The Impact of a Machine Learning Early Warning Score on Hospital Mortality: A Multicenter Clinical Intervention Trial

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OBJECTIVES: To determine the impact of a machine learning early warning risk score, electronic Cardiac Arrest Risk Triage (eCART), on mortality for elevated-risk adult inpatients.

DESIGN: A pragmatic pre- and post-intervention study conducted over the same 10-month period in 2 consecutive years.

SETTING: Four-hospital community-academic health system.

PATIENTS: All adult patients admitted to a medical-surgical ward.

INTERVENTIONS: During the baseline period, clinicians were blinded to eCART scores. During the intervention period, scores were presented to providers. Scores greater than or equal to 95th percentile were designated high risk prompting a physician assessment for ICU admission. Scores between the 89th and 95th percentiles were designated intermediate risk, triggering a nurse-directed workflow that included measuring vital signs every 2 hours and contacting a physician to review the treatment plan.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was all-cause inhospital mortality. Secondary measures included vital sign assessment within 2 hours, ICU transfer rate, and time to ICU transfer. A total of 60,261 patients were admitted during the study period, of which 6,681 (11.1%) met inclusion criteria (baseline period $n = 3{,}191$, intervention period $n = 3{,}490$). The intervention period was associated with a significant decrease in hospital mortality for the main cohort (8.8% vs 13.9%; $p < 0.0001$; adjusted odds ratio [OR], 0.60 [95% CI, 0.52–0.71]). A significant decrease in mortality was also seen for the average-risk cohort not subject to the intervention (0.49% vs 0.26%; $p < 0.05$; adjusted OR, 0.53 [95% CI, 0.41–0.74]). In subgroup analysis, the benefit was seen in both high- (17.9% vs 23.9%; $p = 0.001$) and intermediate-risk (2.0% vs 4.0 %; $p = 0.005$) patients. The intervention period was also associated with a significant increase in ICU transfers, decrease in time to ICU transfer, and increase in vital sign reassessment within 2 hours.

CONCLUSIONS: Implementation of a machine learning early warning score-driven protocol was associated with reduced inhospital mortality, likely driven by earlier and more frequent ICU transfer.

KEY WORDS: decision support techniques; early warning score; machine learning; severity of illness index

In hospital deterioration leading to death is rarely sudden and often heralded by physiologic abnormalities hours to days before the event, which is readily apparent on retrospective chart review (1–3). The advent of electronic health records and growth of machine learning in medicine has yielded numerous models for predicting these deterioration events (4–7). Since many of the common causes of hospital death, such as respiratory failure (8) and

DOI: 10.1097/CCM.0000000000005492

sepsis (9–11), are treatable and benefit from earlier intervention, use of these algorithms for early recognition of deterioration has the potential to speed clinical intervention and decrease mortality. However, data on real-world implementations of machine learning early warning scores are limited (5, 12, 13).

In our prior work, we developed and validated the electronic Cardiac Arrest Risk Triage (eCART) score, a machine learning algorithm that predicted hospital death in the next 24 hours with an area under the curve of 0.93, in a multicenter dataset of over a quarter million patients (14). We then demonstrated in the same retrospective dataset that hospital mortality was increased for patients with delays to ICU transfer following their first high-risk score. These data led us to hypothesize that the clinical implementation of this tool could lead to decreased mortality for elevated-risk patients. Therefore, in this study, we sought to measure the real-world impact on provider behavior and patient outcomes of prospectively integrating a machine learning early warning analytic into clinical workflows at four hospitals. Some of the results of this study have been previously reported in the form of an abstract (15).

METHODS

Study Design

The study was conducted over the same 10-month period in 2 consecutive years at the NorthShore University HealthSystem (NSUHS), an electronically integrated four-hospital community-academic network in north suburban Chicago. The baseline period ran from July 1, 2016, to April 30, 2017. The intervention period ran from July 1, 2017, to April 30, 2018. Between these periods was a 2-month pilot period in which eCART was implemented at one of the four hospitals to optimize workflows and refine educational procedures. This study was approved by the Institutional Review Board of the NSUHS, which waived the need for informed consent (EH17-182).

Study Population

All patients greater than or equal to 18 years old admitted to a medical or surgical ward were eligible for inclusion. We excluded patients who died in the emergency department (ED) prior to admission or who were discharged directly from the ED. Women admitted to Labor and Delivery (L&D) were excluded. However, women transferred from L&D to a medical or surgical service became eligible, and risk scores were displayed in the chart, upon transfer. Patients directly admitted to the ICU were excluded but became eligible upon transfer to the ward. eCART scores continued to calculate while in the ICU but providers were instructed that eCART scores were not validated for decision making in the ICU. Subjects without risk score calculation during an eligible admission were considered missing, as were patients without resulted laboratory values.

Score Calculation and Trigger Thresholds

We used eCARTv2, a 27 variable discrete time survival analysis logistic regression model composed of demographic, mental status, vital sign, and laboratory inputs designed to identifying subjects on the wards at risk of death, cardiac arrest, or unexpected transfer to the ICU (14). The model we implemented was identical to the published model. Calculation was automated and integrated into the electronic health record (EPIC, Verona, WI). Scores were recalculated hourly throughout the inpatient stay. Any available new data element was incorporated in the next hourly calculation. Starting with the patient's first ED or ward vital sign, the score was recalculated with each new data element using a last value carried forward approach and normal imputation for missing values (2). All automated measures of vital signs were verified by the bedside nurse prior to incorporation into the risk score. Once patients were transferred to a Hospice service, scores were no longer calculated because death was anticipated and ICU transfer was inconsistent with the goals of care. Deaths that occurred during inpatient Hospice care were included in the analysis. Hospice patients discharged home or to another inpatient facility were counted as living.

During the baseline period, risk scores were calculated but were not available to treating clinicians and staff. Scores from this time were used to establish trigger thresholds for the intervention period after discussions with clinical champions related to the number of alerts that could be responded to per day to balance detection while minimizing alarm fatigue. Threshold scores were rounded for ease of recall. Specifically, eCART scores greater than or equal to 100 exceeded the 95th percentile of all scores. These were considered high-risk scores and were color-coded red. This corresponded to an average of 10 patients with red scores per day across the four-hospital system. eCART scores between 50 and

99 were between the 89th and 95th percentiles. These scores were deemed intermediate risk and were color-coded yellow. This corresponded to an average of 19 patients per day across the four-hospital system. The remaining were considered average risk and color-coded green.

Workflow Development and Implementation

During the 2-month pilot period, risk scores were presented on the assignment lists of all healthcare providers (HCPs), including physicians, nonphysician providers, and nurses, at one of the four hospitals (**eFig. 1**, http://links.lww.com/CCM/G991; **legend**, http://links.lww.com/CCM/G995). Additionally, each patient's chart contained a graphic display of scores over time, with a table showing the constitutive vital signs and laboratory values that contributed to each score (**eFig. 2**, http://links.lww.com/CCM/G992; legend, http://links.lww.com/CCM/G995). During the first week of the pilot period, educational sessions were conducted by three of the authors (C.J.W., M.T., M.K.) explaining score calculation and presenting workflows for high- and intermediate-risk scores. New high scores prompted a physician-directed workflow that recommended assessment for ICU admission for all patients (**eFig. 3**, http://links.lww.com/CCM/G993; legend, http://links.lww.com/CCM/G995). Treating physicians could decline ICU transfer if intensive care was either inconsistent with the patient's goals of care or if the high score was felt to be attributable to an easily correctable cause that could be managed on the ward. A new intermediate-risk score triggered a bedside nurse-directed workflow that included measuring vital signs every 2 hours, ordering a serum lactic acid if a diagnosis of sepsis was considered, and contacting the provider to review the treatment plan (**eFig. 4**, http://links.lww.com/CCM/G994; legend http://links.lww.com/CCM/G995). At the conclusion of the pilot period, physician and nurse input regarding workflows was solicited and trigger thresholds were reviewed. No changes were made. Thus, during the first week of the intervention period, similar educational sessions were conducted for staff at the three remaining hospitals and hourly updated risk scores were revealed to all HCPs at all hospitals.

During the baseline and intervention periods, all hospitals had a physician-directed rapid response team that could be triggered by any HCP. No specific vital sign triggers were used to activate the teams. Do not resuscitate orders precluded intubation and cardiopulmonary resuscitation but not ICU transfer.

Study Outcomes

The primary outcome was all-cause hospital mortality among patients who ever had an elevated eCART score. Secondary outcomes consisted of subgroup analyses of all-cause hospital mortality among patients whose maximum eCART score during the admission put them at high risk, intermediate risk, and average risk, both respectively and collectively. Additional subgroup analyses were performed to assess process metrics from the recommended workflows, including ICU transfer rate, time to ICU transfer following the first eCART elevation, the frequency of vital sign reassessment within 2 hours of the first elevation, placement of a lactic acid order within 2 hours of first elevation, and the number of new code status orders placed within 24 hours of the first score elevation.

Data Analysis

Categorical variables were reported using frequency counts with percentages and were compared using a chi-square test or Fisher exact test for cell counts less than 5. Continuous variables were reported as medians with interquartile ranges and compared using the Wilcoxon rank-sum test. A two-sided p value of less than 0.05 was considered statistically significant. Adjusted multivariable logistic regression was performed with mortality as the main outcome and the study time periods as the main exposure variable. Potential confounding parameters included in the model were age at admission, sex, race, hospital unit, first eCART score, and whether or not the patient had been in the ICU prior to any risk score elevation. Stratified analyses were performed to measure the impact of the intervention in the following subgroups: high-risk versus intermediate-risk patients and patients with prior ICU admission versus no prior ICU admission. Last, we conducted an interrupted time series analysis (16) to examine the level change and slope change of the mortality rate between the baseline and intervention periods using Poisson regression with the total number of patients each month as the offset variable. We assessed autoregression by examining the plot of residuals and the partial autocorrelation function and conducting the Breusch-Godfrey test (17). All analyses were conducted using SAS 9.4 (Statistical Analysis System, Cary, NC).

RESULTS

A total of 6,681 patients met inclusion criteria, with 3,191 in the baseline and 3,490 in the intervention

periods, respectively (**Fig. 1**). Of those, a total of 3,075 patients (46.0%) had at least one high-risk score and were included in the high-risk subgroup. The remaining 3,606 patients (54.0%) composed the intermediate-risk subgroup (**Table 1**). Patients in the baseline and intervention groups were similar in age, sex, hospital length of stay, and distribution among the hospitals. The prevalence of medical conditions preceding the index admission was also similar between the groups (18). The initial eCART score was significantly higher in the intervention period, and the percent of patients who had been in an ICU prior to score elevation was higher in the baseline period. Characteristics and outcomes stratified by hospital are provided in **eTable 1** (http://links.lww.com/CCM/G995).

Mortality

Compared with the baseline, hospital mortality was significantly lower during the intervention period (8.8% vs 13.9%; $p < 0.01$) for the main cohort. This represented a relative risk reduction for death of 36.7% (**Fig. 2**). This decrease in mortality was seen in both the high-risk (17.9% vs 23.9%; $p = 0.001$) and intermediate-risk subgroups (2.0% vs 4.0%; $p = 0.001$). Being in the intervention period was associated with an adjusted odds ratio (aOR) for death of 0.60 (95% CI, 0.52–0.71) across the main study population, with similar benefits across the two risk subgroups. The only patients that did not appear to benefit from the intervention were those whose first eCART elevation occurred after admission to the ICU (aOR, 1.04; 95% CI, 0.75–1.43) (**Fig. 3**). Overall mortality for all hospitalized patients was 1.96% for the baseline period and 1.19% in the intervention period ($p < 0.01$). Mortality for patients without an eCART elevation was 0.49% (125/25,671) during the baseline period and 0.26% (71/27,452) in the intervention period ($p < 0.05$; **eTable 2**, http://links.lww.com/CCM/G995). The percentage with an ICU transfer was also lower during the intervention period (11.6% vs 10.4%; $p < 0.05$). An interrupted time series analysis confirmed the mortality benefit by exhibiting both a significant level change ($p < 0.0001$) and slope change ($p = 0.0001$) between the baseline and intervention periods for the study cohort. During the baseline period, mortality was increasing in the study cohort over time. This trend reversed after implementing eCART. Similar analysis of the average-risk group confirmed the risk of mortality was reduced by 45% (incidence rate ratio, 0.55; $p < 0.0001$) for the intervention period without a slope change (**eFig. 5**, http://links.lww.com/CCM/G996; legend, http://links.lww.com/CCM/G995).

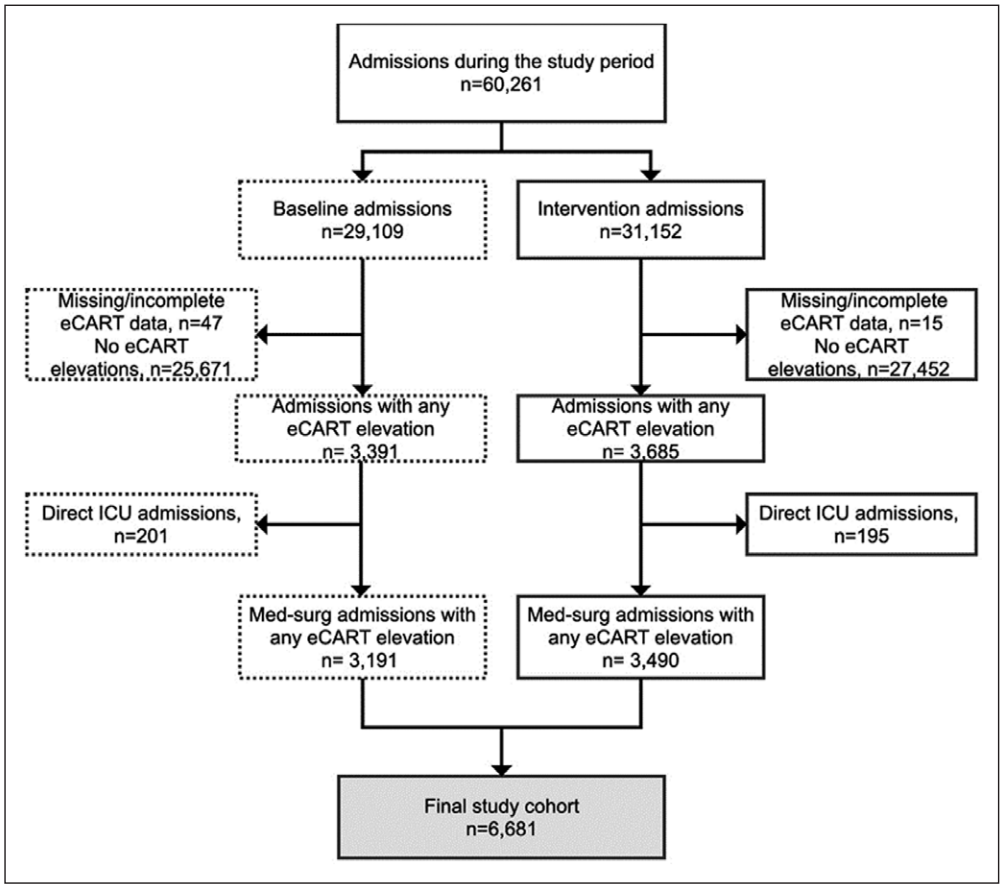

Figure 1. Study inclusion flow diagram. eCART = electronic Cardiac Arrest Risk Triage.

Process Measures

Compared with baseline, more patients in the intervention period were transferred to the ICU after the first

TABLE 1.
Baseline Characteristics for the Target Cohort and the Average Risk Nontargeted Cohort

Variable Name	Nontarget Cohort		Target Cohort	
	Baseline, *n* = 25,671	Intervention, *n* = 27,452	Baseline, *n* = 3,191	Intervention, *n* = 3,490
Age, yr, median (IQR)	67.3 (49.9–80.3)	67.2 (47.2–80.0)[a]	81.2 (70.2–88.8)	80.2 (69.3–88.6)
Hospital length of stay, d, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)[a]	6.0 (4.0–10.0)	6.0 (3.0–10.0)[b]
Admission electronic Cardiac Arrest Risk Triage score, median (IQR)	6.0 (4.0–10.0)	6.0 (4.0–11.0)	20.0 (10.0–41.0)	23.0 (11.0–53.0)[b]
Female	15,186 (59.1)	16,955 (61.7)[a]	1,687 (52.9)	1,820 (52.1)
Number with surgery performed during admission	10,158 (39.6)	10,809 (39.4)[a]	735 (23.0)	759 (21.7)
Hospital distribution				
Hospital A	9,409 (36.6)	9,749 (35.5)	813 (25.5)	817 (23.4)
Hospital B	6,717 (26.1)	7,063 (25.7)	1,014 (31.8)	1,103 (31.6)
Hospital C	4,293 (16.7)	5,697 (20.7)	618 (19.4)	744 (21.3)
Hospital D	5,478 (21.3)	5,982 (21.8)	746 (23.4)	826 (23.7)
Comorbidities				
Atrial fibrillation	8,394 (32.7)	9,257 (33.7)	1,728 (54.2)	1,849 (53.0)
Cancer	9,148 (35.6)	9,986 (36.3)	1,493 (46.8)	1,568 (44.9)
Chronic obstructive pulmonary disease	5,375 (20.9)	5,759 (21.0)	1,017 (31.9)	1,071 (30.7)
Heart failure	4,074 (15.9)	4,330 (15.8)	1,165 (36.5)	1,231 (35.3)
Neurologic conditions	4,360 (17.0)	4,865 (17.7)	798 (25.0)	791 (22.7)[b]
Peripheral vascular disease	4,513 (17.6)	4,872 (17.7)	989 (31.0)	1,002 (28.7)[b]
Stroke	2,745 (10.7)	2,991 (10.9)	627 (19.6)	602 (17.2)[b]
Vascular heart disease	4,378 (17.0)	4,756 (17.3)	945 (29.6)	978 (28.0)
Venous thromboembolism	3,071 (12.0)	3,283 (12.0)	577 (18.1)	600 (17.2)

IQR = interquartile range (25–75%).
[a]$p < 0.05$ comparing intervention with baseline for the nontarget cohort.
[b]$p < 0.05$ comparing intervention with baseline for the target cohort.

eCART score elevation (21.2% vs 12.3%; $p < 0.001$; **Table 2**). Patients in both risk subgroups were nearly twice as likely to be transferred to the ICU following their first eCART elevation in the intervention period compared with the baseline period (32.7% vs 16.6%, $p < 0.01$, for high-risk patients; 12.7% vs 7.9%, $p < 0.01$, for intermediate-risk patients). In addition, median time to ICU transfer decreased by 13.6 hours in the high-risk cohort and 9.4 hours in the intermediate-risk cohort. They were more than twice as likely to have a lactate ordered and significantly more likely to have vital signs reassessed within 2 hours. There was no significant difference in ICU length of stay or need for mechanical ventilation between the two periods. Comparing the Intervention with the baseline period, the number of new code status order increased from 312 of 3,191 (9.8%) to 612 of 3,490 (17.5%; $p < 0.001$).

DISCUSSION

We implemented a machine learning early warning score-driven clinical workflow within the electronic health record at four acute care hospitals and demonstrated a significant decrease in mortality associated with an increase in nursing assessments and timely ICU transfer for both intermediate- and high-risk

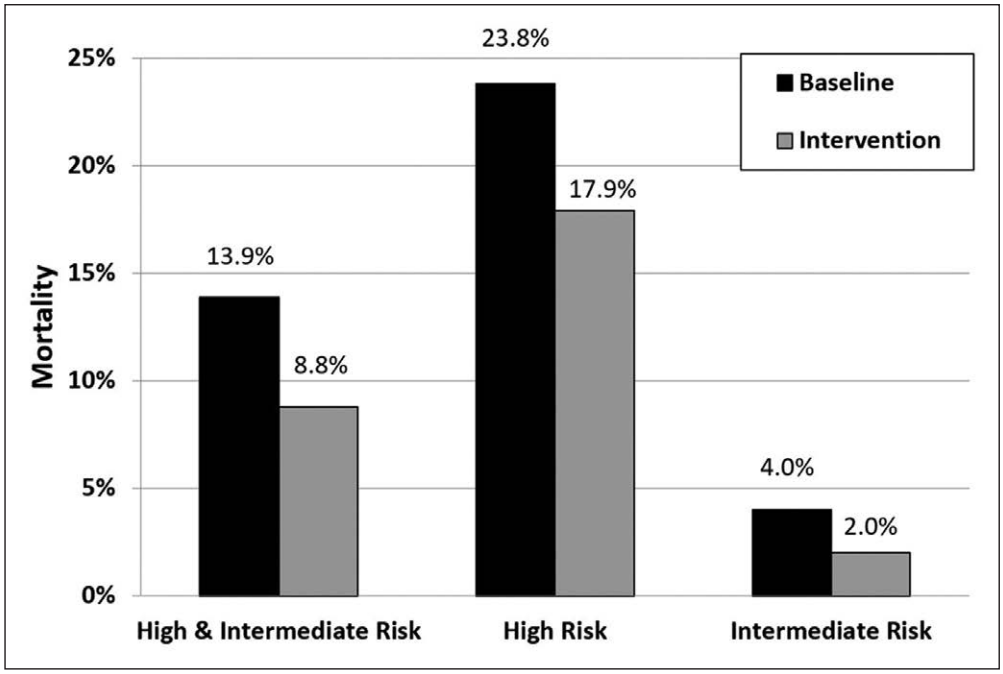

Figure 2. Mortality among patients with high- and intermediate-risk scores. Significance for the mortality difference between baseline and intervention for intermediate- and high-risk patients, $p < 0.01$; for high-risk patients, $p < 0.01$; for intermediate-risk patients, $p < 0.01$.

adult inpatients. Our study results are consistent with the findings of Escobar et al (12) who reported similar inhospital mortality rates of 9.9% in the intervention cohort versus 14.4% in the comparison cohort and Subbe et al (13) population who reported a baseline mortality of 8.1% and an intervention period mortality of 6.5% across the entire patient population.

The proliferation of electronic health records has produced volumes of patient data that can be used to derive machine learning models. As datasets get larger and statistical tools become more robust, the accuracy of these tools will continue to improve. However, a predictive tool by itself is of little value if not tied to actionable interventions and imbedded within the workflow of frontline providers. In this implementation, scores displayed within the patient list and treatment algorithms prioritized more frequent assessments and earlier ICU transfer, which the process measures confirmed occurred more frequently in the intervention period. It is likely that both the earlier identification of deterioration made possible by eCART and the structured approach to at-risk patients drove the mortality benefit seen in this study, but we cannot exclude a secular trend toward lower mortality over time, given that the mortality rate for patients who did not trigger an alert also decreased significantly. In contrast, most prior studies that showed no benefit from the implementation of an early warning score, such as the MERIT study (19) and the EPOCH trial (20), used simple single-parameter or aggregate weighted scores, which are less accurate than machine learning models (21). Other studies implementing more advanced statistically derived models (5) demonstrated that merely showing them to providers without tying them to specific interventions does not improve outcomes. These data, combined with our study, suggest that improving both model accuracy and the response to alerts are critical to improving the outcomes of deteriorating patients. This is also consistent with our prior work (22) and that of others (23, 24) demonstrating that earlier transfer to the ICU can improve outcomes for high-risk patients.

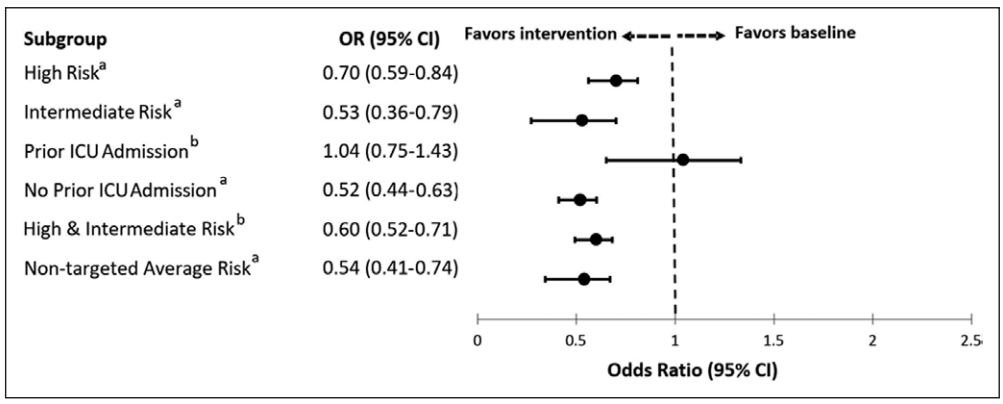

Figure 3. Adjusted mortality risk between baseline and intervention periods among various subgroups. [a]Adjusted for admission electronic Cardiac Arrest Risk Triage (eCART) score, age, sex, race, and prior ICU admission. [b]Adjusted for admission eCART score, age, sex, and race. OR = odds ratio.

TABLE 2.
Process Measures for High- and Intermediate-Risk Patients

Variable Name	High-Risk Patients			Intermediate-Risk Patients		
	Baseline, *n* = 1,590	Intervention, *n* = 1,485	*p*	Baseline, *n* = 1,601	Intervention, *n* = 2,005	*p*
ICU transfers after eCART elevation, *n* (%)	264 (16.6)	486 (32.7)	< 0.01	127 (7.9)	254 (12.7)	< 0.01
Time to ICU transfer after first eCART elevation, hr, median (IQR)	17.2 (4.7–54.8)	3.6 (1.4–23.4)	< 0.01	12.1 (1.8–46.6)	2.7 (1.0–19.8)	< 0.01
ICU length of stay, d, median (IQR)	2.9 (1.4–5.4)	2.7 (1.6–5.9)	0.71	2.3 (1.2–4.3)	2.5 (1.4–4.4)	0.33
Lactate ordered within 2 hr of first eCART elevation, *n* (%)	64 (4.0)	119 (8.0)	< 0.01	35 (2.2)	94 (4.7)	< 0.01
Repeat vital signs within 2 hr of first eCART elevation, *n* (%)	896 (56.4)	1,259 (84.8)	< 0.01	974 (60.8)	1,730 (86.3)	< 0.01
Required mechanical ventilation, *n* (%)	171 (10.8)	188 (12.7)	0.11	101 (6.3)	128 (6.4)	0.98

eCART = electronic Cardiac Arrest Risk Triage, IQR = interquartile range (25–75%).

The relative benefit appeared to be slightly higher in intermediate- compared with high-risk patients. It is noteworthy that the high-risk patients also had longer delays to ICU transfer than the intermediate-risk patients in the baseline period (17 vs 12 hr) despite more profound physiologic derangement. It is possible that those patients who developed high-risk scores after hours spent on the wards after an elevated score may have less reversible deterioration, although this deserves further study. In addition, the one subgroup without apparent benefit was the group whose first elevation occurred following ICU transfer. One potential explanation for these findings is that a higher percentage of those patients have irreversible disease and may be more suitable to end of life care. Alternatively, these patients may be more obvious to the providers so that there was heightened concern for these patients in the baseline period even without eCART. We also found that average-risk patients had decreased mortality after eCART implementation. This may relate to either culture change or clinicians using the full range of the score to assist with clinical decisions, which although outside the educational initiatives that were employed, would have been possible because the score was shown for all patients. Other potential explanations include a general trend toward lower severity of illness not accounted for by the adjusted models or some other systematic difference between the two time periods.

Our study has several strengths. Most importantly, it was a multicenter prospective clinical study over the same months, which represents a real-world implementation study of a machine learning model. We also found that many characteristics were similar between the baseline and intervention periods, and we adjusted for important potential confounders that were determined a priori. In addition to finding improvements in an important outcome, mortality, we also identified changes in process metrics by which that outcome improvement was achieved. Last, in contrast to Escobar et al (12) who used remote reviewing of risk scores, we opted to reveal scores to all treating HCPs. Informal feedback consistently confirmed that the risk score empowered bedside nurses by creating an objective language of risk that facilitated discussions with other members of the healthcare team regarding the potential deterioration of their patients.

The main limitation of this study is that it is not a randomized clinical trial. The setting for this study was an electronically integrated health system where all HCPs have privileges across four hospitals and typically care for patients at more than one campus. This precluded randomization by hospital. We attempted to mitigate the potential bias introduced by a pre- and post-intervention design by planning the study around identical calendar months, 1 year apart, to avoid a seasonal effect. We also employed adjusted

analyses to account for patient differences between the two cohorts and included an interrupted time series analysis to account for secular trends. Second, although we included four hospitals, they were all in one health system, using one electronic health record. The results will need to be confirmed in additional settings. Finally, we did not test different eCART thresholds or alternate treatment protocols. It is possible that a different treatment algorithm would have produced different outcomes, and it is not possible to disentangle the benefit of the machine learning algorithm from the treatment pathways or culture change that occurs when implementing early warning systems.

We conclude that implementation of a machine learning early warning score across a multicenter health system was associated with an increase in timely ICU transfer and a decrease in hospital mortality. Future work will be needed to refine thresholds and workflows to maximize benefit.

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Dr. Winslow had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Winslow, Dr. Taneja, Dr. Shah, Mr. McNulty, Dr. Kharasch, and Dr. Halasyamani were involved in concept and design. Dr. Winslow, Dr. Taneja, Dr. Shah, Dr. Datta, Dr. Wang, Dr. Ravichandran, Mr. McNulty, Dr. Kharasch, and Dr. Halasyamani were involved in acquisition of data and access to database. Drs. Winslow, Edelson, Churpek, Taneja, Shah, Datta, Wang, and Halasyamani were involved in analysis and interpretation of data. Dr. Winslow was involved in initial draft of the article. Drs. Datta and Wang were involved in statistical analysis. All authors were involved in critical revision of the article.

Drs. Edelson and Churpek received funding from EarlySense (Tel Aviv, Israel) and have a patent pending (ARCD. P0535US. P2) through the University of Chicago for risk stratification algorithms for hospitalized patients. Dr. Edelson received funding from Philips Healthcare (Andover, MA) and has ownership interest in AgileMD (San Francisco, CA) that holds the licensing rights to electronic Cardiac Arrest Risk Triage. Dr. Churpek's institution received funding from the National Institutes of Health (NIH) (R01 GM123193) and EarlySense; he received support for article research from the NIH; and he is also supported by an R01 from National Institute of General Medical Sciences (R01 GM123193). Dr. Ravichandran disclosed that she is funded by the Daniel F. and Ada L. Rice foundation. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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This study was conducted at the four hospitals of the NorthShore University HealthSystem.

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