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Original Contributions

USING VITAL SIGNS TO PLACE ACUTELY ILL PATIENTS QUICKLY AND EASILY INTO CLINICALLY HELPFUL PATHOPHYSIOLOGIC CATEGORIES: DERIVATION AND VALIDATION OF EIGHT PATHOPHYSIOLOGIC CATEGORIES IN TWO DISTINCT PATIENT POPULATIONS OF ACUTELY ILL PATIENTS

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□ **Abstract—Background: Early warning scores reliably identify patients at risk of imminent death, but do not provide insight into what may be wrong with the patient or what to do about it. Objective: Our aim was to explore whether the Shock Index (SI), pulse pressure (PP), and ROX Index can place acutely ill medical patients in pathophysiologic categories that could indicate the interventions required. Methods: A retrospective post-hoc analysis of previously obtained and reported clinical data for 45,784 acutely ill medical patients admitted to a major regional referral Canadian hospital between 2005 and 2010 and validated on 107,546 emergency admissions to four Dutch hospitals between 2017 and 2022. Results: SI, PP, and ROX values divided patients into eight mutually exclusive physiologic categories. Mortality was highest in patient categories that included ROX Index value < 22, and a ROX Index value < 22 multiplied the risk of any other abnormality. Patients with a ROX Index value < 22, PP < 42 mm Hg, and SI > 0.7 had the highest mortality and accounted for 40% of deaths within 24 h of admission, whereas patients with a PP ≥ 42 mm Hg, SI ≤ 0.7, and ROX Index value ≥ 22 had the lowest risk of death. These results were the same in both the Canadian and Dutch patient cohorts. Conclusions: SI, PP, and ROX Index values can place acutely ill medical patients into eight mutually exclusive pathophysiologic categories with different mortality rates. Future studies will assess the interventions needed by these categories and their value in guiding treatment and disposition decisions.** **© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)**

□ **Keywords—vital signs; ROX Index; pulse pressure; shock index; pathophysiology; acute illness; pathophysiologic category**

INTRODUCTION

Although the National Early Warning Score (NEWS) and similar early warning scores reliably identify patients at risk of imminent death, they do not provide insight into what may be wrong with the patient and what to do about it (1,2). Therefore, when a physician is called to the bedside of a patient with an elevated NEWS, he or she must "deconstruct" the score to try and work out why the score is elevated. Hypoxia or hypoperfusion are the usual antecedents of death, and identifying their underlying cause is vital; sustained hypoxia commonly causes a viscous cycle of circulatory failure, hypoperfusion, and tissue hypoxia, which results in death if not reversed (3–5).

Several protocols and care bundles of time-dependent interventions that address respiratory function, cardiac

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function, and intravascular volume have been proposed to salvage acutely ill patients. However, randomized controlled trials have failed to show their benefit, possibly because they promote "one size fits all" interventions for all sick patients that may not adequately consider different underlying pathophysiologic derangements (6). For example, inappropriate fluid replacement may cause cardiac compromise and increase the work of breathing, which may explain why the optimal volume of fluid replacement for different patient populations remains unclear (7). The "standard of care" alternative to protocols and care bundles is intensive patient monitoring and adjustment of therapy according to the patient's responses and their underlying diagnoses and comorbidities (8). However, the information, time, expertise, and tacit skills to make these bespoke adjustments may not be available (9). Therefore, a rapid system is needed to identify a patient's dominant pathophysiologic derangement and help indicate the best treatment. Such a system would be particularly useful for therapeutic options, such as noninvasive ventilation and high-flow oxygen, which must be provided promptly to achieve their maximum benefit (10,11).

In non–critical care settings, the traditional bedside vital signs are most often used as proxies to assess organ perfusion, intravascular volume, and cardiac function. Several indices, such as the Shock Index (SI) and pulse pressure (PP), have been suggested to assist clinicians to interpret the cause of physiologic derangements (12–14). The SI is the ratio of heart rate to systolic blood pressure; it is a proxy for decreased intravascular volume and has been used to guide fluid replacement and other interventions (12). The PP is the pressure difference between the systolic and diastolic blood pressure and is a proxy for the left ventricular stroke volume and arterial stiffness (13,14). In addition, the ROX Index has been proposed to support clinicians with the bedside assessment of respiratory function (15). ROX Index is calculated from the patient's oxygen saturation, their inspired oxygen concentration, and their respiratory rate, and has been found to be an independent predictor of mortality in acutely ill patients (16–19).

By using a combination of these three proxies for respiratory function, cardiac function, perfusion, and intravascular volume, patients can be placed in different pathophysiologic categories, potentially providing greater understanding for clinicians when interpreting deranged bedside physiology and help indicate the optimal interventions required. Therefore, the aim of this hypothesis-generating study was to determine, in two separate and different patient cohorts, whether the SI, PP, and ROX Index can consistently place acutely ill patients into physiologic categories with the same mortality ranking.

METHODS

This observational cohort study tested a hypothesis by means of retrospective analysis of previously obtained and reported clinical data from a major regional referral Canadian hospital between 2005 and 2010, which we used as a derivation cohort (20). We validated our findings on routinely collected quality of care data for patients admitted as emergencies to four Dutch hospitals between 2017 and 2022 (21). The study adhered to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) methodology and a flow chart of how we derived both study cohorts is shown in Supplementary Figure 1 (22).

Derivation Cohort

We used historical data from Thunder Bay Regional Health Sciences Centre (TBRHSC), a 375-bed hospital in northwestern Ontario, to define the optimal SI, PP, and ROX Index values (see the Data Analysis section). We then used these values to place patients into eight mutually exclusive categories. We extracted age, temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, inspired oxygen concentration, length of stay, and mortality of every patient 16 years and older admitted to TBRHSC from January 1, 2005 to December 31, 2010 from the hospital's Meditech system; this age is a commonly used transition between children and adults. Because the system only recorded length of stay by the calendar day, a patient with a length of stay of 1 day could have been in hospital for only a few minutes or up to 48 h.

Validation Cohort

We validated the performances of the TBRHSC-derived categories using data from the Netherlands Emergency Department Evaluation Database (NEED). This database contains clinical data from all emergency department (ED) visits to the participating hospitals and is used to benchmark quality of care (www.stichting-need.nl). Only the vital signs and mental status measured at the beginning of ED presentation, before ED treatment, are recorded in the NEED, and only one set of vital signs is recorded per patient. Further details on the NEED have been published previously (21). We included all consecutive ED patients 16 years and older attending the EDs of four participating hospitals (Catharina Hospital Eindhoven, Elisabeth-Tweesteden Hospital Tilburg, Medical Center Leeuwarden, and Adrz Hospital Goes). Inclusion periods in the available database varied from January 1 to December 31, 2019; January 1, 2019 to January 12, 2020;

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and for two hospitals from January 1, 2017 to March 31, 2022.

Bias

We only included patients with a complete set of data. Because this was a hypothesis-generating study, we made no attempt to correct for this by imputation or other potential causes of bias.

Study Size

The number of patients included in the study was determined by the available data collected from previous studies.

Data Analysis

We performed analysis on the first observations recorded on acutely ill patients admitted to all of the participating hospitals. We excluded all patients with missing data.

We calculated SI by dividing heart rate (beats/min) by systolic blood pressure (mm Hg), and the PP by the difference between systolic and diastolic pressure (mm Hg). We calculated the ROX Index value by dividing the patient's oxygen saturation (O_2sat) by their inspired oxygen concentration (FiO_2), and then by the respiratory rate (RR, in breaths/min) (i.e., ROX = O_2sat% / FiO_2 / RR; e.g., 95% / 0.21 / 16 = 28.3).

We calculated descriptive statistics including mean (SD) or percentages and tested statistical significance using Student's *t*-test and χ^2 analysis with a p value < 0.05.

We determined the optimal sensitivity and specificity for the association of in-hospital mortality with different values or SI, PP, and ROX Index in the TBRHSC derivation cohort using Youden's J statistic (i.e., sensitivity + specificity – 1) (23). We then dichotomized the SI, PP, and ROX Index according to their value with the highest Youden's J statistic; a worked example is provided in Supplementary Table 1. Once dichotomized, we placed these three variables into eight mutually exclusive categories.

We performed survival analysis of the TBRHSC derivation cohort using OASIS (Online Application for the Survival Analysis; https://sbi.postech.ac.kr/oasis/surv/) software and compared Kaplan-Meier survival curves using the log-rank test (24).

Ethical Approval

We obtained ethical approval for use of data from the Research Ethics Board for TBRHSC and the medical ethics committee of the Máxima MC (no. 21.007). The study conforms to the principles outlined in the Declaration of Helsinki (25).

RESULTS

Differences between the Derivation and Validation Cohorts

There were marked differences between the TBRHSC derivation and the NEED validation cohorts (Table 1). The TBRHSC derivation cohort was composed entirely of medical patients, had a longer length of hospital stay, and fewer intensive care unit (ICU) admissions than the NEED validation cohort, of which 21% were surgical patients.

Categorization

We derived eight mutually exclusive pathophysiologic categories from the TBRHSC derivation cohort. Death prior to hospital discharge occurred in 1893 (4.1%) of the TBRHSC study cohort of 45,784 acutely ill medical patient admissions with complete data. This in-hospital mortality was associated with increasing SI and falling PP and ROX Index values; the highest Youden's J statistics associated with in-hospital mortality for SI, PP, and ROX Index were 0.70, 42 mm Hg, and 22, respectively. Using these values, patients were divided into eight mutually exclusive categories according to whether the SI was > 0.70, or the PP was < 42 mm Hg, or ROX Index value was < 22. Categories were arranged in ascending order of in-hospital mortality (Table 2).

Category Performance in the TBRHSC Derivation Cohort

The mortality for all eight categories increased throughout the time patients were in hospital; apart from categories 1 and 2 ($p = 0.41$) and categories 6 and 7 ($p = 0.12$), the Kaplan-Meier survival curves for all categories were all significantly different from each other (Figure 1 and Supplementary Table 2). More than 40% of deaths that occurred within 24 h of admission were category 8 patients (i.e., those with a ROX Index < 22, PP < 42 mm Hg, and SI > 0.7), whereas these patients only accounted for 20% of deaths at 30 days. In contrast, category 1 patients (i.e., those with PP ≥ 42 mm Hg, SI ≤ 0.7, and ROX ≥ 22) accounted for only 3.4% of deaths within 24 h of admission.

Comparison of Category Performance in the TBRHSC Derivation and the NEED Validation Cohort

The proportion of patients in each category and the in-hospital mortality rates associated with each category

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Table 1. Characteristic of Thunder Bay Regional Health Science Centre and NEED Cohorts

Variable	TBRHSC Derivation Cohort	NEED Validation Cohort
All patients in database (n)	46,925	138,651
Excluded as data missing (%)	2.40	22.40
Final study population (n)	45,784	107,546
Participating hospitals (n)	1	4
Dates of data collection	1/1/2005–12/31/2010	1/1/2017–3/31/2022
Sex, male, n (%)	22,251 (48.60)	56,283 (52.30)
Age (y), mean (SD)	67.7 (17.8)	66.4 (17.4)
Length of hospital stay (d), mean (SD)	9.5 (14.5)	2.8 (7.7)
Admitted to surgical ward,* n (%)	0 (0)	22,206 (21)
ICU admission, n (%)	1056 (2.30)	4548 (4.20)
In-hospital mortality, n (%)	1893 (4.1)	5573 (5.2)

ICU = intensive care unit; NEED = Netherlands Emergency Department Evaluation Database; TBRHSC = Thunder Bay Regional Health Science Centre.
* All other patients admitted to medical wards.

Table 2. Eight Mutually Exclusive Categories According to PP, SI, and ROX Index Derived from Analysis of 45,784 Acutely Ill Patients Admitted to the Medical Wards of Thunder Bay Regional Health Sciences Centre (Derivation Cohort) Between 2005 and 2010

Category	n	In-Hospital Mortality (%)	PP < 42 mm Hg*	SI > 0.7†	ROX Index <22‡
ROX, PP, and SI normal	22,132	1.46	No	No	No
Low PP, normal SI and ROX	1850	1.51	Yes	No	No
High SI, normal PP and ROX	4413	3.01	No	Yes	No
High SI and low PP, normal ROX	3189	4.14	Yes	Yes	No
Low ROX, normal PP and SI	7921	5.81	No	No	Yes
Low ROX and PP, normal SI	474	8.44	Yes	No	Yes
Low ROX and high SI, normal PP	3641	11.18	No	Yes	Yes
Low ROX and PP and high SI	2164	17.10	Yes	Yes	Yes
Total	45,784	—	—	—	—

PP = pulse pressure; SI = Shock Index.
* PP was "low" if < 42 mm Hg.
† SI > 0.7 was "high."
‡ ROX Index was "low" if < 22.

were similar in both the TBRHSC and the NEED cohorts. In both cohorts, category 1 was the largest (44.5–48.3% of patients), followed by category 5 (15.3–17.3% of patients); category 6 was the smallest and only 1–2% of the total. In-hospital mortality increased progressively from category 1 to 8 in both cohorts (Figure 2). In both the TBRHSC and the NEED cohorts, there were statistically significant differences in the odds ratio for in-hospital mortality between category 1 and all of the other categories except for category 2 (Table 3).

DISCUSSION

Through this hypothesis-generating study, we found that vital sign measurement can be used to place patients into eight mutually exclusive pathophysiologic categories with increasing mortality. The proportion of patients in each category and the in-hospital mortality rates associated with each category were similar in two separate patient cohorts, which were distinctly different because of different enrollment criteria. This suggests

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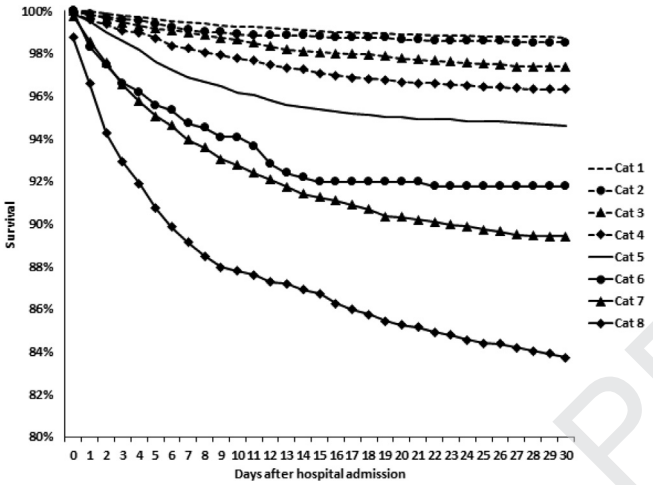

Figure 1. The 30-day Kaplan-Meier survival curves of patients admitted to medical wards of Thunder Bay Regional Health Sciences Centre. Dotted lines show survival curves of all patients with a ROX Index ≥ 22 and solid lines show survival curves of all patients with a ROX Index < 22.

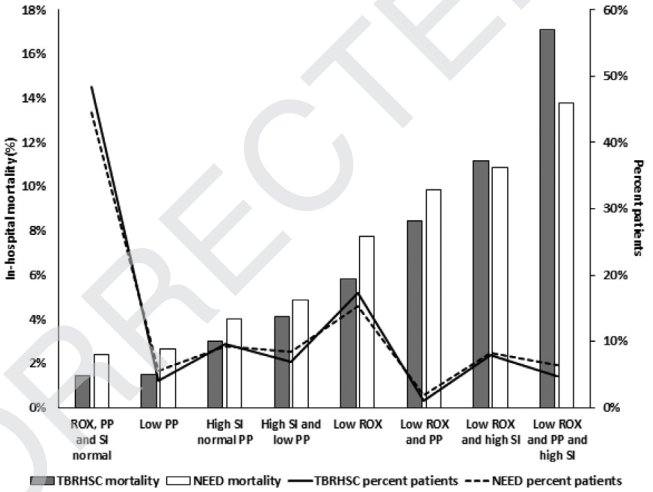

Figure 2. In-hospital mortality according to the eight categories in Thunder Bay Regional Health Sciences Centre (TBRHSC) medical patients (derivation cohort) and medical and surgical patients in the Netherlands Emergency Department Evaluation Database (NEED) (validation cohort). Pulse pressure (PP) was "low" if < 42 mm Hg and the ROX Index "low" if < 22. A Shock Index (SI) > 0.7 was "high." In both cohorts, mortality increases progressively from category 1 patients (i.e., normal ROX Index, SI, and PP), to category 8 (i.e., low ROX Index, low PP, and high SI).

that the mortality and distribution of categories observed can be applied to many patient populations.

Our proposed categories offer the following potential advantages:

1. allow care bundles and protocols to be tailored more precisely to each patient's pathophysiology;
2. require less supplemental information, expertise, tacit skill, and resources than are currently required to make appropriate bespoke adjustments to the care of acutely ill patients;
3. allow future studies to compare interventions given to patients with the same pathophysiologic derangements (i.e., compare like with like); and

help identify patients likely to benefit from new technology, such as high-flow nasal oxygen, which helps reduce the work of breathing.

Categories with a ROX Index value < 22 had the highest mortality. However, the accurate prediction of mortality was not the proposed purpose of the categories identified by this study. On the contrary, it is hoped that they will direct clinical interventions that more accurately address underlying pathophysiologic derangements and thus save patients who would have been expected to die. These categories should supplement NEWS and similar early warning scores, not replace them. The vital sign data required to calculate NEWS are the same as for the eight categories. The categories could be automatically

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Table 3. Unadjusted Odds Ratio for In-Hospital Mortality for Patient Categories 2–8 Compared with Category 1 in the TBRHSC (Derivation Cohort) and NEED (Validation Cohort)

Category*	TBRHSC Derivation Cohort			NEED Validation Cohort		
	Odds Ratio	95% CI	*p* Value	Odds Ratio	95% CI	*p* Value
ROX, SI and PP normal	1.00					
Low PP, normal SI and ROX	1.04	0.69 to –1.55	0.93	1.12	0.94 to 1.32	0.21
High SI, normal PP and ROX	2.10	1.70 to –2.59	< 0.0001	1.71	1.52 to 1.93	< 0.0001
High SI, low PP, normal ROX	2.92	2.36 to –3.60	< 0.0001	2.08	1.86 to 2.33	< 0.0001
Low ROX, normal PP and SI	4.16	3.59 to –4.82	< 0.0001	3.42	3.15 to 3.71	< 0.0001
Low ROX and PP, normal SI	6.22	4.35 to –8.87	< 0.0001	4.44	3.79 to 5.19	< 0.0001
Low ROX, high SI, normal PP	8.50	7.29 to –9.91	< 0.0001	4.97	4.54 to 5.44	< 0.0001
Low ROX, low PP and high SI	13.93	11.87 to–16.34	< 0.0001	6.51	5.95 to 7.13	< 0.0001

PP = pulse pressure; SI = Shock Index; NEED = Netherlands Emergency Department Evaluation Database; TBRHSC = Thunder Bay Regional Health Science Centre.
* PP was "low" if < 42 mm Hg, ROX Index was "low" if < 22, and SI > 0.7 was "high."

determined and presented by electronic systems used to collect vital signs and calculate early warning scores (26). Currently, acutely ill patients are usually given supplemental oxygen and a fluid challenge. The efficacy of this approach is unclear; it probably works well in patients who are hypovolemic without underlying respiratory or cardiac problems, provided the underlying cause of hypovolemia (e.g., bleeding and sepsis) is also addressed. However, for patients with respiratory or cardiac compromise, new interventions, such as noninvasive ventilation and high-flow nasal oxygen, may provide safer and more effective treatment (10).

Although we do not know whether patients in this study with each pathophysiologic category needed or received different interventions, we consider it unlikely, for example, that a patient with a high SI and normal ROX Index will require the same treatment as one with a normal SI and a low ROX Index, even if both patients have the same NEWS. The physiologic responses to life-threatening illness can vary according to the compensatory reserve of each individual patient (27,28). Although much of the research has been on trauma patients and not those with acute medical illness, numerous reports have found that vital sign changes may occur late in critical illness; pulse and blood pressure can remain clinically normal for some time, even in bleeding patients who have lost 20% of their blood volume (27,29). Therefore, many of the current legacy criteria for assessing vital sign derangement, which are based largely on heart rate and blood pressure, occur too late to save many patients, are not supported by clinical experience, and should be revised (30). Although the Advanced Trauma Life Support classification of shock suggests that increased respiratory rate is a late sign, this study of the first vital signs recorded on acutely ill medical patients found that the most common vital sign derangement was a low ROX Index and not a high SI. This supports previous reports that found respiratory changes are among the earliest signs of clinical deterioration (18,31–34).

Acutely ill patients with life-threatening illness require effective treatments to be delivered at the optimal time (35). Prospective trials are required to determine the optimal interventions required by each pathophysiologic category, as well as the speed and urgency of their delivery. Although nearly all of the patients above category 2 will have an elevated NEWS, the differences in their imminent and subsequent mortality in hospital were marked. For some of these patients, simple observation to allow the body time to further compensate may be all that is required; others will need immediate lifesaving interventions. We found mortality was highest in patient categories with a ROX Index < 22, and a ROX Index < 22 multiplied the risk of any other abnormality. ROX Index values have been reported to guide the response to oxygen therapy and indicate when assisted ventilation is needed[36]; a falling ROX Index value should prompt interventions that protect the patient's airway, maintain oxygen saturation and ventilation, and reduce the work of breathing (10,36–38). SI levels correlate with fluid and blood transfusion requirements, ICU admission, and mortality in trauma patients (39). However, some patients are more tolerant of high SI levels and survive, whereas patients with a low tolerance can die with near-normal values (31). Unless there is either an SI > 0.70 or ROX Index < 22, a PP < 42 mm Hg carried no additional risk. Nevertheless, because a low PP indicates that a low stroke volume is likely, it seems reasonable to use this easily available finding as a "red flag" to prompt further cardiovascular

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assessment and cautious administration of i.v. fluids and inotropes.

Limitations

Strengths of this hypothesis-generating study include the large sample size and validation in a different cohort. However, there are several limitations. First, as a retrospective study, it is prone to information bias; we did not consider confounders such as patient age, ethnicity, diagnoses, and comorbidities, or identify those patients receiving end-of-life care. Only patients with a complete set of data were included. This may have introduced selection bias into our findings, as patients without a complete set of data may be a different patient population who, for example, may have been less sick or admitted at a different time of day. The hospital length of stay in TBRHSC was much longer than in Dutch hospitals. Unfortunately, comparing mortality at different times was not possible, as only the in-hospital mortality of Dutch patients was available. Therefore, the similarity in absolute in-hospital mortality, but not the trend in increasing mortality, should be considered as little more than a coincidence and requires further evaluation. Second, we were not able to determine how RR was measured in participating centers or verify the accuracy of these measurements; all other vital signs were measured electronically. How FiO_2 was determined was not recorded and, in many cases, may have been estimated from the oxygen flow rate of the venturi mask used. Third, the TBRHSC Meditech System recorded length of stay by the calendar day only. Therefore, a patient with a length of stay recorded as < 24 h could have been in hospital for only a few minutes or up to 48 h. The length of time patients spent in the hospital's ED before admission was not available nor were data on follow-up after hospital discharge. Finally, the Youden's J statistic may not be the optimal method of cutoff selection; future studies may identify better trigger points for clinical interventions.

CONCLUSIONS

Acutely ill medical patients can be placed into eight mutually exclusive physiologic categories according to their SI, PP, and ROX Index values. In two separate patient cohorts, these categories had a similar prevalence, in-hospital mortality was highest in all patient categories with a ROX Index < 22, and a ROX Index < 22 multiplied the risk of any other abnormality. Patients with a ROX Index < 22, PP < 42 mm Hg, and SI > 0.7 had the highest mortality and accounted for 40% of deaths within 24 h of admission, whereas patients with a PP ≥ 42 mm Hg, SI ≤ 0.7, and ROX Index ≥ 22 had the lowest mortality. Future studies will assess the interventions needed for these categories and their value in guiding treatment and disposition decisions.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jemermed.2022.12.024.

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ARTICLE SUMMARY

1. Why is this topic important?

Early warning scores do not provide insight into what is wrong with a patient or how to treat a patient, and they need to be deconstructed to uncover the core physiologic derangement.

2. What does this study show?

In two large separate cohorts of acutely ill patients, eight mutually exclusive physiologic categories defined by ROX Index, Shock Index (SI), and pulse pressure (PP) have similar distribution and in-hospital mortality.

3. What are the key findings?

The categories with the highest in-hospital mortality have a ROX Index < 22. A ROX Index < 22 multiplies the risk of SI > 0.7 or a PP < 42 mm Hg.

4. How is patient care impacted?

These categories can help clinicians to focus on the nature and severity of underlying physiologic derangement in sick patients.

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