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Incidence and factors associated with newly implemented do-not-attempt-resuscitation orders among deteriorating patients after rapid response system activation: A retrospective observational study using a Japanese multicenter database

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Abstract

Aim: The rapid response system (RRS) was initially aimed to improve patient outcomes. Recently, some studies have implicated that RRS might facilitate do-not-attempt-resuscitation (DNAR) orders among patients, their families, and healthcare providers. This study aimed to examine the incidence and factors independently associated with DNAR orders newly implemented after RRS activation among deteriorating patients.

Methods: This observational study assessed patients who required RRS activation between 2012 and 2021 in Japan. We investigated patients' characteristics and the incidence of new DNAR orders after RRS activation. Furthermore, we used multivariable hierarchical logistic regression models to explore independent predictors of new DNAR orders.

Results: We identified 7904 patients (median age, 72 years; 59% male) who required RRS activation at 29 facilities. Of the 7066 patients without pre-existing DNAR orders before RRS activation, 394 (5.6%) had new DNAR orders. Multivariable hierarchical logistic regression analyses revealed that new DNAR orders were associated with age category (adjusted odds ratio [aOR], 1.56; 95% confidence interval, 1.12–2.17 [65–74 years old reference to 20–64 years old], aOR, 2.56; 1.92–3.42 [75–89 years old], and aOR, 6.58; 4.17–10.4 [90 years old]), malignancy (aOR, 1.82; 1.42–2.32), postoperative status (aOR, 0.45; 0.30–0.71), and National Early Warning Score 2 (aOR, 1.07; 1.02–1.12 [per 1 score]).

Conclusion: The incidence of new DNAR orders was one in 18 patients after RRS activation. The factors associated with new DNAR orders were age, malignancy, postoperative status, and National Early Warning Score 2.

KEYWORDS
clinical deterioration, hospital rapid response team, patient care planning, resuscitation orders, terminal care

INTRODUCTION

The concept of a rapid response system (RRS) has been implemented worldwide to urgently respond to deteriorating patients in the wards and prevent in-hospital cardiopulmonary arrest (CPA), morbidity, and unexpected mortality.[1] Recently, some researchers have shifted their focus to other outcomes, such as the placement of do-not-attempt-resuscitation (DNAR) orders and discussion of end-of-life (EOL) care, which may be initiated following RRS activation.[2,3]

In Japan, which leads the world in terms of aging, the concept of RRS has been gradually accepted. Chronic illness, frailty, and disability are expected to become more prevalent as the Japanese population ages leading to acute deterioration in the general condition.[4] RRS may play an important role in the aging Japanese population. In the most recent studies, following RRS activations, 8% of patients (median, range 2.1%–25%) had DNAR orders implemented.[5] However, previous studies have mainly involved hospitals in Western countries, making the results difficult to generalize to other countries with cultural differences in patients' and physicians' attitudes toward DNAR order and EOL care. Therefore, these findings should be confirmed by other studies conducted in different health and institutional settings, especially in Asian countries with few previous studies.

Furthermore, few reports systematically clarify incidence and factors influencing physicians' and patients' decisions regarding DNAR order changes after RRS activation. Knowledge of predictive factors for shared decision-making of DNAR orders between physicians and patients may help RRS or healthcare providers address patient comfort more frequently and initiate discussions about the limits of medical treatment with patients and their families.

This study aimed to examine the incidence of new DNAR orders and explore the independent factors associated with new DNAR orders after RRS activation among deteriorating patients.

MATERIALS AND METHODS

Ethical approval

This study was conducted in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" guidelines. This study was approved by the Institutional Review Board of Nagoya City University Graduate School of Medical Sciences and Nagoya City University Hospital (approval number: 60210077, August 24, 2021). The requirement for informed consent from patients was waived because of the retrospective nature of this study.

Study design and data source

This study was performed retrospectively using observational data collected through the In-Hospital Emergency Registry in Japan (IHER-J), which was organized in the University Hospital Medical Information Network-Clinical Trials Registry (UMIN000012045).[6] The number of facilities in the IHER-J online database increased to 43 in 2021. All facilities used similar predefined criteria for RRS activation, including thresholds for airway, breathing, circulation, consciousness, and other factors. Rapid response team varied depending on the participating facilities in the registry, and each team included doctors and/or nurses and/or respiratory therapists who were available either 24 h per day, 7 days per week or during in-hours only.

Participation in the registry and data analysis methods was approved by the institutional review board of each participating facility. The registration items were revised in November 2017 with minor classification changes (e.g., outpatient categories, triggers, and state of consciousness). The first author (T. Tsuji) prepared a cross-reference table between old and new registries. The agreement between the two reviewers (Y.S. and T. Naito) regarding the consistency of variables in the cross-reference table was established, and disagreements were resolved by discussing these variables among the three authors (T. Tsuji, Y.S., and T. Naito).

Study population

All patients with activated RRS from the old database, which operated from January 2012 to March 2018, and the new database, which operated from November 2017 to June 2021, were eligible for inclusion in our study. Both databases were open for registration as a transitional period during the 5-month window from November 2017 to March 2018. The exclusion criteria were as follows: (i) registered from long-term care facilities or facilities with <50 cases or <1 year of enrollment; (ii) patients age <20 years; and (iii) incomplete data for a date or DNAR orders. For patients who required RRS activation several times during the study period, we considered each case of RRS activation independently.

Variables

We obtained the following patient characteristics for the study cohort: demographic characteristics (age and sex), existing comorbidities (malignancy, postoperative status, or sepsis), admitted department (medical, surgical, minor [urology, otolaryngology, dermatology, and ophthalmology], obstetrics/gynecology, or others [emergency, radiology, and other than above]), setting (inpatient or outpatient), time of day (night [5 p.m.–7:59 a.m.] or day [8 a.m.–4:59 p.m.]),[6] professions who activated RRS (doctors, nurses, or others [laboratory technician, physiotherapist, biomedical equipment technician, medical clerk, and other personnel]), according to clinical experience and previous registry studies.[6–8] Ages were divided into four categories (20–64 years [young and middle], 65–74 years [pre-old], 75–90 years [old], and ≥90 years old [super-old])

according to the proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society.[9] Patients with the care directive of "full code" order (i.e., patients who wish to have cardiopulmonary resuscitation performed in a CPA) and "partial code" order (i.e., patients who allow some, but not all resuscitation procedures) were merged into the "without DNAR" (i.e., patients whose code status is non-DNAR) category. Patients with the care directive of the "DNAR" order (i.e., patients who wish not to have cardiopulmonary resuscitation performed in a CPA) were classified in the "with DNAR" (i.e., patients whose code status is DNAR) category. Moreover, DNAR orders that had already existed before RRS activation were termed "pre-DNAR." In our study, those newly implemented following RRS activation were termed "new DNAR" (i.e., patients whose code status changed from non-DNAR to DNAR because of RRS activations).

We also collected vital signs (heart rate, systolic and diastolic blood pressure, Glasgow coma scale [GCS], respiratory rate [RR], percutaneous oxygen saturation [SpO_2], and body temperature), Quick Sequential Organ Failure Assessment (qSOFA) score,[10] and National Early Warning Score 2 (NEWS2)[11] at the time of RRS activation. GCS was substituted using the following rules adopted from a previous study: GCS, 13–15 was considered as "alert," 9–12 was "voice," 6–8 was "pain," and 3–5 was "unresponsive" on the alert, voice, pain, unresponsive (AVPU) scale.[12] The NEWS has been validated in the Japanese RRS setting.[13] In recent studies, NEWS, NEWS2, and qSOFA scores have been used to assess the disease severity for predicting prognosis in deteriorating patients who required RRS activation.[14,15] Furthermore, we used hospital type (university or non-university hospitals), hospital volume (small [1–500 beds], medium [501–800 beds], or large [801–1200 beds]) according to the previous study,[16] and calendar year as variables. Triggers of RRS activation and intervention content were similar to those of previous IHER-J registry studies.[6,8,13,16]

Outcomes

The primary outcome was code change after RRS activation (from "with DNAR" to "without DNAR" and from "without DNAR" to "with DNAR"). Typically, members from the rapid response team and the doctor of the primary treating team jointly make management decisions in consultation with patients and their families (including patient disposition and goals of care, DNAR orders) on a case-by-case basis with a guideline, protocol, or decision-making support for each facility. The secondary outcomes were CPA on arrival and during RRS intervention, dispositions after RRS activation (death, intensive care unit [ICU] transfer, high dependency unit [HDU] transfer, stay in the ward, and others [transfer to other hospitals or unknown]), and outcomes after 30 days (death, hospitalization, and discharge alive), regarding previous studies.[6,8,13,16]

Statistical analysis

Descriptive statistics were calculated to summarize baseline covariates and the percentage of activation triggers, interventions, and outcomes for patients with and without pre- and new DNAR orders, respectively. Continuous variables were expressed as mean and standard deviation (SD) or medians and interquartile ranges and were compared using a *t*-test or a Mann–Whitney *U* test, as appropriate. Categorical variables summarized as numbers and percentages were analyzed using a χ^2 test or a Fisher's exact test, where applicable.

A multivariable hierarchical logistic regression model, with a random effect for each facility, was used to calculate crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for the incidence of new DNAR orders after RRS activation. Based on biological plausibility, clinical experience, and the previous studies,[15,16] we adjusted for potential confounders as follows; patients' factors (characteristics, existing comorbidities, admitted department, inpatient or outpatient, time of the day, professions who activated RRS, and clinical severity scores) and facility factors (hospital type and volume). Possible collinearity between variables was examined by computing variance inflation factors. We assigned the mean values to missing data (Model 1: imputing mean values) of qSOFA score and NEWS2.[17]

Sensitivity and subgroup analysis

Multivariable hierarchical logistic regression analyses were performed as a sensitivity analysis by adding all covariates after excluding missing data (Model 2: complete case analysis). We also considered the possibility that perspectives for DNAR orders differ between patients who suffered CPA and patients who did not at the time of RRS activation. Therefore, we conducted a subgroup analysis to explore the relationship between new DNAR orders and each variable in the cohort excluding patients with CPA (Model 3: subgroup analysis excluding patients with CPA using mean value imputation).

We used SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA) for statistical analysis. Statistical significance was set at p-value < 0.05.

RESULTS

Patient characteristics of the overall cohort

Between 2012 and 2021, there were 7904 patients in the study cohort (Figure 1). The median age was 72 (interquartile range, 61–80) years, and 59.3% (n = 4691) of the patients were male (Table 1). The proportions of patients with existing malignancy and postoperative patients were 21.5% (n = 1699) and 12.4% (n = 977), respectively. The percentage of time of day at RRS activation was 37.7% (n = 2526) at night. The mean values of the qSOFA score and NEWS2 calculated from vital signs at RRS activation were 1.5 (SD, 0.8) and 7.4 (SD, 4.0), respectively (Table 1).

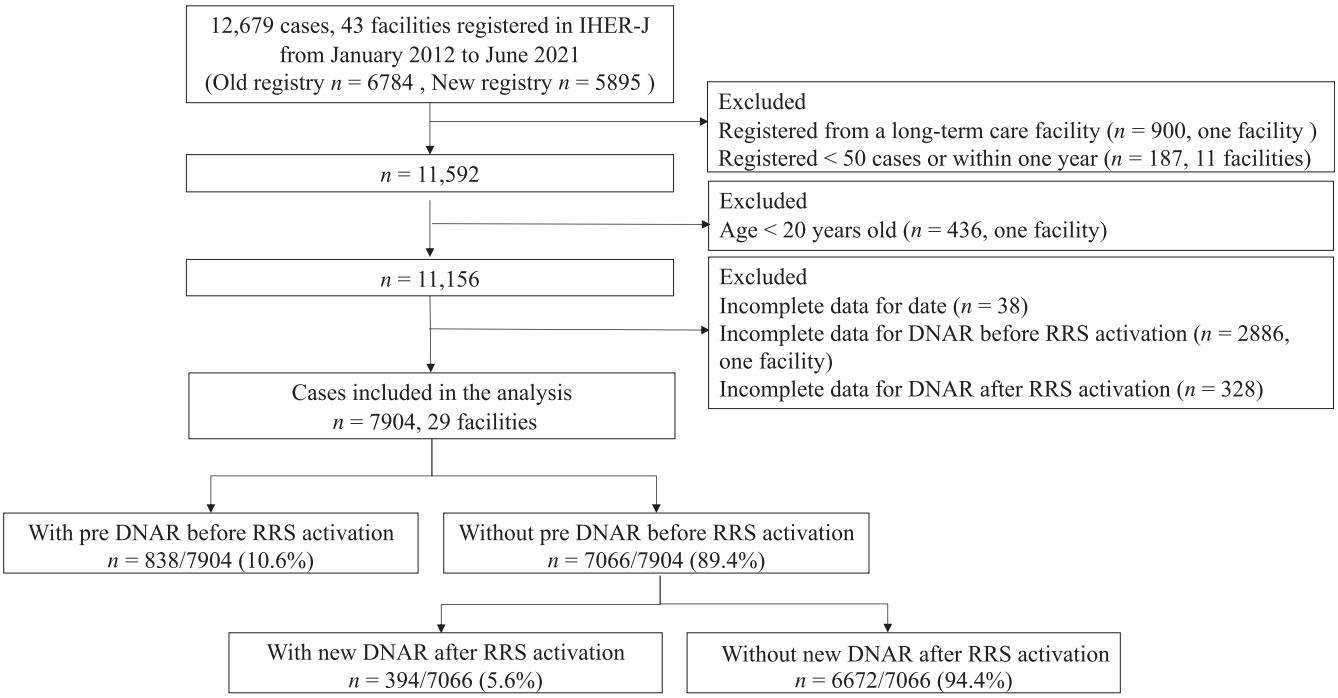

FIGURE 1 Patients flow chart (from January 2012 to June 2021). DNAR, do-not-attempt-resuscitation; IHER-J, In-Hospital Emergency Registry in Japan; RRS, rapid response system.

Details of patients with and without pre-DNAR orders and new DNAR orders

Of the 7904 patients, 838 (10.6%) had DNAR orders before RRS activation (pre-DNAR). Of 7066 patients without a pre-DNAR order, DNAR orders were newly implemented for 394 patients (5.6%) (Figure 1, Table 1). Patients with new DNAR orders were older (78 years versus 71 years), had more cases of malignancy (30.7% versus 20.6%), and had higher clinical severity scores (qSOFA score [mean 1.8 versus 1.5], and NEWS2 [mean 9.7 versus 7.1]) than patients without new DNAR orders (Table 1).

Triggers and interventions by DNAR order

Triggers and interventions by DNAR order are shown in Appendix S1. In the overall study cohort, the major triggers for RRS activation were desaturation ($n = 2622$, 33.2%), and the proportions of patients who required tracheal intubation and cardiopulmonary resuscitation were 15.6% ($n = 1231$) and 6.9% ($n = 546$), respectively (Appendix S1).

Outcomes by DNAR order

Table 2 presents the frequency and proportion of primary and secondary outcomes, excluding missing data. The proportion of code status change after RRS activation from pre-DNAR to "full code" or "partial code" was 6.7% (56/838). The details of the code status change around the RRS activation are listed in Appendix S2.

The patients with new DNAR orders were less likelihood of ICU transfer (25.2% [99/393] versus 37.7% [2488/6608], $p < 0.001$), and higher 30-day mortality (75.8% [279/368] versus 21.6% [1298/6001], $p < 0.001$) than patients without new DNAR orders.

Multivariable hierarchical logistic regression analysis

The association between the placement of the new DNAR orders and each variable is shown in Table 3. In the multivariable hierarchical logistic regression analysis (Model 1), positive predictors significantly associated with new DNAR orders were age-category (aOR, 1.56; 95% CI, 1.12–2.17, [pre-old reference to young and middle] aOR, 2.56 [1.92–3.42], [old], and aOR, 6.58; 95% CI, 4.17–10.4 [super-old]), malignancy (aOR, 1.82 [1.42–2.32]), activation at night (aOR, 1.32 [1.04–1.67]), qSOFA score (aOR, 1.37 [1.13–1.67]), and NEWS2 (aOR, 1.07 [1.02–1.12]). Negative predictors were postoperative status (aOR, 0.45 [0.30–0.71]) and activation by a profession other than doctors or nurses (aOR, 0.29 [0.11–0.73]). The results of logistic regression analyses in Model 2, performed as sensitivity analysis, are shown in Appendix S3. Subgroup analysis excluding patients with CPA using mean value imputation also confirmed these associations (Appendix S4). The qualitative directions of the aORs in Model 2 and Model 3

TABLE 1 Characteristics of the study cohort, *n* (%).

		With pre-DNAR	Without pre-DNAR *n* = 7066/7904 (89.4)	
	Total *n* = 7904	***n* = 838/7904 (10.6)**	**With new DNAR *n* = 394/7066 (5.6)**	**Without new DNAR *n* = 6672/7066 (94.4)**
Age median (IQR), years	72 (61, 80)	79 (70, 86)	78 (69, 84)	71 (59, 79)
Young and middle (20–64 years)	2428 (30.7)	123 (14.7)	69 (17.5)	2236 (33.5)
Pre-old (65–74 years)	2006 (25.4)	155 (18.5)	91 (23.1)	1760 (26.4)
Old (75–89 years)	3131 (39.6)	450 (53.7)	199 (50.5)	2482 (37.2)
Super-old (90– years)	339 (4.3)	110 (13.1)	35 (8.9)	194 (2.9)
Sex				
Male	4691 (59.3)	490 (58.5)	230 (58.4)	3971 (59.5)
Existing comorbidity				
Malignancy	1699 (21.5)	204 (24.3)	121 (30.7)	1374 (20.6)
Postoperative status	977 (12.4)	39 (4.7)	30 (7.6)	908 (13.6)
Sepsis	1158 (14.7)	129 (15.4)	67 (17.0)	962 (14.4)
Admitted department[a]				
Medical	3744 (52.0)	540 (67.8)	187 (51.8)	3017 (49.9)
Surgical	2389 (33.2)	160 (20.1)	114 (31.6)	2115 (35.0)
Minor[m]	532 (7.4)	53 (6.7)	31 (8.6)	448 (7.4)
Obstetrics/gynecology	214 (3.0)	12 (1.5)	14 (3.9)	188 (3.1)
Others[n]	321 (4.5)	31 (3.9)	15 (4.2)	275 (4.6)
Setting				
Inpatient	7094 (89.8)	792 (94.5)	353 (89.6)	5949 (89.2)
Outpatient	810 (10.2)	46 (5.5)	41 (10.4)	723 (10.8)
Time of day[b]				
Day (8:00–16:59)	4169 (62.3)	412 (58.0)	188 (55.0)	3569 (63.3)
Night (17:00–7:59)	2526 (37.7)	298 (42.0)	154 (45.0)	2074 (36.7)
Professions activating RRS[c]				
Doctors	1865 (29.3)	151 (21.4)	96 (32.3)	1618 (30.2)
Nurses	4083 (64.1)	540 (76.5)	196 (66.0)	3347 (62.4)
Others[o]	418 (6.6)	15 (2.1)	5 (1.7)	398 (7.4)
Vital signs at time of RRS activation				
Heart rate[d] median (IQR), /min	93 (72, 116)	100 (75, 120)	84 (40, 111)	93 (72, 115)
Systolic blood pressure[e] median (IQR), mm Hg	111 (82, 138)	114 (87, 140)	90 (46, 124)	112 (83, 138)
Diastolic blood pressure[f] median (IQR), mm Hg	65 (49, 80)	67 (50, 82)	53 (0, 70)	65 (50, 80)
Glasgow coma scale[g] median (IQR)	12 (8, 15)	12 (8, 15)	7 (3,13)	13 (8, 15)
Respiratory rate[h] median (IQR), /min	22 (16, 30)	24 (18, 30)	30 (20, 36)	22 (17, 30)
SpO_2[i] median (IQR), %	95 (88,98)	93 (81, 97)	88 (54, 96)	95 (89, 98)
Body temperature[j] median (IQR), °C	36.9 (36.5, 37.6)	37 (36.5, 37.8)	37.0 (36.5, 37.8)	36.9 (36.5, 37.6)
qSOFA score[k] mean (SD)	1.5 (0.8)	1.6 (0.8)	1.8 (0.7)	1.5 (0.9)
NEWS2[l] mean (SD)	7.4 (4.0)	8.6 (3.6)	9.7 (4.2)	7.1 (4.0)
Hospital type				
University hospital	4245 (53.7)	327 (39.0)	193 (49.0)	3725 (55.8)
Non-University hospital	3659 (46.3)	511 (61.0)	201 (51.0)	2947 (44.2)

(Continues)

TABLE 1 (Continued)

	Total *n* = 7904	With pre-DNAR *n* = 838/7904 (10.6)	Without pre-DNAR *n* = 7066/7904 (89.4)	
			With new DNAR *n* = 394/7066 (5.6)	Without new DNAR *n* = 6672/7066 (94.4)
Hospital volume				
Small (1–500 beds)	1690 (21.4)	195 (23.3)	73 (18.5)	1422 (21.3)
Medium (501–800 beds)	1672 (21.1)	227 (27.1)	108 (27.4)	1337 (20.0)
Large (801–1200 bed)	4542 (57.5)	416 (49.6)	213 (54.1)	3913 (58.7)

Note: With pre-DNAR, Patients with pre-existing do-not-attempt-resuscitation orders before rapid response system activation. Without pre-DNAR, patients without pre-existing do-not-attempt-resuscitation orders before rapid response system activation. With new DNAR, patients who were implemented do-not-attempt-resuscitation orders after rapid response system activation. Without new DNAR, patients who were not implemented do-not-attempt-resuscitation orders after rapid response system activation.

Abbreviations: DNAR, do-not-attempt-resuscitation; IQR, interquartile range; NEWS2, National Early Warning Score 2; qSOFA, Quick-Sequential Organ Failure Assessment; RRS, rapid response system; SD, standard deviation.

[a]Data from 7200 patients.

[b]Data from 6695 patients.

[c]Data from 6366 patients.

[d]Data from 6974 patients.

[e]Data from 6848 patients.

[f]Data from 6371 patients.

[g]Data from 6963 patients.

[h]Data from 5825 patients.

[i]Data from 6556 patients.

[j]Data from 4186 patients.

[k]Data from 5161 patients.

[l]Data from 3238 patients.

[m]Urology, otolaryngology, dermatology, and ophthalmology.

[n]Emergency, radiology, other than above.

[o]Laboratory technician, physiotherapist, biomedical equipment technician, medical clerk, and other personnel.

TABLE 2 Event outcomes of patients after RRS activation, *n* (%).

	Total *n* = 7904	With pre-DNAR *n* = 838/7904 (10.6)	Without pre-DNAR *n* = 7066/7904 (89.4)		*p*-Value[d]
			With new DNAR *n* = 394/7066 (5.6)	Without new DNAR *n* = 6672/7066 (94.4)	
Code change after RRS activation	450 (5.7)	56 (6.7)			
CPA on arrival	562 (7.1)	41 (4.9)	93 (23.6)	428 (6.4)	<0.001
CPA during RRS intervention	123 (1.6)	20 (2.4)	16 (4.1)	87 (1.3)	<0.001
Dispositions after RRS activation[a]					
Death	289 (3.7)	70 (8.4)	84 (21.4)	135 (2.0)	<0.001
ICU transfer	2718 (34.7)	131 (15.7)	99 (25.2)	2488 (37.7)	
HDU transfer	2105 (26.9)	299 (35.9)	98 (24.9)	1708 (25.9)	
Stay in ward	2485 (31.7)	314 (37.7)	105 (26.7)	2066 (31.3)	
Other[c]	237 (3.0)	19 (2.3)	7 (1.8)	211 (3.2)	
Outcomes after 30 days[b]					
Death	2045 (28.5)	466 (58.6)	279 (75.8)	1298 (21.6)	<0.001
Hospitalization	2175 (30.4)	166 (20.9)	57 (15.5)	1952 (32.5)	
Discharge	2946 (41.1)	163 (20.5)	32 (8.7)	2751 (45.8)	

Note: With pre-DNAR, patients with pre-existing do-not-attempt-resuscitation orders before rapid response system activation. Without pre-DNAR, Patients without pre-existing do-not-attempt-resuscitation orders before rapid response system activation. With new DNAR, patients who were implemented do-not-attempt-resuscitation orders after rapid response system activation. Without new DNAR, patients who were not implemented do-not-attempt-resuscitation orders after rapid response system activation.

Abbreviations: CPA, cardiopulmonary arrest; DNAR, do-not-attempt-resuscitation; ICU, intensive care unit; HDU, high dependency unit; RRS, rapid response system.

[a]Data from 7834 patients.

[b]Data form 7166 patients.

[c]Transfer to other hospitals or unknown.

[d]Compared patients with new DNAR orders and without DNAR orders.

were consistent with Model 1 in age category, malignancy, postoperative status, and NEWS2.

DISCUSSION

Key findings

Our data highlight the incidence and factors associated with new DNAR orders in 29 facilities involving 7904 patients with RRS activation for clinical deterioration in Japan. We found that new DNAR orders were implemented for one in 18 patients without pre-DNAR orders after RRS activation. Factors associated with new DNAR orders that were consistent with the three models in our study were age, malignancy, postoperative status, and NEWS2.

Relationship to previous studies

The incidence of new DNAR orders after RRS activation in our study (5.6%, 394/7066 of excluding patients with pre-existing DNAR orders [10.6%, 838/7904 of total cohort]) was lower than that reported in previous studies (approximately 8% [median, range 2.1%–25%] of prevalence in the most recent studies from Australia, the United States [US], and other countries).[5,18–20] The lower incidence of new DNAR orders in Japan may reflect differences in local healthcare practices, culture, and availability of ICU or HDU resources between international countries.[21] Another possible explanation for the lower incidence of new DNAR orders is that guidelines regarding DNAR orders have not been established with legal justification, and physicians in most Japanese facilities are not obligated to order code status for patients.[22] However, our findings revealed that the Japanese RRS also plays a role in making decisions on DNAR orders for deteriorating patients.

In contrast to new DNAR orders, there were even fewer reports on withdrawals of pre-existing DNAR orders after RRS activation. The previous study reported that 13% (15/115) of RRS-implemented changes of code status involved reversing status from "DNAR" to "full code"[23] in a single US hospital. Consistent with this study, among patients with pre-existing DNAR orders, 6.7% (56/838) had a shift in status from "DNAR" to "full code" or "partial code" after RRS activation in our study. These data suggest that the RRS does not simply provide an opportunity to implement new DNAR orders but also provides an opportunity to withdraw pre-existing DNAR orders for deteriorating patients.

In our main results of the multivariable hierarchical regression model (Model 1), age, malignancy, activation at night, and higher qSOFA score and NEWS2 were positively associated with new DNAR orders after RRS activation, whereas postoperative patients and activation from professions other than physicians and nurses were negatively associated. This is consistent with previous studies, in which age was strongly associated with early DNAR orders placement after RRS activation[24] and in other specific settings (emergency department, and inpatient).[25,26] In our study, factors associated with new DNAR orders seemed closely related to predictors of mortality after RRS activation because more than three in four patients with new DNAR orders died within 30 days. Indeed, positive predictors of mortality after RRS activation in previous studies included deterioration of vital signs at the time of RRS activation,[27] malignancy, and activation at night, whereas negative predictors included postoperative status,[16] which is also consistent with our research outcomes.

Strengths and limitations

This study has several strengths, including being conducted across multiple centers in Japan, a large sample size, and a longitudinal analysis over the past decade. To our knowledge, this multicenter study is the first to explore independent factors affecting DNAR orders after RRS activation.

However, this study has several limitations. First, although the decision-making of DNAR orders is an important outcome, it could be strongly influenced by healthcare providers' perspectives and patients' or their family's wishes for EOL care. Therefore, our findings may not be generalizable to patients in Japanese facilities not included in our study and other countries with different RRS practices.

Second, a substantial amount of vital sign data necessary to calculate the qSOFA score and NEWS2 were missing (24.5% and 59.0%, respectively). Missing vital signs data is a frequent problem in such a kind of research, and it has been reported that the frequency of missing values is high (e.g., up to 77% for the absence of RR in general wards).[28] However, the concordant results of our sensitivity analyses (complete case analysis) assured the robustness of the main results.

Third, unmeasured confounding factors are inherent risks in all observational studies. Several factors might have influenced DNAR order decisions, including the patient's existing comorbidity (e.g., chronic obstructive pulmonary disease, chronic heart failure, cerebrovascular accident, or neurodegenerative disease), the composition of RRS, the status of the patient's cognitive function, the presence of proxy, primary care physicians' or RRS members' perspectives on DNAR orders, and previous EOL discussions.

Fourth, this database does not have information on whether the discussion of the DNAR order was held among members of RRS, primary care physicians, patients, or patients' families. Moreover, the decision to attempt resuscitation is only one of many essential decisions physicians are encouraged to make when discussing the preference for EOL care with patients and their families.[29]

TABLE 3 Multivariable hierarchical logistic regression analysis of characteristics associated with new DNAR orders after RRS activation (Model 1: imputing mean value), $n = 7066$.

Characteristic	cOR	95% CI	*p*-Value	aOR	95% CI	*p*-Value
Young and middle (20–64 years)	Ref.			Ref.		
Pre-old (65–74 years)	1.68	1.22, 2.31	<0.001	1.56	1.12, 2.17	0.009
Old (75–89 years)	2.60	1.96, 3.44	<0.001	2.56	1.92, 3.42	<0.001
Super-old (90 years)	5.85	3.79, 9.01	<0.001	6.58	4.17, 10.4	<0.001
Male	0.95	0.78, 1.17	0.654	0.97	0.78, 1.20	0.764
Existing comorbidity						
Malignancy	1.71	1.37, 2.13	<0.001	1.82	1.42, 2.32	<0.001
Postoperative status	0.52	0.36, 0.76	<0.001	0.45	0.30, 0.71	<0.001
Sepsis	1.22	0.93, 1.60	0.158	0.95	0.71, 1.26	0.699
Admitted department						
Medical	Ref.			Ref.		
Surgical	0.87	0.51, 1.51	0.253	0.93	0.72, 1.21	0.597
Minor[a]	1.12	0.75, 1.65	0.583	1.09	0.72, 1.65	0.684
Obstetrics/gynecology	1.20	0.69, 2.11	0.522	1.56	0.84, 2.90	0.163
Others[b]	0.88	0.51, 1.51	0.643	1.26	0.72, 2.20	0.424
Missing	0.85	0.58, 1.23	0.390	1.06	0.70, 1.61	0.772
Setting						
Inpatient	1.05	0.75, 1.56	0.789	1.15	0.78, 1.70	0.466
Time of day						
Day	Ref.			Ref.		
Night	1.41	1.13, 1.76	0.002	1.32	1.04, 1.67	0.022
Missing	0.96	0.70, 1,31	0.80	1.00	0.72, 1.39	0.989
Professions activating RRS						
Doctors	Ref.			Ref.		
Nurses	0.99	0.77, 1.27	0.917	1.10	0.84, 1.45	0.481
Others[c]	0.21	0.09, 0.52	<0.001	0.29	0.11, 0.73	0.011
Missing	1.25	0.93, 1.67	0.135	1.31	0.90, 1.91	0.163
qSOFA score (per 1 score)	1.73	1.49, 2.02	<0.001	1.37	1.13, 1.67	0.004
NEWS2 (per 1 score)	1.14	1.10, 1.18	<0.001	1.07	1.02, 1.12	0.001
Hospital type						
University hospital	0.76	0.62, 0.93	0.008	0.67	0.44, 1.00	0.064
Hospital volume						
Small (1–500)	Ref.			Ref.		
Medium (501–800)	1.57	1.16, 2.14	0.004	1.23	0.74, 2.05	0.438
Large (801–1200)	1.06	0.81, 1.39	0.677	1.15	0.72, 1.85	0.555

Note: Missing continuous values (qSOFA score [1.5] and NEWS2 [7.4]) were imputed to the mean value.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; DNAR, do-not-attempt-resuscitation; NEWS2, National Early Warning Score 2; qSOFA, Quick-Sequential Organ Failure Assessment; Ref., reference; RRS, rapid response system.

[a]Urology, otolaryngology, dermatology, and ophthalmology.

[b]Emergency, radiology, other than above.

[c]Laboratory technician, physiotherapist, biomedical equipment technician, medical clerk, and other personnel.

Implications and future research

Patients who required RRS activation were high-risk populations, with a mortality rate of approximately one in four. Our findings on incidence and predictors of new DNAR orders after RRS activation should provide an opportunity to improve the implementation of DNAR orders or EOL care discussions among healthcare provider, patients, or their families.

Further studies on the epidemiology of RRS are required, especially to help distinguish between patients who would benefit from intensive care and those who might be shifted

to comfortable care after appropriate DNAR orders and EOL discussions.[30] Furthermore, for our study to expand, research is also necessary to investigate whether using predictors identified in our study would promote appropriate DNAR orders and encourage discussion of EOL care.

Conclusions

We found that the incidence of new DNAR orders was one in 18 patients after RRS activation. We identified factors associated with new DNAR orders after RRS activation among deteriorating patients: age, malignancy, postoperative status, and NEWS2. Knowledge of predictive factors for DNAR orders may help healthcare providers withhold futile medical treatment and improve patients' EOL care.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data in this manuscript were provided by the In-Hospital Emergency Committee in Japan under license. The datasets used and analyzed during this study are available from the corresponding author on reasonable request with the permission of the In-Hospital Emergency Committee in Japan.

ETHICS STATEMENT

Approval of the research protocol: The Institutional Review Board of Nagoya City University Graduate School of Medical Sciences and Nagoya City University Hospital approved this study (approval number: 60210077, August 24, 2021).
Informed consent: The need for written informed consent was waived because of the observational nature of the study.
Registry and the registration no. of the study/trial: The IHER-J was organized in the University Hospital Medical Information Network–Clinical Trials Registry (UMIN000012045).
Animal studies: Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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