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Clinical paper

Impact of dynamic parameter of trends in vital signs on the prediction of serious events in hospitalized patients -a retrospective observational study

Rimi Tanii[a,b], *Kuniyoshi Hayashi*[c], *Takaki Naito*[b], *Zoie Shui-Yee Wong*[d], *Toru Yoshida*[b], *Koichi Hayashi*[a], *Shigeki Fujitani*[b,*]

Abstract

Aim: Although early detection of patients' deterioration may improve outcomes, most of the detection criteria use on-the-spot values of vital signs. We investigated whether adding trend values over time enhanced the ability to predict adverse events among hospitalized patients.

Methods: Patients who experienced adverse events, such as unexpected cardiac arrest or unplanned ICU admission were enrolled in this retrospective study. The association between the events and the combination of vital signs was evaluated at the time of the worst vital signs 0–8 hours before events (near the event) and at 24–48 hours before events (baseline). Multivariable logistic analysis was performed, and the area under the receiver operating characteristic curve (AUC) was used to assess the prediction power for adverse events among various combinations of vital sign parameters.

Results: Among 24,509 in-patients, 54 patients experienced adverse events(cases) and 3,116 control patients eligible for data analysis were included. At the timepoint near the event, systolic blood pressure (SBP) was lower, heart rate (HR) and respiratory rate (RR) were higher in the case group, and this tendency was also observed at baseline. The AUC for event occurrence with reference to SBP, HR, and RR was lower when evaluated at baseline than at the timepoint near the event (0.85 [95%CI: 0.79–0.92] vs. 0.93 [0.88–0.97]). When the trend in RR was added to the formula constructed of baseline values of SBP, HR, and RR, the AUC increased to 0.92 [0.87–0.97].

Conclusion: Trends in RR may enhance the accuracy of predicting adverse events in hospitalized patients.

Keywords: In-hospital cardiac arrest, Rapid response systems, Vital signs, Delta values, Adverse events, Clinical deterioration

Introduction

In-hospital cardiac arrest (IHCA) is one of the most serious adverse events with a high mortality rate[1,2] and is reported to occur at a rate of 1 to 5 events per 1,000 hospital admissions.[1–4] Furthermore, clinical deterioration of patients' status is commonly seen before the occurrence of IHCA,[5] and the alterations in physiological parameters, including vital signs, have often been documented 6 to 8 hours preceding these events.[6–8] Hence, early detection of patients' clinical deterioration and timely intervention are crucial to prevent IHCA and unplanned transfer to the intensive care unit (ICU). The rapid response system (RRS) is a global standard system that is intended to improve patient safety by identifying and intervening in patients'

Abbreviations: IHCA, in-hospital cardiac arrest, RRS, Rapid Response System, NEWS, National Early Warning Score, MEWS, Modified Early Warning Score, EWS, early warning scores, EHR, Electronic health records, ICU, intensive care unit, IQR, interquartile range, ROC, receiver operating characteristic, AUC, area under the curve, HR, heart rate, RR, respiratory rate, SpO2, saturation of percutaneous oxygen, SBP, systolic blood pressure, OR, odds ratio

* Corresponding author at: Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan.

E-mail address: shigekifujitani@gmail.com (S. Fujitani).

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clinical deterioration in hospital wards and preventing serious events.[9] Although RRS is considered to be associated with a reduced incidence of IHCA,[10–12] its process always starts with crisis detection, and how to identify patients at risk has been studied to build reliable criteria for activating RRS.[13,14] Hence there have been developed many criteria for activating RRS, including a single parameter criterion,[15] National Early Warning Score (NEWS),[16] Modified Early Warning Score (MEWS),[17] and more recently, Machine Learning-based Early Warning System (ML-EWS).[18,19] While there is no doubt that these criteria contribute to the early detection of patients' deterioration, the development of these scoring systems suggests a teleological need for some challenges to be improved in predicting the occurrence of serious events.

Vital signs are core components of predicting adverse events and the activation criteria for early warning scores (EWS).[15–19] Although the values of vital signs at specific time points count highly in the EWS,[16–19] the concept that the changes in the value may also reflect patients' vital sign severity has not been fully substantiated. Indeed, whether systolic blood pressure (SBP) remains stable or gradually decreases should affect the clinical implication even though the initial SBP is the same. Most of the existing criteria, however, allow activation of RRS based exclusively on absolute values of vital signs at one-time point but do not reflect the changes in vital signs over time. Furthermore, very few articles have been published that focus on the changes in vital signs over time before adverse events, and those are all retrospective cohort studies without controls.[20,21] Thus, the trend or the predicted value of the changes in vital signs before adverse events has not hitherto been evaluated fully.

This study aimed to characterize the vital sign profiles in critical inpatients at two time points, i.e., 24–48 hours and 0–8 hours before serious adverse events, and to compare the results with those in patients who survived to discharge with no adverse events. Furthermore, whether the change in vital signs during the two time points enhanced the ability to predict adverse events and served as a novel parameter in combination with the conventional static parameters was evaluated.

Methods

We conducted a retrospective observational study at St. Marianna University Hospital (Kawasaki, Kanagawa, Japan) with 1,175 beds, including ten intensive care unit (ICU) beds and 30 high care unit beds. RRS has been implemented since 2010 and covers all general wards. The hospital also operates the code blue system, which targets all patients with unexpected cardiac arrest.

The study was approved by the Institutional Review Board and Ethics Committee of St. Marianna University School of Medicine (approval No. 5703) and was conducted in accordance with the Declaration of Helsinki. The need for patient consent was waived because of the observational nature of this study; the opt-out information was published on our university website. Information from the electronic health records (EHR) was anonymized before final analyses. The study was registered at UMIN (UMIN000051847).

Primary outcomes

The primary outcomes of interest were adverse events, defined as a composite outcome of unexpected cardiac arrest and unplanned ICU admission. We defined "unexpected" cardiac arrest as the condition without the DNAR (Do Not Attempt Resuscitation) order mentioned in the EHR. "Unplanned" ICU admission was determined as unscheduled ICU admission from a general ward; when unplanned ICU admission was recorded following RRS activation, we defined the time of RRS activation as the time when the events occurred. If patients experienced more than one adverse event during the same hospital stay, we treated these episodes as different events. We obtained the patient list of the primary outcome and RRS/code blue system activation from the administrative database of the hospital's patient safety division. The list was manually checked to meet the defined criteria by the EHR.

Study populations and data sources

We included all patients aged 16 and over who were admitted to our hospital from January to December 2019. Among them, the patients who experienced the primary outcome were defined as cases, and the remaining as controls (Fig. 1).

The data on patients' vital signs and demographic information were extracted from the EHR. No imputation method was applied to the datasets with missing values, which were excluded from the study (exclusion-2 and 3, Fig. 1). The patients who developed unexpected cardiac arrest in the ICU were excluded since ICU patients are not a target for RRS. Furthermore, the patients with end-stage chronic disease, including malignancies, expressed DNAR orders and had been dead at discharge. Along with these populations, the patients whose outcome at discharge was unknown were excluded from data analysis. The reasons for these exclusions are detailed in Supplementary Table 1.

Vital sign parameters

We used five fundamental vital signs: SBP, heart rate (HR), respiratory rate (RR), saturation of percutaneous oxygen (SpO_2), and body temperature (Temp). As a predictive parameter for impending events, we obtained each vital sign's "worst value" within 8 hours before an event. This is because clinical deterioration appears 6 to 8 hours before adverse events,[6–8] and vital signs are usually evaluated thrice daily in general wards. Then, we collected the values from 48 to 24 hours before the event. Because several vital signs were recorded during the period in most cases, we used the average of these values as a "baseline value." Finally, the change in vital signs (i.e., Δ) was calculated as

Δ = [the worst vital value] - [the baseline value].

For controls, hospital discharge was regarded as an event. The Δ values were calculated as follows:

Δ = [the worst vital value up to 8 hours before discharge] - [the baseline value].

Patients for whom proper calculation of Δ was unavailable for any reason (e.g., occurrence of events within 24 hours after admission, insufficient data recorded for the worst value period or the baseline value period) were excluded (Supplementary Table 1).

Statistical analysis

Continuous variables were expressed as median [IQR1-IQR3], and categorical variables as numbers (%). Comparison between cases and controls was made using the Mann-Whitney U test or chi-square test. Multivariable analysis was performed using the logistic regression model to assess the association between vital sign values and the primary outcome.

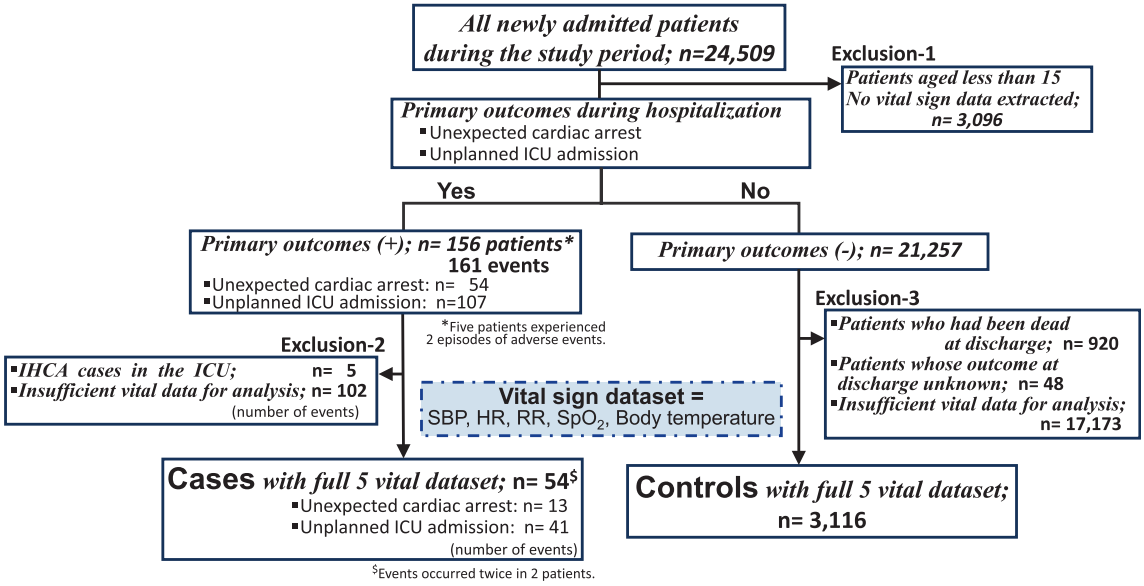

Fig. 1 – Flow chart for inclusion of cases and controls. IHCA; in-hospital cardiac arrest, SBP; systolic blood pressure, HR; heart rate, RR; respiratory rate, SpO2; saturation of percutaneous oxygen.

We used receiver operating characteristic curve (ROC) analysis and calculated the area under the curve (AUC) values to clarify the performance of the prediction of adverse events. AUC was determined with the Youden index. Furthermore, the vital sign data were dichotomized based on the criteria adopted in the NEWS (score 2),[16] and multivariable logistic regression analysis was performed with each vital sign variable as an explanatory parameter. Finally, to minimize the confounding effects of the baseline covariables on primary outcomes, the source data were re-analyzed after propensity score matching. A logistic regression model was applied to generate propensity scores with age and the baseline data, including SBP, HR, RR, and SpO2, as covariables, and caliper width was set at 0.2 or less of the standard deviation of the logit of the propensity score. The matched pairs were then analyzed with the Wilcoxon signed rank test. We used R (version 4.1.1) for data manipulation and performed statistical analysis with JMP Pro (v.16.2.0, SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

Results

Enrollment of cases and controls

A total of 24,509 patients were newly admitted to our hospital between January 2019 and December 2019 (Fig. 1). During the study period, 156 patients aged $\geq$ 16 experienced the primary outcome of an adverse event. Among them, five patients experienced adverse events twice during the same hospital stay, and we confirmed 161 adverse events. Among them, 54 cases experienced unexpected cardiac arrest (2.2 patients/1,000 hospital admission), and 107 cases had unplanned ICU admission. We then excluded 5 ICU patients and 102 patients with insufficient data for calculating the Δ values. Ultimately, 54 cases were included for further evaluation.

After the exclusion of the patients under 16 years of age, there were 21,257 patients with no experience of the primary outcomes during hospitalization (Fig. 1). We then excluded 920 patients who had been dead at hospital discharge and 48 patients with unknown outcomes. Although ten explanatory variables (baseline_SBP/_HR/_RR/_SpO2/_Temp and worst_SBP/_HR/_RR/_SpO_2/_Temp) were required to evaluate the association between vital sign data and the primary outcomes, some of the vital sign data were missing in 17,173 patients (Supplementary Table 1). Thus, 3,116 controls were included for full set analysis.

Vital sign data at the worst values

There were no statistical differences in sex or age between the cases and the controls (Table 1). Among the variables entailing the worst vital sign measurements, SBP and SpO2 were lower, whereas HR and RR were higher in the case group. A modest difference in Temp was observed between these groups. When the association between these parameters and the primary outcomes was evaluated, SBP, HR, and RR constituted important variables for predicting the outcome (Table 2A).

Baseline data and D values of vital sign data

At baseline, SBP was lower, and HR and RR were higher in the case group than in the control group (Fig. 2). No difference in SpO2 or Temp was seen between these groups. Absolute Δ values for SBP, HR, RR, and SpO2 were greater in the case group.

We further examined whether the vital sign data at baseline were associated with the occurrence of adverse events. Both HR and RR were associated with primary outcomes (Table 2B). However, the AUC for adverse events was less than that observed at the time of the worst values ($p = 0.012$).

Impact of D values on AUC and event occurrence

The AUC, with SBP, HR, and RR as explanatory variables, was less when evaluated at baseline than at the time of the worst values (0.850 [95%CI: 0.785–0.915] vs. 0.925 [95%CI: 0.876–0.974], $p = 0.010$, Fig. 3A). Then, we introduced various Δ parameters into the calculation formula and found that adding Δ_RR, rather than Δ_SBP or Δ_HR, increased the AUC to 0.917 [95%CI: 0.866–0.968]

Table 1 – Patients' demographics and various parameters obtained 0–8 hours before adverse events (case) or hospital discharge (control).

Parameters	Control (n = 3,116)	Case (n = 54)	p value
Male (n, %)	1,823 (58.5)	38 (70.4)	0.094
Age (y/o), median [IQR]	73.0 [62.8, 81.0]	72.0 [60.3, 77.0]	0.242
Worst values			
SBP (mmHg), median [IQR]	119 [106, 132]	101 [88, 126]	<0.001
HR (beats/min), median [IQR]	72 [64, 82]	104 [83, 126]	<0.001
RR (/min), median [IQR])	16.0 [16.0, 18.0]	24.0 [20.0, 31.8]	<0.001
SpO_2 (%), median [IQR]	97 [96, 98]	95 [91, 98]	<0.001
Temp (C), median [IQR]	36.6 [36.4, 36.8]	36.9 [36.6, 37.5]	<0.001

SBP; systolic blood pressure, HR; heart rate, RR; respiratory rate, SpO2; saturation of percutaneous oxygen, Temp; body temperature, IQR; interquartile range.

Table 2 – Adjusted OR for event occurrence in association with various parameters.

A. At the time of the worst values (0–8 h before events)

Parameters	Adjusted OR per each unit	95%CI	p value	AUC: 0.925
SBP	0.97 (/mmHg)	0.96–0.99	<0.001	**[95%CI: 0.876–0.974]**
HR	1.04 (/beats/min)	1.02–1.05	<0.001	Sensitivity: 87.0%
RR	1.30 (/min)	1.22–1.38	<0.001	Specificity: 91.6%
SpO2	1.01 (/%)	0.93–1.10	0.750	

B. At baseline (24-48h before events)

Parameters	Adjusted OR per each unit	95%CI	p value	AUC: 0.849*
SBP	0.99 (/mmHg)	0.97–1.00	0.138	**[95%CI: 0.784–0.914]**
HR	1.06 (/beats/min)	1.04–1.08	<0.001	Sensitivity: 66.7%
RR	1.30 (/min)	1.21–1.40	<0.001	Specificity: 90.5%
SpO2	0.96 (/%)	0.82–1.12	0.564	

SBP; systolic blood pressure, HR; heart rate, RR; respiratory rate, SpO2; saturation of percutaneous oxygen, OR; odds ratio, CI; confidence interval, AUC; area under the curve.

* ; p = 0.012 vs. at the time of the worst values (A).

(p = 0.001), a value nearly identical to that seen at the time of the worst values (p = 0.635). In contrast, the static parameters (baseline_SpO2, baseline_Temp) had no additive effects on the AUC.

When the three baseline parameters (SBP, HR, and RR) and Δ_RR were incorporated in the multivariable logistic regression analysis, Δ_RR ≥ 5/min and baseline_RR ≥ 20/min contributed more greatly to the prediction of adverse events (Fig. 3B).

Impact of D values on event occurrence among propensity score-matched patients

Because there existed marked differences in baseline vital sign data between cases and controls (Fig. 2), these patient groups were matched using the propensity score method, with inclusion of age and the baseline data (HR, RR, SBP, and SpO2) as covariables. Thus, the baseline data of all these parameters were nearly the same between the propensity score-matched control and the case subgroup (n = 54, Table 3A). In contrast, marked differences in the Δ values of these parameters were noted between the case and the control subgroup. Furthermore, Δ_HR ≥ 10 beats/min and Δ_RR ≥ 5/min were associated with a higher occurrence of adverse events (Table 3B).

Discussion

Many risk-scoring systems have developed to attempt to predict the occurrence of critical events early and mortality in hospitalized patients.[13–19] Although early prediction of serious events could prevent the actual occurrence with appropriate care and treatment, it remains controversial which of the EWS is more reliable[22,23] or whether additional modalities can enhance the accuracy of the prediction.[20,21]

Vital sign parameters and event occurrence

Our study revealed that critical patients presented abnormal vital signs several hours (within 8 hours) before the occurrence of serious events (Table 1). Thus, increased RR and HR and reduced SBP constituted the substantial risk factors that preceded critical events and through which we could predict their occurrence (Table 2A), and the high AUC value (i.e., 0.925) indicated that the logistic regression model for the ROC was well constructed for discrimination of event occurrence. These observations support the principle proved by the established EWS, including NEWS[16] and MEWS.[17]

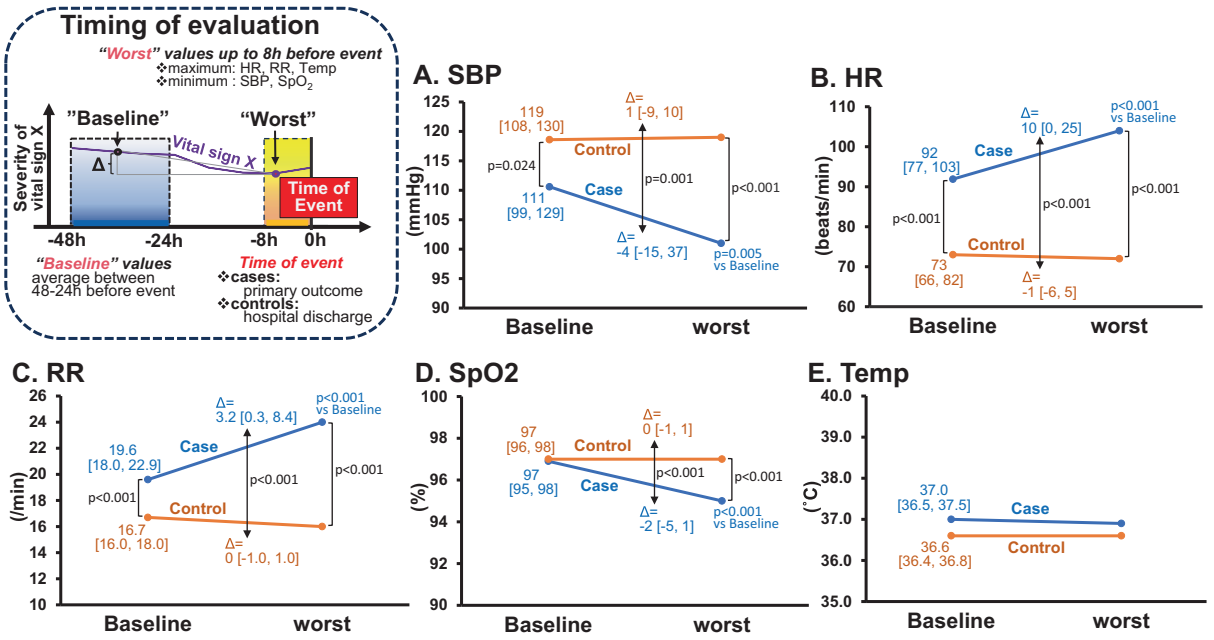

Fig. 2 – Changes in various parameters during the clinical course. SBP; systolic blood pressure, HR; heart rate, RR; respiratory rate, SpO2; saturation of percutaneous oxygen. Brackets indicate interquartile ranges (25% and 75%).

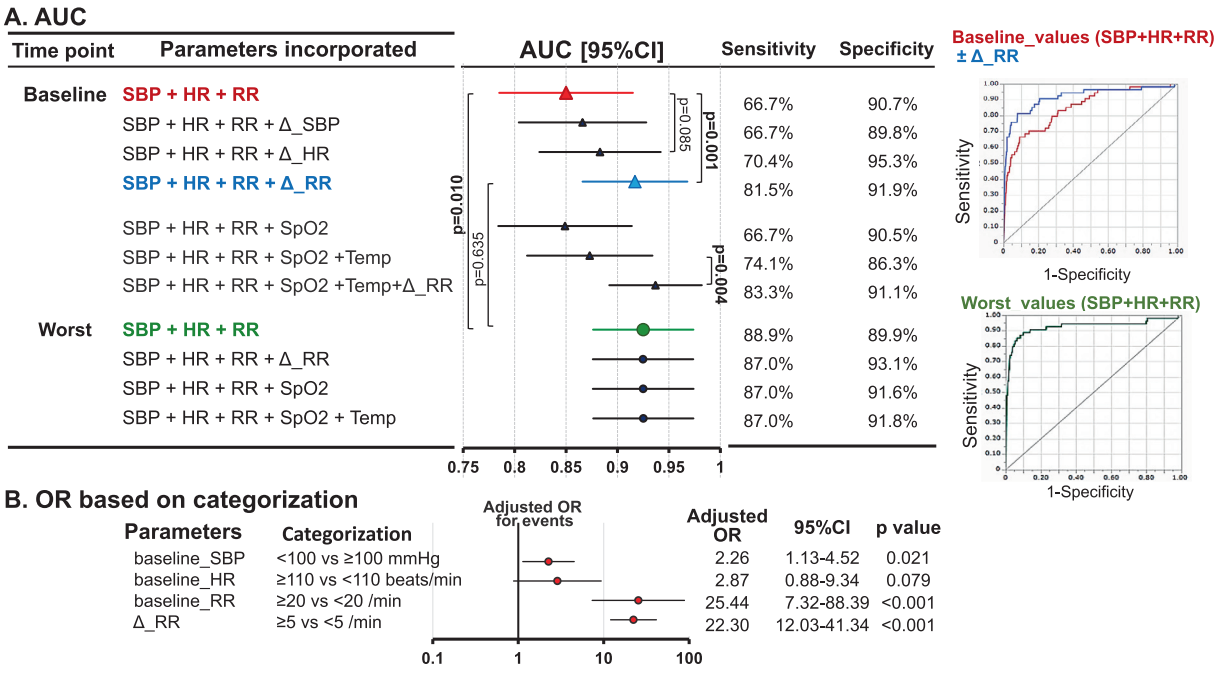

Fig. 3 – ROC analysis and multivariable logistic regression analysis. SBP; systolic blood pressure, HR; heart rate, RR; respiratory rate, OR; odds ratio.

Whilst the prediction of critical events could offer the opportunity for improving patients' conditions, it remains undetermined whether the earlier evaluation may retain the accuracy of the prediction. We therefore assessed the vital sign data observed 24–48 hours before critical events (i.e., at baseline) and compared the results with the worst data obtained 0–8 hours before events. Thus, SBP was lower, and HR and RR were higher at baseline (Fig. 2). These findings indicate that abnormal vital signs appeared as early as 24–48 hours before the events. The logistic regression analysis showed greater contributions of high RR and HR to the occurrence of the events (Table 2B). The AUC, however, was lower than that observed at the time of the worst data (0.849 [95%CI: 0.784–0.914] vs 0.925

Table 3 – Changes in vital sign parameters and adjusted OR for events among propensity score-matched patients (n = 54).

A. Changes in vital sign parameters.

		Baseline [95%CI] (24–48 h before events)	**Worst** [95%CI] (0–8 h before events)	**p value** (baseline vs worst)	**Δ (difference)** [95%CI]
SBP	**case**	111 [99, 129]	101 [88, 126]	0.005	−4 [-15, 3]
	control	109 [99, 122]	113 [100, 132]	0.344	0.3 [-8, 14]
	p value (case vs control)	0.608	0.042		0.012
HR	**case**	92 [77, 103]	104 [83, 126]	<0.001	10 [0, 25]
	control	93 [76, 108]	84 [74, 99]	0.083	−1.1 [-12, 4]
	p value (case vs control)	0.888	0.083		<0.001
RR	**case**	19.6 [18.0, 22.9]	24 [20.0, 31.8]	<0.001	3.2 [0.2, 8.6]
	control	19 [17.3, 24.0]	17 [16.0, 21.5]	0.021	−1.3 [-3.1, 1.3]
	p value (case vs control)	0.517	<0.001		<0.001
SpO2	**case**	97 [96, 98]	95 [91, 98]	<0.001	−2 [-5, 1]
	control	97 [96, 98]	97 [95, 98]	0.915	0 [-1, 1]
	p value (case vs control)	0.667	<0.001		0.001

B.Adjusted odds ratios.

Parameters	**Categorization**	**Odds ratio [95%CI]**	**p value**
Δ_SBP	**<-10 vs ≥-10 mmHg**	**3.22 [0.82–12.65]**	**0.094**
Δ_HR	**≥10 vs <10 beats/min**	**6.36 [2.19–18.48]**	**<0.001**
Δ_RR	**≥5 vs <5 /min**	**6.35 [1.85–21.76]**	**0.003**
Δ_SpO2	**<-3 vs ≥-3%**	**7.35 [0.78–69.06]**	**0.081**

SBP; systolic blood pressure, HR; heart rate, RR; respiratory rate, SpO2; saturation of percutaneous oxygen. Δ; difference in each parameter between baseline and the worst values.

[95%CI: 0.876–0.974]). Hence, these findings would allow us to introduce novel ideas that could improve the accuracy of the prediction of the event occurrence.

Of note, Churpek et al.[20] demonstrated that RR was the most accurate vital sign, using univariate analysis. Kellett et al.[21] also showed that the incorporation of RR into the ViEWS[24] improved the prediction performance for 30-day mortality. In this regard, we found that 48.1% of the cases manifested RR ≥ 20/min at baseline whereas only 9.3%, 25.9% and 7.4% had HR ≥ 110 beats/min, SBP < 100 mmHg and SpO2 ≤ 93%, respectively (Supplementary Fig. 1). Thus, abnormal RR is more closely associated with the occurrence of events and may appear earlier than other vital signs.

Changes in vital sign parameters and event occurrence

Although the conventional EWS (e.g., NEWS, MEWS) uses static parameters in which the data are obtained at specific time points, the trend in the values of the parameters over time (i.e., dynamic parameters) may offer additional benefits for the assessment of patients' risk. In the present study, we found that adding Δ_RR to the baseline parameters (baseline_SBP, baseline_HR, and baseline_RR) improved the accuracy for predicting the events (AUC: from 0.850 [95%CI: 0.785–0.915] to 0.917 [95%CI: 0.866–0.968], Fig. 3). Furthermore, Δ_RR ≥ 5/min, along with baseline_RR ≥ 20/min, constituted major determinants of the occurrence of adverse events, and the propensity score-matched model suggested an important association between Δ_RR and the event occurrence (Table 3B). In this regard, Bell et al.[25] demonstrated that the addition of vital signs and laboratory trend values to the logistic model increased the AUC and the sensitivity for predicting adverse events. Their findings, as well as our current study, would thus endorse the idea that incorporation of the dynamic parameter (e.g., Δ_RR) can improve the accuracy of prediction of adverse events. A similar notion has been proposed among cardiac arrest patients in whom acute changes in vital signs and laboratory parameters evolve, including regional cerebral oxygen saturation (StO2),[26,27] dynamic (Δ_StO2) together with static (initial_StO2) parameters are closely associated with the return of spontaneous circulation. Collectively, the enrollment of both static and dynamic parameters could act in concert to enhance the capability and precision of predicting the occurrence of critical events.

Limitations

Because the present study was conducted in a single center, careful interpretation is required regarding external validity. Some concern remains regarding sampling/selection bias. In most general wards, patients' vital signs were obtained thrice a day, but in some wards where patients' conditions were stable, only one measurement was done. Because Δ values (=worst-baseline values) were unavailable, these cases were excluded, particularly from the control population. Similarly, patients with short hospital stays (<1 day) or whose occurrence of adverse events within 24 hours after admission cannot have baseline data. Furthermore, 920 patients with chronic and/or malignant disease expressed DNAR orders. Consequently, a large num-

ber of the population were excluded (Supplementary Table 1). Second, because of the retrospective nature of this observational study, we could not take into consideration the therapeutic intervention, including oxygen and fluid administration, which might affect vital signs and their related parameters.

The timing of the data acquisition remains a matter of controversy. Our study shows that the Δ value of vital signs appears useful for the prediction of adverse events. However, the Δ value calculation herein required the worst and the baseline data observed at a relatively long interval (16–48 hours). If we set Δ values of shorter duration, we could obtain a more practical result in predicting adverse events. Furthermore, in the control group, we adopted the worst data within 8 hours of discharge as the "worst value" when the vital signs were stable. This selection bias might exaggerate the differences in the role of vital sign parameters between cases and controls.

Finally, we assessed the AUC for the determination of event occurrence based on the raw data, but not the scores, for each parameter because of a more straightforward evaluation. When assessed with a new scoring system (Mari-MEWS, Supplementary Fig. 2), the AUC was increased by incorporating dynamic parameters (e.g., Δ_RR). Furthermore, "efficiency curves",[16,24] which assessed the association between the aggregate scores and the number of events, suggested greater need for workload when evaluated at baseline but adding Δ_RR scores improved this shift (Supplementary Fig. 3). Since EWSs are more conveniently available in clinical settings, our novel challenge needs to be more thoroughly investigated.

Conclusion

The trend in vital signs, particularly RR, may help predict serious adverse events in hospital wards when combined with the existing criteria using static parameters. Further studies are required to clarify how the trend values are determined in clinical practice.

Declaration of AI and AI-assisted technologies in the writing process

No AI technologies were used during the preparation of this work.

Availability of data and materials

The datasets used in the current study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Rimi Tanii: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kuniyoshi Hayashi:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Takaki Naito:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Zoie Shui-Yee Wong:** Writing – review & editing, Methodology. **Toru Yoshida:** Writing – review & editing, Methodology. **Koichi Hayashi:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Shigeki Fujitani:** Writing – review & editing, Supervision, Project administration, Methodology.

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.

Appendix A. Supplementary data

Supplementary Table 1.
Supplementary Fig. 1.
Supplementary Fig. 2.
Supplementary Fig. 3.
Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100628.

Author details

[a]*Department of Emergency and Critical Care Medicine, St Marianna University Yokohama Seibu Hospital, 1197-1 Yasushi-cho, Asahi-ku, Yokohama, Kanagawa, Japan* [b]*Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa, Japan* [c]*Faculty of Data Science, Kyoto Women's University, 35 Kitahiyoshi-cho, Imakumano, Higashiyama-ku, Kyoto, Japan* [d]*Graduate School of Public Health, St. Luke's International University Omura Susumu & Mieko Memorial St.Luke's Center for Clinical Academia, 5th floor, 3-6-2 Tsukiji, Chuo-ku, Tokyo, Japan*

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