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Original Article

Early enteral nutrition in patients with out-of-hospital cardiac arrest under target temperature management was associated with a lower 7-day bacteremia rate: A post-hoc analysis of a retrospective cohort study

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Bacteremia;
Critical care;
Hypothermia;
Heart arrest

Abstract *Introduction:* Early enteral nutrition (EN) is a nutritional strategy for reducing the incidence of in-hospital infections. However, the benefits of early EN, under targeted temperature management (TTM) in patients with out-of-hospital cardiac arrest (OHCA), remain unclear. We aimed to evaluate the effect of early EN on the infective complications of OHCA patients who underwent TTM.
Methods: We retrospectively searched the clinical databases of two adult emergency tertiary referral hospitals in southern Taiwan and identified patients admitted for OHCA who underwent TTM between 2017 and 2022. The 85 enrolled patients were divided into two groups based on timing: early EN (EN within 48 h of admission) and delayed EN (EN $>$ 48 h after admission). Clinical outcomes of 7-day infective complications between the two groups were analyzed.
Results: Early EN was provided to 57 (67 %) of 85 patients and delayed EN was provided to the remaining 28 (33 %) patients. No significant differences in baseline patient characteristics were observed between the two groups. In addition, no differences in clinical outcomes were observed, except that the early EN group had a lower 7-day bacteremia rate (5.3 % vs. 26.9 %, $p = 0.013$). Gram-negative bacteria were the major pathogen among the 7-day infective complications.
Conclusion: In OHCA patients treated with TTM, early EN was associated with a lower 7-day bacteremia rate. Furthermore, the application of early EN in this population was well tolerated without significant adverse events.

Introduction

Enteral nutrition (EN) is widely used in critical care because of its ease of use, cost-effectiveness, maintenance of intestinal mucosal integrity, activation of the gastrointestinal immune system, and reduction in intestinal bacterial translocation.[1] Early EN (within 48 h of admission) has also been associated with reducing the incidence of in-hospital infections, with a trend towards lowering mortality.[2] Therefore, current critical care guidelines recommend that critically ill patients immediately start EN as nutritional support unless there are obvious contraindications.[2–4]

In Taiwan, targeted temperature management (TTM) is widely used for patients with out-of-hospital cardiac arrest (OHCA). Infectious diseases, such as pneumonia, are common fatal complications in this population.[5,6] EN support appears to be a reasonable option for patients with OHCA; however, the optimal timing of EN administration in these patients remains unknown. Moreover, hypothermia may temporarily reduce nutritional requirements in patients with TTM[7] because it slows gastrointestinal motility.[7,8] Furthermore, establishing intestinal feeding in this group could be challenging; this is because EN may increase gastrointestinal blood flow, thereby affecting systemic hemodynamics and causing adverse effects in patients with hemodynamic instability after cardiac arrest.

Therefore, this study aimed to examine whether early EN can decrease infective complications and provide clinical benefits in patients with OHCA undergoing TTM.

Materials and methods

Data for this study were derived from the clinical databases of two adult emergency tertiary referral hospitals in Kaohsiung City, southern Taiwan. The data used included age, sex, medical history, reason for admission, emergency room treatment, tests and treatments after admission, prescriptions, and discharge diagnoses. Diseases were coded according to the International Classification of Diseases, 10th edition (ICD-10).

This study was approved by the Ethics Committee of the Kaohsiung Veterans General Hospital (KSVGH22-CT10-03). In accordance with the Declaration of Helsinki and the principles of the International Conference on Uniform Clinical Medicine Standards, the privacy of the patients included in the study was fully protected.

Study population

The inclusion criteria were as follows: 1) adult patients (aged $\geq$18 years); 2) patients hospitalized due to OHCA between January 2017 and January 2022; and 3) patients who received TTM during hospitalization. As ventricular tachycardia and fibrillation are common heart rhythms in patients with OHCA on admission,[9] we used ICD-10 codes for cardiac arrest (I46.2, I46.8, and I46.9), ventricular tachycardia (I47.2), ventricular fibrillation (I49.01), and ventricular flutter (I49.02) to identify patients with OHCA. The exclusion criteria were as follows: 1) received no nutritional feeding during hospitalization; 2) discharged within 2 days of admission; 3) abdominal surgery, gastrointestinal bleeding, ileus, intestinal ischemia, or any infection (e.g., evident pneumonia and urinary tract infection [UTI]) presented within the first 2 days of admission; and 4) received any antimicrobial therapy during the past 4 weeks before admission.

A total of 1098 adult patients with ICD-10 codes I46.2, I46.8, I46.9, I47.2, I49.01, and I49.02 were enrolled from 2017 to 2022. Of these, 104 experienced in-hospital cardiac

arrest, and 72 were miscoded. Ten patients did not receive food during admission. Additionally, 475 patients were admitted to the hospital for <2 days. Sixty-six patients were excluded for undergoing abdominal surgery within 2 days of admission, occurrence of intestinal ischemia or gastrointestinal bleeding, contracting any infectious disease within 2 days of admission, or a medical history of antimicrobial therapy within 4 weeks before admission. Another 320 patients did not undergo TTM. The remaining 85 patients were included in the final analysis: 57 (67 %) in the early EN group and 28 (33 %) in the delayed EN group (Fig. 1).

Protocols of TTM and EN

Both study hospitals followed the same protocol for TTM use in adult patients with OHCA and return of spontaneous circulation after resuscitation (i.e., patients with stable hemodynamics after emergency resuscitation but still comatose, defined as a Glasgow Coma Scale score of <9).[10] Patients with life-threatening hemorrhage (i.e., intracranial hemorrhage) or terminal disease who signed a "Do Not Attempt Resuscitation" status consent form were excluded. The protocol involved a target temperature of 33—34 °C for 24 h, a rewarming target temperature of 36 °C, and a rewarming rate of 0.2—0.25 °C per hour. To prevent tremors in patients during TTM, sedatives and muscle relaxants were used to maintain the patients' Richmond Agitation Sedation Scale score at −5. Patients' vital signs, electrolytes, and coagulation function were regularly monitored during the hypothermia treatment. Vasopressors were used in evident cases of shock (mean arterial pressure <65 mm Hg).

EN was established by using nasogastric or duodenal tubes. After placement, the feeding tube position was confirmed by radiography and physical examination. Clinical nutritionists, nurses, and physicians discussed patients' nutritional feeding goals and established feeding protocols. EN was initiated at 10—30 mL/h[11] with a final calorie target of 25 kcal/kg/day[12] if the patient could tolerate the feeding strategy. The proportions of early EN and delayed EN provided by the two hospitals are illustrated in Appendix 1.

Neurologists and intensivists changed the treatment policies for patients with OHCA, based on clinical and laboratory information, 1 week after the end of TTM. Palliative care was discussed with the family if the prognosis was poor.

Data collection

We divided the 85 enrolled patients into two groups based on the timing of EN administration: those who received EN within 48 h of admission (early EN group) and those who received EN 48 h after admission (delayed EN group). We calculated the Charlson Comorbidity Index (CCI) based on the patient's medical history. Acute Physiological Assessment and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and modified Nutrition Risk in Critically ill (m-NUTRIC) scores were calculated based on the vital signs and laboratory data first recorded when the patient entered the intensive care unit.[13,14] The m-NUTRIC score was derived from the original NUTRIC formula, excluding the level of interleukin-6.[14]

Since high-dose vasopressors may contraindicate EN,[2—4] we used the norepinephrine equivalence (NEE) to quantify vasopressor use in each patient. The NEE was calculated using the latest dose of each vasopressor required at 48 h post-admission as follows: norepinephrine dose (μg/kg/min) +

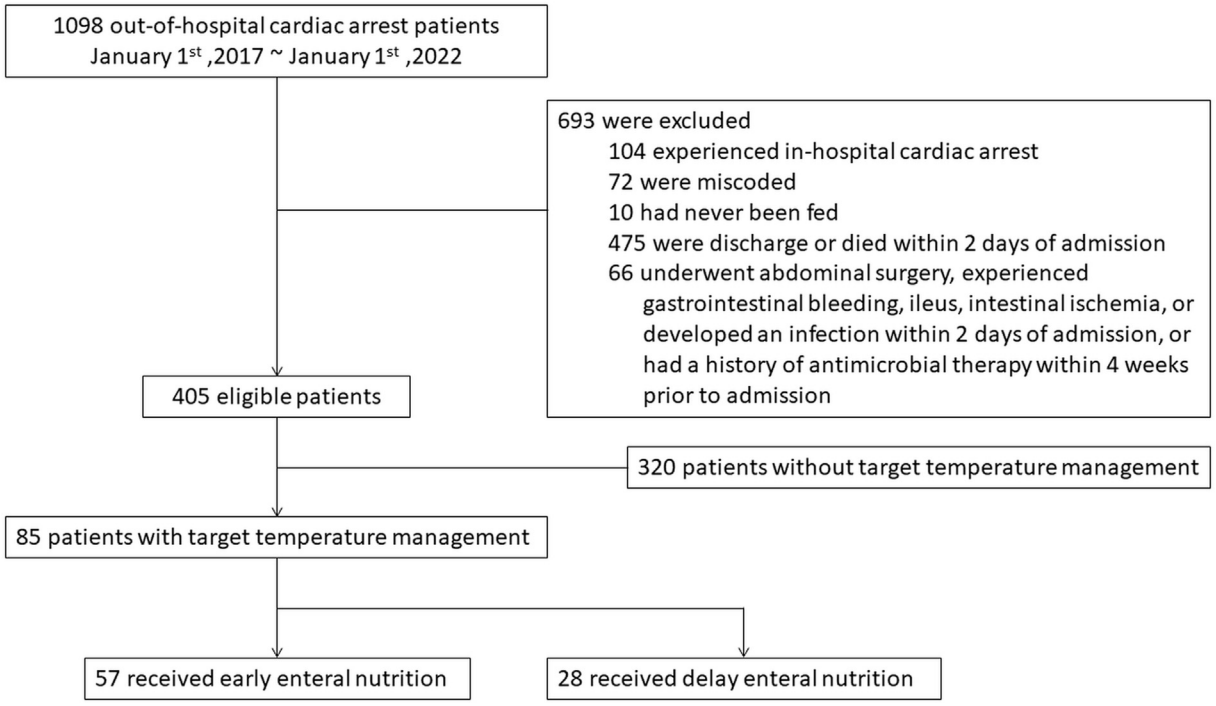

Figure 1. Flow chart of patient selection.

epinephrine dose (μg/kg/min) + 1/10 × phenylephrine dose (μg/kg/min) + 1/100 × dopamine dose (μg/kg/min) + 1/8 × metaraminol (μg/kg/min) + 2.5 × vasopressin dose (U/min) + 10 × angiotensin II dose (μg/kg/min).[15,16]

Outcomes

The primary outcomes were 7-day infective complications, including bacteremia, pneumonia, UTI, or any other documented infectious disease. The secondary outcomes included 7-day and 30-day mortality; length of hospital stay; ventilator dependence rate; and fair neurological outcome rate. Safety monitoring items included the incidence of gastrointestinal bleeding, ileus, and occurrence of intestinal ischemia within 7 days of admission.

Both medical institutions adhered to a standardized protocol for the management of patients presenting signs of infection. When infection-associated symptoms manifested, including fever, elevated or left-shifted white blood cell counts, and heightened oxygen requirements, patients were consistently subjected to a range of diagnostic measures, such as collection of blood cultures and specimens from suspected infection sites. The practice of obtaining blood cultures was notably consistent across both hospitals, revealing comparable positivity rates that fluctuated within the range of 15%—20 % over the last 5 years. Furthermore, it is noteworthy that both hospitals strictly adhered to the guidelines established by The Clinical and Laboratory Standards Institute, ensuring the issuance of reliable and substantiated reports and underscoring the commitment to maintaining high accuracy and credibility in the realm of clinical laboratory practices.

All-cause infections, including pneumonia; any site of infection such as UTI; and bacteremia, were retrospectively identified by ICD-10 codes and chart review by two physicians. Pneumonia was defined as a condition in which a patient presents with fever, hypoxia, and acute lower respiratory symptoms, combined with new inflammatory infiltrates observed on chest imaging and microbiological evidence (e.g., a positive culture of lower respiratory tract specimen) or serological diagnosis (e.g., a positive urinary pneumococcal antigen) of infection.[17] UTI was defined as a condition in which a patient exhibits acute urinary symptoms such as dysuria, hematuria, frequency, and pyuria in urine analysis, with a positive urine culture.[18] Bacteremia was defined as one positive blood culture that grew non-skin flora or two positive blood cultures that grew skin flora determined by sampling blood from different sites. Blood cultures with the growth of only a single set of coagulase-negative staphylococci, *Bacillus* species, *Micrococcus* species, *Cutibacterium* species, or gram-positive bacilli were considered contaminant samplings.[19,20] The calculation of final bacteremia rates only included patients who had blood culture samples drawn during their hospital stay. Early infection was defined as an infective episode within 7 days of admission, with documented clinical, microbiological, and radiologic evidence.[21]

Patients who could not be successfully weaned from ventilator assistance in 21 days were defined as ventilator-dependent patients based on previous expert consensus.[22] A fair neurological outcome was defined as a modified Rankin Scale score of 0, 1, or 2 at discharge. Gastrointestinal bleeding was defined as a positive occult blood test of the gastrointestinal tract material and documented positive esophagogastroduodenoscopy findings. Ileus and intestinal ischemia were retrospectively confirmed through imaging, which was reviewed by two physicians.

Covariates

Patient-related characteristics were collected anonymously for analysis, including age, sex, height, weight, medical history, shockable rhythm in emergency department, type of intensive treatment received, and type of drugs received after admission. Laboratory data, including complete blood count, liver and kidney function, lipoproteins, albumin, uric acid, inflammatory index, and lactate levels, were also included in the analysis.

Statistical analyses

Demographic and clinical characteristics were summarized for the early and delayed EN groups and expressed as median (interquartile range) or number (percentage), as appropriate. Differences owing to non-parametric data between the two groups were calculated using the independent Mann—Whitney U test and Chi-squared test or Fisher's exact test for continuous and categorical variables, respectively. Logistic regression was employed to assess the collected parameters for progression. All statistical analyses were performed using Statistical Analysis Software (SAS; version 9.4; SAS System for Windows) and SPSS (version 20; SPSS Inc., Chicago, Illinois, USA). Statistical significance was set at $p < 0.05$.

Results

The median patient age was 62.0 years, and the majority were male (75.3 %) (Table 1). The median body mass index (BMI) was 24.2 kg/m^2, indicating slight overweight according to the Asian criteria. The median CCI was 4.0 (interquartile range, 2.0—6.0). Underlying diseases did not differ between the two groups. The early EN group exhibited a higher APACHE II score than the delayed EN group (28.0 vs. 22.5, $p = 0.020$). Similarly, SOFA scores were slightly higher in the early than the delayed EN group, although this difference did not reach statistical significance (9.0 vs. 8.0, $p = 0.538$). The median m-NUTRIC score was 5.0 (interquartile range, 4.0—6.0), indicating that most patients had a high risk of nutrition deficiency.[14] The NEE at 48 h of admission was 0.11 (interquartile range, 0.00—0.28). Most patients (77.6 %) reached the caloric target of 25 kcal/kg/day on day 7 after starting EN. The early EN group had lower blood sodium ion (137.0 vs. 140.0 mmol/L, $p = 0.046$) and higher blood glutamic oxaloacetic transaminase (65.0 vs. 48.0 U/L, $p = 0.044$) levels than the delayed EN group (Table 2).

The study outcomes are summarized in Table 3. A total of 83 patients had blood culture samples drawn within the first 7 days of hospitalization due to suspected infections. Among them, 57 patients were classified as the early EN group, and the remaining 26 were in the delayed EN group. The overall positivity rate of blood cultures within 7 days was 12.0 %. The rate of early onset bacteremia in the early EN group was

Table 1 Baseline characteristics of out-of-hospital cardiac arrest patients with target temperature management.

Variable (Median, IQR)	Total	Early EN	Delay EN	p-value
	n = 85 (%)	n = 57 (%)	n = 28 (%)	
Age, years	62.0 (49.5–72.5)	59.0 (50.0–71.5)	68.0 (49.0–79.5)	0.442
Male	64 (75.3)	41 (71.9)	23 (82.1)	0.305
BMI	24.2 (21.6–28.6)	24.4 (21.6–29.2)	23.6 (21.7–26.5)	0.877
Charlson comorbidity Index	4.0 (2.0–6.0)	4.0 (2.0–5.0)	4.0 (1.0–7.0)	0.765
Hypertension	43 (50.6)	28 (49.1)	15 (53.6)	0.700
Myocardial infarction	24 (28.2)	16 (28.1)	8 (28.6)	0.962
Heart failure	6 (7.1)	4 (7.0)	2 (7.1)	1.000
CVA or TIA	14 (16.5)	9 (15.8)	5 (17.9)	0.809
Dementia	4 (4.7)	4 (7.0)	0 (0.0)	0.297
Peptic ulcer disease	5 (5.9)	3 (5.3)	2 (7.1)	1.000
Diabetes	33 (38.8)	21 (36.8)	12 (42.9)	0.593
ESRD (dialysis)	12 (14.1)	8 (14.0)	4 (14.3)	0.975
Chronic kidney disease	10 (11.8)	6 (10.5)	4 (14.3)	1.000
COPD	4 (4.7)	3 (5.3)	1 (3.6)	1.000
APACHE II (admission)	27.0 (21.0–33.0)	28.0 (22.5–35.0)	22.5 (20.0–27.8)	0.020
SOFA	8.0 (8.0–11.0)	9.0 (7.0–11.5)	8.0 (8.0–9.0)	0.538
modified NUTRIC	5.0 (4.0–6.0)	6.0 (4.0–6.5)	5.0 (3.0–6.0)	0.277
Norepinephrine equivalence	0.11 (0.00–0.28)	0.10 (0.00–0.23)	0.17 (0.06–0.31)	0.883
Shockable rhythm in ED	24 (28.2)	16 (28.1)	8 (28.6)	0.962
Bystander CPR	35 (41.2)	23 (40.4)	12 (42.9)	0.825
ROSC time (minutes)	13.0 (9.0–20.5)	14.0 (8.0–21.5)	11.5 (9.0–19.8)	0.883
Feeding goal reached	66 (77.6)	44 (77.2)	22 (78.6)	0.886
ECMO	7 (8.2)	4 (7.0)	3 (10.7)	0.679
PCI	37 (43.5)	21 (36.8)	16 (57.1)	0.076

APACHE, acute physiological assessment and chronic health evaluation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CVA, cerebral vascular accident; ECMO, extracorporeal membrane oxygenation; ED, emergency department; EN, enteral nutrition; ESRD, end-stage renal disease; IQR, interquartile range; NUTRIC, nutrition risk in critically ill; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment; TIA, transient ischemia attack.

significantly lower than that in the delayed EN group (5.3 % vs. 26.9 %, $p = 0.013$); however, no other items differed significantly. To mitigate the influence of various hospital-associated factors, we attempted to stratify by hospital when testing the impact of feeding time on early onset bacteremia. The results showed that, while not reaching statistical significance, there was a trend similar to that observed before hospital stratification (Appendix 2). Notably, intestinal ischemia was not observed in any of the patients.

Table 4 shows logistic regression analysis for the 7-day bacteremia occurrence rate with the timing of EN. Univariate analysis revealed a significant difference for early EN between 7-day bacteremia occurrence and the lack thereof. Age, sex, BMI, shockable rhythm in emergency department, APACHE II score on admission, SOFA score, NEE, m-NUTRIC score, and treatment with extracorporeal membrane oxygenation were independent predictors of the 7-day bacteremia rate.

Table 5 displays the outcomes of pathogen analysis in patients with early onset infection in the early and delayed EN groups. *Klebsiella pneumoniae* infection (41.67 %) was the predominant pathogen associated with pneumonia. *Escherichia coli* (36.36 %) constituted the primary pathogen in UTIs. Gram-positive bacteria accounted for 60 % of bloodstream infections. The strains of late onset infections are included in Appendix 3.

Discussion

Main finding

To our knowledge, this is the first study to demonstrate that early EN in OHCA patients under TTM is associated with a reduced 7-day bacteremia rate compared to delayed EN. The time of EN did not affect the incidences of pneumonia or UTI. Among the 10 patients in the cohort with bacteremia, 2 had pneumonia, 1 had UTI, and 7 could not be identified. Notably, bacteremia was caused by enterobacteria in 2 of the 10 patients and by anaerobic bacteria in another 2 patients. Generally, anaerobic bacteria are difficult to grow when exposed to air, making their cultivation on human skin challenging. Contrastingly, these intestinal anaerobes are presumably translocated from the intestinal anaerobic flora due to the collapse of the intestinal barrier after resuscitation.[23]

Patients with cardiac arrest may experience shock, hypoxia, and other adverse events that are detrimental to gastrointestinal blood flow. Intestinal mucosal cells are susceptible to damage in the hypoperfused state.[24] Delayed EN may aggravate villus atrophy in injured intestinal mucosal cells during the first few hours to days of illness.[1,25] Disrupting the tight junctions of intestinal cells can challenge intestinal integrity.[26] Moreover, delayed EN can also affect

Table 2 Laboratory data of out-of-hospital cardiac arrest patients with target temperature management.

Variable (Median, IQR)	Total n = 85	Early EN n = 57	Delay EN n = 28	p-value
WBC (10^3/uL)	13.1 (10.5–16.4)	12.9 (10.7–17.8)	13.1 (10.4–16.0)	0.877
Hb (g/dL)	12.5 (10.5–14.9)	12.1 (10.4–14.8)	13.5 (11.4–15.3)	0.357
PLT (10^3/uL)	214.0 (172.5–271.5)	214.0 (183.0–278.5)	213.5 (159.5–264.5)	0.877
BUN (mg/dL)	21.0 (15.0–34.0)	21.0 (15.0–34.0)	21.0 (16.0–38.8)	0.872
Cr (mg/dL)	1.5 (1.1–2.6)	1.5 (1.1–2.5)	1.6 (1.3–2.7)	0.759
Na (mmol/L)	138.0 (135.0–141.0)	137.0 (134.5–140.0)	140.0 (136.3–143.8)	0.046
K (mmol/L)	4.0 (3.4–4.7)	3.8 (3.4–4.7)	4.2 (3.4–4.7)	0.217
GOT (U/L)	62.0 (42.0–95.0)	65.0 (52.0–96.5)	48.0 (20.0–66.8)	0.044
GPT (U/L)	53.0 (31.5–87.0)	59.0 (37.0–96.0)	40.5 (12.3–66.8)	0.281
Total bilirubin (mg/dL)	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.5 (0.4–0.6)	0.872
Total cholesterol (mg/dL) n = 72	144.5 (112.5–167.0)	143.5 (107.5–171.0)	144.5 (122.5–162.3)	0.809
Triglyceride (mg/dL) n = 72	99.5 (67.0–157.8)	101.0 (65.0–161.3)	75.5 (67.0–134.8)	0.227
HDL (mg/dL) n = 72	36.0 (27.3–45.8)	35.5 (27.0–41.0)	41.5 (29.8–49.5)	0.361
LDL (mg/dL) n = 72	84.0 (55.5–104.0)	79.0 (47.3–100.8)	88.5 (59.8–108.3)	0.809
Glucose (mg/dL)	228.0 (163.0–310.0)	224.0 (146.0–303.5)	244.5 (167.5–319.5)	0.442
Albumin (g/dL)	3.2 (2.8–3.5)	3.1 (2.7–3.4)	3.3 (2.9–3.8)	0.541
Uric acid (mg/dL) n = 66	6.0 (4.3–7.4)	4.8 (3.4–7.0)	6.9 (5.2–8.7)	0.109
HbA1c (%) n = 73	6.0 (5.7–6.6)	6.1 (5.8–7.0)	6.0 (5.5–6.2)	0.110
CRP (mg/dL)	0.9 (0.3–4.2)	0.9 (0.3–4.5)	0.9 (0.2–3.7)	0.877
Lactic acid (mmol/L)	5.9 (3.5–9.6)	6.1 (3.4–10.0)	4.9 (3.6–7.9)	0.281

BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; EN, enteral nutrition; GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamic Pyruvic Transaminase; Hb, hemoglobin; HbA1c, Glycated Hemoglobin; HDL, High-density lipoprotein; IQR, interquartile range; K, potassium; LDL, Low-density lipoprotein; Na, sodium; PLT, platelet; WBC, white blood cell.

Table 3 Study outcome by feeding group.

Variable (Median, IQR)	Total	Early EN	Delay EN	p-value
	n = 85 (%)	n = 57 (%)	n = 28 (%)	
Early onset pneumonia	40 (47.1)	28 (49.1)	12 (42.9)	0.586
Early onset urinary tract infection	10 (11.8)	7 (12.3)	3 (10.7)	1.000
Early onset bacteremia[a]	10 (12.0)	3 (5.3)	7 (26.9)	0.013
Early onset all-cause infection	47 (55.3)	31 (54.4)	16 (57.1)	0.810
7-day mortality	7 (8.2)	3 (5.3)	4 (14.3)	0.211
30-day mortality	34 (40.0)	22 (38.6)	12 (42.9)	0.706
Length of hospital stay (days)	20.0 (11.5–41.5)	21.0 (12.0–43.0)	18.0 (10.0–36.25)	0.877
Gastrointestinal bleeding	7 (8.2)	5 (8.8)	2 (7.1)	1.000
Ileus	1 (1.2)	0 (0.0)	1 (3.6)	0.329
Intestinal ischemia	0 (0)	0 (0)	0 (0)	1.000
Ventilator dependence	34 (40.0)	23 (40.4)	11 (39.3)	0.925
Neurologic favorable outcome	17 (20)	10 (17.5)	7 (25.0)	0.149

EN, enteral nutrition; IQR, interquartile range.
[a] In the entire cohort of 85 patients, a total of 83 patients had blood cultures performed within 7 days of admission. Among them, 57 were in the early EN group, while the remaining 26 were in the delayed EN group.

intestinal peristalsis, as it reduces the amount of bile salts and immunoglobulin A adhering to the intestinal mucosa, resulting in the excessive reproduction of bacteria attached to the intestinal wall.[1,24,25] A compromised intestinal barrier increases the entry of gut pathogens into the human body, amplifying systemic inflammatory responses.[1]

However, although early EN can reduce the incidence of bacteremia within 7 days, the timing does not affect mortality rates on the 7th and 30th days. We speculate that this may be related to the fact that the prognosis of patients with OHCA is mainly affected by hypoxic encephalopathy severity.[21,27,28] Early mortality in patients with cardiac arrest is additionally associated with circulatory failure,[27] and late (>7 days) mortality may be associated with patients receiving palliative care who have been withdrawn from life support systems.[29] Additionally, although early EN was not associated with significant differences in hospitalization length, ventilator dependence, or neurologic outcome, reducing the incidence of 7-day bacteremia may still be crucial for OHCA patients. Delayed diagnosis and treatment of bacteremia increase patients' mortality and long-term comorbidity.[23,30] Effectively reducing the occurrence of early onset bacteremia remains an indispensable part of post-resuscitation care.

Table 4 Univariate logistic regression analysis for the 7-day bacteremia occurrence rate with the timing of enteral nutrition.

Variables	OR	95 % CI	p-value
Early enteral nutrition	0.17	0.04—0.71	0.015
Age	0.99	0.96—1.03	0.981
Male	0.74	0.17—3.15	0.680
BMI	0.92	0.79—1.08	0.301
Charlson comorbidity index	0.98	0.77—1.25	0.890
APACHEII (admission)	0.98	0.90—1.07	0.630
SOFA score	0.99	0.76—1.28	0.908
Norepinephrine equivalence	4.42	0.16—123.45	0.381
modified NUTRIC score	0.90	0.61—1.32	0.576
Shockable rhythm in ED	0.25	0.03—2.10	0.202
Bystander CPR	0.32	0.06—1.60	0.165
ROSC time	1.05	0.98—1.12	0.138
ECMO	3.50	0.58—21.08	0.171

APACHE, acute physiological assessment and chronic health evaluation; BMI, body mass index; CI, confident interval; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ED, emergency department; NUTRIC, nutrition risk in critically ill; OR, odds ratio; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment.

Bacteria profile of early onset infectious disease

Since patients with OHCA lose the ability to protect their airways after unconsciousness, oropharyngeal flora may be carried into the lungs during emergency intubation. Additionally, deep sedation during TTM may increase the risk of hidden respiratory aspirations.[21] The early (<7 days) infectious disease of patients after resuscitation is mainly pulmonary infection (followed by UTI or bacteremia). The pathogenic bacteria are gram-positive bacteria dominated by *Streptococcus species* and *Staphylococcus aureus*, or gram-negative bacteria dominated by *Haemophilus influenzae*, *enterobacteriaceae* (such as *E. coli* and *K. pneumoniae*).[5,6,31] Streptococcal pneumonia is the main form of community-acquired pneumonia in Taiwan.[17] The proportion of gram-negative enteric pathogens, such as *Klebsiella pneumonia* or oral anaerobes, may increase based on different patients' comorbidities and disease complications.[17]

These results indicate that *Klebsiella* spp. was the major pathogen for pneumonia in patients with cardiac arrest within 7 days, accounting for a higher proportion than in previous findings.[5,21] Moreover, Chinese ethnicity may be associated with a higher risk of intestinal colonization[32] (all patients in this study were Chinese). Additionally, the influence of local epidemiology on the infectious strain should be considered.[33]

Safety concerns regarding infection, intestinal ischemia, and drawback from hypothermia

A concern with early EN is whether it increases the risk of aspiration pneumonia. However, a meta-analysis showed that early EN can reduce the risk of developing pneumonia[34] or infective complications[2,35] in critically ill patients. In this analysis, early EN did not increase the risk of developing pneumonia (49.1 % vs. 42.9 %, $p = 0.586$) or other infective complications (54.4 % vs. 57.1 %, $p = 0.810$). Alternatively, hypothermia therapy may slow gastrointestinal motility,[7] suggesting that such patients are at higher risk of ileus.[8] Severely ill patients reportedly have an approximately 50%—80 % chance of developing delayed gastric emptying, ileus, or gut dysfunction.[8] However, the mean incidence of ileus within 7 days of admission in our study was <10 %, indicating that early EN did not increase the risk of ileus (0 % vs. 3.6 %, $p = 0.329$).

Patients who undergo TTM after a cardiac arrest have an elevated risk of hemodynamic instability, multiple organ failure, and coagulation deficits.[7] Additionally, gastrointestinal bleeding and ischemia are worrisome complications associated with EN. The odds of overt bleeding without clinically significant events reportedly range from 8.5% to 15 % in critically ill patients.[36] The overall incidence of gastrointestinal bleeding in our analysis was 8.2 %, which is not higher than previous reports. Nevertheless, nutritional feeding treatment guidelines discourage early EN in critically ill patients with hemodynamic instability and incomplete intravascular volume resuscitation[2—4] because EN may infuse blood into the gastrointestinal tract, exacerbating the insufficient supply of systemic tissue perfusion.[37] Such patients may be at high risk of intestinal ischemia induced by intestinal feeding. Currently, there is no direct evidence that early intestinal feeding may cause intestinal ischemia, and its reported prevalence in critically ill patients is low (2 %).[37] However, owing to the potential consequences, cautious application of EN is recommended for patients who are hemodynamically unstable or are taking high doses of vasopressors (epinephrine or norepinephrine >30 μg/min in the EDEN trial[11] and >0.4 μg/kg/min in the PERMIT study[38]).[2—4]

In summary, we believe that the lower rate of 7-day bacteremia in the early EN group in this study may be due to the maintenance of the immune barrier of the intestinal wall to avoid translocation of intestinal bacteria. Furthermore, gram-negative enteric pathogens were the major causes of 7-day pneumonia. Early EN was safe with no major adverse events in this group.

Study limitations

This retrospective and non-randomized study has some limitations. Despite including OHCA cases from two adult emergency tertiary referral hospitals in southern Taiwan over 5 years, the small final sample hindered certain subgroup analyses (e.g., extremely underweight or obese patients). Treatment strategy variations among medical teams could not be ruled out due to the retrospective nature of the study. Data capture through disease classification codes and manual medical record reviews could have introduced errors. Collaborations with domestic and international centers are planned for an extended prospective study, aiming to address current research limitations and potentially overcome these challenges.

Conclusions

In patients with OHCA treated with TTM, early EN was associated with a lower rate of 7-day bacteremia.

Table 5 Pathogen profile of early onset infectious complications.

Pneumonia		Total n = 48	%
Gram-positive bacteria	*Pneumococcus* antigen (+)	3	6.25
	Staphylococcus aureus	5	10.42
Gram-negative bacteria	*Acinetobacter baumannii*	3	6.25
	Escherichia coli	2	4.17
	Haemophilus influenzae	1	2.08
	Klebsiella aerogenes	1	2.08
	Klebsiella ozaenae	1	2.08
	Klebsiella pneumoniae	20	41.67
	Pseudomonas aeruginosa	9	18.75
	Stenotrophomonas maltophilia	3	6.25
Urinary tract infection		Total n = 11	%
Gram-positive bacteria	*Enterococcus faecalis*	3	27.27
Gram-negative bacteria	*Escherichia coli*	4	36.36
	Morganella morganii	1	9.09
	Proteus mirabilis	1	9.09
	Pseudomonas aeruginosa	1	9.09
Others	*Candida albicans*	1	9.09
Bacteremia		Total n = 10	%
Gram-positive bacteria	*Atopobium parvulum*	1	10
	Parvimonas micra	1	10
	Staphylococcus aureus	1	10
	Staphylococcus capitis	1	10
	Staphylococcus haemolyticus	1	10
	Streptococcus parasanguinis	1	10
Gram-negative bacteria	*Escherichia coli*[a]	1	10
	Klebsiella pneumoniae[b]	1	10
	Pseudomonas aeruginosa[b]	1	10
	Serratia marcescens	1	10

[a] A patient was diagnosed as concurrent urinary tract infection and bacteremia.
[b] Two patients were diagnosed as concurrent pneumonia and bacteremia.

Furthermore, early EN was well-tolerated in this population, with no significant adverse events.

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Research ethics

This study was approved by the Ethics Committee of Kaohsiung Veterans General Hospital (KSVGH22-CT10-03).

Patient consent

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Authors' contributions

YCT, CHY, JSC, YSC, and JKC designed this study. YCT, CHY, and JKC were involved in the data acquisition. YCT, CHY, and JKC were involved in statistical analysis and data interpretation. YCT drafted the manuscript. YCT, CHY, JSC, SCH, and JKC made final revisions. All the authors have read and approved the final manuscript.

Declarations of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Jabbar A, Chang WK, Dryden GW, McClave SA. Gut immunology and the differential response to feeding and starvation. *Nutr Clin Pract: official publication of the American Society for Parenteral and Enteral Nutrition* 2003;**18**(6):461—82.
2. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). *JPEN - J Parenter Enter Nutr* 2016;**40**(2): 159—211.
3. McClave SA, DiBaise JK, Mullin GE, Martindale RG. ACG clinical guideline: nutrition therapy in the adult hospitalized patient. *Am J Gastroenterol* 2016;**111**(3):315—34. quiz 335.
4. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019;**38**(1):48—79.
5. Mortensen SJ, Hurley M, Blewett L, Uber A, Yassa D, MacDonald M, et al. Infections in out-of-hospital and in-hospital post-cardiac arrest patients. *Intern Emerg Med* 2020; **15**(4):701—9.
6. Tsai MS, Chiang WC, Lee CC, Hsieh CC, Ko PC, Hsu CY, et al. Infections in the survivors of out-of-hospital cardiac arrest in the first 7 days. *Intensive Care Med* 2005;**31**(5):621—6.
7. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med* 2009;**37**(7 Suppl):S186—202.
8. Williams ML, Nolan JP. Is enteral feeding tolerated during therapeutic hypothermia? *Resuscitation* 2014;**85**(11):1469—72.
9. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol* 2018;**72**(14):e91—220.
10. Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, et al. European resuscitation Council and European society of intensive care medicine guidelines 2021: post-resuscitation care. *Intensive Care Med* 2021;**47**(4):369—421.
11. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012; **307**(8):795—803.
12. Compher C, Bingham AL, McCall M, Patel J, Rice TW, Braunschweig C, et al. Guidelines for the provision of nutrition support therapy in the adult critically ill patient: the American Society for Parenteral and Enteral Nutrition. *JPEN - J Parenter Enter Nutr* 2022;**46**(1):12—41.
13. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care* 2011;**15**(6):R268.
14. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the "modified NUTRIC" nutritional risk assessment tool. *Clin Nutr* 2016;**35**(1):158—62.
15. Goradia S, Sardaneh AA, Narayan SW, Penm J, Patanwala AE. Vasopressor dose equivalence: a scoping review and suggested formula. *J Crit Care* 2021;**61**:233—40.
16. Kotani Y, Di Gioia A, Landoni G, Belletti A, Khanna AK. An updated "norepinephrine equivalent" score in intensive care as a marker of shock severity. *Crit Care* 2023;**27**(1):29.
17. Chou CC, Shen CF, Chen SJ, Chen HM, Wang YC, Chang WS, et al. Recommendations and guidelines for the treatment of pneumonia in Taiwan. *J Microbiol Immunol Infect* 2019;**52**(1): 172—99.
18. Chiu CC, Lin TC, Wu RX, Yang YS, Hsiao PJ, Lee Y, et al. Etiologies of community-onset urinary tract infections requiring hospitalization and antimicrobial susceptibilities of causative microorganisms. *J Microbiol Immunol Infect* 2017;**50**(6): 879—85.
19. Lin CH, Chen PL, Huang YT, Ho CY, Hsieh CC, Wang WYC, et al. Blood cultures and appropriate antimicrobial administration after achieving sustained return of spontaneous circulation in adults with nontraumatic out-of-hospital cardiac arrest. *Antibiotics (Basel)* 2021;**10**(7).
20. Boman J, Nilson B, Sunnerhagen T, Rasmussen M. True infection or contamination in patients with positive Cutibacterium blood cultures-a retrospective cohort study. *Eur J Clin Microbiol Infect Dis* 2022;**41**(7):1029—37.
21. François B, Cariou A, Clere-Jehl R, Dequin PF, Renon-Carron F, Daix T, et al. Prevention of early ventilator-associated pneumonia after cardiac arrest. *N Engl J Med* 2019;**381**(19): 1831—42.
22. MacIntyre NR, Epstein SK, Carson S, Scheinhorn D, Christopher K, Muldoon S. Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. *Chest* 2005;**128**(6):3937—54.
23. Coba V, Jaehne AK, Suarez A, Dagher GA, Brown SC, Yang JJ, et al. The incidence and significance of bacteremia in out of hospital cardiac arrest. *Resuscitation* 2014;**85**(2):196—202.
24. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. *Am J Surg* 2002;**183**(4):390—8.
25. Hermsen JL, Sano Y, Kudsk KA. Food fight! Parenteral nutrition, enteral stimulation and gut-derived mucosal immunity. *Langenbeck's Arch Surg* 2009;**394**(1):17—30.
26. Moonwiriyakit A, Pathomthongtaweechai N, Steinhagen PR, Chantawichitwong P, Satianrapapong W, Pongkorpsakol P. Tight junctions: from molecules to gastrointestinal diseases. *Tissue Barriers* 2023;**11**(2):2077620.
27. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Med* 2013;**39**(11):1972—80.
28. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004;**30**(11):2126—8.
29. O'Leary MJ. Comment on "Mode of death after admission to an intensive care unit following cardiac arrest" by Laver et al. *Intensive Care Med* 2005;**31**(6):888.
30. Abou Dagher G, Bou Chebl R, Safa R, Assaf M, Kattouf N, Hajjar K, et al. The prevalence of bacteremia in out of hospital cardiac arrest patients presenting to the emergency department of a tertiary care hospital. *Ann Med* 2021;**53**(1): 1207—15.
31. Kakavas S, Mongardon N, Cariou A, Gulati A, Xanthos T. Early-onset pneumonia after out-of-hospital cardiac arrest. *J Infect* 2015;**70**(6):553—62.
32. Lin YT, Siu LK, Lin JC, Chen TL, Tseng CP, Yeh KM, et al. Seroepidemiology of Klebsiella pneumoniae colonizing the intestinal tract of healthy Chinese and overseas Chinese adults in Asian countries. *BMC Microbiol* 2012;**12**:13.
33. Muengtaweepongsa S, Puengcharoen S. Infections in out-of-hospital and in-hospital post-cardiac arrest patients: comment. *Intern Emerg Med* 2020;**15**(7):1349—50.
34. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive

care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Med* 2009;**35**(12):2018—27.
35. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001;**29**(12): 2264—70.
36. Saeed M, Bass S, Chaisson NF. Which ICU patients need stress ulcer prophylaxis? *Cleve Clin J Med* 2022;**89**(7):363—7.
37. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet (London, England)* 2018;**391**(10116): 133—43.
38. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med* 2015;**372**(25): 2398—408.

Appendix 1. Feeding time comparison by hospital.

Hospital	Early enteral nutrition	%	Delay enteral nutrition	%
A	52	94.5	3	5.5
B	5	16.7	25	83.3

Appendix 2. Early onset bacteremia rate by feeding group and the hospital.

Hospital A[1]	Total n = 55 (%)	Early EN n = 52 (%)	Delay EN n = 3 (%)	p-value
Early onset bacteremia	4 (7.3)	3 (5.8)	1 (33.3)	0.206
Hospital B[1]	Total n = 28 (%)	Early EN n = 5 (%)	Delay EN n = 23 (%)	p-value
Early onset bacteremia	6 (21.4)	0 (0)	6 (26.1)	0.553

EN, enteral nutrition.
1. Only patients who had undergone blood cultures were included.

Appendix 3. Pathogen profile of late onset infectious complications.

Pneumonia		Total n = 37	%
Gram-positive bacteria	*Staphylococcus aureus*	2	5.41
Gram-negative bacteria	*Acinetobacter baumannii*	5	13.51
	Burkholderia cepacia	1	2.7
	Escherichia coli	2	5.41
	Klebsiella aerogenes	1	2.7
	Klebsiella pneumoniae	5	13.51
	Proteus mirabilis	1	2.7
	Pseudomonas aeruginosa	14	37.84
	Stenotrophomonas maltophilia	5	13.51
Others	Nontuberculous mycobacteria	1	2.7
Urinary tract infection		Total n = 14	%
Gram-positive bacteria	*Enterococcus faecalis*	2	14.29
	Entercoccus faecium	1	7.14
Gram-negative bacteria	*Acinetobacter baumannii*	1	7.14
	Escherichia coli	3	21.43
	Klebsiella aerogenes	1	7.14
	Pseudomonas aeruginosa	5	35.71
Others	*Candida albicans*	1	7.14

(*continued*)

Bacteremia		Total n = 7	%
Gram-positive bacteria	*Staphylococcus epidermidis*	1	14.29
Gram-negative bacteria	*Escherichia coli*	1	14.29
	Fusobacterium varium	1	14.29
	Klebsiella pneumoniae	1	14.29
	Pseudomonas aeruginosa	1	14.29
	Stenotrophomonas maltophilia	2	28.57