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Clinical paper

Frequency, clinical characteristics, and outcomes of pneumonia in patients with out-of-hospital cardiac arrest undergoing extracorporeal cardiopulmonary resuscitation ☆

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Abstract

Aim: This study aimed to describe the frequency, clinical characteristics, and outcomes of pneumonia in OHCA patients treated with ECPR in a multicenter setting.

Methods: This is a secondary analysis of the SAVE-J II study, which was a multicenter, retrospective cohort of OHCA patients treated with ECPR. Age, sex, comorbidities, presence of witnessed CA, presence of bystander CPR, initial rhythm, cause of CA, low-flow time, initiation of targeted temperature management, details of sputum culture, pneumonia, and prophylactic antibiotic use were recorded. Pneumonia was diagnosed when the patients met all the clinical, radiologic, and microbiologic criteria acquired after hospitalization.

Results: In total, 1,986 patients were included in the analysis, and 947 (48%) died during the first 2 days of admission. A prophylactic antibiotic was used in 712 (35.9%) patients. Overall, the hazard of death was high on days 1 and 2 of admission, exceeding 20% on both days; 251 (12.6%) patients developed pneumonia during hospitalization, and the hazard of pneumonia development remained high (>2%) in the first 7 days of admission. *Staphylococcus aureus* and *Klebsiella* species were commonly identified in the sputum culture. Among patients who survived the first 7 days, the odds ratio (OR) of those with pneumonia and unfavorable neurological outcomes defined by cerebral performance category 3–5 was approximately 1. In those who survived the first 10 days, the OR was greater than 1 with a wide confidence interval.

Conclusions: This is the first study describing details of pneumonia in OHCA patients treated with ECPR using a large dataset.

Keywords: Cardiopulmonary resuscitation, Out-of-hospital cardiac arrest, Pneumonia, Death, Antibiotics

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) followed by targeted temperature management (TTM) has demonstrated better results in patients with out-of-hospital cardiac arrest (OHCA).[1–6] Despite this great achievement, severe complications such as bleeding, infection, and ischemia can occur during ECPR.[7,8]

Despite studies that have discussed the epidemiology and prognosis of pneumonia in patients with OHCA without ECPR followed by TTM,[9–11] only a few have reported the details of pneumonia in OHCA patients treated with ECPR.[12,13] In a single-center study, Shiba et al. reported that ECPR was associated with early-onset pneumonia (EOP) compared with conventional CPR.[12] Tagami et al. examined OHCA patients treated with ECPR using national insurance claims data; however, they did not have detailed clinical information relevant

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to pneumonia.[13] Moreover, no studies have described the frequency, clinical characteristics, and outcomes of pneumonia in OHCA patients treated with ECPR in a multicenter setting.

This study aimed to describe the frequency, clinical characteristics, and outcomes of pneumonia in OHCA patients with ECPR using a dataset from 36 sites in Japan.

Methods

SAVE-J II study

The SAVE-J II study was conducted as a multicenter, retrospective study of OHCA patients treated with ECPR, involving 36 participating institutions in Japan.[14] The SAVE-J II study included consecutive patients with OHCA aged ≥18 years who were admitted to the emergency department between January 1, 2013, and December 31, 2018, and received ECPR.

This study was approved by the institutional review board of Kagawa University and each participating institution, including St. Luke's International Hospital. The SAVE-J II study was registered at the University Hospital Medical Information Network Clinical Trials Registry and the Japanese Clinical Trial Registry (Registration no. UMIN000036490).

Study design and participants

This study was a secondary analysis of the SAVE-J II study.[14] The inclusion criteria were patients with OHCA aged ≥18 years who received ECPR and were admitted to the participating institutions between January 1, 2013, and December 31, 2018. The exclusion criteria were patients who introduced venoarterial-extracorporeal membrane oxygenation (VA-ECMO) after ICU admission, those who achieved return of spontaneous circulation (ROSC) either before ECMO initiation or at hospital arrival, and those transferred from another hospital.

This secondary analysis was approved by the institutional review board of St. Luke's International Hospital (Approval no. 21-R140, 1: December 23, 2021, title: Clinical characteristics and outcomes of pneumonia in out-of-hospital cardiac arrest patients undergoing extracorporeal cardiopulmonary resuscitation) that waived the need for additional informed consent. Procedures were followed in accordance with the ethical standards of the review board of St. Luke's International Hospital on human experimentation and with the Helsinki Declaration of 1975.

Data collection and processing

The following parameters were recorded for each patient: age, sex, comorbidities (hypertension, diabetes mellitus, hyperlipidemia, heart disease, and chronic kidney disease), presence of witnessed CA, presence of bystander CPR, initial rhythm, cause of CA (cardiogenic and hypothermia defined as cardiac arrest following environmental cold exposure), low-flow time, TTM initiation, details of sputum culture, pneumonia, and prophylactic antibiotic use.

Definitions

Low-flow time was defined as the time from circulatory collapse to the establishment of adequate ECMO flow. Prophylactic antibiotic use was defined as antibiotic administration within 24 h after admission before the emergence of any signs of infection. Pneumonia was diagnosed when the patients met all the clinical, radiologic, and microbiologic criteria that were acquired after hospitalization. The clinical criteria were met when the patients showed at least one of three clinical features (i.e., fever ≥ 38.0 °C, leukocytosis [>12,000 cells/μL], and purulent tracheobronchial secretions).[15,16] The radiologic criteria were met by the presence of a new or progressive and persistent infiltrate characteristic of bacterial pneumonia or the presence of a new consolidation on chest X-ray imaging. The microbiologic criteria were met by a positive respiratory culture that did not contain normal bacterial flora. Hypothermia was diagnosed as a body temperature on admission of <30 °C.

Study endpoints

The primary outcome was unfavorable neurological outcomes based on the cerebral performance category (CPC)[17] at hospital discharge, which was defined as a CPC of 3–5, whereas favorable outcomes were defined as a CPC of 1 or 2. The secondary outcome was survival at hospital discharge.

Statistical analysis

For each day, with the first day of admission being day 1, the hazards of death and pneumonia were calculated as the proportion of patients who died or were diagnosed with pneumonia on the day among those who were alive at the beginning of the day. Among patients who survived until the beginning of each day, the odds ratios (ORs) of suffering pneumonia by then were calculated for unfavorable neurological outcomes and hospital mortality.

Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for binary and categorical variables, and p-values <0.05 were considered statistically significant. Statistical analysis was performed using JMP Pro 17.1.0 (SAS, USA). Missing data in the initial cardiac rhythm and cause of CA were treated as unknown, whereas missing data in the other items were treated as no or none.

Results

Of the 2,157 adult OHCA patients treated with ECPR in SAVE-J II, 1,986 were included in the analysis (Fig. 1).

Baseline characteristics

The median patient age was 61 years, and 82.1% were men. A medical history of hypertension was recorded in 30.1% of the patients, 76.4% had witnessed CA, and 56.4% received bystander CPR. The initial cardiac rhythm at the scene was shockable, pulseless electrical activity, and asystole in 62.4%, 26.5%, and 10.0% of cases, respectively. A cardiogenic cause was found in 71.5% of the cases, and 5.6% had hypothermia. The low-flow time was 57 (48–70) [median (IQR)] min. Prophylactic antibiotics use was noted in 35.9% of the patients (Table 1).

The hazard of death was high on days 1 and 2 of admission and exceeded 20% on both days, resulting in 947 (47.8%) deaths (Fig. 2a). Among cases with cardiogenic and hypothermic causes, the hazard of death exceeded 10% during the first 3 days of admission (Fig. 2b,c).

Demographic, medical, and prehospital features of patients with pneumonia

In total, 251 (12.6%) patients developed pneumonia during hospitalization. The hazard of pneumonia development remained high (>2%) during the first 7 days of admission (Fig. 2a). Among cardiogenic

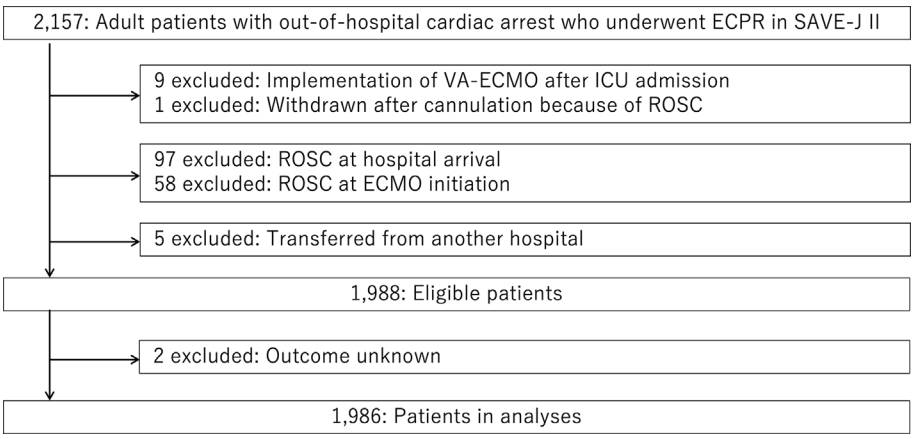

Fig. 1 – Patient flow. ROSC, return of spontaneous circulation; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

Table 1 – Characteristics of the patients at baseline.

	All patients (*n* = 1986)	Pneumonia group (*n* = 251)	Non-pneumonia group (*n* = 1735)	*p* value
Age (years)	61 [49–69]	60 [48–67]	61 [49–69]	0.101
Male	1631 (82.1)	213 (84.5)	1418 (81.8)	0.252
Comorbidities				
Hypertension	597 (30.1)	81 (32.1)	516 (29.8)	0.418
Diabetes mellitus	371 (18.7)	61 (24.2)	310 (17.9)	0.019
Hyperlipidemia	207 (10.4)	34 (13.5)	173 (10.0)	0.083
Heart disease	454 (22.9)	55 (21.8)	399 (23.0)	0.702
CKD	96 (4.8)	10 (4.0)	86 (5.0)	0.636
Witnessed cardiac arrest	1518 (76.4)	193 (76.9)	1325 (76.4)	0.937
Bystander CPR	1121 (56.4)	141 (56.2)	980 (56.5)	0.946
Initial cardiac rhythm				0.183
Shockable rhythm	1240 (62.4)	172 (68.3)	1068 (61.6)	
PEA	526 (26.5)	58 (23.0)	468 (27.0)	
Asystole	199 (10.0)	19 (7.5)	180 (10.4)	
Unknown	21 (1.1)	2 (0.8)	19 (1.1)	
Cause of cardiac arrest				0.001
Cardiogenic	1420 (71.5)	192 (76.5)	1228 (70.8)	
Hypothermia	112 (5.6)	26 (10.3)	86 (5.0)	
Others	454 (22.9)	33 (13.1)	421 (24.3)	
Low flow time (min)	57 [48–70]	53 [43–63]	58 [48–71]	0.001
TTM initiation	354 (17.8)	27 (10.8)	327 (18.8)	0.001
Prophylactic antibiotic use	712 (35.9)	129 (51.4)	583 (33.6)	0.001

Data are presented as median [interquartile range] for continuous variables and as *N* (percentage) for categorical variables.
CKD, chronic kidney disease; CPR, cardiac pulmonary arrest; PEA, pulseless electrical activity;
TTM, targeted temperature management.

cases, the hazard of pneumonia development was relatively low during the first 2 days and high from day 3 to week 1 (Fig. 2b). On the contrary, in hypothermic cases, the hazard of pneumonia development decreased progressively from day 1 and was observed during the first 8 days (Fig. 2c).

The baseline characteristics of patients with and without pneumonia were compared, and patients with pneumonia had a higher prevalence of diabetes mellitus (24.2% vs. 17.9%, $p = 0.019$) and shorter low-flow time (median 53 min [IQR, 43–63] vs. 58 (48–71), $p < 0.001$) than those without pneumonia (Table 1).

Microbiological results of sputum cultures

Details of the sputum culture are provided in supplemental file. The most common bacteria in the sputum culture were *Staphylococcus aureus* (26.3%) followed by *Klebsiella* species (20.3%), *Candida* species (15%), and *Pseudomonas aeruginosa* (13.5%).

Correlation of pneumonia and outcomes

Among patients who survived the first 7 days, ORs (95% CI) of those with pneumonia for unfavorable neurological outcomes and hospital death were 1.0 (95% CI 0.7–1.4; $P = 0.973$) and 0.8 (95% CI 0.6–1.1; $P = 0.155$), respectively (Fig. 3). Among those who survived the first 10 days, ORs were 1.1 (95% CI 0.8–1.6; $P = 0.441$) and 1.0 (95% CI 0.7–1.4; $P = 0.849$). Results were similar when limited to cardiogenic cases. When limited to patients with hypothermia who survived the first 7 days, the ORs of those with pneumonia resulting in unfavorable neurological outcomes and hospital death were 1.2 (95% CI 0.4–3.5; $P = 0.682$) and 8.5 (95% CI 1.0–74.4; $P = 0.02$),

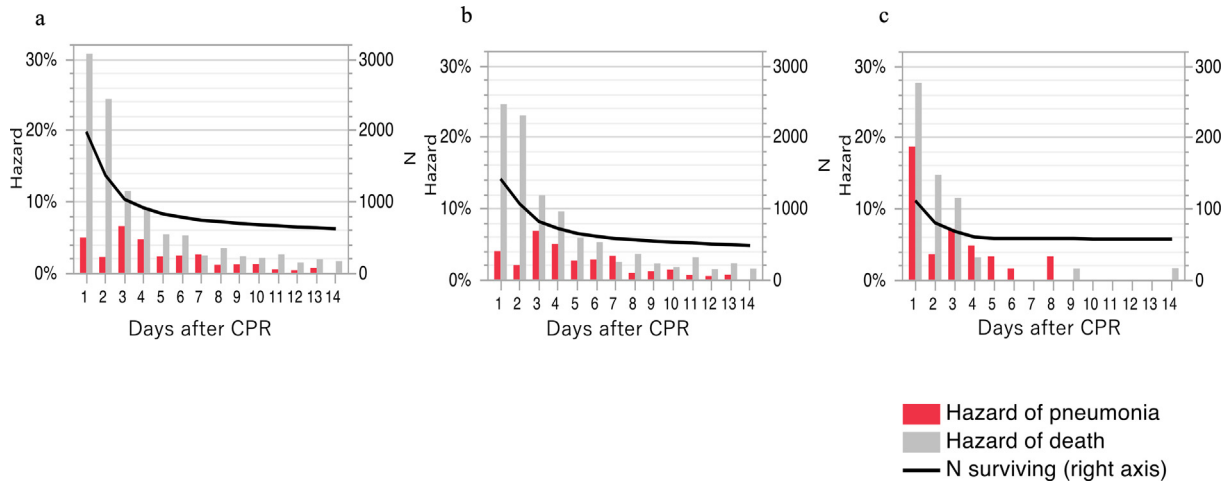

Fig. 2 – Hazards of death and pneumonia. The hazards of death and pneumonia were calculated as the proportion of patients who died or were diagnosed with pneumonia on the day among those who were alive at the beginning of the day. A. All. B. Cardiogenic only. C. Hypothermia only.

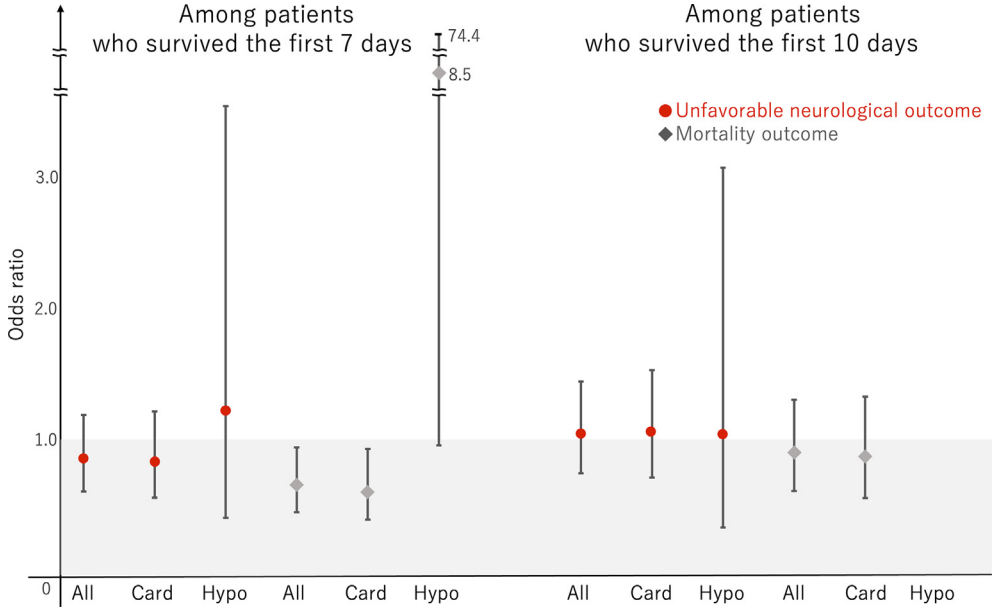

Fig. 3 – OR of patients with pneumonia resulting in unfavorable neurological outcomes and hospital death. A ORs of patients who survived the first 7 days with pneumonia resulting in unfavorable neurological outcomes and hospital death. The ORs in all cause (all the patients in the analysis cohort), cardiogenic only (subset of patients with cardiogenic cardiac arrest), and hypothermia only (those with hypothermia) were provided with 95% confidence intervals. B OR of patients who survived the first 10 days with pneumonia resulting in unfavorable neurological outcomes and hospital death. OR of all cause, cardiogenic only, and hypothermia only were provided with 95% confidence intervals. In the case of hypothermia, after day 9, all patients not suffering from pneumonia survived to the time of discharge; therefore, the odds are infinite, and not shown. All, all patients; Card, cardiogenic only; Hypo, hypothermia only; OR, odds ratio.

respectively, and among those who survived the first 10 days, the OR was 1.1 (95% CI 0.4–3.0; $P = 0.912$) for unfavorable neurological outcomes. The OR of hospital death was infinite and was not calculated because no patients with pneumonia during the first 10 days survived to the time of discharge. Sensitivity analyses with different time thresholds for defining both excluded early death and pneumonia revealed that observed correlation between pneumonia and outcomes was affected by such thresholds (Figs. 4 and 5).

Sensitivity analysis: correlation of pneumonia and neurological outcomes at hospital discharge

Among those who survived the first day of admission (n = 1,375), paradoxically, patients with pneumonia tended to have more favorable neurological outcomes (Fig. 4a, left end). However, when patients who died within the first 7 days were excluded, those with pneumonia by then tended to have unfavorable neurological outcomes (Fig. 4a). The same trend was observed when limited to

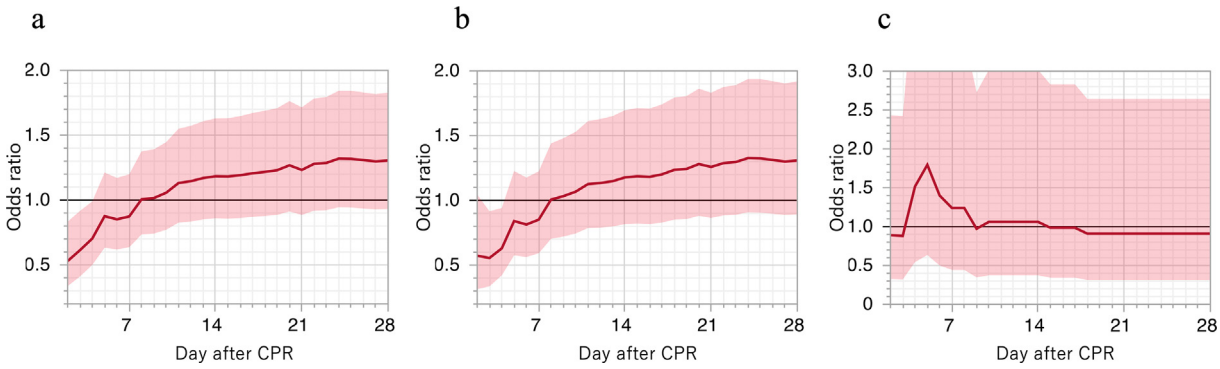

Fig. 4 – Correlation of pneumonia and neurological outcomes. Among patients who survived until the beginning of each day, the odds ratio (OR) of suffering pneumonia by then and unfavorable neurological outcomes at discharge were calculated. A. All. B. Cardiogenic only. C. Hypothermia only.

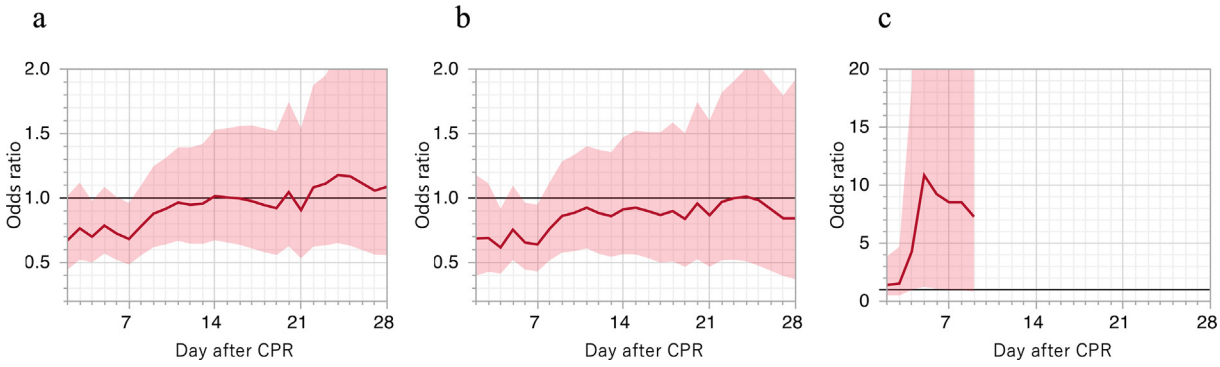

Fig. 5 – Correlation of pneumonia and hospital mortality. Among patients who survived until the beginning of each day, the odds ratio (OR) of suffering pneumonia by then and hospital mortality were calculated. A. All. B. Cardiogenic only. C. Hypothermia only. In the case of hypothermia, after day 9, all patients not suffering from pneumonia survived to the time of discharge; therefore, the odds are infinite, and not shown.

cardiogenic cases (Fig. 4b). Similarly, among patients with hypothermia who survived the first day of admission, the correlation between pneumonia, and neurological outcomes was unclear with an OR of 0.9 having a wide confidence interval (Fig. 4c). However, when limited to patients with hypothermia who survived the first 3 days, patients with pneumonia tended to have unfavorable neurological outcomes. Among patients with hypothermia who survived the first 7 days, those with pneumonia had similar neurological outcomes to those without pneumonia.

Sensitivity analysis: correlation of pneumonia and hospital mortality

Among patients who survived the first day of admission (n = 1,375), again paradoxically, patients with pneumonia tended to survive the hospital stay compared with those without pneumonia (Fig. 5a, left end). However, when those who died within the 10 days of hospitalization were excluded, the ORs were approximately 1.0 with wide confidence intervals, indicating no association between pneumonia and hospital mortality. The same trend was observed in cardiogenic cases (Fig. 5b).

Among patients with hypothermia who survived the first day of admission, those with pneumonia were more prone to hospital mortality compared with those without pneumonia; however, this was not statistically significant (Fig. 5c, left end). The same trend was observed when patients with hypothermia who died within the first days of admission were excluded, whereas the confidence interval was wide due to the limited number of observations.

Discussion

This study was the first to describe the details of pneumonia development using a large registry with 1,986 OHCA patients treated with ECPR. A prophylactic antibiotic was used in 35.9% of the patients. The hazard of death was high on days 1 and 2 of admission and exceeded 20% on both days resulting in 947 (47.7%) deaths. Pneumonia was diagnosed in 12.6% of the patients during hospitalization, and the hazard of pneumonia development remained high (>2%) during the first 7 days of admission. In the sputum culture, *S. aureus* and *Klebsiella* species were frequently identified. Among patients who survived the first 7 days, the OR of those with pneumonia resulting in unfavorable neurological outcomes was approximately 1, and in those who survived the first 10 days, the OR was more than 1 with a wide confidence interval.

Shiba et al. examined the EOP (hospitalization period of >48 h and within 7 days of admission) in OHCA patients treated with ECPR, and 20 of 55 (36.4%) patients developed EOP.[15] This was much higher than the result of the present study, i.e., 12.6%. How-

ever, they excluded patients who died within the first 48 h of admission; therefore, based on the hazard of death on the first 2 days in the present study, approximately half of the OHCA patients with ECPR were supposed to be excluded in this analysis. Thus, the observed frequency of pneumonia development in patients who received ECPR was affected by the inclusion criteria due to the high mortality rate in the early phase.

Overall, the prophylactic antibiotics use rate was 35.9% in the present study. Patients with pneumonia were more likely to receive prophylactic antibiotics than those without pneumonia (51.4% vs. 33.6%, p = 0.001). This might be because clinicians selectively administer antibiotics to patients at high risk of developing pneumonia. In the sputum culture, not only *S. aureus* or *Klebsiella* species but also *Candida* species *or P. aeruginosa* were also identified in patients who received ECPR with the current large cohort and first described herein. The ILCOR recommendation suggests against the use of prophylactic antibiotics in patients following ROSC with a weak recommendation; however, they do not mention patients limited to ECPR.[18] In a randomized controlled trial, the 2-day course of antibiotic therapy in patients with OHCA without ECPR resulted in a lower incidence of early ventilator-associated pneumonia than placebo.[9] Moreover, the rate of pneumonia was higher in OHCA patients with ECPR than in those without ECPR.[16] In another large cohort of patients with cardiogenic OHCA undergoing TTM, antibiotics appear to improve survival in a subgroup of patients that required ECMO.[13] Considering the high risk of pneumonia in patients who received ECPR, prophylactic antibiotic administration may be warranted, and antimicrobial agents against *P. aeruginosa* and antifungal agents against *Candida* may be indicated.

In this study, we found that (1) patients with pneumonia had shorter low-flow time, (2) pneumonia on the first few days of admission was associated with favorable neurological outcomes, and (3) patients with pneumonia tended to have worse neurological outcomes when those who died within 7 days of admission were excluded. In combination these may indicate different thresholds for diagnostic tests applied to these patients depending on their perceived risks. For example, sputum culture may be less likely obtained when the patient has a poor overall condition. Furthermore, the radiological criteria of pneumonia may not be met in patients already suffering from acute respiratory distress syndrome. This may also explain the higher proportion of favorable neurological outcomes among patients with EOP than in those without EOP previously reported (45% vs. 25.7%, p = 0.143) (13).

This highlights the importance of (1) a systematic exploratory analysis and (2) transparency regarding analytical procedures in observational studies. While methodological specifics such as exclusion criteria can affect the results of analysis, these are often arbitrarily decided by researchers with limited exploratory analysis, and the reason for such decisions is rarely disclosed.

Limitations

First, the diagnosis of pneumonia was not uniform. Specifically, the implementation of culture, and other tests was dependent on the policies of the institutions and the decision of physicians. Second, only the first development of pneumonia was recorded for each patient in the present dataset; therefore, the second, and further episodes of pneumonia during admission were not examined. Finally, enteral feeding was not examined because another study group examined the association between enteral feeding and clinically outcomes including pneumonia development.

Conclusions

To our knowledge, this study is the first to describe the details of pneumonia in patients with ECPR-treated OHCA using a large dataset. The observed frequency of pneumonia and its association with clinical outcomes vary greatly depending on how early deaths are addressed in the analysis.

CRediT authorship contribution statement

Eiki Iida: Formal analysis, Writing – review & editing. **Nao Ichihara:** Formal analysis, Writing – review & editing. **Toru Hifumi:** Conceptualization, Writing – original draft, Supervision. **Kasumi Shirasaki:** Investigation. **Katsuhiro Horie:** Investigation. **Shutaro Isokawa:** Investigation. **Akihiko Inoue:** Project administration. **Tetsuya Sakamoto:** Project administration. **Yasuhiro Kuroda:** Project administration. **Norio Otani:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resplu.2023.100474.

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