantly higher neurological favourable outcomes compared to SC in the overall cohort (AOR 1.56, 95% CI 1.03–2.37). This trend was no longer apparent among the initial shockable patients, while the trend was constant among initial non-shockable patients (AOR 1.45, 95% CI 0.81–2.60; AOR 2.13, 95% CI 1.10–4.13, among initial shockable and non-shockable patients, respectively). In the propensity score analysis, no difference was observed between the two cooling methods in the overall cohort (OR 1.36, 95% CI 0.96–1.94) and among the initial shockable patients (OR 1.40, 95% CI 0.83–2.36), while EC was associated with better neurological outcomes among the initial non-shockable patients (OR 1.87, 95% CI 1.01–3.47). In addition, the impact of SC and EC on the outcome of the patients showed, though not significant, heterogeneity in different initial rhythms (P for interaction = 0.053), and the heterogeneity was significant among those patients who received PCI (P for interaction = 0.023) (Fig. 2).

Discussion

In this study, we assessed the impact of cooling methods at different initial rhythms on the outcome of 1082 OHCA patients, using the database of the JAAM-OHCA registry which included patients from 87 institutions in Japan. The main results of this study are summarised as follows: First, EC was associated with significantly better 30-day neurological outcomes compared with SC in patients with an initial non-shockable rhythm. Second, this difference was no longer apparent in patients with an initial shockable rhythm. Third, this association was constant in terms of patient mortality.

The impact of SC and EC on the neurological outcome of OHCA patients is well-compared in several studies, including three randomised controlled trials showing similar non-significant trends towards the beneficial effect of EC.[7–9] Our overall result is consistent with these studies. Furthermore, our study first focused on the heterogeneity of the effectiveness of the cooling method between patients with different initial rhythms and demonstrated that the optimal cooling method for TTM after OHCA may differ depending on the initial rhythm.

Initial non-shockable rhythm is known to be associated with longer no-flow time, which means longer exposure to global ischaemia.[12] Patients with an initial non-shockable rhythm are also associated with older age and a higher rate of co-existing chronic conditions that predispose to deterioration in underlying conditions and depletion of physiologic reserves,[13] can be more susceptible to ischaemic injury. As ischaemic injury progresses, patients are imminently threatened with reperfusion injury.[20, 21] Therefore, the advantages of rapid and tighter temperature control of EC may be more prominent in patients with non-shockable rhythm. Furthermore, our data showed that the initial non-shockable patients treated with PCI benefited more from EC, suggesting that rapid reperfusion with intensive reperfusion injury protection may be more feasible. Consequently, our data might show heterogeneity in the effectiveness of SC and EC in patients with different initial rhythms. Together with recent data that demonstrate the superiority of induced hypothermia to normothermia for the outcome of initial non-shockable patients,[22] a certain proportion of initial non-shockable patients may benefit more from intensive treatment strategies.

Our overall cohort showed similar patient demographics with a previous report from a large international registry, while the percentages of patients who presented with shockable rhythm (47% vs. 51%) and those treated with TTM-low (67% vs. 73%) were slightly decreased, possibly because of the secular change in the implementation of TTM.[23] However, it is worth mentioning that there was significant heterogeneity in the targeted temperature between the cooling method groups. Clinicians prefer TTM-high when they use SC; this trend was prominent in patients with non-shockable rhythm, whereas there was no significant heterogeneity in patients with shockable rhythm. These results should be interpreted with caution. In our study, as in most observational studies, the decision for the TTM strategy is fully entrusted to the treating clinicians. Aside from various individual indication criteria that affect the decision, it is natural for clinicians to choose a minimally invasive strategy for patients who are or may become critically ill on the presupposition that the target temperature and cooling method do not have a significant impact on the outcome. Our analysis showed that non-shockable patients treated with SC are likely to be targeted at TTM-High; previous trials have shown that patients with several factors known to be associated with poor prognosis, such as absence of bystander CPR, absence of witness, initial non-shockable rhythm, older age, and longer time to return of spontaneous circulation, may tend to be treated with SC at TTM-High.[6, 23] However, it can be difficult to retrospectively adjust all of the factors that designate highly vulnerable patients because of the dramatic clinical course of OHCA. From another point of view, clinicians' decision to treat non-shockable patients with SC at TTM-high itself may occasionally reflect the patients' desperate status assessed dynamically through primary resuscitation which could not be revealed by retrospective static data. Therefore, clinicians should be aware that a certain proportion of the most severe patients may tend to be included in the group of non-shockable patients treated with SC at TTM-High, the least invasive TTM implementation strategy. Our results imply that there is a need for a randomised clinical trial on the efficacy of cooling methods for TTM among certain groups of patients, given the real-world selection bias observed in those who received this treatment.

At present, guidelines do not recommend a cooling method for the implementation of TTM due to lack of evidence indicating that any specific cooling method improves outcomes after cardiac arrest when compared with any other cooling method.[1, 2, 24, 25] Meanwhile, our results suggest that the TTM implementation strategy in accordance with the initial rhythm might be important. Considering the results of recent trials that focused on initial non-shockable patients,[24, 26] the optimal TTM strategy may be different in this group of patients. As the mortality of this group of patients is still high,[22, 23, 26] they may benefit more from improvement in the TTM strategy. Furthermore, the suggestion to consider TTM for non-shockable patients was reinforced in the latest guideline,[1] and the number of patients receiving TTM may increase. Therefore, our results underscore the need for further studies in this patient group.

Our study has several limitations. First, if methods to control the temperature were duplicated, the TTM procedure category was defined as EC in this case. Therefore, several patients treated with both EC and SC were included in the EC group. However, in a real-world setting, SC is often added to the EC to achieve the target temperature more rapidly. Furthermore, since previous studies compared relatively limited cooling methods (e.g. endovascular device vs. conventional cooling method, endovascular device vs. SC device, endovascular device vs. single SC devices) on the outcome of patients showed similar trends without significant difference,[5, 6, 9, 10] we believe it is important to focus on the interaction of different mechanisms of heat exchange and initial rhythm on the outcome. Second, we excluded patients requiring ECMO because of completely different invasiveness, effect of cardiac support, and baseline patient severity who needed ECMO. Therefore, our findings cannot be applied to the management and outcomes of OHCA in these patient groups. Third, as mentioned above, patient selection bias may have occurred.

Conclusions

From the nationwide OHCA registry in Japan, we demonstrated that the use of EC was associated with better outcomes in OHCA patients with an initial non-shockable rhythm, while no such association was observed in those with initial shockable rhythm.

List Of Abbreviations

TTM, target temperature management; OHCA, out-of-hospital cardiac arrest; SC, surface cooling; EC, endovascular cooling; JAAM, Japanese Association for Acute Medicine; ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; EMS, emergency medical service; PCI, percutaneous coronary intervention; CPC, cerebral performance category; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; IPW, inverse probability weighting.

Declarations

Ethics approval and consent to participate

The protocol was approved by the institutional review board of each participating hospital. The registry was approved by the Ethics Committee of Kyoto University; each hospital approved the JAAM-OHCA Registry protocol as necessary.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the JAAM-OHCA registry committee. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission from the JAAM-OHCA registry committee.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MW drafted the manuscript; HO, MK, YN, YM, and NO helped draft the manuscript. TM, TK, and BO have revised the manuscript. TM provided statistical advice on the study design and analysed the data. All authors contributed fully to all aspects of the study and approved the final manuscript. TM takes responsibility for the paper as a whole.

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Tables

Due to technical limitations, tables 1 and 2 is only available as a download in the Supplemental Files section.

Figures

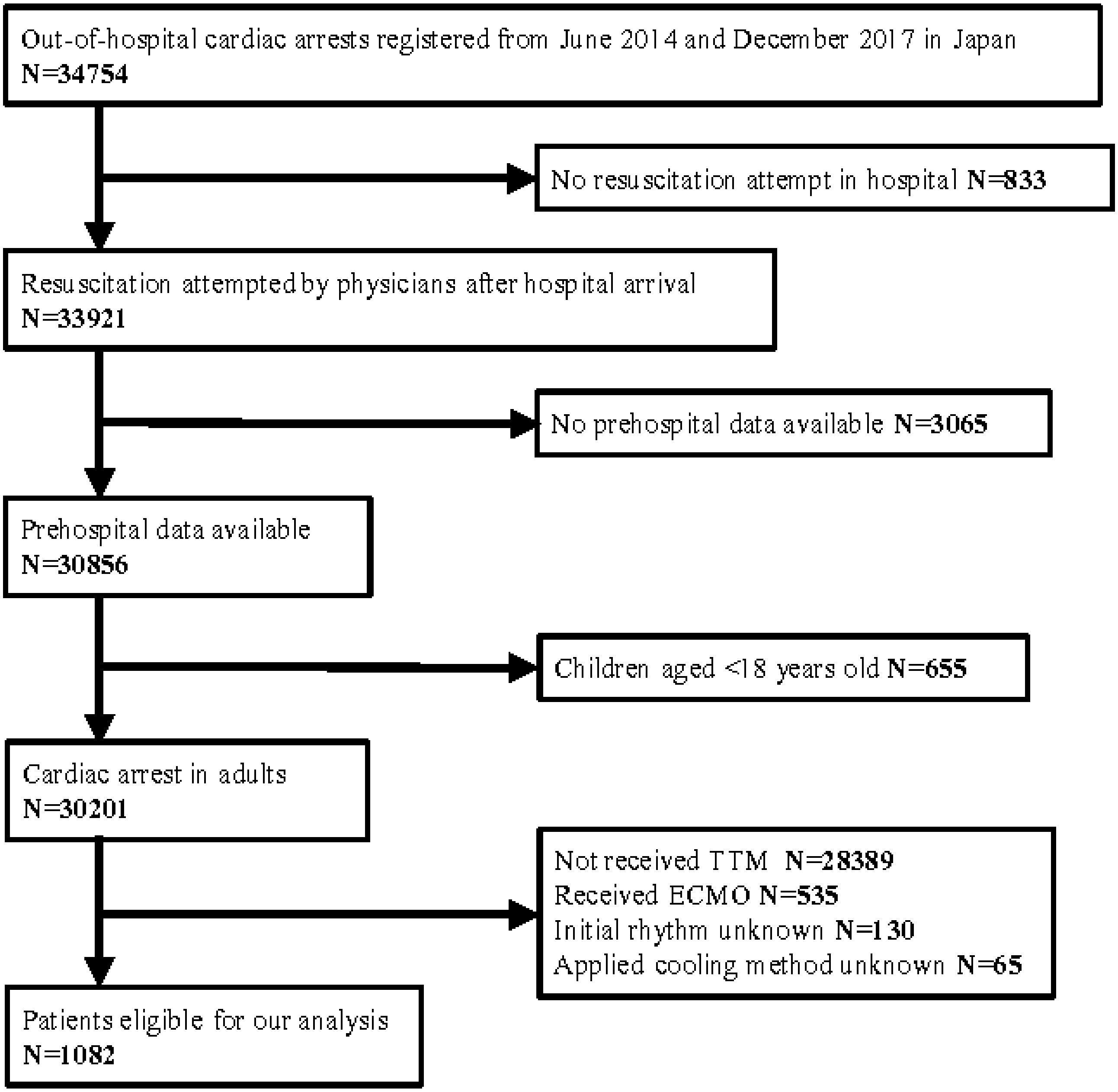

Figure 1

Study flow chart. TTM, target temperature management; ECMO, extracorporeal membrane oxygenation.

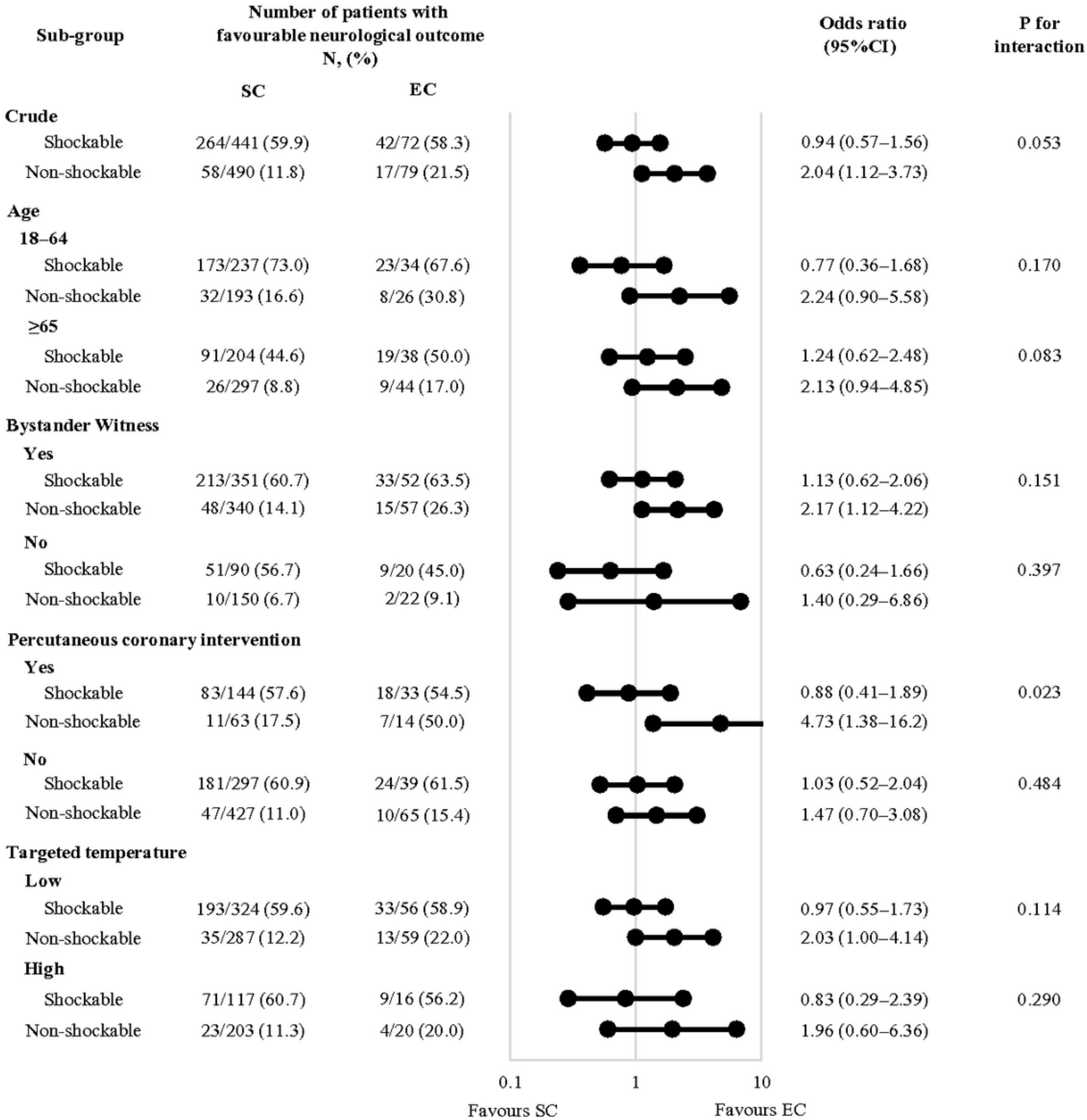

Figure 2

Interaction between initial rhythm and cooling method on the neurological favourable outcome of the patients. Values are expressed as numbers (percentages) unless indicated otherwise; SC, surface cooling; EC, endovascular cooling; CI, confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1Patientcharacteristicfinal.xlsx
- Table2Outcomefinal.xlsx
- TableS1PatientcharacteristicwithSMDfinal.xlsx