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Research paper

The impact of door to extracorporeal cardiopulmonary resuscitation time on mortality and neurological outcomes among out-of-hospital cardiac arrest acute myocardial infarction patients treated by primary percutaneous coronary intervention

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ABSTRACT

Background: Few previous studies evaluated the impact of time from the hospital arrival to the implementation of extracorporeal cardiopulmonary resuscitation (ECPR) (door to ECPR time) on outcomes among out-of-hospital cardiac arrest (OHCA) acute myocardial infarction (MI) patients.

Methods: 50 patients with OHCA who received both ECPR and percutaneous coronary intervention (PCI) at Cardiovascular Division, NHO Osaka National Hospital were analyzed. Patients were divided into 2 groups according to the median of door to ECPR time. The primary outcome was all-cause death. Survival analyses were conducted to compare all-cause mortality at 90 days between 2 groups. Neurological outcome at 30 days was also compared between 2 groups using the Cerebral Performance Category (CPC).

Results: The multivariable Cox proportional-hazards model showed that all-cause mortality at 90 days was significantly higher among patients with door to ECPR time $\geq$ 25 min compared with those with door to ECPR time $<$ 25 min (adjusted hazard ratio [HR]: 3.14; 95 % confidence interval [CI]: 1.21–8.18). The proportion of patients with CPC at 30 days $\leq$ 2 was significantly higher among patients with shorter door to ECPR time (P = 0.048).

Conclusion: Among patients with OHCA due to acute MI who received ECPR and PCI, the shorter door to ECPR time was associated with the lower mortality and favorable neurological outcomes.

1. Introduction

Low flow duration is defined as the interval from the beginning of resuscitation to extracorporeal cardiopulmonary resuscitation (ECPR) or return of spontaneous circulation (ROSC) among patients with out-of-hospital cardiac arrest (OHCA) [1,2]. The implementation of ECPR and a decrease in low flow duration were reported to be associated with better neurological outcomes among OHCA patients [2–11]. Although OHCA due to acute myocardial infarction (MI) has several different characteristics compared with OHCA due to other causes including the frequency of shockable rhythm [12] and the importance of time from hospital arrival to treatment [13], previous studies on low flow duration did not focus on OHCA patients due to acute MI. Low flow duration is divided into 2 periods: time from the beginning of resuscitation to the hospital arrival, and time from the hospital arrival to the implementation of ECPR (door to ECPR time). The healthcare professionals at hospitals can shorten the latter period by their efforts. Although shorter low flow duration has already been reported to be associated with better

Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; MI, myocardial infarction; PCI, percutaneous coronary intervention; CPC, Cerebral Performance Category; CPR, Cardio-pulmonary resuscitation; BLS, basic life support; CABG, Coronary artery bypass grafting.

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neurological outcomes [2–11], it is still unknown if the latter period is associated with the neurological outcomes. In the present study, we aimed to evaluate the association between door to ECPR time and outcomes among patients with OHCA due to acute MI who received PCI.

2. Materials and methods

The flow diagram of data processing is presented in Fig. 1. In the present study, patients who were diagnosed as type 1 acute MI by coronary angiography between January 2009 and December 2020 at Cardiovascular Division, NHO Osaka National Hospital were retrospectively analyzed [14,15]. MI was defined according to the fourth universal definition [14–16]. Among those patients with acute MI, those with OHCA who received ECPR and PCI were included in the present analysis. The study patients were divided into 2 groups according to the median of door to ECPR time. The present study was approved by the NHO Osaka National Hospital Institutional Review Board #2 (Approval No. 21045). Informed consent from each patient was waived because this was a retrospective cohort study [14,15].

The following data were collected from clinical records; age, sex, body mass index (BMI), ST-segment elevation myocardial infarction (STEMI) (yes/no), history of smoking, medical history, laboratory data including peak creatine kinase (peak CK) and peak creatine kinase myocardial band (peak CK-MB), blood gas data at hospital arrival including pH and lactate, culprit vessel of MI, number of diseased vessels, chronic total occlusion (CTO) (yes/no), electrocardiogram waveform at hospital arrival (ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)/pulseless electrical activity (PEA)/asystole), the bystander cardio-pulmonary resuscitation (CPR) (yes/no), the witness of OHCA (yes/no).

The primary outcome was defined as the all-cause death at 90 days from the date of admission to the hospital. The observation period was from the date of hospital admission to the date of death, the date when the patient was lost to follow-up, at 90 days from the hospital admission, whichever occurred first [14,15].

The baseline characteristics of the study patients were compared between 2 groups. Categorical variables were presented by count and proportion and were compared by the chi-squared test. Continuous variables including age, BMI and blood gas data were presented by mean and standard deviation (SD) and were compared by the Kruskal-Wallis test. Continuous variables including peak CK, peak CK-MB, time interval from the start of CPR to the arrival at the hospital, and door to ECPR time were presented by median and interquartile range (IQR) and were compared by the Kruskal-Wallis test. Kaplan-Meier method was applied to calculate the cumulative probability of events, and the difference in mortality between 2 groups was compared by the log-rank test. The univariate and multivariable Cox proportional-hazards model were applied to evaluate the impact of door to ECPR time on 90-day mortality. Hazard ratio (HR) and 95 % confidence interval (CI) were calculated. The multivariable Cox proportional-hazards model was adjusted for age and history of smoking, which were independently associated with all-cause mortality in the present population.

Neurological outcomes were assessed by the universal classification of neurological outcomes; cerebral performance category (CPC) [17–19]. CPC is a part of the Glasgow-Pittsburg Outcome Categories and is applied to evaluate the neurological status of patients with cardiac arrest. CPC consists of 5 categories: 1 (Good Cerebral Performance), 2 (Moderate Cerebral Disability), 3 (Severe Cerebral Disability), 4 (Coma/Vegetative State), and 5 (Brain Death). In the present study, the distribution of 30-day CPC was compared between 2 groups by the chi-squared test.

The incidence of complications associated with ECPR including limb ischemia, stroke, cerebral bleeding, sepsis and vessel injury was summarized and was compared between 2 groups by the chi-squared test.

All the analyses were conducted by R software (version 4.1.1). *P* values were two-sided, and P value < 0.05 was considered as statistically significant.

3. Results

The baseline characteristics of the study patients are presented in Table 1. The patients with door to ECPR time $\geq$ 25 min were significantly older compared with those in door to ECPR time $<$ 25 min. Other characteristics were not significantly different between the 2 groups.

The average of the observation period was 39 days. The all-cause mortality at 90 days was significantly higher among patients with

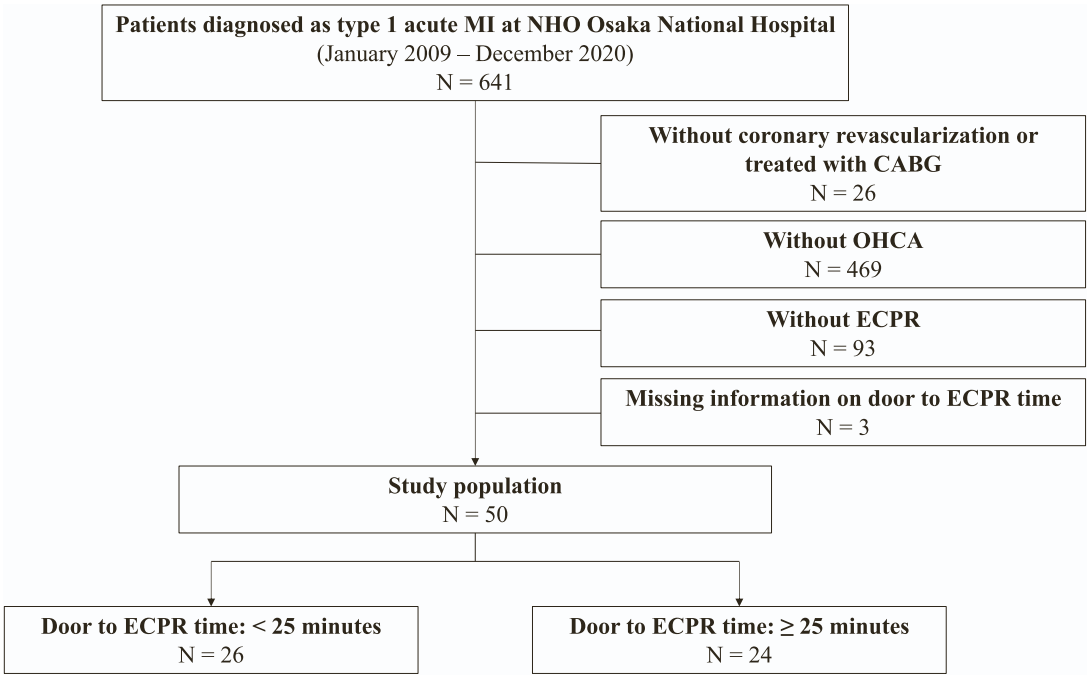

Fig. 1. The flow diagram of data processing.

Table 1
Baseline characteristics of the study population.

	Door to ECPR time		*P*-value	Missing
	<25 min *N* = 26	≥25 min *N* = 24		N (%)
Age	54.8 ± 8.9	60.7 ± 12.2	0.03	0 (0.0 %)
Male	24 (92.3 %)	21 (87.5 %)	0.57	0 (0.0 %)
BMI	26.9 ± 3.8	25.0 ± 4.5	0.11	6 (12.0 %)
STEMI	25 (96.2 %)	21 (87.5 %)	0.26	0 (0.0 %)
History of smoking	19 (73.1 %)	17 (70.8 %)	0.86	0 (0.0 %)
Medical history				
Diabetes mellitus	10 (38.5 %)	10 (41.7 %)	0.82	0 (0.0 %)
Hypertension	10 (38.5 %)	10 (41.7 %)	0.82	0 (0.0 %)
Hypercholesterolemia	10 (38.5 %)	7 (29.2 %)	0.49	0 (0.0 %)
Laboratory data				
Peak CK, U/L	8536 (2271–16,720)	6988 (2411–13,886)	0.64	0 (0.0 %)
Peak CK-MB, U/L	605 (214–1283)	572 (301–1134)	0.95	0 (0.0 %)
Blood gas data at the hospital arrival				
pH	6.97 ± 0.15	6.99 ± 0.16	0.87	1 (2.0 %)
Lactate, mg/dL	152.1 ± 51.7	143.4 ± 43.6	0.69	1 (2.0 %)
Culprit lesion				
RCA	6 (23.1 %)	5 (20.8 %)	0.85	0 (0.0 %)
LMT	4 (15.4 %)	3 (12.5 %)	0.77	0 (0.0 %)
LAD	14 (53.8 %)	14 (58.3 %)	0.75	0 (0.0 %)
LCX	4 (15.4 %)	2 (8.3 %)	0.44	0 (0.0 %)
Number of diseased vessels			0.17	0 (0.0 %)
1 vessel	9 (34.6 %)	11 (45.8 %)		
2 vessels	13 (50.0 %)	6 (25.0 %)		
3 vessels	4 (15.4 %)	7 (29.2 %)		
Multivessel disease	17 (65.4 %)	13 (54.2 %)	0.42	0 (0.0 %)
Chronic total occlusion	8 (30.8 %)	7 (29.2 %)	0.90	0 (0.0 %)
Time from the start of CPR to the hospital arrival, min	22.0 (16.3–30.0)	22.0 (17.0–27.5)	0.88	0 (0.0 %)
Door to ECPR time, min	17.0 (14.0–20.0)	43.5 (35.0–65.5)	<0.01	0 (0.0 %)
Electrocardiogram waveform at the hospital arrival				
VF/Pulseless VT	24 (92.3 %)	19 (79.2 %)	0.18	0 (0.0 %)
PEA	1 (3.8 %)	4 (16.7 %)	0.13	0 (0.0 %)
Asystole	1 (3.8 %)	1 (4.2 %)	0.95	0 (0.0 %)
Presence of bystander CPR	17 (65.4 %)	15 (62.5 %)	0.83	0 (0.0 %)
Witness of OHCA	26 (100.0 %)	23 (95.8 %)	0.29	0 (0.0 %)

BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; peak CK, peak creatine kinase; peak CK-MB, peak creatine kinase myocardial band; RCA, right coronary artery; LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; CTO, chronic total occlusion; CPR, cardio-pulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.
Categorical variables were summarized by count and proportion (%) and compared by chi-squared test. Continuous variables were summarized by mean and standard deviation (SD) or median and interquartile range (IQR), and compared by the Kruskal-Wallis test.

door to ECPR time ≥ 25 min compared with those with door to ECPR time < 25 min even after the adjustment for age and history of smoking (Fig. 2, Table 2).

Better neurological outcomes at 30 days were observed among patients with door to ECPR time < 25 min compared with those with door to ECPR time ≥ 25 min (Table 3). Especially, the proportion of the patients with CPC ≤ 2, which indicates the sufficient cerebral function to lead independent daily lives [17–19], was significantly higher among patients with door to ECPR time < 25 min than those with door to ECPR time ≥ 25 min. The association between door to ECPR time and CPC among the study population was described by using the scatter plot (Fig. 3).

The incidence of complications associated with ECPR was not significantly different between 2 groups of door to ECPR time, except for sepsis. The incidence of sepsis was significantly higher among patients with door to ECPR time < 25 min than those with door to ECPR time ≥ 25 min ($P = 0.048$) (Table 4).

4. Discussion

The present study among patients with OHCA due to MI who received ECPR and PCI showed that the shorter door to ECPR time was associated with the lower mortality and better neurological outcome. The results of the present study suggested that efforts and countermeasures to shorten door to ECPR time by healthcare professionals at hospitals may be important to achieve lower mortality and better neurological outcomes among patients with OHCA due to acute MI receiving ECPR.

While most of the previous studies on ECPR focused on the association of low flow duration and mortality or neurological outcomes [2–11], only a few of them evaluated the association of door to ECPR time and mortality or neurological outcomes [8,11]. An observational study [8] including 28 OHCA patients who received ECPR revealed that door to ECPR time < 30 min was significantly associated with an improvement in mortality at 30 days. Since detailed information on the timing of the start of resuscitation or timing of the hospital arrival were not available in previous studies [2,4], analyses on the association between door to ECPR time and mortality or neurological outcomes have not been conducted. In the present study, detailed information on those timings were available, which enabled us to elucidate the association between door to ECPR time and mortality or neurological outcomes

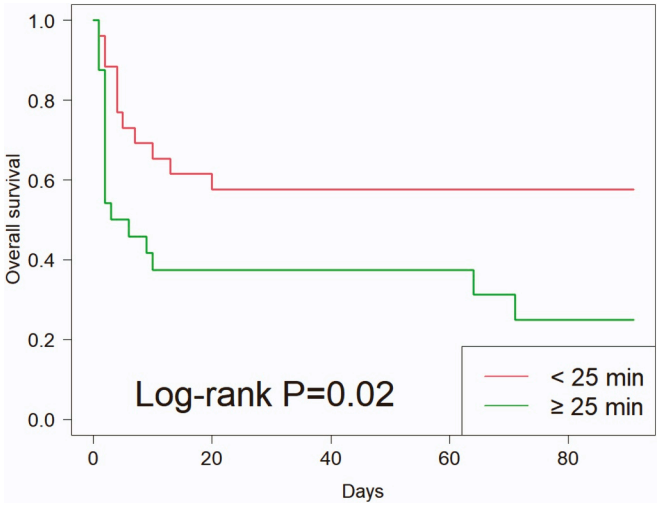

Fig. 2. Kaplan-Meier curve for the primary outcome.

Table 2
The association between door to ECPR time and all-cause mortality using the Cox proportional-hazards model.

Outcome	Univariate model		Multivariable model[a]	
	HR	95%CI	HR	95%CI
All-cause death	2.44	1.10–5.41	3.14	1.21–8.18

HR, hazard ratio; CI, confidence interval.
[a] The multivariable Cox proportional-hazards model was adjusted for age and history of smoking.

Table 3
The distribution of cerebral performance at 30 days category according to door to ECPR time.

Cerebral performance category at 30 days[a]	Door to ECPR time		P-value	Missing
	<25 min N = 26	≥25 min N = 24		N (%)
1 (Good Cerebral Performance)	10 (38.5 %)	3 (12.5 %)	0.21	0 (0.0 %)
2 (Moderate Cerebral Disability)	1 (3.9 %)	1 (4.2 %)		
3 (Severe Cerebral Disability)	1 (3.9 %)	0 (0.0 %)		
4 (Coma/Vegetative State)	3 (11.5 %)	5 (20.8 %)		
5 (Brain Death)	11 (42.3 %)	15 (62.5 %)		

[a] The distribution of cerebral performance was summarized by count and proportion (%) and compared by chi-squared test.

among patients with OHCA receiving ECPR. While time from the beginning of resuscitation to the arrival at the hospital is affected by factors in which healthcare professionals at hospitals cannot intervene such as the local emergency medical service [20] and the location where the OHCA occurred, there is room for shortening door to ECPR time thanks to the efforts by healthcare professionals at hospitals, which we believe is clinically important.

Most of the previous studies on ECPR targeted all of the OHCA patients, whereas the present study targeted only the patients with OHCA due to acute MI. It is shown that type 1 acute MI is the leading cause of refractory OHCA [21,22]. Causes of OHCA arrest other than acute MI include cardiovascular disease such as aortic dissection and pulmonary embolism, cerebrovascular diseases, and trauma [21]. We believe it is clinically important to focus on OHCA due to acute MI when we conduct analyses on patients receiving ECPR, because acute MI may have 2 following distinct characteristics compared with other causes of OHCA. First, acute MI patients with OHCA often present refractory ventricular fibrillation, and previous studies on OHCA patients treated with ECPR have shown that the proportion of patients with better neurological outcomes was higher among patients with refractory ventricular fibrillation than those with cardiac rhythm changed to PEA or asystole [23,24]. Since one of the common causes of refractory ventricular fibrillation is acute MI [23], patients with OHCA due to acute MI may be one of the best candidates for ECPR. Second, time from the arrival at the hospital to the treatment of diseases causing OHCA is more strictly associated with mortality among the patients with OHCA due to acute MI compared with those due to other causes of diseases. Time from the arrival at the hospital to treatment among patients with acute MI receiving PCI is called as door to balloon time [25,26], and some observational studies have shown that the shorter door to balloon time was significantly associated with the lower mortality among the patients with acute MI receiving PCI [13,25,26]. Door to ECPR time is part of door to balloon time, therefore efforts by healthcare professionals at hospitals to shorten door to ECPR time would be important to achieve better outcomes among patients with OHCA receiving ECPR and PCI due to acute MI.

Since this was a single-center retrospective cohort study, we were able to identify reasons why it took time to implement ECPR among patients with longer door to ECPR time. The most common reason was that the decision and the preparation to implement ECPR were not made before the patient arrival at the hospital. The average age of these patients was 71 years, which was significantly older than patients with shorter door to ECPR time. Considering the higher mortality and poorer neurological outcomes among older patients with OHCA receiving ECPR [27], healthcare professionals at hospitals would hesitate to decide

Table 4
The incidence of complications associated with ECPR according to door to ECPR time.

Complication[a]	Door to ECPR time		P-value	Missing
	<25 min N = 26	≥25 min N = 24		N (%)
Limb ischemia	4 (15.4 %)	3 (12.5 %)	0.77	0 (0.0 %)
Stroke	2 (7.7 %)	1 (4.2 %)	0.60	0 (0.0 %)
Cerebral bleeding	1 (3.9 %)	0 (0.0 %)	0.33	0 (0.0 %)
Sepsis	8 (30.8 %)	2 (8.3 %)	0.05	0 (0.0 %)
Vessel injury	2 (7.7 %)	4 (16.7 %)	0.33	0 (0.0 %)

[a] The incidence of each complication was summarized by count and proportion (%) and compared between the two groups by chi-squared test.

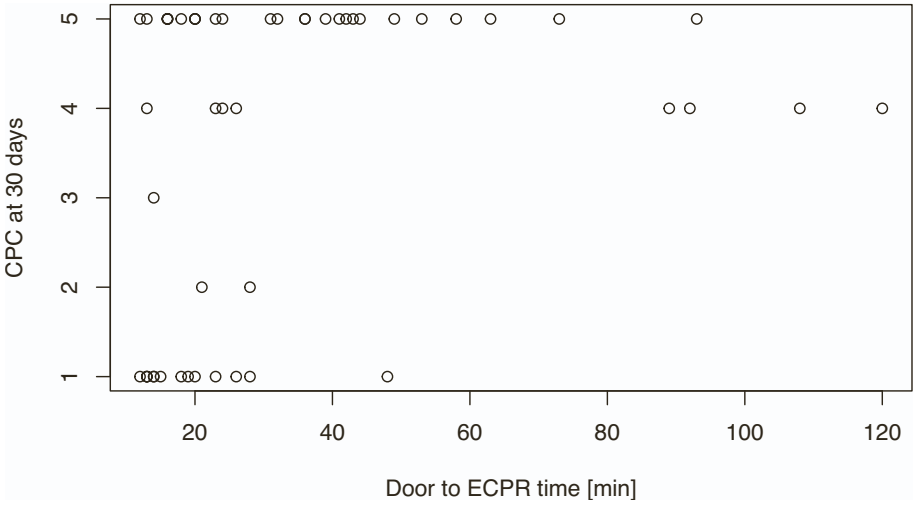

Fig. 3. The association between door to ECPR time CPC at 30 days.

implementing ECPR for elderly patients with OHCA and therefore the decision to implement ECPR would likely to delay among these patients [28]. However, given that survival rate is reportedly to be around 20 % even among patients with OHCA over 70 years of age [27] and neurological outcomes have been improving even among elderly patients with OHCA [29], and the present study showed that shorter door to ECPR time was associated with lower mortality regardless of age (Table 2), it may be important to decide rapidly and prepare in advance to implement ECPR for patients with OHCA regardless of their age.

In ECPR, the healthcare professionals combat with numerous complications associated with ECPR. In the present study, the incidence of each complication was similar to that of previous studies on ECPR [30]. In the present study, the incidence of sepsis was significantly higher among patients with door to ECPR time < 25 min than those with door to ECPR time ≥ 25 min. This may be due to longer survival time among patients with shorter door to ECPR time. Longer survival time may have led to longer detention of devices including percutaneous cardiopulmonary support (PCPS), which may have elevated the risk of infection [31,32].

5. Study limitations

The present study had several limitations: 1) this study was a single-center study, therefore the number of patients included were limited. Despite this limitation, we believe that the present study is one of the largest single-center studies of patients with out-of-hospital cardiac arrest acute myocardial infarction, since NHO Osaka National Hospital is one of the largest emergency hospitals in Osaka City and it is estimated that it covers >20 % of OHCA patients in Osaka City [14]; 2) Impella had not been introduced in our hospital during the study period, therefore we could not compare mortality and neurological outcomes among the study population with or without Impella; 3) information on left ventricular ejection fraction (LVEF) at baseline and hospital discharge was not available; 4) more refined indicator of neurological outcomes including the modified Rankin scale was not and available; 5) pre-hospital factors [33] including the location where the OHCA occurred, time from cardiac arrest to beginning of resuscitation (no flow duration), and time from the beginning of resuscitation to the hospital arrival were not adjusted in the present study, which may have affected the results of the study; 6) the present study was a retrospective cohort study, and unmeasured confounding would have affected the study results [14,15].

6. Conclusions

Among patients with OHCA due to acute MI who received both ECPR and PCI, shorter time from the arrival at the hospital to the implementation of ECPR was associated with lower mortality and better neurological outcomes.

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CRediT authorship contribution statement

Taro Takeuchi: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yasunori Ueda:** Writing – review & editing, Conceptualization. **Shumpei Kosugi:** Writing – review & editing. **Kuniyasu Ikeoka:** Writing – review & editing. **Haruya Yamane:** Writing – review & editing. **Takuya Ohashi:** Writing – review & editing. **Takashi Iehara:** Writing – review & editing. **Kazuki Oozato:** Writing – review & editing. **Satoshi Oosaki:** Writing – review & editing. **Masayuki Nakamura:** Writing – review & editing. **Tatsuhisa Ozaki:** Writing – review & editing. **Tsuyoshi Mishima:** Writing – review & editing. **Haruhiko Abe:** Writing – review & editing. **Koichi Inoue:** Writing – review & editing. **Yasushi Matsumura:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yasunori Ueda reports a relationship with Abbott, Daiichi-Sankyo, Teijin, Japan Lifeline, OrbusNeich, Janssen, Otsuka, Ono, Eli Lilly, Astellas, Amgen, Boehringer Ingelheim, and Novartis that includes: funding grants. Yasunori Ueda reports a relationship with Abbott, Kowa, Bayer, Daiichi-Sankyo, Nipro, Takeda, AstraZeneca, Japan Lifeline, Novartis, Ono, Boehringer Ingelheim, and Amgen that includes: speaking and lecture fees. If there are other authors, they 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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