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Clinical paper

Effectiveness and safety of early enteral nutrition for patients who received targeted temperature management after out-of-hospital cardiac arrest

Woo Jin Joo[a], *Kazuki Ide*[a,b], *Yohei Kawasaki*[c], *Chikashi Takeda*[a,d], *Tomotsugu Seki*[a], *Tomoko Usui*[e], *Koji Kawakami*[a,b,*]

[a] *Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoecho, Sakyo-ku, Kyoto-city, Japan*

[b] *Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto, Japan*

[c] *Biostatistics Section, Clinical Research Center, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-city, Japan*

[d] *Department of Anesthesia, Kyoto University Hospital, Kyoto, Japan*

[e] *Division of Nephrology and Endocrinology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan*

Abstract

Aim: Early enteral nutrition (EN) is recommended for critically ill patients; however, few reports have examined early EN for patients who received targeted temperature management (TTM) after out-of-hospital cardiac arrest (OHCA). We investigated the effectiveness and safety of early EN for patients who received TTM after OHCA.

Methods: We used a nationwide Japanese administrative database to identify OHCA patients who received TTM from April 2008 to March 2017. The primary outcome was 30-day mortality; secondary outcomes were incidences of all-cause infection, pneumonia, and intestinal ischemia.

Results: Of the 1932 OHCA patients who received TTM, 1682 met the inclusion criteria. Of these, 294 received early EN within 2 days from the initiation of TTM and 266 propensity-score matched pairs were generated. Cox regression analyses revealed no significant difference in 30-day mortality between groups (hazard ratio (HR): 0.90; 95% confidence interval (95% CI): 0.65–1.25). There was no significant difference in the incidence of all-cause infection (odds ratio (OR): 0.98; 95% CI: 0.66–1.46) or pneumonia (OR: 1.02; 95% CI: 0.68–1.55). Subgroup analyses of patients with a low body mass index (BMI; kg/m2) ($<$ 18.5) revealed a significant decrease of 30-day mortality in the early EN group (HR: 0.30; 95% CI: 0.092–0.97) but no significant difference among patients with a BMI $\geq$ 18.5 (HR: 1.01; 95% CI: 0.72–1.43).

Conclusion: Among patients who received TTM after OHCA, there was no significant association between early EN and 30-day mortality; however, early EN could be beneficial for patients with a low BMI.

Keywords: Body mass index, Early enteral nutrition, Malnutrition, Out-of-hospital cardiac arrest, Propensity score matching, Targeted temperature management, Therapeutic hypothermia

* Corresponding author at: Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-cho, Sakyo-ku, Kyoto-city, Japan.

E-mail address: kawakami.koji.4e@kyoto-u.ac.jp (K. Kawakami).

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Introduction

Nutritional support is essential for critically ill patients, since most critically ill patients have a hyper metabolic and immune response to the underlying disease, which can lead to malnutrition associated with mortality and complications.[1] When there is no clear reason not to use the gastrointestinal tract, enteral nutrition (EN) is preferred to parenteral nutrition.[2] Early EN within 24–48 h after admission is recommended in European and American guidelines.[3,4] For critically ill patients, early EN can prevent malnutrition and maintain gut barrier function, which may lead to reduction of infection and bacterial translocation.[5–7] However, the effectiveness and safety of early EN for hemodynamically unstable patients are still uncertain.[8] For such patients, there is a concern that early EN can cause negative results, including intestinal ischemia and worsen hemodynamic instability.

Therapeutic hypothermia or targeted temperature management (TTM) is recommended for comatose patients after cardiac arrest,[9] and it is becoming more common practice in intensive care units (ICUs). Hypothermia sometimes causes hypotension and intestinal dysfunction, which provoke hesitation to start EN. Early EN for TTM patients may be recommended like other critically ill patients[10,11]; however, there are few reports about the topic.[12] Further, energy demands may be lower during TTM because of deep sedation and hypothermia[13]; therefore, the risk of malnutrition and the effectiveness of early EN may be low. However, some reports showed that energy expenditures were higher than expected during TTM.[13,14] Nonetheless, it is still unclear whether early EN for patients on TTM is beneficial.

In sum, we examined the effectiveness and safety of early EN during TTM and the association between early EN and outcome of patients who received TTM after out-of-hospital cardiac arrest (OHCA).

Methods

Data source

This was a retrospective cohort study using an administrative claims database in Japan. The data were provided by Medical Data Vision Co., Ltd (MDV; Tokyo, Japan), which contains anonymous information mainly from diagnosis procedure combination (DPC) claims. The DPC is a Japanese case-mix classification system that is linked to a lump-sum payment system.[15] Approximately 1500 hospitals use DPC in acute medical care, and the MDV database covers about 17% of Japanese acute care hospitals. It contains patient characteristics such as age, sex, comorbidities, admission precipitating disease, medical procedures, clinical examination, prescriptions, and in-hospital outcomes. Disease names are coded using the International Classification of Diseases, 10th Revision (ICD-10) codes.

The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (No. R1189; August 29, 2017). This study followed the guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Study population and outcomes

The inclusion criteria were adult patients who received TTM after OHCA between April 2008 and March 2017; aged $\geq$ 20 years; received TTM on day 0 or day 1; and were diagnosed with cardiac arrest (I46), ventricular tachycardia (I472), or ventricular fibrillation (I490) at admission. Exclusion criteria were having abdominal surgery, abdominal bleeding, ileus on day 0 or day 1, or discharged within 2 days from admission.

The primary outcome was 30-day mortality. Secondary outcomes included incidence of pneumonia, all-cause infection, and gastrointestinal ischemia. Patients were divided into two groups according to the day when EN was started. Those who received EN within 2 days from the start of TTM comprised the 'early EN group', and the remaining patients comprised the control group.

Covariates

We collected information concerning patients' characteristics such as age, sex and comorbidities, cardiogenic or not, organ-supportive therapies (intra-aortic balloon pumping (IABP), extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy), drugs used after admission, and hospital volume (Table 1). We defined non-cardiogenic arrest the same as a previous study, according to ICD-10 codes at admission or primary diagnosis[16] (Supplementary Table 1). Post-admission therapy within 2 days of admission were used as covariates because it may represent patient severity, which influence the decision to proceed with early EN. Hospital volume was defined per the average number of patients treated with TTM per year and divided into tertiles.

Statistical analysis

Age was expressed as median (interquartile range), and other continuous variables were expressed as means (standard deviations). Categorical variables were described as numbers (percentages). We used propensity score matching approach to adjust for differences in patients' characteristics and severity.

We used age, sex, body mass index (BMI), Charlson Comorbidity Index score (CCI), cardiogenic arrest or not, cardiac arrest on admission, and post-admission therapy as covariates for estimating propensity score. Then, propensity score matching was performed using the nearest neighbour matching without replacement, and a caliper width of 0.1 of the standard deviation was used. Those with missing values of any covariates were excluded from matching. Cox proportional hazard model was used to compare 30-day mortality between the early EN group and control group. Death within 30 days after admission was identified by DPC records, and discharge within 30 days was treated as censored. We performed logistic regression analyses to compare categorical outcomes such as incidence of pneumonia.

Malnutrition has been associated with worse clinical outcomes of critically ill patients, and early EN may be more effective for such patients.[17] The World Health Organization considers a BMI (kg/m2) $<$ 18.5 as underweight, and most studies use a BMI $<$ 18.5 to diagnose malnutrition.[18] Therefore, we performed post-hoc subgroup analyses using BMI ($<$ 18.5 and $\geq$ 18.5) to assess the effect of early EN for patients with malnutrition.

All analyses were performed with SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC). For each analysis, the two-sided significant level was set at $P < .05$.

Sensitivity analysis

We performed sensitivity analyses to confirm the results. First, we used inverse-probability weighting (IPW) instead of matching. Second, we imputed the missing data using the multiple imputation model by monotone regression.[19] We created 25 complete datasets

Table 1 – Characteristics of patients and hospitals.

	Before propensity score matching					After propensity score matching				
	Early EN		Control		Standardized difference (%)	Early EN		Control		Standardized difference (%)
Total	n = 294		n = 1388			n = 266		n = 266		
Age (years), median (IQR)	65.0	(54, 72)	63.0	(51, 72)		65.0	(55, 72)	65.0	(54, 73)	
Male sex, n (%)	213	(72.4)	1071	(77.2)	11.1	191	(71.8)	191	(71.8)	0.0
BMI (kg/m^2), mean (SD)	22.8	(3.9)	23.5	(4.2)	16.5	22.8	(3.9)	22.8	(3.6)	0.8
Charlson comorbidity index score, mean (SD)	2.1	(2.2)	2.0	(2.0)	6.4	2.2	(2.3)	2.2	(2.1)	1.9
Non-cardiogenic arrest, n (%)	56.0	(19.1)	251.0	(18.1)	2.6	49.0	(18.4)	42.0	(15.8)	6.9
Cardiac arrest on admission, n (%)	114.0	(38.8)	609.0	(43.9)	10.4	108.0	(40.6)	112.0	(42.1)	3.0
Postadmission therapy, n (%)										
Steroid	24	(8.2)	103	(7.4)	3.0	20	(7.5)	22	(8.3)	3.0
Muscle relaxants	228	(77.6)	1064	(76.7)	2.1	203	(76.3)	205	(77.1)	1.9
Dopamine	119	(40.5)	600	(43.2)	5.5	104	(39.1)	102	(38.3)	1.6
Dobutamine	61	(20.7)	314	(22.6)	4.6	52	(19.5)	56	(21.1)	4.0
Noradrenaline	138	(46.9)	697	(50.2)	6.6	126	(47.4)	136	(51.1)	7.4
Antiarythmia	112	(38.1)	640	(46.1)	16.3	103	(38.7)	116	(43.6)	10.0
Vasopressin	10	(3.4)	49	(3.5)	0.5	10	(3.8)	12	(4.5)	3.5
IABP	70	(23.8)	391	(28.2)	10.0	67	(25.2)	66	(24.8)	0.9
ECMO	41	(13.9)	269	(19.4)	14.8	38	(14.3)	39	(14.7)	1.1
PCI	83	(28.2)	429	(30.9)	5.9	79	(29.7)	75	(28.2)	3.3
CRRT	34	(11.6)	187	(13.5)	5.7	32	(12.0)	24	(9.0)	9.8
Blood transfusion, n (%)										
Red blood cells	27	(9.2)	1822	(13.1)	12.4	25	(9.4)	22	(8.3)	3.9
Fresh frozen plasma	30	(10.2)	198	(14.3)	12.5	28	(10.5)	26	(9.8)	2.3
Platelets	9	(3.1)	72	(5.2)	10.5	8	(3.0)	7	(2.6)	2.4
Hospital information, n (%)										
TTM volume (mean cases/year)										
Low volume (< 1.7)	9	(3.1)	88	(6.3)	15.2	10	(3.7)	9	(3.3)	2.2
Middle volume (1.7–4.8)	57	(19.4)	373	(26.9)	17.9	47	(17.2)	48	(17.5)	0.8
High volume (> 4.8)	228	(77.6)	927	(66.8)	24.3	217	(79.2)	217	(79.2)	0.0

All data were described as number (%), except for age, BMI, and Charlson comorbidity index score.
The definition of non-cardiogenic arrest according to International Classification of Diseases, 10th Revision codes at admission or primary diagnosis is shown in Supplementary Table 1.
EN, enteral nutrition; IQR, interquartile range; SD, standard deviation; BMI, body mass index; IABP, intra-aortic balloon pumping; ECMO, extracorporeal membrane oxygenation; PCI, percutaneous coronary intervention; CRRT, continuous renal replacement therapy; TTM, Therapeutic temperature management.

under the assumption that data were missing at random, and combined the effect estimates from the imputed datasets using Rubin's rule. We performed propensity score matching and Cox regression analysis after imputation.

Results

A flow diagram of the cohort is shown in Fig. 1. Overall, 1932 patients received TTM after OHCA between April 2008 and March 2017. Of these, 250 (10 with abdominal surgery, 30 with ileus, 119 with gastrointestinal bleeding on day 0 or day 1, and 116 were discharged within 2 days; some patients met two or more exclusion criteria) were excluded. Eligible patients (n = 1682) were divided into the early EN group (n = 294) or control group (n = 1388). The median number of days to start EN among all eligible patients was 4 (see the histogram in Supplementary Fig. 1). Because BMI were missing among 28 (9.5%) participants in the early EN group and 213 (15.3%) participants in the control group, 266 propensity score matched pairs were generated (Fig. 1). Table 1 shows the baseline characteristics of study patients before and after propensity score matching. Patients in the early EN group were less likely to receive anti-arrhythmic drugs, ECMO, and blood transfusions. In addition, most patients in the early EN group were treated at high-volume hospitals. After matching, baseline characteristics of both groups were well balanced.

Fig. 2 shows the Kaplan-Meier survival plots for propensity score matched patients. The Cox regression analysis did not show significant differences of 30-day mortality between groups (hazard ratio (HR): 0.90; 95% confidence interval (CI): 0.65–1.25).

For the sensitivity analysis, the results of IPW were similar to the main analysis (HR: 0.94; 95% CI: 0.82–1.07). Using multiple imputation method for missing values of BMI, 294 propensity score matched pair were generated. The Cox regression analysis of the 294 matched pair after imputation was similar to the main results (HR: 0.84; 95% CI: 0.58–1.21).

Table 2 shows the results of the secondary outcomes. The incidence proportion of all-cause infection and pneumonia did not significantly differ between the two groups. The complication of intestinal ischemia occurred among one patient in the early EN group, while there was no intestinal ischemia in the control group. This patient in the early EN group had chronic heart failure, and the cause of cardiac arrest was acute myocardial infarction. The patient received a blood transfusion, IABP, ECMO, percutaneous coronary intervention, and a high dose of vasopressor after admission.

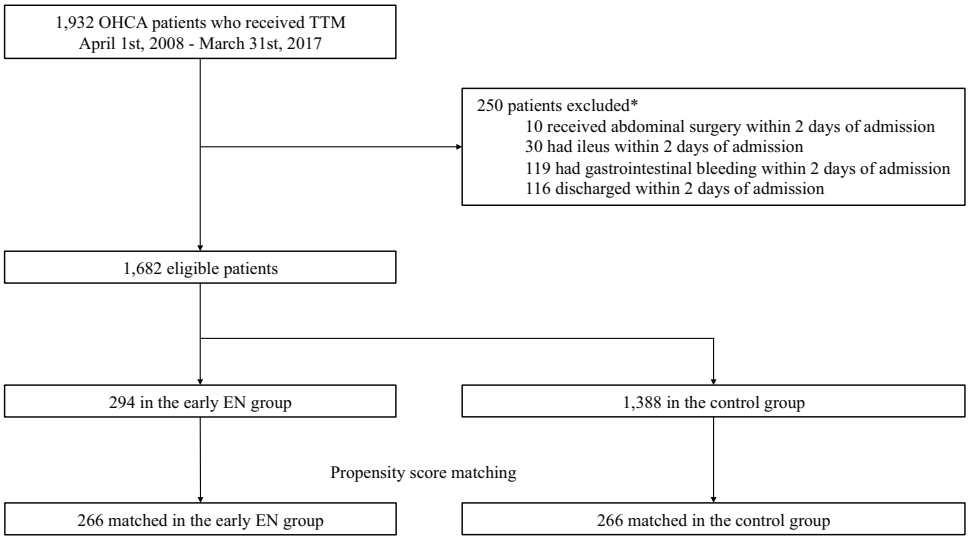

Fig. 1 – Study flow diagram.
OHCA, out-of-hospital cardiac arrest; TTM, therapeutic temperature management; EN, enteral nutrition. *Some patients met two or more exclusion criteria.

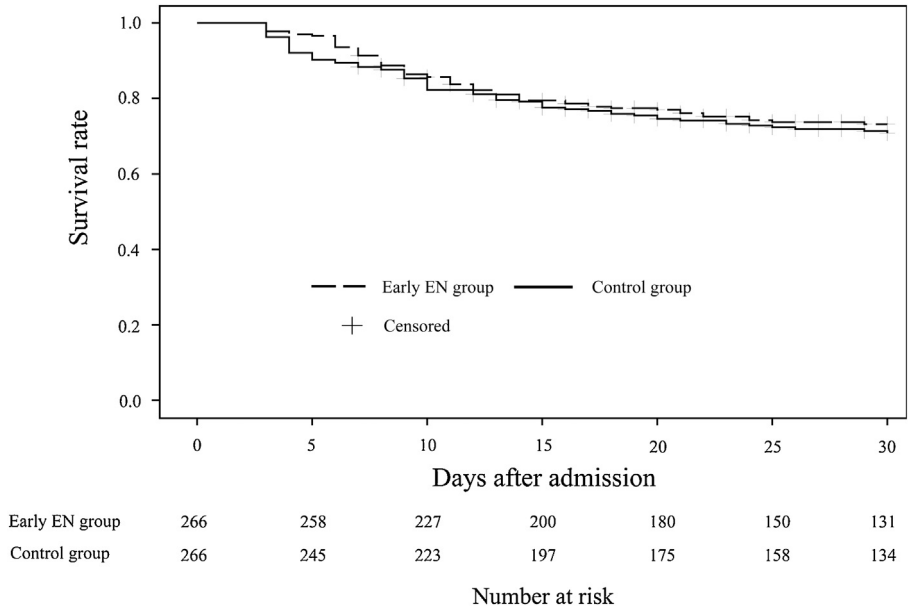

Fig. 2 – Survival plots for propensity score matched patients in the early EN group and control group.
EN, enteral nutrition.

Table 2 – Secondary outcomes after propensity score matching.

	Early EN		Control			
	n = 266		n = 266		OR	(95% CI)
All-cause infection, n (%)	203	(76.3)	204	(76.7)	0.98	(0.66–1.46)
Pneumonia, n (%)	58	(21.8)	57	(21.4)	1.02	(0.68–1.55)
Intestinal ischemia, n (%)	1	(0.4)	0	(0.0)	–	–

EN, enteral nutrition; OR, odds ratio; CI, confidence interval.

Subgroup analyses about BMI are shown in Fig. 3. Among patients with a low BMI (< 18.5), the early EN group showed significantly lower 30-day mortality compared to the control group (HR: 0.30; 95% CI: 0.092–0.97), while no significant difference among patients with BMI ≥ 18.5 were observed (HR: 1.01; 95% CI: 0.72–1.43).

Discussion

We examined the association between early EN and 30-day mortality in patients who received TTM after OHCA. There was no significant

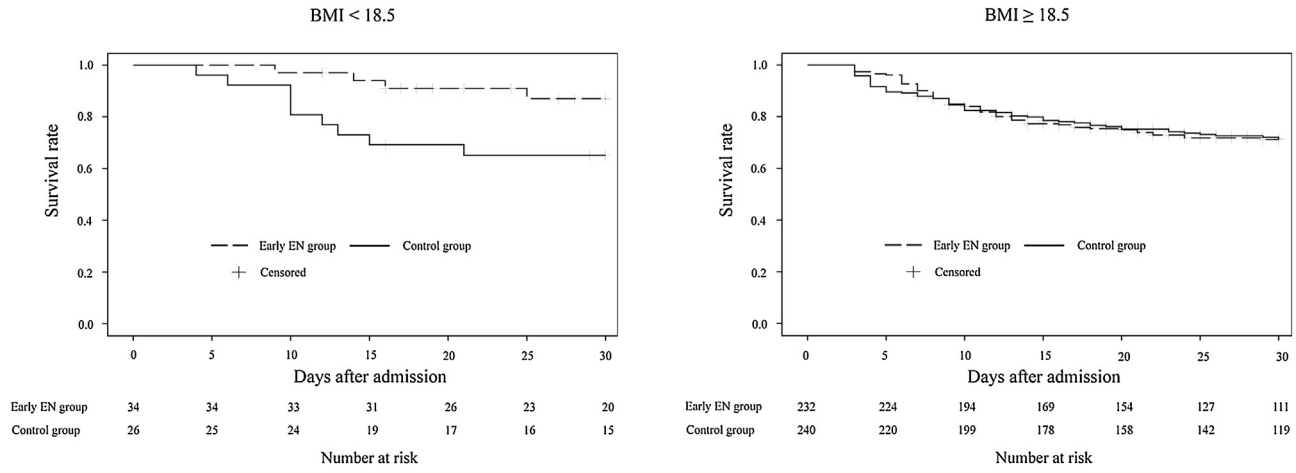

Fig. 3 – Survival plots for propensity score matched patients stratified by BMI in the early EN group and control group. EN, enteral nutrition; BMI, body mass index.

difference in mortality, and no significant increase of adverse events such as pneumonia among propensity-score matched patients. Subgroup analyses showed a significant reduction of mortality among patients with a low BMI. This is the first study to report the association between early EN during TTM and patients' outcomes.

A prior meta-analysis of six randomized controlled trials showed the effect of early EN for reduction of mortality among ICU patients.[7] However, the size of each study was small, and the recent updated meta-analysis showed no significant reduction of mortality and a significant reduction of infection.[11] Strong evidence is still absent about the effect of early EN among critically ill patients.[20] Previous studies focused on trauma and ventilated patients in ICU, and most studies excluded patients with TTM. There is only one case series study about TTM patients, which reported that early EN during TTM may be safe.[12] The present study showed no significant effect to reduce mortality and all cause infection rate of early EN among TTM patients. The metabolic rate of TTM patients may be lower than other critically ill patients such as trauma or sepsis; therefore, they may benefit less from early EN.

Early EN during TTM may cause some adverse events. Some studies showed delayed gastric emptying, representing a concern for critically ill patients,[21,22] and TTM may induce intestinal paralysis. Therefore, early EN during TTM may increase silent pulmonary aspiration, which can lead to pneumonia. On the other hand, recent studies suggested that early EN was related to lower incidence of septic complications, including pneumonia.[23,24] This study showed no significant increase of the incidence of pneumonia and infection. Another possible adverse event of early EN during TTM is intestinal ischemia. Though intestinal ischemia is a rare complication, mortality is high.[25,26] In our study, only one patient in the EN group (0.4%) developed intestinal ischemia. The incidence proportion of intestinal ischemia was similar a previous study that examined patients after cardiopulmonary bypass.[26] Because the number of patients who developed intestinal ischemia in our study was small, we could not estimate the association between early EN and the development of intestinal ischemia.

Further, this study showed that early EN was associated with a significant decrease of mortality among TTM patients with a low BMI. When we start nutritional support for patients with malnutrition, we should be aware of the risk of overfeeding and re-feeding syndrome. On the other hand, enough nutritional support may be beneficial, especially among patients with malnutrition.[27] In this study, BMI may reflect the baseline nutritional status of the patients, and it may modify the effect of early EN on mortality. Even during TTM, patients with malnutrition may require early nutrition supports. However, there is limited evidence, and further studies focused on this topic are needed.

Our study has several limitations. First, because of the nature of the database, no detailed data about pre-hospital information such as witness, bystander cardiopulmonary resuscitation, advanced airway management, and automated external defibrillator use was available. The pre-hospital background would be similar among patients who received TTM, because there were usually similar adaptation criteria for induction of TTM in each hospital. We used propensity score matching to match the patients' severity, and the patients' characteristics between groups were well balanced about the identified covariates. However, this may be insufficient, and further study is required to adjust for more covariates such as the detailed data of pre-hospital condition.[28] Second, there was no detailed data about EN and TTM. The formula and the amount of EN, and the details of the TTM protocol at each hospital, such as the accurate degree and duration of target temperature and the speed of cooling or rewarming, were not available from the database. The dates when TTM was performed or when EN commenced were available; however, the detailed time relationship was unclear. Further studies with more detailed data about EN and TTM are required. Third, pneumonia and intestinal ischemia were defined using disease codes; therefore, misclassification might occur. The incidence of pneumonia was lower than that reported in a previous study[29]; therefore, it may have been underdiagnosed. Fourth, because this was a not randomized controlled trial, there may be unmeasured confounders. However, conducting a randomized controlled trial with this population would prove difficult.

Conclusion

There were no significant associations between early EN and mortality among patients who received TTM after OHCA. However, subgroup analyses showed significant reduction of mortality among patients with a low BMI. Early EN may be beneficial, especially among patients on TTM with malnutrition. Further prospective studies with more detailed data and larger cohorts are needed to examine the effect of early EN for patients treated with TTM.

Conflicts of interest

T. Seki received personal fees from Pfizer.inc, outside the submitted work. K. Kawakami received honoraria from Shin Nippon Biomedical Laboratories, Ltd.; research funds from Olympus Corporation, Sumitomo Dainippon Pharma Co., Ltd., Bayer Yakuhin Ltd., Stella Pharma Corporation, Novartis Pharma K.K., CMIC Co., Ltd., Amgen Astellas BioPharma K.K., Suntory Beverage & Food Ltd., and Medical Platform Co., Ltd.; and holds stocks in School Health Record Center Co., Ltd. and Real World Data, Co., Ltd. There are no patent products under development or marketed products to declare, relevant to those companies.

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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.2019.01.007.

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