

Association of Time to Rapid Response Team Activation With Patient Outcomes Using a Range of Physiologic Deterioration Thresholds

OBJECTIVES: Clinical deterioration of hospitalized patients is common and can lead to critical illness and death. Rapid response teams (RRTs) assess and treat high-risk patients with signs of clinical deterioration to prevent further worsening and subsequent adverse outcomes. Whether activation of the RRT early in the course of clinical deterioration impacts outcomes, however, remains unclear. We sought to characterize the relationship between increasing time to RRT activation after physiologic deterioration and short-term patient outcomes.

DESIGN: Retrospective multicenter cohort study.

SETTING: Three academic hospitals in Pennsylvania.

PATIENTS: We included the RRT activation of a hospitalization for non-ICU inpatients greater than or equal to 18 years old.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary exposure was time to RRT activation after physiologic deterioration. We selected four Cardiac Arrest Risk Triage (CART) score thresholds a priori from which to measure time to RRT activation (CART score ≥ 12 , ≥ 16 , ≥ 20 , and ≥ 24). The primary outcome was 7-day mortality—death or discharge to hospice care within 7 days of RRT activation. For each CART threshold, we modeled the association of time to RRT activation duration with 7-day mortality using multivariable fractional polynomial regression. Increased time from clinical decompensation to RRT activation was associated with higher risk of 7-day mortality. This relationship was nonlinear, with odds of mortality increasing rapidly as time to RRT activation increased from 0 to 4 hours and then plateauing. This pattern was observed across several thresholds of physiologic derangement.

CONCLUSIONS: Increasing time to RRT activation was associated in a nonlinear fashion with increased 7-day mortality. This relationship appeared most marked when using a CART score greater than 20 threshold from which to measure time to RRT activation. We suggest that these empirical findings could be used to inform RRT delay definitions in further studies to determine the clinical impact of interventions focused on timely RRT activation.

KEY WORDS: cardiac arrest; decompensation; deterioration; early warning scores; rapid response teams

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OBJECTIVE

Clinical deterioration of hospitalized patients is common and can lead to progressive critical illness, in-hospital cardiac arrest (IHCA), and death. Rapid response teams (RRTs) are specialist teams that assess and treat high-risk patients with signs or symptoms of clinical deterioration outside of the ICU to prevent further worsening and subsequent adverse outcomes. The

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KEY POINTS

Question: Is there a relationship between increasing time to rapid response team (RRT) activation after physiologic deterioration and short-term patient outcomes?

Findings: In this multicenter, retrospective study, increasing time to RRT activation was associated in a nonlinear fashion with increased 7-day mortality. This relationship appeared most marked when using a Cardiac Arrest Risk Triage score greater than 20 threshold from which to measure time to RRT activation.

Meaning: We suggest that these empirical findings could be used to inform RRT delay definitions in further studies to determine the clinical impact of interventions focused on timely RRT activation.

presumed benefit of the RRT is predicated on the ability to detect patients who are in early stages of deterioration, often using a vital sign–based track and trigger approach. Such approaches typically use threshold values of individual vital signs or an Early Warning Score (EWS) to trigger activation of the RRT. Early involvement of the RRT is hypothesized to be particularly important because many of the leading causes for deterioration, including acute respiratory failure and sepsis, affect patient populations in which delays in specific therapies are associated with increased mortality (1–4).

Whether activation of the RRT early in the course of clinical deterioration impacts outcomes, however, remains unclear. Although previous attempts to study this question have suggested that delays in RRT activation may be associated with adverse patient outcomes, the generalizability and clinical utility of these findings have been hindered by methodological limitations (5–14). Specifically, approaches to defining both the time at which deterioration has occurred (T_0) and what duration of time after T_0 constitutes a clinically relevant delay are particularly challenging. Studies to date have defined T_0 using institution-specific single vital sign thresholds for RRT activation (5–14). In addition to limiting generalizability, these study designs prevented empiric assessment of which physiologic derangement threshold best defines the time from which increased

time to RRT activation may have negative clinical consequences. Further, prior studies have typically categorized RRTs a priori as “delayed” and “nondelayed” based on somewhat arbitrary time thresholds—most typically 15–60 minutes after T_0 (5–14). One such study included a secondary analysis suggesting that RRT delay duration greater than 4 hours from a single vital sign abnormality may be associated with increased in-hospital mortality compared with shorter delays (6). The relationship between progressive time from T_0 to RRT activation and patient outcomes remains incompletely characterized—is the relationship linear, or is there a threshold beyond which time to RRT activation may have clinical impact? In sepsis, an inverse relationship between progressive treatment delays and survival is well described and has been key to informing standards of care in this population (3, 15, 16). An empiric approach to defining both T_0 and the nature of the time-outcome relationship among patients prompting RRT activation is crucial to understanding how to best use the RRT for deteriorating inpatients.

We therefore sought to characterize the functional form of the relationship between increasing time to RRT activation after physiologic deterioration and short-term patient outcomes across strata of physiologic deterioration in a retrospective multicenter cohort study of hospitalized non-ICU patients who had RRT activations. We hypothesized that increasing time to RRT activation from physiologic deterioration activation would be associated with progressively increased risk of either death or discharge to hospice care within 7 days of RRT activation, that this relationship would

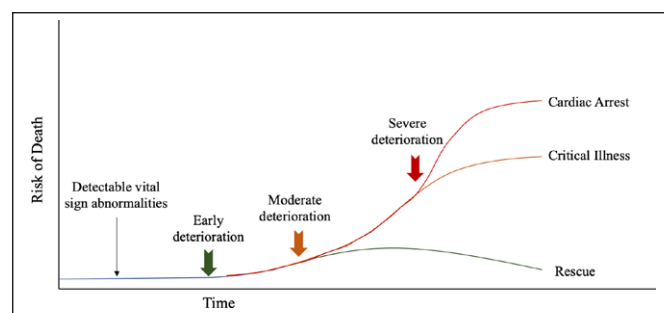


Figure 1. Hypothesized progression of deterioration over time. As physiologic deterioration progresses over time, there is a corresponding increase in the risk of critical illness and death. Early intervention (*green arrow and line*) may be associated with higher odds of clinical rescue than interventions after deterioration has progressed (*orange arrow and line*) or after severe deterioration is apparent (*red arrow and line*).

be nonlinear, and more marked in patients with more advanced deterioration (Fig. 1).

DESIGN

Full details of study design and statistical analyses are in the **Supplementary Content** (<http://links.lww.com/CCX/B83>). In brief, we performed a multicenter retrospective analysis of prospectively collected quality improvement (QI) RRT data.

SETTING

We included RRT data from three Penn Medicine hospitals. At each site, the RRT consisted of a respiratory therapist, attending physician in either internal medicine or critical care, and a dedicated RRT nurse, available 24 hours a day, 7 days per week. RRTs were well established at each site, having been created in 2006 or earlier.

PATIENTS

We included all RRT activations for non-ICU inpatients greater than or equal to 18 years old. For patients with multiple RRT activations over their hospital course, we included only the first RRT activation and excluded subsequent events. Index RRT events from separate hospitalizations for a given patient were considered independent, as such we did not exclude patients with greater than one hospitalization over the study period. RRT activations within 24 hours of hospitalization were excluded to avoid immortal time bias. Due to variations in the timing of QI database launches, the dates of inclusion overlapped but varied by site: Hospital of the University of Pennsylvania (HUP): December 31, 2018 to December 31, 2020; Pennsylvania Hospital (PAH): January 1, 2017 to December 31, 2020; and Penn Medicine Princeton Health (PMC): July 1, 2017 to December 31, 2020. RRT members prospectively entered data after each event into a QI database maintained by the local Clinical Emergencies Committee. We collected additional data from the electronic medical record (EMR). The study was deemed exempt by the University of Pennsylvania's Institutional Review Board (In-Hospital Clinical Emergencies, no. 844850, approved January 15, 2021). All procedures followed the ethical standards of the responsible institutional committee on human experimentation and the 1975 Helsinki Declaration.

MEASUREMENTS AND MAIN RESULTS

The primary exposure was time to RRT activation after physiologic deterioration, defined as the time from the first instance when the patient met a specified threshold Cardiac Arrest Risk Triage (CART) score (T_0) to the documented time of RRT activation. We only considered vital signs in the 24 hours prior to RRT activation, and the time to RRT activation was measured from T_0 regardless of CART score at the time of the RRT activation. Patients who did not meet the CART score threshold either at the time of or in the 24 hours prior to RRT were excluded from the primary analysis but included in a sensitivity analysis with a time to RRT activation of 0 minutes. We selected a priori four CART score value thresholds from which to measure time to RRT activation to represent physiologic abnormality strata ranging from mild to severe (CART score ≥ 12 , ≥ 16 , ≥ 20 , and ≥ 24). An illustrative example of time to RRT activation calculation is presented in **Supplemental Figure 1** (<http://links.lww.com/CCX/B83>). The primary outcome was 7-day mortality—measured as death or discharge to hospice care within 7 days of RRT activation.

Statistical Approach

For each prespecified CART threshold, we first modeled the association of time to RRT activation duration with 7-day mortality using multivariable fractional polynomial regression. We visually examined fractional polynomial regression curves to identify clinically relevant categories of time to RRT activation, which were then used as primary exposure variables in multivariable logistic regression models with the outcome of 7-day mortality. Confounders included in the model were selected based on biological and clinical plausibility and included age, gender, hospital of admission, admission Elixhauser comorbidity score (17), and calendar year, presence of a do-not-resuscitate order, service, and CART score. A robust estimator of covariance was used to account for correlation among measurements. We performed sensitivity analyses using alternative primary endpoints, study cohorts, and definitions of time to RRT activation. The study period overlapped with the first year of the COVID-19 pandemic in 2020. Although we did observe an increase in RRT events during this period, many of these

events occurred in the first wave of COVID-19, and testing was not widely available (18). Given the potential of an altered relationship between patient deterioration and RRT activation during this period, we performed a post hoc sensitivity analysis excluding RRTs that occurred after 2020, thus excluding the COVID-19 pandemic period.

Main Results

Over the study period, a total of 5,309 RRT activations were captured in the QI databases. After exclusion of RRT activations that were not matched to the EMR and did not meet study inclusion criteria, a total of 2,725 RRT activations remained for the primary analysis (Fig. 2). Characteristics of the study population are displayed in Table 1. In the 7 days after RRT activation, 591 patients (22%) met the primary endpoint of mortality (394 died, 136 transitioned to inpatient hospice, and 61 were discharged to home hospice). Most patients were “full code” (no limitations on the use of cardiopulmonary resuscitation) at the time they exceeded the threshold CART value (Table 1). In the 24 hours after RRT activation, 1,213 patients (45%) were transferred to the ICU.

Results of the fractional polynomial multivariable logistic regression are presented in graphical format to highlight the relationship between progressive increases in time to RRT activation and 7-day mortality (Fig. 3). There was an increase in the probability of 7-day mortality with progressive time to RRT activation. Predicted risk of 7-day mortality appeared to rise with the first hour, with increase up to 4 hours and a subsequent plateau. This was most apparent when using CART thresholds of greater than 16 and greater than 20 (Fig. 3, B and C) and least apparent when using a CART threshold of greater than 24. Sensitivity analyses tracking CART for 48 hours prior to RRT activation, not considering those discharged to hospice as having reached the primary outcome and including only patients who had no limitations on cardiopulmonary resuscitation at the time that they exceeded the CART threshold, showed a similar overall pattern relationships between time to RRT activation and outcomes (Supplemental Figs. 2–4, <http://links.lww.com/CCX/B83>). We performed three additional sensitivity analyses. One included patients who never reached the specified CART threshold as having a time to RRT activation of zero (Supplemental Fig. 5, <http://links.lww.com/CCX/B83>). We performed a sensitivity

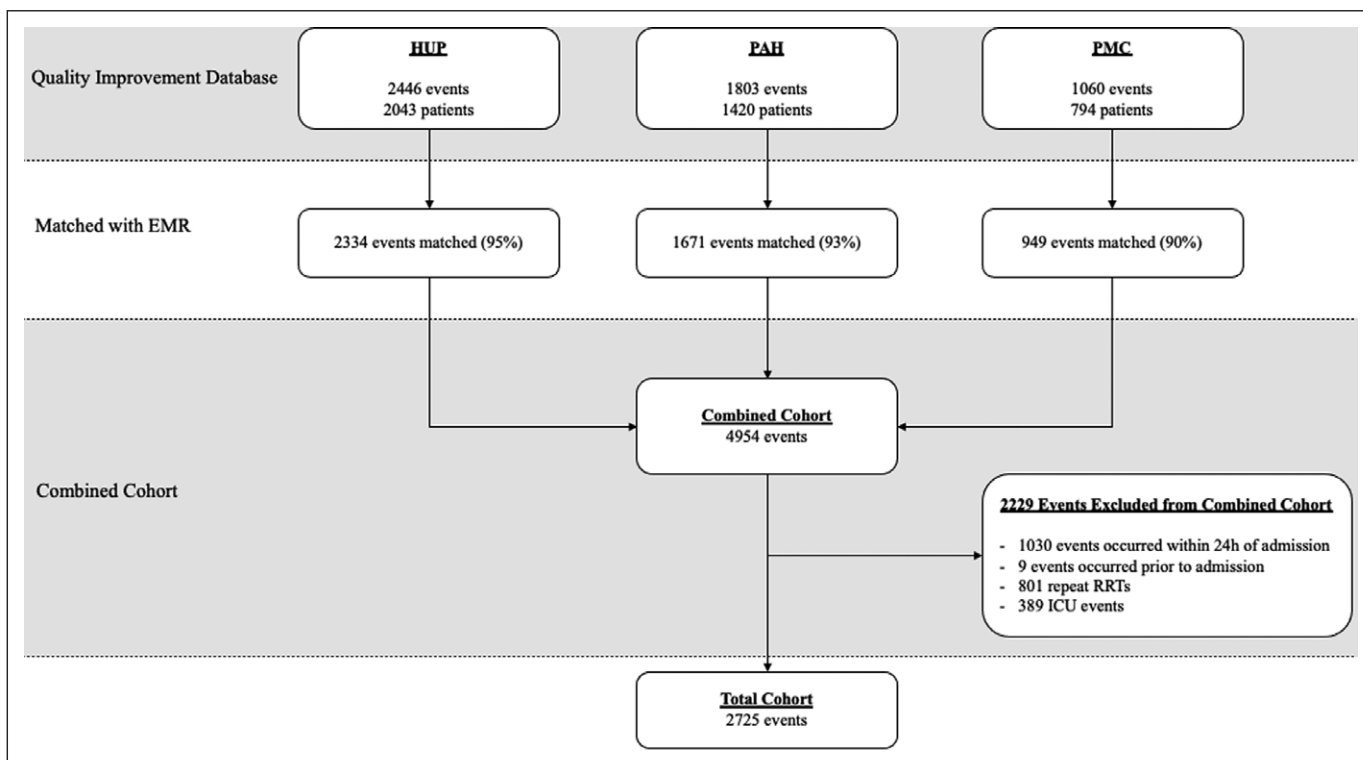


Figure 2. Consolidated Standards of Reporting Trials flow diagram. EMR = electronic medical record, HUP = Hospital of the University of Pennsylvania, PAH = Pennsylvania Hospital, PMC = Penn Medicine Princeton Health, RRT = rapid response team.

TABLE 1.
Characteristics of Patients With Rapid Response Team Activations That Were Included for Analysis

Demographics		Number (Total Cohort N = 2,725)
Age, median (interquartile range)	Years	67 (56–75)
Gender, n (%)	Male	1,423 (52)
	Female	1,302 (48)
Race, n (%)	White	1,559 (60)
	Black	794 (31)
	Other	228 (9)
	Unknown	144 (< 1)
Hospital, n (%)	Hospital of the University of Pennsylvania	1,364 (50)
	Penn Medicine Princeton Health	457 (17)
	Pennsylvania Hospital	904 (33)
Year, n (%)	2017	202 (8)
	2018	326 (13)
	2019	1,148 (44)
	2020	938 (36)
Service, n (%)	Medical	1,966 (72)
	Surgical	602 (22)
	Emergency Department	2 (< 1)
	Unknown	155 (< 1)
Admission Elixhauser score, median (interquartile range)		4 (3–6)
Length of stay on day of RRT activation, median (interquartile range)	Days	5 (2–12)
Exceeded CART threshold in 24 hr before RRT activation, n (%)	CART ≥ 12	1,607 (59)
	CART ≥ 16	1,267 (47)
	CART ≥ 20	889 (33)
	CART ≥ 24	625 (23)
Interval between meeting or exceeding CART threshold and RRT (hr) , median (interquartile range)	CART ≥ 12	18 (3–24)
	CART ≥ 16	15 (2–24)
	CART ≥ 20	10 (1–21)
	CART ≥ 24	5 (1–19)
Restrictions on resuscitative measures at the time when CART threshold was met or exceeded, n (%)	Do-not-resuscitate order present at time of RRT activation	423 (17)
	None	2,127 (83)
	Unknown	175 (6)

CART = Cardiac Arrest Risk Triage score, IQR = interquartile range, RRT = rapid response team.

analysis using an alternative EWS, the National Early Warning Score (NEWS). Again, we demonstrated a rapid rise over the first 4 hours in predicted risk of mortality with increased time to RRT activation that

was more evident using a moderate (NEWS ≥ 3) rather than an advanced (NEWS ≥ 5) deterioration threshold (**Supplemental Fig. 6**, <http://links.lww.com/CCX/B83>). A sensitivity analysis that excluded the year 2020

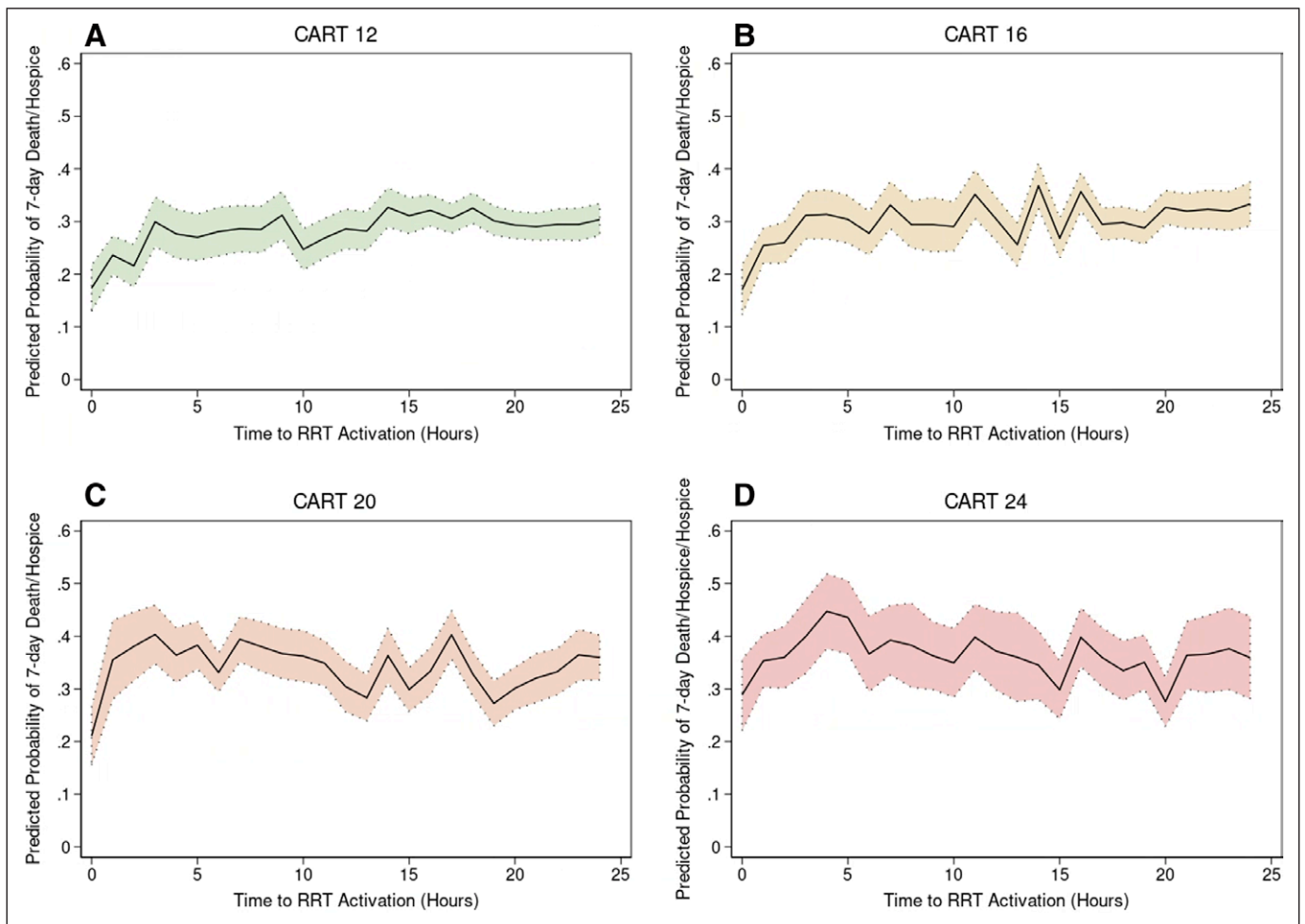


Figure 3. Predicted probabilities of 7-d death or discharge to hospice with increasing time to rapid response team (RRT) activation in RRT activation after Cardiac Arrest Risk Triage (CART) score of greater than 12 (*green, A*), greater than 16 (*yellow, B*), greater than 20 (*orange, C*), or greater than 24 (*red, D*). Duration of time to RRT activation in the 24 hr prior to RRT activation was modeled using multivariable logistic regression with fractional polynomials with a robust estimator of variance and adjusted for age, gender, hospital of admission, calendar year, and Elixhauser comorbidity score as well as the presence of a do-not-resuscitate order, whether the patient was admitted to a medical service, and the CART score at the time of reaching CART threshold (T_0).

due to the COVID-19 pandemic showed a similar relationship between time to RRT activation and 7-day mortality (**Supplemental Fig. 7**, <http://links.lww.com/CCX/B83>).

We visually inspected the primary analysis fractional polynomial models to identify inflection points that could be used to categorize time to RRT activation. We prioritized evident inflection points from the model using a CART threshold greater than 20, since it showed the most marked relationship between increasing time to RRT activation and mortality, although the model using a CART threshold of greater than 16 demonstrated inflection points at similar time points. **Table 2** shows the resultant categories and their adjusted odds of 7-day mortality, presented for each CART threshold. We repeated this using CART greater than 16 and CART greater than 12 fractional

polynomial models to inform time to RRT activation categories (**Supplemental Table 1**, <http://links.lww.com/CCX/B83>). We found an association of increased odds of 7-day mortality with increasing categories of time to RRT activation after meeting deterioration criteria. This association was not observed when using a CART threshold of greater than 24 to define deterioration and was consistent when time to RRT activation of less than 1 hour or less than 2 hours was used as the reference time category. A similar association was observed between increasing categories of time to RRT activation and 30-day mortality (**Supplemental Table 2**, <http://links.lww.com/CCX/B83>).

Of the 1,607 patients with a CART score greater than 12 in the 24 hours prior to RRT activation, 457 (28%) met the threshold of CART greater than 20 at the same time, 432 (27%) progressed to a CART score greater

TABLE 2.**Association Between Time to Rapid Response Team (RRT) Activation Categories With Odds of 7-d Death or Transfer to Hospice**

Threshold CART Score Used		Never Met CART Threshold	< 1 hr	1–3 hr	4–11 hr	> 12 hr
CART ≥ 12	<i>N</i>	1,118	219	193	206	989
	7-d mortality, <i>n</i> (%)	153 (14)	39 (18)	46 (24)	58 (28)	295 (30)
	aOR	NA	Reference	1.5 (0.9–2.6)	2.1 (1.3–3.6)	1.9 (1.2–2.9)
CART ≥ 16	<i>N</i>	1,458	212	170	172	713
	7-d mortality, <i>n</i> (%)	228 (16)	36 (17)	45 (26)	51 (30)	231 (32)
	aOR	NA	Reference	2.1 (1.2–3.7)	2.5 (1.4–4.3)	2.7 (1.7–4.2)
CART ≥ 20	<i>N</i>	1,836	195	147	128	419
	7-d mortality, <i>n</i> (%)	307 (17)	40 (21)	52 (35)	47 (37)	145 (35)
	aOR	NA	Reference	2.3 (1.3–3.9)	2.5 (1.4–4.3)	2.1 (1.4–3.4)
CART ≥ 24	<i>N</i>	2,100	155	129	98	243
	7-d mortality, <i>n</i> (%)	375 (18)	44 (28)	45 (35)	37 (38)	90 (37)
	aOR	NA	Reference	1.4 (0.8–2.5)	1.5 (0.8–2.8)	1.6 (1.0–2.6)

aOR = adjusted odds ratio, CART = Cardiac Arrest Risk Triage, NA = not available.

Association between time to rapid response team (RRT) activation categories with odds of 7-d death or transfer to hospice. Time to RRT activation was measured from the first instance that threshold CART score was met or exceeded (in 24 hr prior to RRT) until the documented time of RRT activation. Categories selected based on inflection points observed from the fractional polynomial regression model using a CART threshold of ≥ 20. Each model was adjusted for age, gender, hospital of admission, calendar year, and Elixhauser comorbidity score as well as the presence of a do-not-resuscitate order, whether the patient was admitted to a medical service, and the CART score at the time of reaching CART threshold (T_0). Unadjusted mortality for patients seen by the RRT who did not meet the specified CART threshold in the 24 hr prior to the RRT are also presented.

than 20 after they reached CART greater than 12, and 718 (45%) never progressed to a CART score greater than 20. Among the 432 patients who progressed to a CART score greater than 20, it took a median of 16 hours (interquartile range, 6–24 hr) for CART scores to increase from greater than or equal to 12 to greater than or equal to 20. The relationship between increasing time to RRT activation and increased mortality was most marked among patients who progressed from a CART score greater than 12 to subsequent CART score greater than 20 and was much less apparent among those who never progressed to CART greater than 20 or those who exceeded the threshold of CART greater than 12 and CART greater than 20 at the same time (**Supplemental Fig. 8**, <http://links.lww.com/CCX/B83>).

CONCLUSIONS

In our retrospective multicenter cohort study, we found that increased time from clinical decompensation to RRT activation was associated with higher risk of 7-day

mortality. This relationship was nonlinear, with odds of mortality increasing rapidly as time to RRT activation increased from 0 to 4 hours and then plateauing after 4 hours. We demonstrated that this pattern was observed across several thresholds of physiologic derangement, although it was not observed in advanced deterioration and was robust to sensitivity analyses. Additionally, there appeared to be a more marked increase in probability of mortality with shorter time to RRT activation when using higher CART thresholds to define T_0 , a relationship that appeared most evident with a CART score threshold of greater than 20. Our findings lend empirical evidence to support future definitions of RRT delay, until now largely selected a priori without outcomes-based justification and have the potential to inform future study design and targeted interventions to optimize RRT deployment timing.

Delays in RRT activation have been proposed as a potential explanation for the heterogeneous outcomes of studies investigating the impact of establishing RRTs on patient mortality (5). Studies attempting to answer

TABLE 3.
Characteristics of Patients With Shorter (< 1 hr) Versus Longer (> 1 hr) Time to Rapid Response Team Activation After Meeting Deterioration Criteria (Cardiac Arrest Risk Triage \geq 20)

Demographics		Shorter Time to RRT Activation, N = 195	Longer Time to RRT Activation, N = 694
Age, median (IQR)	Years	71 (61–79)	72 (64–78)
Gender n (%)	Male	111 (57)	374 (53)
	Female	84 (43)	320 (47)
Race n (%)	White	112 (57)	425 (61)
	Black	53 (27)	202 (29)
	Other	29 (15)	63 (9)
	Unknown	1 (< 1)	4 (< 1)
Hospital n (%)	Hospital of the University of Pennsylvania	95 (49)	410 (59)
	Penn Medicine Princeton Health	52 (22)	87 (13)
	Pennsylvania Hospital	58 (30)	197 (28)
Year n (%)	2017	14 (7)	57 (8)
	2018	26 (13)	69 (10)
	2019	82 (42)	316 (46)
	2020	73 (37)	252 (36)
Service n (%)	Medical	146 (75)	454 (82)
	Surgical	48 (25)	103 (15)
	Unknown	1 (< 1)	24 (4)
Admission Elixhauser score, median (IQR)		4 (3–6)	5 (4–6)
Maximum CART score in 24 hr prior to RRT activation, median (IQR)		25 (22–30)	26 (23–31)
Code status at the time when threshold CART was exceeded n (%)	Do-not-resuscitate order present at time of RRT activation	37 (18)	151 (22)
	Full code	153 (79)	530 (76)
	No code status	5 (3)	13 (2)
Mortality n (%)	7-d mortality	40 (21)	244 (35)
	30-d mortality	56 (29)	323 (47)

CART = Cardiac Arrest Risk Triage Score, IQR = interquartile range, RRT = rapid response team.

Characteristics of patients who had a “delayed” RRT activation. For the purposes of this comparison, longer time to RRT activation was defined as > 1 hr between the first instance when a patient’s CART score was \geq 20 and the time when the RRT was activated.

whether RRT delay impacts mortality have been limited by their design and almost exclusively considered time to RRT activation as a binary exposure, present or absent after 15–60 minutes after reaching the institutional RRT vital sign threshold (5–13). In this study, we instead took a broader approach, using an aggregate weighted EWS (the CART score) to quantify degree of deterioration, analyzing multiple CART thresholds and

quantifying the predicted mortality associated with progressive time to RRT activation, from 0 to 24 hours of time from deterioration. We were thus able to identify a nonlinear relationship between increasing time to RRT activation and short-term mortality. Beyond providing a detailed characterization of the relationship between increasing time to RRT activation and patient mortality, varying our definition of T_0 allowed us to demonstrate

that the relationship between increasing time to RRT activation and mortality differed across strata of deterioration severity. The risk of mortality with increasing time to RRT activation varied by CART threshold and appeared most marked after moderate deterioration, where even 1-hour increases in time to RRT activation were associated with substantial increases in mortality (particularly $CART \geq 20$). Although we are unable to determine causality, it is possible, and biologically plausible, that this observed relationship was due to delays in time-sensitive interventions that could have been performed by the RRT. These findings thus represent a first step in empirically informing what deterioration and time thresholds could be used in future studies of delay RRT activation. We did not observe a relationship with mortality of increasing time to RRT activation from the time of severe deterioration ($CART \geq 24$). We hypothesize that patients with significant vital sign abnormalities may have already experienced substantial clinical deterioration, rendering any intervention by the RRT less likely to alter outcomes. It is also possible that we were not adequately powered to detect the association of increased time to RRT activation with mortality among patients with CART scores greater than 24, as the number of patients with such deterioration represented less than one quarter of the study sample.

More study is needed to identify which threshold is most suitable for clinical practice. The RRT is a limited resource, and lower activation thresholds would likely impact the workload of the team, potentially affecting outcomes of other patients. One observational before and after study of automated RRT activation using an EWS-based approach demonstrated an increased volume of RRT activations in parallel with an improvement in several patient-centered outcomes (19). This highlights the potential benefit of earlier RRT involvement, the associated risk of an increased RRT workload, and the need for robust and thoughtful study of such interventions. Further, our data do not shed light on patients who did not have an RRT within 24–48 hours after meeting the tested CART thresholds. It remains unclear if the lack of RRT involvement with such patients relates in any way to their outcomes, but this is important to understand since they would be included in any prospective efforts to use CART thresholds as part of the RRT activation process. Ultimately, a sequence of pragmatic randomized controlled trials may be required to definitively determine the impact

of both RRT threshold criteria and of RRT activation timing on patient outcomes.

Our exploratory analysis of factors associated with time to RRT activation greater than 1 hour in those with moderate vital sign abnormalities ($CART \geq 20$) prior to RRT identified several factors worthy of further study (Table 3). We found that those with longer time to RRT activation had higher pre-RRT maximum CART score and higher admission Elixhauser scores. This finding may reflect greater challenges in identifying deterioration in patients who have multiple comorbidities. Future work aimed at identifying patients with deterioration who are at risk of delayed RRT activation, and how risk factors for delayed RRT activation vary across hospital systems might facilitate the identification of a target population for intervention in future studies.

Examining trajectory in those who reached CART greater than 12, we found that patients who progressed over time to severe deterioration before RRT activation ($CART \geq 20$) had a stronger time-mortality relationship than in those whose vital sign derangements did not progress. This highlights the potential benefits of early identification of patients with deterioration and suggests that predicting the trajectory of deterioration could plausibly inform the utility of RRT activations for patients meeting lower CART thresholds.

Our findings must be interpreted within the context of several limitations. First, we limited our inclusion criteria to patients who were seen by the RRT during their hospitalization. Selecting this subpopulation of hospitalized adult patients as our cohort precludes the extension of our findings to the general hospital population (e.g., creating an intervention automating RRT activation 1 hr after a CART score of ≥ 20) as patients not included in our present study would necessarily be included in any hospital-wide intervention. Although we considered using the entire population of hospitalized adults as our cohort, we expected that many patients would meet CART score thresholds without a subsequent RRT. We reasoned that the way we characterized the “time to RRT activation” in such patients would overwhelm any time-outcome association present among patients with more evident ultimate deterioration. A key future step is predicting which patients will experience ongoing clinical deterioration. We also only considered only the first RRT of each hospitalization, and it is possible that for the subset of patients who had repeated RRTs that timing of the second RRT activation may have

affected outcome. Due to the retrospective nature of our study, we were unable to characterize interventions that occurred in between the time of deterioration and the time of RRT activation, including who was aware of the deterioration, how and when the primary team was informed of the abnormal vital signs, how they responded, and which interventions were directed or performed by the RRT. These details will be important considerations for future interventions in the area and will likely require thoughtful prospective observational study. Such a prospective approach would also allow for detailed characterization of RRT details, including the indication for activation, who activated the RRT, and whether family members were involved. Finally, our study was not designed to establish causality, and although hypothesis generating, we have only demonstrated an association between time to RRT activation after deterioration and mortality. Although we adjusted for potential confounders of the relationship between increasing time to RRT activation and mortality, our findings may have been impacted by residual confounding. It is possible, for example, that certain etiologies of deterioration—for example acute respiratory failure—are both more likely to result in increased time to RRT activation and higher RRT mortality (6, 20). As such, these results should not be used as evidence that RRT deployment at a specific CART threshold will improve outcomes. Intervention studies are needed to determine the impact of RRT timing on patient outcomes among groups with varied degrees and trajectories of physiologic decompensation. Such trials could more adequately account for the effect of excess alert activations, both for RRT patients and the larger hospital population that may be impacted by diversion of resources.

In this multicenter, retrospective study, increasing time to RRT activation was associated in a nonlinear fashion with increased 7-day mortality. This relationship appeared most marked when using a CART score greater than 20 threshold from which to measure time to RRT activation. We suggest that these empirical findings could be used to inform RRT delay definitions in further studies to determine the clinical impact of interventions focused on timely RRT activation. There is a need for further study to better characterize optimal CART thresholds for use in clinical practice, to understand the impact of decompensation trajectory on outcomes, and to identify low- and high-risk patient subgroups of hospitalized patients meeting specific CART thresholds.

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