

Original Article

Prevalence and predictors of direct discharge home following hospitalization of patients with serious adverse events managed by the rapid response system in Japan: a multicenter, retrospective, observational study

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Aim: The rapid response system (RRS) is an in-hospital medical safety system. To date, not much is known about patient disposition after RRS activation, especially discharge home. This study aimed to investigate the prevalence, characteristics, and outcomes of patients with adverse events who required RRS activation.

Methods: Retrospective data from the In-Hospital Emergency Registry in Japan collected from April 2016 to November 2020 were eligible for our analysis. We divided patients into Home Discharge, Transfer, and Death groups. The primary outcome was the prevalence of direct discharge home, and independently associated factors were determined using multivariable logistic regression.

Results: We enrolled 2,043 patients who met the inclusion criteria. The prevalence of discharge home was 45.7%; 934 patients were included in the Home Discharge group. Age (adjusted odds ratio [AOR] 0.96; 95% confidence interval [CI], 0.95–0.97), malignancy (AOR 0.69; 95% CI, 0.48–0.99), oxygen administration before RRS (AOR 0.49; 95% CI, 0.36–0.66), cerebral performance category score on admission (AOR 0.38; 95% CI, 0.26–0.56), do not attempt resuscitation order before RRS (AOR 0.17; 95% CI, 0.10–0.29), RRS call for respiratory failure (AOR 0.50; 95% CI, 0.34–0.72), RRS call for stroke (AOR 0.12; 95% CI, 0.03–0.37), and intubation (AOR 0.20; 95% CI, 0.12–0.34) were independently negative, and RRS call for anaphylaxis (AOR 15.3; 95% CI, 2.72–86.3) was positively associated with discharge home.

Conclusion: Less than half of the in-hospital patients under RRS activation could discharge home. Patients' conditions before RRS activation, disorders requiring RRS activation, and intubation were factors that affected direct discharge home.

Key words: discharge to home, DNAR, RRS, serious adverse event

*See Appendix 1.

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INTRODUCTION

ADVERSE EVENTS DURING hospitalization have influenced increased mortality, hospital stays, and costs, which is unfortunate for patients and/or their families.^{1,2} The rapid response system (RRS) is shown to effectively function as an in-hospital medical safety system to identify signs of

imminent clinical deterioration on nonintensive care wards with the purpose of prevention of further life-threatening events.^{3,4} Patients with in-hospital adverse events are less likely to be discharged home.⁵ Nevertheless, discharge to home is the ultimate goal for all clinicians and patients and/or their families due to patient satisfaction, quality of life, and socioeconomic costs.^{6–9} Although the Japanese government has proposed constructing a comprehensive home medical care system due to its rapidly aging society, few studies have investigated the outcomes of in-hospital serious adverse events requiring RRS; limited data exist, especially regarding discharge to home in this cohort.^{5,10}

We undertook a large-scale, retrospective, cohort study using data from a Japanese RRS registry to investigate the prevalence, characteristics, and outcomes focused on discharge home for patients with serious adverse events who received RRS activation. Sharing our study could help emergency physicians make better patient care plans for those suffering from unfortunate in-hospital adverse events.

METHODS

In-Hospital Emergency Registry in Japan

THE In-Hospital Emergency Registry in Japan (IHER-J) is a registered database for the RRS in Japan (UMIN000012045) managed by the Japanese Society of Intensive Care Medicine and the Japanese Society of Emergency Medicine. The number of institutions comprising the IHER-J online registry has increased to 32 in Japan (nine university hospitals and 23 community hospitals). All participating hospitals used similar, predefined criteria for RRS activation, including thresholds for breathing, airway status, consciousness, circulation, and other factors (e.g., inability to contact the patient's physician or staff concern).¹¹ All patients with RRS activation were entered into the IHER-J database at each participating hospital.

Study design, setting, and subjects

This study was approved by a suitably constituted ethics committee of our institution (Committee of Okayama Saiseikai General Hospital, ID 201201), and it conforms to the provisions of the Declaration of Helsinki. Patient consent was waived.

This study was undertaken using retrospective, observational data collected through the IHER-J online registry form. Patients with activated RRS from April 2016 to November 2020 were eligible for our analysis. Cases involving outpatients, patients with cerebral performance category (CPC) scores of 3 or higher on admission, patients under

20 years old, and patients with incomplete outcome data were excluded.

Data collection

We collected the following data from the RRS registry: baseline patient data (age, sex, admitted disorder, admitted department, intensive care unit [ICU] admissions, oxygen administration, do not attempt resuscitation [DNAR] order, operation before RRS, and CPC score on admission), RRS activation data (time course, medical status of the caller, activated reason, diagnosed disorder after activation, interventions by medical emergency teams [METs]), and outcomes (CPC score, length of hospital stay, DNAR orders after RRS, and disposition after RRS activation and at discharge).

Patient grouping and end-point

We compared three patient groups who received RRS activation in the participating hospitals: the Home Discharge group (patients who were directly discharged home), the Transfer group (patients who were discharged to other hospitals or nursing facilities), and the Death group (patients who died in the hospital) based on discharge status. The primary outcome was the prevalence of direct discharge home. Secondary outcomes included CPC score, length of hospital stay, DNAR orders, and disposition after RRS activation. Additionally, factors associated with discharge home were evaluated.

Data analysis

Continuous variables were described using medians with interquartile ranges (IQR). Categorical variables were described using percentages. We compared variables across groups using one-way ANOVA for numerical variables and the χ^2 -test for categorical variables. Multivariable logistic regression was used to adjust covariates (age, sex, post-ICU, oxygen administration, CPC score, DNAR order, pre-existing conditions, time course of RRS, diagnosed disorder related to RRS, and interventions by METs) to evaluate factors contributing to discharge home. Logistic regression analysis results were expressed using odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analysis was carried out using Stata version 17 (StataCorp, College Station, TX, USA). *P*-values below 0.05 were considered statistically significant.

RESULTS

FIGURE 1 shows our study design flow chart. During the approximately 4-year period, 4,782 cases were

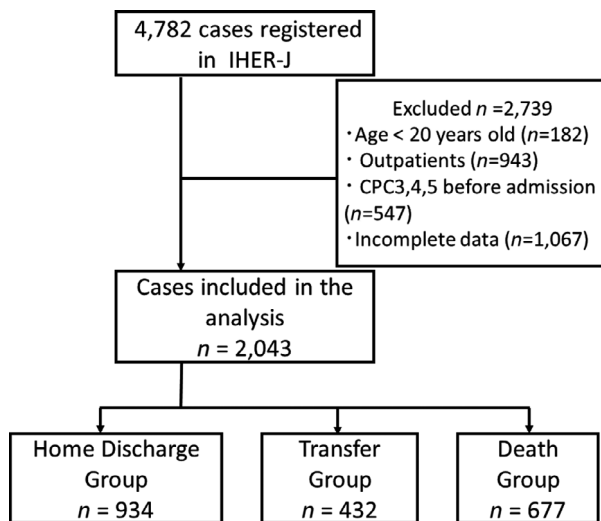


Fig. 1. Flowchart of the cohort study design to determine the prevalence and predictors of direct discharge home of inpatients managed by the rapid response system in Japan. CPC, cerebral performance category; IHER-J, In-Hospital Emergency Registry in Japan.

registered. After excluding patients under 20 years of age ($n = 182$), outpatients ($n = 943$), and cases with CPC score 3–5 ($n = 547$) and incomplete data ($n = 1,067$), 2,043 cases met the inclusion criteria; prevalence of discharge home was 45.7%; 934 patients were included in the Home Discharge group. The Transfer group and Death group included 432 patients (21.1%) and 677 patients (33.2%), respectively.

Table 1 shows the patients' baseline characteristics. The Home Discharge group was younger (median age, 71 years [IQR, 56–79 years]), had a higher proportion of CPC scores of 1 (90.7%), and had fewer DNAR orders before RRS (3.5%) than the Transfer and Death groups. The proportions of patients in the Home Discharge group with malignancy and oxygen administration before RRS were 14.2% and 35.1%, respectively. Overall, approximately half of the cases (1,075/2,043 [52.6%]) were admitted to medical departments.

Table 2 shows the baseline characteristics of patients who received RRS activation. The RRS activation call criteria including agitation (2.4%) was higher, while desaturation (22.2%) was lower in the Home Discharge group. There were multiple criteria for RRS activation; the median number of RRS activation call criteria was 1 (IQR, 1–2) in the Home Discharge group. Rapid response system activation disorders including anaphylaxis (3.3%) were higher, while asphyxia (3.7%), respiratory failure (14.8%), and stroke (1.3%) were lower in the Home Discharge group. Table 3 shows outcomes after RRS. The proportion of CPC scores

of 1 was 85.1% in the Home Discharge group. Length of hospital stay was shorter in the Home Discharge group (17 days (IQR, 10–28)). Furthermore, the proportion of newly announced DNAR orders (0.8%) was lower in the Home Discharge group. In multivariable analysis, age (adjusted odds ratio [AOR] 0.96; 95% CI, 0.95–0.97; $P < 0.001$), malignancy (AOR 0.69; 95% CI, 0.48–0.99; $P = 0.050$), oxygen administration before RRS (AOR 0.49; 95% CI, 0.36–0.66; $P < 0.001$), CPC score on admission (AOR 0.38; 95% CI, 0.26–0.56; $P < 0.001$), DNAR order before RRS (AOR 0.17; 95% CI, 0.10–0.29; $P < 0.001$), RRS call for respiratory failure (AOR 0.50; 95% CI, 0.34–0.72; $P < 0.001$), RRS call for stroke (AOR 0.12; 95% CI, 0.03–0.37; $P < 0.001$), and intubation (AOR 0.20; 95% CI, 0.12–0.34; $P < 0.001$) were independently negatively associated with discharge home. Rapid response system call for anaphylaxis (AOR 15.3; 95% CI, 2.72–86.3; $P = 0.002$) was positively associated with discharge home (Table 4).

DISCUSSION

IN THIS population-based study of IHER-J data, we found that the prevalence of direct return home on discharge was only 45.7%. Age, malignancy, oxygen administration before RRS, CPC score on admission, DNAR order before RRS, and RRS call for respiratory failure and stroke were independently negatively associated with discharge home, while RRS call for anaphylaxis was independently positively associated with discharge home.

Few published reports describe the outcomes of patients with adverse events who required RRS activation and were discharged home.⁵ In prospective data, the prevalence of discharge home after receiving RRS activation was approximately 50%, consistent with our results, while the prevalence of discharge home after hospitalization was 86.8%.^{5,12} These results indicate that adverse events were associated with less frequency of discharge home. There might be several reasons for the low frequency of discharge home after hospitalization. First, patients who recover from in-hospital serious adverse events might suffer from impaired activities, generating a reduced perception of well-being in affected individuals.^{6,8} Physical function, health status, and socioeconomic status at hospital discharge have been identified as risk factors affecting patients' return to home.^{6,8} Our results revealed that CPC scores on hospital discharge were different between the groups. Second, the potential lack of medical staff or other resources needed, including financial issues, might prevent home-based long-term care for these patients nationwide in our medical system.¹³

Our study revealed that malignancy and code status were negatively associated with home discharge. Approximately

Table 1. Characteristics of inpatients treated by medical emergency teams ($n = 2,043$)

	Home discharge ($n = 934$)	Transfer ($n = 432$)	Death ($n = 677$)	All ($n = 2,043$)	<i>P</i> -value
Clinical information					
Male gender	525 (56.2)	233 (53.9)	424 (62.6)	1,182 (57.8)	0.006
Age, years	71 (56–79)	79 (70–86)	76 (67–83)	75 (64–83)	<0.001
Postoperative	196 (21.0)	106 (24.5)	471 (6.9)	349 (17.1)	<0.001
Post-ICU	44 (4.7)	32 (7.4)	29 (4.2)	105 (4.9)	0.052
Oxygen administration	324 (35.1)	184 (32.4)	446 (66.8)	954 (47.2)	<0.001
CPC score on admission					
CPC1	848 (90.7)	318 (73.6)	524 (77.4)	1,689 (82.7)	<0.001
CPC2	87 (9.3)	114 (26.4)	153 (22.6)	354 (17.3)	<0.001
DNAR order	24 (3.5)	38 (13.4)	128 (23.0)	190 (12.6)	<0.001
Admitted department					
Medical	470 (50.3)	168 (38.8)	437 (64.6)	1,075 (52.6)	<0.001
Surgical	202 (21.6)	65 (15.0)	113 (16.6)	380 (18.6)	0.004
Neurosurgery	33 (3.5)	39 (9.0)	24 (3.5)	90 (4.7)	<0.001
Psychiatric, <i>n</i>	5(0.5)	1 (0.2)	2 (0.2)	8 (0.3)	0.624
Obstetrics and gynecology	65 (6.9)	5 (1.1)	19 (2.8)	89 (4.3)	<0.001
Emergency	13 (1.3)	21 (4.8)	16 (2.3)	50 (2.4)	0.001
Others ^a	122 (13.0)	131 (30.3)	55 (8.1)	308 (15.0)	<0.001
Pre-existing conditions					
Infection	62 (6.6)	25 (5.7)	51 (7.5)	138 (6.7)	0.518
Malignancy	133 (14.2)	32 (7.4)	168 (24.8)	333 (16.2)	<0.001

Note: Continuous variables are presented as median (interquartile range), categorical variables are shown as *n* (%). *P*-values were calculated using χ^2 analysis or ANOVA.

^aIncluding Dermatology, Urology, and Orthopedics.

CPC, cerebral performance category; DNAR, do not attempt resuscitation; ICU, intensive care unit.

31.1% of patients with end-of-life care who received RRS activation received limited medical therapy; only 22.4% of these patients were discharged home in the prospective study.⁵ Brown et al. described 30.0% of in-hospital patients with end-of-life care due to advanced cancer who received RRS activation.¹⁴ Other studies indicated the effectiveness of MET intervention for increased completion of limited medical treatment orders, DNAR orders, instigation of patient and family meetings, and end-of-life discussions.^{14,15} Our study revealed that patients who were not discharged home were more likely to have a DNAR order established. Medical emergency teams could help improve end-of-life care by communicating the goals for quality end-of-life, and accepting end-of-life for patients with malignancy and DNAR orders.

Our results showed that patients with adverse events who suffered from respiratory failure and stroke requiring RRS activation had a lower chance of home return. Va et al. described the incidence of home discharge as 163/279 (58.4%) in patients 50–70 years old and 18/96 (18.8%) in those over 80 years old with the use of mechanical ventilation.¹⁶ The diagnosis of polyneuropathy and/or myopathy,

including ICU-acquired weakness caused by respiratory failure, is another general factor strongly associated with reduced discharge home.¹⁷ The influence of stroke on daily functioning and quality of life can affect discharge home. Time is a critical factor in the treatment of acute strokes, both hemorrhagic and ischemic.¹⁸ Rapid response systems specialized in stroke help to reduce in-hospital treatment delay, although the effect of discharge home is unknown.¹⁸

Our results also revealed that patients with RRS call for anaphylaxis had a higher chance of home return regardless of the pathology. There has been a worldwide increase in all-cause anaphylaxis cases, primarily driven by food and medication-related anaphylaxis; fatal anaphylaxis constitutes less than 1% of mortality risk.¹⁹ However, delayed adrenaline injection is associated with fatal outcomes.²⁰ In general, pediatric METs were frequently required for anaphylaxis.²¹

The RRS is designed for early recognition of deterioration and administration of resuscitation to clinically unstable patients. Previous studies have indicated that RRS implementation could reduce the incidence of unplanned ICU admission, cardiac arrest, hospital death, and hospital mortality.^{3,4} We could not compare the institutions with or

Table 2. Characteristics of patients with rapid response system (RRS) activation ($n = 2,043$)

	Home discharge ($n = 934$)	Transfer ($n = 432$)	Death ($n = 677$)	All ($n = 2,043$)	P- value
RRS call					
Weekday	764 (81.7)	346 (80.1)	539 (79.6)	1,649 (80.7)	0.512
Weekend	170 (18.3)	86 (19.9)	138 (20.4)	394 (19.3)	0.512
Call occupation					
Physician	257 (27.8)	66 (15.3)	202 (30.9)	525 (26.2)	<0.001
Nurse	634 (68.8)	353 (82.2)	442 (67.7)	1,429 (71.3)	<0.001
Time course					
Time from call to MET arrival, min	5 (3–8)	3 (5–10)	4 (2–8)	5 (3–8)	0.192
Duration of MET activation, min	30 (18–53)	30 (20–55)	35 (20–59)	31 (20–56)	0.311
Call criteria for RRS					
Respiratory					
Dyspnea	92 (9.8)	41 (9.4)	82 (12.1)	215 (10.5)	0.252
Bradypnea	17 (1.8)	10 (2.3)	60 (8.8)	87 (4.2)	<0.001
Tachypnea	119 (12.7)	53 (12.2)	131 (19.3)	303 (14.8)	<0.001
Desaturation	208 (22.2)	130 (30.0)	279 (41.2)	617 (30.1)	<0.001
Circulatory					
Hypotension	285 (30.4)	95 (21.9)	214 (31.6)	594 (29.0)	0.001
Bradycardia	52 (5.5)	10 (2.3)	77 (11.3)	139 (6.8)	<0.001
Tachycardia	95 (10.1)	63 (14.5)	69 (10.1)	227 (11.1)	0.035
Neurology					
Altered mental status	205 (21.9)	110 (25.4)	258 (38.1)	573 (28.0)	<0.001
Seizure	24 (2.5)	10 (2.3)	10 (1.4)	44 (2.1)	0.318
Agitation	23 (2.4)	3 (0.6)	5 (0.7)	31 (1.5)	0.006
Other					
Nurse concern	157 (16.7)	81 (18.7)	95 (14.0)	333 (16.2)	0.099
Delayed reaction	32 (3.4)	12 (2.7)	10 (1.4)	54 (2.6)	0.054
Decreased urine output	21 (2.2)	10 (2.3)	19 (2.8)	50 (2.4)	0.759
Chest pain	23 (2.4)	15 (3.4)	3 (0.4)	41 (2.0)	0.001
Number of RRS activation	1 (1–2)	1 (1–2)	2 (1–3)	1 (1–2)	<0.001
reasons					
Disorder for RRS					
Anaphylaxis	31 (3.3)	3 (0.6)	0 (0)	34 (1.6)	<0.001
Asphyxia	35 (3.7)	45 (10.4)	67 (9.8)	147 (7.1)	<0.001
Respiratory failure	139 (14.8)	76 (17.5)	205 (30.2)	420 (20.5)	<0.001
Hemorrhagic shock	74 (7.9)	20 (4.6)	39 (5.7)	133 (6.5)	0.045
Sepsis	138 (14.7)	43 (9.9)	123 (18.1)	304 (14.8)	0.001
Heart failure	52 (5.5)	24 (5.5)	47 (6.9)	123 (6.0)	0.467
Myocardial infraction	21 (2.2)	4 (0.9)	15 (2.2)	40 (1.9)	0.219
Pulmonary embolism	8 (0.8)	4 (0.9)	10 (1.4)	22 (1.0)	0.464
Stroke	12 (1.2)	21 (4.8)	20 (2.9)	53 (2.5)	<0.001
Intervention					
Test order	436 (49.1)	210 (50.6)	308 (48.6)	954 (49.3)	0.821
Oxygen administration	274 (31.1)	134 (32.8)	309 (48.5)	717 (37.2)	<0.001
Fluid bolus	199 (22.6)	72 (17.6)	200 (31.6)	471 (24.5)	<0.001
Medication	280 (31.7)	111 (27.0)	249 (39.7)	640 (33.3)	<0.001
Suction	45 (5.1)	54 (13.3)	142 (22.8)	241 (12.6)	<0.001
BVM	60 (6.8)	37 (9.0)	173 (27.5)	270 (13.9)	<0.001
NPPV	30 (3.4)	18 (4.4)	44 (6.9)	92 (4.8)	0.006
Intubation	52 (5.9)	23 (5.6)	175 (27.7)	250 (13.0)	<0.001

Table 2. (Continued)

	Home discharge (<i>n</i> = 934)	Transfer (<i>n</i> = 432)	Death (<i>n</i> = 677)	All (<i>n</i> = 2,043)	<i>P</i> - value
CPR	13 (1.4)	4 (0.9)	90 (14.2)	107 (5.5)	<0.001
Defibrillation	9 (1.0)	6 (1.4)	28 (4.4)	43 (2.2)	<0.001
Transfusion	52 (5.9)	16 (3.9)	31 (4.9)	99 (5.1)	0.311

Note: Continuous variables are presented as median (interquartile range); categorical variables are shown as *n* (%). *P*-values were calculated using χ^2 analysis or ANOVA. BVM, bag valve mask; CPR, cardiopulmonary resuscitation; MET, medical emergency team; NPPV, noninvasive positive pressure ventilation.

Table 3. Outcomes of patients who were treated by medical emergency teams (*n* = 2,043)

	Home discharge (<i>n</i> = 934)	Transfer (<i>n</i> = 432)	Death (<i>n</i> = 677)	All (<i>n</i> = 2,043)	<i>P</i> -value
Outcomes					
Disposition after RRS activation					
ICU transfer	257 (27.5)	87 (20.1)	246 (36.4)	590 (28.9)	<0.001
Stay in ward	550 (58.9)	290 (67.1)	274 (40.6)	1,114 (54.6)	<0.001
Death	0 (0)	0 (0)	107 (15.8)	107 (5.2)	<0.001
DNAR order after RRS	29 (3.8)	45 (13.4)	236 (37.8)	310 (18.0)	<0.001
New DNAR order after RRS	5 (0.8)	4 (1.6)	66 (15.8)	75 (5.8)	<0.001
CPC score					
CPC1	790 (85.1)	190 (44.3)	0 (0.0)	980 (48.2)	<0.001
CPC2	123 (13.2)	147 (34.3)	0 (0.0)	270 (13.2)	<0.001
CPC3	15 (1.6)	85 (19.8)	0 (0.0)	100 (4.9)	<0.001
CPC4	0 (0.0)	6 (1.4)	0 (0.0)	6 (0.2%)	<0.001
CPC5	0 (0.0)	0 (0.0)	677 (100)	677 (33.3)	<0.001
Hospital length of stay, days	17 (10–28)	27 (18–38)	22 (10–39)	21 (12–33)	0.001

Note: Continuous variables are presented as median (interquartile range); categorical variables are shown as *n* (%). *P*-values were calculated using χ^2 analysis or ANOVA. CPC, cerebral performance category; ICU, intensive care unit; DNAR, do not attempt resuscitation; RRS, rapid response system.

without the RRS registry in this study; however, the effectiveness of RRS in contributing to return home on discharge following in-hospital adverse events should be evaluated in the future.

Our study has several limitations. First, we could not obtain detailed information about the patients' residence (home/nursing facility/hospital) before hospital admission; some of RRS activated patients could have been transported from other hospitals or nursing facilities. Second, this study analyzed national registry data, which included records from only 32 participating institutions. Thus, some of the study findings might not be generalizable to all institutions. Third, home discharge is not necessarily synonymous with

functional recovery; however, it can be a summative measure of short-term outcomes representing restoration of quality of life. Fourth, we could not obtain sufficient detailed follow up information on deterioration on discharge. Finally, the cases discharged to nursing homes or transferred to another hospital might eventually return home.

CONCLUSIONS

IN OUR ANALYSIS, less than half of in-hospital patients who received RRS activation could directly discharge home from the hospital. Age, malignancy, code status, CPC score on admission, respiratory failure, and stroke before

Table 4. Multivariable logistic regression for predicting discharge home following hospitalization of patients with serious adverse events managed by the rapid response system (RRS)

Factor	AOR (95% CI)	P-value
Discharge home		
Age	0.96 (0.95–0.97)	<0.001
Malignancy	0.69 (0.48–0.99)	0.050
Oxygen administration before RRS	0.49 (0.36–0.66)	<0.001
CPC score on admission	0.38 (0.26–0.56)	<0.001
DNAR order before RRS	0.17 (0.10–0.29)	<0.001
RRS call for respiratory failure	0.50 (0.34–0.72)	<0.001
RRS call for stroke	0.12 (0.03–0.37)	<0.001
RRS call for anaphylaxis	15.3 (2.72–86.3)	0.002
Intubation	0.20 (0.12–0.34)	<0.001

Note: Variables for the outcomes in the multivariable logistic regression included age, sex, post-intensive care unit, oxygen administration, cerebral performance category (CPC) score on admission, do not attempt resuscitation (DNAR) order, pre-existing conditions, time course of RRS, disorder related to RRS, intervention by RRS including intubation, noninvasive positive pressure ventilation, transfusion, fluid bolus, and test order. CI, confidence interval; OR, odds ratio.

RRS activation were negative factors and anaphylaxis before RRS activation was a positive factor affecting direct discharge home from the hospital.

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DISCLOSURES

APPROVAL OF THE research protocol: The study protocol for this research project was approved by a suitably constituted ethics committee at our institution (registration no. 201201), and it conforms to the provisions of the Declaration of Helsinki.

Informed consent: Informed consent was waived.

Animal studies: N/A.

Conflict of interest: None.

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APPENDIX 1

COLLABORATORS OF THE IN-HOSPITAL EMERGENCY STUDY GROUP

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Medical Center General Hospital (Kazuma Nagata); Fukushima Medical University Aizu Medical Center (Takuro Saito); Tomishiro Central Hospital (Masahiro Tamashiro); St. Luke’s International Hospital (Kazuhiro Aoki); Hyogo College Of Medicine College Hospital (Atsushi Miyawaki); Jichi Medical University Saitama Medical Center (Tomoyuki Masuyama); Shizuoka Children’s Hospital (Tatsuya Kawasaki); Japanese Red Cross Musashino Hospital (Takuya Kawaguchi); Seirei Hamamatsu General Hospital (Takahiro Atsumi); Hikone Municipal Hospital (Tomoyuki Ikeda); Shimane Prefectural Central Hospital (Yuji Yamamori); Kameda Medical Center (Yoshiro Hayashi); Kurashiki Central Hospital (Takanao Otake); Gunma University Hospital (Masaru Tobe); Okayama Saiseikai General Hospital (Toshifumi Fujiwara); Ibaraki Prefectural Central Hospital (Ryosuke Sekine); Chiba University Graduate School of Medicine (Takaaki Nakada); Chikamori Hospital (Kazuhiko Sugimoto); Northern Okinawa Medical Center (Hiroshi Onozawa); Kainan Hospital (Kentaro Miyake); National Hospital Organization Nagasaki Medical Center (Chikaaki Nakamichi); Hitachi General Hospital (Naraba Hiromu); Yokosuka General Hospital Uwamachi (Jun Makino); Fukuyama City Hospital (Kenzo Ishii); Nara City Hospital (Yasunobu Goto); Mito Saiseikai General Hospital (Hitoshi Kikuchi); Tokushima Red Cross Hospital (Tadaaki Takada); Kin-ikyo Chuo Hospital (Dai Taguchi); Fukuyama City Hospital (Kenzo Ishii); Dokkyo Medical University (Eisei Hoshiyama); Daiyukai General Hospital (Hiromichi Miyabe); Tottori Prefectural Central Hospital (Masaru Okamoto); Kyoto Okamoto Memorial Hospital (Masahiro Koide); Jikei University School of Medicine Kashiwa Hospital (Yoichi Kase); Jikei University School of Medicine (Yoichi Kase); Kansai Electric Power Hospital (Takuya Hashino); Saitama Children’s Medical Center (Takehiro Niitsu); Shinshu University Hospital (Hiroshi Kamijo).