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Sample entropy predicts lifesaving interventions in trauma patients with normal vital signs☆

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ABSTRACT

Introduction: Heart rate complexity, commonly described as a "new vital sign," has shown promise in predicting injury severity, but its use in clinical practice is not yet widely adopted. We previously demonstrated the ability of this noninvasive technology to predict lifesaving interventions (LSIs) in trauma patients. This study was conducted to prospectively evaluate the utility of real-time, automated, noninvasive, instantaneous sample entropy (SampEn) analysis to predict the need for an LSI in a trauma alert population presenting with normal vital signs.
Methods: Prospective enrollment of patients who met criteria for trauma team activation and presented with normal vital signs was conducted at a level I trauma center. High-fidelity electrocardiogram recording was used to calculate SampEn and SD of the normal-to-normal R-R interval (SDNN) continuously in real time for 2 hours with a portable, handheld device. Patients who received an LSI were compared to patients without any intervention (non-LSI). Multivariable analysis was performed to control for differences between the groups. Treating clinicians were blinded to results.
Results: Of 129 patients enrolled, 38 (29%) received 136 LSIs within 24 hours of hospital arrival. Initial systolic blood pressure was similar in both groups. Lifesaving intervention patients had a lower Glasgow Coma Scale. The mean SampEn on presentation was 0.7 (0.4-1.2) in the LSI group compared to 1.5 (1.1-2.0) in the non-LSI group ($P < .0001$). The area under the curve with initial SampEn alone was 0.73 (95% confidence interval [CI], 0.64-0.81) and increased to 0.93 (95% CI, 0.89-0.98) after adding sedation to the model. Sample entropy of less than 0.8 yields sensitivity, specificity, negative predictive value, and positive predictive value of 58%, 86%, 82%, and 65%, respectively, with an overall accuracy of 76% for predicting an LSI. SD of the normal-to-normal R-R interval had no predictive value.
Conclusions: In trauma patients with normal presenting vital signs, decreased SampEn is an independent predictor of the need for LSI. Real-time SampEn analysis may be a useful adjunct to standard vital signs monitoring. Adoption of real-time, instantaneous SampEn monitoring for trauma patients, especially in resource-constrained environments, should be considered.

1. Introduction

Traditional vital sings often fail to reflect the true severity of injury in trauma patients until compensatory mechanisms have been exhausted [1-5]. In fact, heart rate (HR) may even decrease in response to severe trauma, which carries a risk of undertriage and, consequently, increased mortality [4]. Heart rate variability (HRV) analysis, commonly described as a "new vital sign," has shown promise in predicting injury severity, but its use in clinical practice, despite availability of real-time data [4,6-8], has not been widely adopted.

The primary goal of trauma triage is to identify high-risk patients who would benefit from aggressive, resource-unlimited medical care (appropriate triage) while limiting exclusion of those who could benefit from such care (undertriage) [8]. Specificity of screening criteria for trauma team activation is often sacrificed for an increased sensitivity. Furthermore, current triage systems are supported by little evidence and commonly reflect expert opinion [9,10]. These triage limitations are particularly apparent in combat casualty care, in which an additional need to minimize the operational risk for responding medics has led to the concept of "remote triage" [3,11]. The application of remote triage may also play a role in civilian prehospital trauma triage during mass casualty and tactical interactions. For remote triage to be useful, data need

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to be automated and provide valuable information for rapid clinical decision making. Heart rate variability analysis could possibly serve that purpose, as it has shown promise in the reported literature as a potential objective triage tool [2-4,6-8,11-14]. Some studies, using an alternative approach for quantifying cardiac variability based on the amount of irregularity or fractal dimension by curve length, have indicated a superior diagnostic performance to predict poor outcome [3-5]. As biologic systems are inherently complex, a decreased irregularity or loss of complexity measured by sample entropy (SampEn) has been suggested to reflect early changes to occult and nonoccult physiologic stress [3,4,15], perhaps making SampEn a more powerful predictor of impending physiologic compromise.

In a previous investigation, we examined the diagnostic utility of real-time SampEn analysis for predicting the need of lifesaving interventions (LSIs) in trauma patients upon hospital arrival [16], many of whom had grossly abnormal vital signs. In the present prospective study, we restricted the study population to only patients with normal vital signs upon presentation as well as narrowed the definition of LSI to avoid risking overfitting the diagnostic usefulness of SampEn. We hypothesized that SampEn is decreased in trauma patients with normal presenting vital signs who undergo LSIs.

2. Methods

Patients who met criteria for trauma team activation (6 AM-9 PM, convenience sample) were prospectively enrolled in our study between April 2012 and January 2014. Research staff responded to trauma activations to determine if a new patient was eligible for enrollment. Trauma team activation at our institution is a 2-tiered system based upon mechanism of injury and physiology. Tier 1 activation mobilizes the most resources and includes patients with Glasgow Coma Scale (GCS) less than 8, hypotension of any cause, any penetrating torso injuries, and traumatic arrest, among other criteria. Tier 2 activation includes patients with GCS 9 to 13, any airway support, any patient with a tourniquet applied, suspected pelvic fracture, multiple long bone fractures, and multisystem trauma (eg, chest and long bone injuries), among other criteria. In addition, trauma team activation can be called at the discretion of the prehospital providers if specific criteria are not met. Patients were enrolled who met either tier 1 or tier 2 activation criteria. Patients with a presenting HR greater than 110 beats per minute or systolic blood pressure (SBP) less than 110 mm Hg were excluded. Additional exclusion criteria included age younger than 18 years and transfer from an outside institution. This study was approved by the Massachusetts General Hospital Institutional Review Board with waiver of informed consent.

Upon arrival to the resuscitation bay, research staff monitored the patient with an ICON Noninvasive Cardiac Monitor (Osypka Medical, La Jolla, CA) that has been modified and programmed to calculate and display SampEn and SD of the normal-to-normal R-R interval (SDNN) in real time. Apart from instantaneous SampEn and SDNN that were recorded on a minute-by-minute basis, the monitor also provided continuous measurements of HR, stroke volume, and cardiac output. Sample entropy was calculated through electrocardiographic recordings of 200 consecutive beats in a continuous sliding-window fashion, as previously described [7,16]. Sample entropy is a measure of the likelihood of finding similar patterns in the signal. A lower value implies increased regularity and, likewise, decreased complexity of the signal, thereby limiting the effects of stationarity. For SampEn calculations, the dimension parameter m was 2, and the filter parameter r was 20% of the SD [17,18]. Traditional HRV was determined using standard time-domain analysis, specifically SDNN [14,16,19,20]. Clinical management of the patient occurred at the discretion of the treating physician who was blinded to the ongoing study results.

A standardized data collection sheet was used for all patients. In addition to demographics, other collected data included initial vital signs, injury burden, and laboratory parameters. Comorbidities on admission were noted, such as diabetes mellitus, coronary artery disease, atrial fibrillation, cerebrovascular disease, and use of antiarrythmic medications and sedative medications (benzodiazepines, propofol, fentanyl, morphine, and hydromorphone). The primary outcome was a LSI within 24 hours of arrival to the emergency department (ED). Lifesaving interventions were defined as the following: blood transfusion, cardioversion, tube thoracostomy, cardiopulmonary resuscitation, intubation, cricothyrotomy, thoracotomy, angiography with or without embolization, needle decompression, laparotomy, use of vasoactive medications, hyperosmolar fluid therapy, and other emergent surgical intervention [21]. With respect to blood transfusion, each case was reviewed and excluded if the indication for the transfusion could not be clearly defined and directly attributable to an anatomical injury. In this way, delayed blood transfusions for management of a pelvic fracture after angioembolization would be included, while excluding blood transfusions given empirically in the setting of a nonoperatively managed liver laceration with normal vital signs and stable hemoglobin. Other exceptions that would not constitute an LSI were defined a priori as orthopedic surgery for fractures without apparent or potential for hemodynamic instability (eg, radius fracture) and the use of vasoactive medications for indications other than hemodynamic instability (eg, to augment perfusion of suspected spinal cord injury without hemodynamic instability). *Hospital admission* was defined as a secondary outcome. The occurrence and analysis of an LSI were binary (present or not present, regardless of whether the patient received >1 LSI). A patient was considered to have received sedation if an anxiolytic, sedative/hypnotic, opioid agonist, or dopaminergic antagonist was administered before beginning of the electrocardiographic recording. This was also analyzed in a binary fashion, regardless of dosing.

Continuous data were described using mean with SD or median with interquartiles, whichever more appropriate, and compared using the Student t tests or Wilcoxon rank sum tests, whereas categorical data were summarized using proportions and compared using χ^2 tests. Sample entropy, HR, and SDNN were compared between outcome groups at 1, 5, 10, 60, and 120 minutes. Multiple logistic regression models were constructed to identify independent predictors of LSIs and hospital admission. Two diagnostic approaches were used for the purposes of analysis. First, only the first-minute data that were derived from the monitor were considered, to resemble its use for remote telemetry and triage. Second, additional data that would be available during a primary survey (eg, GCS) were also considered in a separate model. To assess diagnostic performance of the models, receiver operating characteristic (ROC) curves were constructed, and area under curve (AUC) was used to summarize model performance. Cutoff points of SampEn at the first minute were selected to allow determination of sensitivity, specificity, negative predictive value, and positive predictive value. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

One hundred twenty-nine patients were enrolled during the study period; the mean age was 44 ± 17 years and 78% were male. Injury was caused by a blunt mechanism in 112 patients (87%), commonly after a fall (n = 46, 36%), motor vehicle accident (n = 42, 33%), and/or pedestrian struck (n = 12, 9%). Of approximately 3600 trauma activations during the study period, 1722 patients were screened (based upon daily manpower availability of this convenience sample) for enrollment. Upon presentation, the mean HR was 89 ± 20 beats per minute; respiratory rate, 19 ± 4 breaths/min; SBP, 143 ± 25; and initial GCS score, 15 [15-29]; the motor component of GCS was 6 [6-29]. Initial laboratory values indicated mean hemoglobin level of 13.8 ± 1.7 g/dL and a lactate level of 2.9 ± 1.9 mmol/L. Blood gas analysis was performed in 64 patients (50%), which demonstrated a mean pH of 7.35 ± 0.13 units, pO_2 of 120 (80-174) mm Hg, pCO_2 of 45 ± 14 mm Hg, and base deficit of 2 ± 4.0 mEq/L. There were no difference in blood gas or lactate values between groups. Forty-four patients (34%) were discharged home

Table 1
Characteristics of patients that received LSI to those who did not receive an intervention (non-LSI)

Variable	LSI (n = 38)	Non-LSI (n = 91)	*P*
Age (y)	45 ± 20	43 ± 16	.47
Male	28 (74%)	72 (79%)	.64
Blunt mechanism of injury	33 (87%)	79 (87%)	1.00
Diabetes mellitus	1 (3%)	6 (7%)	.45
Coronary artery disease	1 (3%)	4 (4%)	1.00
HR, beats/min	100 ± 22	84 ± 17	.0001
SBP, mm Hg	142 ± 35	144 ± 20	.8
GCS	14.5 (3-15)	15 (15-15)	<.0001
Hemoglobin level, g/dL	12.9 ± 2.0	14.2 ± 1.4	.0006
ICU admission	32 (84%)	6 (7%)	<.0001
ISS	28 (10-35)	4 (1-10)	<.0001
Mortality	7 (18%)	0 (0%)	.0001

from the ED, whereas the remaining 85 patients (66%) required hospital admission; 31 (24%) were initially transferred to the intensive care unit (ICU); 19 (15%), to the operating room; and 35 (27%), to the surgical ward. The median Injury Severity Score (ISS) of the study population was 9 [1-19], and 7 patients (5%) died during hospital stay.

There were 38 patients (29%) who underwent a total of 136 LSIs within 24 hours of arrival to the ED. Lifesaving interventions included blood transfusion (n = 18), chest tube placement (n = 18), cardiopulmonary resuscitation (n = 3), endotracheal intubation (n = 29), operation (n = 11), thoracotomy (n = 1), angioembolization (n = 3), needle decompression of the chest (n = 2), vasoactive medication (n = 21), and hyperosmolar fluid therapy (n = 10). All patients who received an LSI required hospital admission. The 2 groups were similar with respect to demographics, mechanism of injury, and comorbidities (Table 1). With regard to initial laboratory parameters, the LSI group exhibited lower hemoglobin level (12.9 ± 2.0 vs 14.2±1.4 g/dL; P = 0006) as well as lower pH (7.31 vs 7.40 units; P = .001) compared to the non-LSI group. There was a significant difference between the groups in terms of HR (100 ± 22 LSI vs 84 ± 17 beats per minute non-LSI; P = .0001), GCS score (10.6 ± 5.3 LSI vs 14.9 ± 0.3 non-LSI; P < .0001), and oxygen saturation (95% ± 10% LSI vs 98% ± 2% non-LSI; P = .03), but other vital signs, including SBP, were similar (Table 1). Mortality was significantly higher in the LSI group (18% vs 0%; P = .0001).

Mean SampEn at all time points were significantly lower in the LSI group at 1, 5, 10, 60, and 120 minutes (Table 2). In addition, median HR was significantly higher in the LSI group throughout the duration of monitoring except for 120 minutes. SD of the normal-to-normal R-R interval was significantly higher in the LSI group at 60 and 120 minutes. Using a logistic regression model with SampEn at 1 minute (HR complexity at 1 minute) as the sole predictor, the odds ratio of an LSI for a decrease in 0.1 units of SampEn was 1.15 (95% confidence interval [CI], 1.08-1.24; P < .0001). The following equation was constructed: p(LSI) = ek/(1 + ek), where k = 1.33 − 0.22 * ($SampEn_{1min}$), as previously described [16]. This indicates that lower SampEn was significantly associated with an increased likelihood of undergoing an LSI. The AUC was 0.76 (95% CI, 0.66-0.86) (Fig. 1); diagnostic performance of selected cutoff values for $SampEn_{1min}$ is presented in Table 3. The performance of using $SampEn_{1min}$ as the sole predictor of LSI was slightly

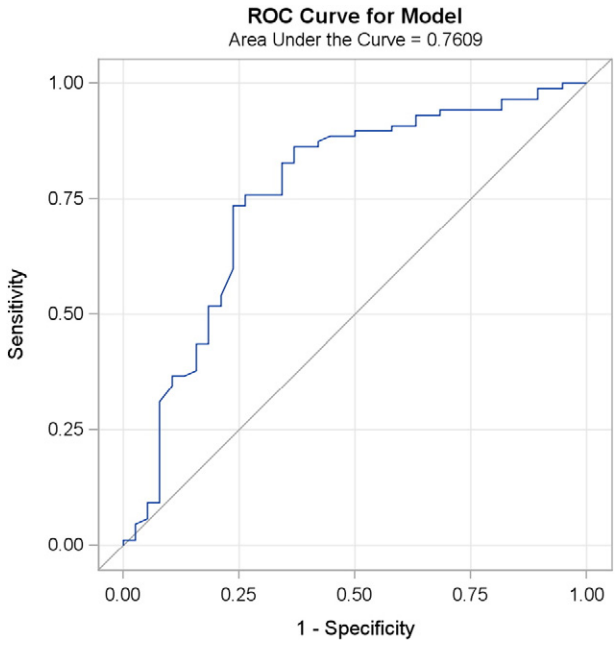

Fig. 1. Receiver operating characteristic curve for model using real-time $SampEn_{1min}$ alone for prediction of LSI. Area under the curve, 0.76.

better than using HR at 1 minute (AUC, 0.70; 95% CI, 0.60-0.80) and GCS (AUC, 0.73; 95% CI, 0.64-0.81) but significantly better than traditional measures such as HR (AUC, 0.53; 95% CI, 0.41-0.65) or SBP (AUC, 0.51; 95% CI, 0.39-0.63). The effects of adding other factors to the model were also explored (Table 4). The addition of HR_{1min} to the model had minimal effect, whereas the inclusion of GCS or sedation greatly improved AUC from 0.76 to 0.87 or 0.95. Heart rate at 1 minute and GCS did not make significant contribution after the inclusion of sedation. A model with HR complexity at 1 minute and sedation produced an AUC of 0.93 (95% CI, 0.89-0.98) (Fig. 2).

With respect to hospital admission, GCS was lower in the admitted group (15 [14-15] vs 15 [15-15]; P < .0001), whereas ISS was higher (13 [9-29] vs 1 [0-1]; P < .0001) (SDC 1). In addition, SampEn was significantly lower in the admitted group at 1, 10, 60, and 120 minutes (SDC 2). SD of the normal-to-normal R-R interval, HR, and blood pressure failed to discriminate between groups. Hemoglobin level was lower in the admitted group (13.6 ± 1.7 vs 14.2 ± 1.5 g/dL; P = .03), but we regard this as a clinically insignificant difference and not useful for decision making. The odds ratio for a 0.1-unit decrease in $SampEn_{1min}$ for predicting hospital admission was 1.09 (95% CI, 1.03-1.15) with an AUC of 0.68 (95% CI, 0.58-0.77), which was slightly better than using HR at 1 minute alone (AUC, 0.52; 95% CI, 0.42-0.63). The inclusion of HR_{1min} and GCS to the $SampEn_{1min}$ model had minimal effect (AUC, 0.74; 95% CI, 0.65-0.83), and neither HR_{1min} nor GCS reached statistical significance. However, addition of sedation to the model increased the AUC from 0.68 to 0.79 (95% CI, 0.71-0.87), with both factors being significant predictors of hospital admission.

Table 2
Real-time variables in patients with and without LSI

	SampEn			SDNN			HR, beats/min		
Time	Non-LSI	LSI	*P*	Non-LSI	LSI	*P*	Non-LSI	LSI	*P*
1 min	1.5 (1.1-2.0)	0.7 (0.4-1.2)	<.0001	40 (25-71)	32 (17-68)	.37	81 (70-91)	92 (82-104)	.0004
5 min	1.5 (1.1-1.9)	0.8 (0.5-1.3)	<.0001	46 (31-65)	38 (14-68)	.27	81 (70-88)	90 (78-104)	.001
10 min	1.5 (1.0-2.0)	1.1 (0.6-1.5)	.001	41 (22-55)	32 (15-61)	.22	79 (68-89)	90 (76-106)	.004
60 min	1.5 (1.1-1.9)	0.8 (0.4-1.2)	<.0001	36 (20-59)	16 (8-41)	.008	79 (68-88)	94 (77-108)	.0005
120 min	1.5 (1.0-0.9)	0.8 (0.5-1.1)	<.0001	33 (22-66)	15 (11-24)	.002	79 (71-90)	91 (76-102)	.065

Table 3
Diagnostic performance of different cutoff values of SampEn for predicting LSI

Value	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
1.7	89 (75-97)	37 (27-48)	89 (74-97)	38 (28-49)	53 (44-62)
1.4	79 (63-90)	54 (43-65)	85 (73-94)	43 (31-55)	62 (52-70)
1.1	74 (57-87)	76 (65-84)	87 (77-94)	57 (42-71)	73 (65-81)
0.8	58 (41-74)	86 (77-93)	82 (73-90)	65 (46-80)	78 (69-85)
0.5	34 (20-51)	93 (86-97)	76 (67-84)	68 (43-87)	75 (67-82)

NPV indicates negative predictive value; PPV, positive predictive value.

4. Discussion

Studies of HRV analysis in trauma patients have been widely published in the literature. In a series of articles, the group at Vanderbilt University Medical Center demonstrated that cardiac uncoupling (reduced HRV) was associated with mortality and deteriorating physiologic reserve in trauma ICU patients [2,15,19,20,22-25]. Subsequent studies in prehospital and inhospital trauma patients have corroborated these results [6,8,14]. For example, a recent study by Ryan et al [6] showed that reduced HRV was an independent predictor of morbidity and mortality in 216 hemodynamically stable trauma patients with evidence of traumatic brain injury upon hospital arrival. Importantly, however, the aforementioned study acknowledges that HRV analysis was completed a few hours to 3 days after initial measurement, which obviates any use for clinical decision making. Similarly, Cancio et al [4] noted that analysis of HRV parameters, albeit easily learned, required long processing times, which limited its clinical utility.

To our knowledge, our group was the first to report on the use of instantaneous HRV and complexity analysis in trauma patients [16]. These results build specifically upon those previously published by Cancio et al [4] and King et al [8]. In their study, prehospital trauma patients with decreased SampEn had significantly increased odds of receiving an LSI. Interestingly, our study also showed that SampEn was lower in patients who were admitted to the hospital compared to those who were discharged home from the ED. Another important finding was the lack of utility of time-domain (SDNN) analysis. This may likely be related to the nonstationarity of the signal, which greatly disturbs calculations of time-domain parameters [7,26,27]. Nonstationarity is defined by the tendency of the mean and SD to vary considerably over time. Physiological parameters are especially prone to nonstationarity in the setting of trauma, which consequently affects the reliability of linear variables such as SDNN [7,26]. On the other hand, SampEn is an alternative approach that quantifies the irregularity in the HR using nonlinear statistics, which are less sensitive to nonstationarity [27]. This may be better suited for analysis of autonomic cardiovascular responses that are inherently complex due to multiple interacting mechanisms [4,5] and ongoing interventions and clinical changes.

Among the several complexity variables that are available, we considered 2 characteristics of SampEn that justified its use in our study.

Table 4
The effects of adding other factors for predicting LSI

Model	Factor	OR (95% CI)	AUC (95% CI)
$SampEn_{1min}$	$SampEn_{1min}$	1.15 (1.08-1.24)	0.76 (0.66-0.86)
$SampEn_{1min}$ + HR_{1min}	$SampEn_{1min}$	1.12 (1.04-1.20)	0.78 (0.68-0.87)
	HR_{1min}	0.97 (0.95-1.002)	
$SampEn_{1min}$ + HR_{1min} + GCS	$SampEn_{1min}$	1.09 (1.001-1.12)	0.87 (0.79-0.94)
	HR_{1min}	0.97 (0.94-1.01)	
	GCS	2.18 (1.03-4.59)	
$SampEn_{1min}$ + HR_{1min} + GCS + sedation	$SampEn_{1min}$	1.10 (0.99-1.21)	0.95 (0.91-0.99)
	HR_{1min}	0.96 (0.92-1.001)	
	GCS	2.18 (1.03-4.59)	
	Sedation	0.03 (0.01-0.12)	
$SampEn_{1min}$ + sedation	$SampEn_{1min}$	1.16 (1.07-1.26)	0.93 (0.89-0.98)
	Sedation	0.02 (0.006-0.08)	

OR indicates odds ratio.

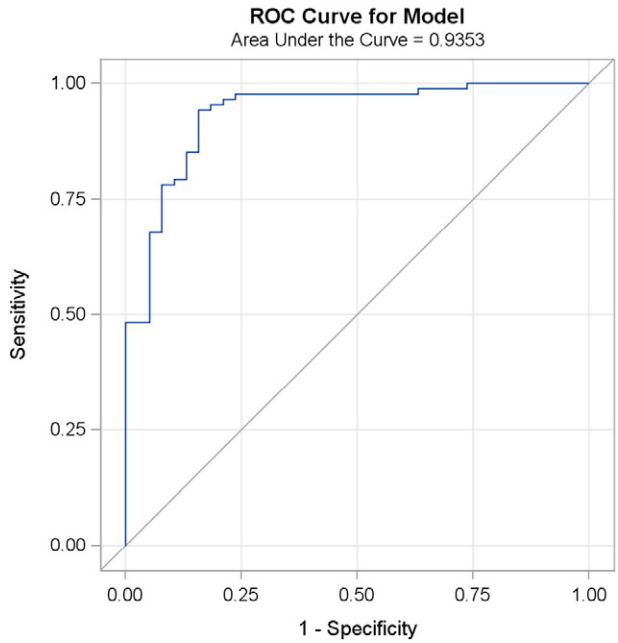

Fig. 2. Receiver operating characteristic curve for model using real-time $SampEn_{1min}$ and sedation for prediction of LSI. Area under the curve, 0.935.

First, SampEn has been shown in several studies to be a reliable and independent predictor of poor outcomes [3,4,7,26-29]. Batchinsky et al [27-29] demonstrated in 3 animal models that SampEn decreased after traumatic injury and hemorrhagic shock. The same author also noted that SampEn was associated with mortality in prehospital trauma patients (1.10 ± 0.05 survivors vs 0.80 ± 0.08 nonsurvivors; $P < .01$) [3]. The study by Cancio et al [4], mentioned earlier, also used SampEn with significant results. Second, SampEn, in contrast to approximate entropy (closely related variable), has been reported by Batchinsky et al [7] to predict mortality with data sets as short as 100 beats. Based on their study, we decided to analyze 200-beat data sets, as they showed the highest value for the area under the ROC curve (0.895), albeit not statistically significantly higher than the 100-beat data set. Considering that mean HR in our LSI group was 100 beats per minute, this means that SampEn values were available after approximately 2 minutes of monitoring. Once the first value was calculated, SampEn was available on a beat-to-beat basis owing to the continuous sliding-window approach that was used by the algorithm.

In our data, the diagnostic performance of SampEn in the first minute, as measured by the AUC, was 0.76. Although summary statistics have consistently demonstrated significant differences between trauma patients with poor and favorable outcomes, the added benefit of HRV monitoring remains unclear [5]. In our data, the AUC for SDNN in the first minute alone was 0.45, and AUC only increased from 0.76 to 0.78

SDC 1
Comparison of patients who were admitted to the hospital (ADMIT) to those who were discharged home from the ED (Non-ADMIT)

Variable	ADMIT (n = 85)	Non-ADMIT (n = 44)	*P*
Age (y)	47 ± 18	37 ± 14	.002
Male	69 (81%)	31 (70%)	.19
Blunt mechanism of injury	73 (86%)	39 (89%)	.79
Diabetes mellitus	5 (6%)	2 (5%)	1
Coronary artery disease	5 (6%)	0 (0%)	.16
HR, beats/min	89 ± 21	88 ± 16	.76
SBP, mm Hg	143 ± 27	143 ± 21	.93
GCS	15 (14-15)	15 (15-15)	<.0001
Hemoglobin level, g/dL	13.6 ± 1.7	14.2 ± 1.5	.03
ISS	13 (9-29)	1 (0-1)	<.0001
Mortality	7 (8%)	0 (0%)	.095

SDC 2
Real-time variables in patients who were admitted to the hospital and those who were discharged home from the ED

	SampEn			SDNN			HR, beats/min		
Time	No-ADMIT	ADMIT	*P*	No-ADMIT	ADMIT	*P*	No-ADMIT	ADMIT	*P*
1 min	1.5 (1.3-2.1)	1.1 (0.6-1.6)	.001	39 (27-57)	37 (18-88)	.91	82 (73-91)	85 (71-96)	.67
5 min	1.6 (1.1-1.8)	1.2 (0.7-1.8)	.071	40 (34-56)	49 (21-69)	.93	82 (72-92)	83 (70-93)	.89
10 min	1.6 (1.0-2.0)	1.3 (0.7-1.8)	.046	41 (24-49)	34 (16-61)	.75	81 (71-92)	80 (69-95)	.68
60 min	1.5 (1.1-1.8)	1.2 (0.7-1.7)	.012	35 (23-56)	33 (13-53)	.43	80 (71-88)	81 (69-94)	.40
120 min	1.5 (1.1-2.0)	1.1 (0.8-1.6)	.013	32 (22-69)	24 (13-54)	.16	78 (71-90)	82 (72-94)	.33

by adding SDNN to the SampEn model. One can imagine that a patient with obvious trauma and low GCS score may be readily identified as needing an LSI without knowledge of these variability metrics; however, few patients fit nicely into this paradigm. Other studies have demonstrated that initial GCS score can distinguish different groups of patients (eg, alive vs dead, LSI vs no-LSI) [3,4,8,13]. Hence, Rickards et al [5] conducted a study to evaluate the added value of complexity measurements for predicting LSIs in prehospital trauma patients who were hemodynamically stable with normal GCS_{motor} scores on presentation. They showed that fractal dimension by curve length was a significant predictor of LSI in a multivariable analysis, but its utility was limited by the very high overlap of individual values between the groups. In our data, the AUC for GCS score alone was 0.73, and AUC increased from 0.76 to 0.86 by adding GCS score to the SampEn model.

Sample entropy could be used for triage; an optimal cutoff value for SampEn should have a high accuracy for LSI to minimize incorrect classification. Based on our results, SampEn less than 0.8 yields sensitivity, specificity, negative predictive value, and positive predictive value of 58% (22/38), 86% (75/87), 82% (75/91), 65% (22/34), respectively, with an overall accuracy of 78% (97/125) for predicting an LSI. Diagnostic performance was further improved to an excellent accuracy (AUC, 0.93) by the addition of sedation to the model—a combination of SampEn less than 1.2 and sedation yields an overall accuracy of 87% (109/125) for predicting an LSI. Determination of an exact cutoff for trauma triage will require further investigation and (likely) inclusion of additional technology-based inputs, such as wearable accelerometers and explosion proximity (overpressure) detectors for this to be useful on the battlefield.

Our results may also be used to support the use of SampEn as a vital sign for remote triage in combat casualty care. The limitations of this environment impose some obvious difficulties in accurate remote triage [21]. Thus, simplified and automated systems are necessary to support decision making in this setting. The future envisions soldiers being equipped with sensors that would transmit data by telemetry to medic for instantaneous notification of the need for an LSI. For this reason, our multivariable models were conducted in 2 stages. First, a model was constructed using variables that would only be available with remote monitoring. Both initial HR and SampEn were associated with LSI in univariate analysis, but only SampEn emerged as a significant predictor on logistic regression; furthermore, the addition of HR made a minimal contribution to the area under the ROC curve. Next, significant factors that required clinical examination, that is, GCS, were added to the model to simulate the natural history of tactical combat casualty care into tactical field care, when this information may become available. We also controlled for patients who were sedated either as a part of rapid sequence intubation or to receive analgesia, and the results showed significant contribution of sedation to the area under the ROC, which could demonstrate the limited utility of SampEn measurement in premedicated patients. Despite certain laboratory parameters (hemoglobin and pH) exhibiting an association with LSI, we did not include these into regression models, as they would likely not be available to the combat medic or hospital clinician during initial triage of trauma care.

The limitations of our study need to be addressed. First, because of logistical reasons, only daytime patients were enrolled, which implies that selection bias could have affected our results because there is known diurnal variation in autonomic function. Second, our results reflect only the specific variability and complexity parameters that were used and we cannot make any assumptions about the utility of other methods that have been described in the literature. Unfortunately, cardiac variability and complexity calculations have not been generally standardized, but based on our understanding of the current trauma literature, SDNN and SampEn are well established and have previously shown significant association with patient outcomes [22,23]. Third, our study has not examined the effects of LSIs on cardiac variability to determine its utility as an end point of resuscitation. Such use has been suggested by Batchinsky et al [27] who noted restoration of complexity measures after resuscitation of swine with hemorrhagic shock. Similarly, another study in patients with severe burns demonstrated increased complexity after 36 hours of resuscitation [26]. Further work will be needed to demonstrate usefulness of instantaneous SampEn as an end point of resuscitation. Fourth, very few of our patients received a toxicology screen, so we cannot comment on the effect that intoxicants may have played in complexity analysis. Finally, because the LSIs represent a heterogeneous group of interventions, which may also vary significantly from the combat population, we cannot reliably extrapolate these findings to another dissimilar population of patients.

In conclusion, this study confirmed the results of our previous, smaller study that reported real-time SampEn can predict LSIs and hospital admission in trauma activation patients. Triage decisions based upon SampEn need to be considered in the context of sedatives and analgesics. Widespread adoption of real-time, instantaneous SampEn monitoring for trauma patients should be considered.

Author contributions

LN, AYM, and DRK contributed to study design, data collection, data analysis, data interpretation, and writing of the manuscript. OAB, CMC, TM, AL, MP, GMV, AMI, and JOH contributed to data collection and data interpretation. YC, GCV, PJF, DY, and MAD contributed to study design, data interpretation, and writing of the manuscript.

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