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Can cardiovascular reserve index (CVRI) on arrival to the trauma unit detects massive hemorrhage and predicts developing hemorrhage?

Observational prospective cohort study

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Ethical Compliance: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Highlights

- The detection of haemorrhage in trauma casualties may be delayed owing to compensatory mechanisms.

- This observational prospective cohort study aimed to evaluate whether the cardiovascular reserve index (CVRI) detects massive haemorrhage and predicts haemorrhage development in trauma casualties.
- The prediction capability had been compared to lactate, haemoglobin, vital signs and shock index.
- Detection of massive haemorrhage on arrival was evident by most variables.
- Prediction of developing haemorrhage was considerable and statistically significant only by lactate (AUC=0.88), CVRI (0.82) and RR (0.73).
- CVRI has advantages over lactate
    - It is feasible in pre-hospital and multi casualties arena
    - Repeated CVRI measurements enable dynamic deterioration detection.
- CVRI may be a useful tool in the evaluation of haemorrhage.

Data statement

Research data supporting this publication is not available due to the hospital regulations.

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Observational prospective cohort study

ABSTRACT

Background: The detection of hemorrhage in trauma casualties may be delayed owing to compensatory mechanisms. This study aimed to evaluate whether the cardiovascular reserve index (CVRI) on arrival detects massive hemorrhage and predicts hemorrhage development in trauma casualties.

Methods: This was an observational prospective cohort study of adult casualties (≥18Y) who were brought to a single level-1 trauma center, enrolled upon arrival and followed until discharge. Vital signs were monitored on arrival, from which the CVRI and shock index (SI) were retrospectively calculated (blinded to the caregivers). The outcome measure was the eventual hemorrhage classification group: massive hemorrhage on arrival (MHOA) (defined by massive transfusion on arrival of ≥6 [O+] packed cells units), developing hemorrhage (DH) (defined by a decrease in Hemoglobin >1g/dL in consecutive tests), and no significant hemorrhage (NSH) noted throughout the hospital stay. The means of each variable on arrival by hemorrhage group were evaluated using the Analysis of Variance. We evaluated the detection of MHOA in the entire population and the prediction of DH in the remainders (given that MHOA had already been detected and treated) by C-statistic predefined strong prediction by area under the curve (AUC)≥0.8, p≤0.05.

Results: The study included 71 patients (after exclusion): males, 82%; average age 37.7Y. The leading cause of injuries was road accident (61%). Thirty-nine (54%) patients required hospital admission; distribution by hemorrhage classification: 5 (7%) MHOA, 5 (7%) DH, and 61 (86%) NSH. Detection of MHOA found a strong predictive model by CVRI and most variables (AUC 0.85-1.0). The prediction of DH on arrival showed that only lactate (AUC=0.88) and CVRI (0.82) showed strong predictive model.

Conclusions: CVRI showed a strong predictive model for detection of MHOA (AUC>0.8) as were most other variables. CVRI also showed a strong predictive model for detection of DH (AUC=0.82), only serum lactate predicted DH (AUC=0.88), while all other variables were not found predictive. CVRI has advantages over lactate in that it is feasible in pre-hospital and mass casualty settings. Moreover, its repeatability enables detection of deteriorating trend. We conclude that CVRI may be a useful additional tool in the evaluation of hemorrhage.

Keywords: Cardiovascular reserve index (CVRI); Detection; Developing hemorrhage; Hemorrhage; Prediction; Trauma;

Abbreviations

ATLS – advanced trauma life support

AUC – area under the curve

BSA – body surface area

CI – confidence interval

CVRI – cardiovascular reserve index

DBP – Diastolic blood pressure

DH – Developing hemorrhage

$etCO_2$ – End tidal CO_2

Hb. – Hemoglobin

HR – Heart rate

MAP – Mean arterial (blood) pressure

MHOA – Massive hemorrhage on arrival

NSH – No significant hemorrhage

OA – On arrival

ROC - Receiver operating characteristics

RR - Respiratory rate

SaO_2 – Oxygen saturation

SBP – Systolic blood pressure

SI – Shock index

INTRODUCTION

The main causes of immediate and early trauma deaths are severe CNS injuries and hemorrhage [1-5]. Hemorrhage can be controlled and reversible; hence, death due to hemorrhage is theoretically considered to be "preventable death." The earlier the hemorrhage is controlled, the better is the odds of a successful outcome.

The mechanism of trauma (especially blunt injuries, high energy injuries, and penetrating injuries) may raise suspicion of bleeding. However, internal hemorrhage may not be evident or detectable on arrival, though initial bleeding does exist, and may further deteriorate toward hemorrhagic shock

When hemorrhage develops, compensatory mechanisms conceal hemodynamic deterioration, which poses a major challenge even for experienced experts. Hence, casualties are closely monitored to detect signs of deterioration. Once compensatory mechanisms are exhausted, uncompensated deterioration and shock develop, which can be relatively easily detected. Accordingly, the intervention is also delayed while the window of opportunities is closing.

Hemorrhage severity evaluation relies on a combination of physical examination, vital signs, laboratory tests, and imaging (e.g., tachycardia, hypotension, tachypnea, decreased pulse pressure, elevated blood lactate levels, or negative base excess). Despite the availability of standardized approaches and various indices that have been proposed over the years, the challenge of detecting and predicting hemorrhages persists.

The shock index SI was first proposed in 1968 as the ratio of heart rate to systolic blood pressure and is still in use, especially in research and hospital based management algorithms, but remains controversial in clinical practice. A meta-analysis published in 2023 concluded that SI may have a limited role as a sole tool for predicting the need for massive transfusions in adult trauma patients [6].

Over the last few decades, several efforts have targeted non-invasive estimates of cardiac output (CO) through echocardiography [7], impedance cardiography [8], pulse contour analysis of the arterial pressure waveform [9], and transcutaneous Doppler [10]. However, the compensatory mechanisms maintain sufficient CO even with considerable hemorrhage until the compensatory mechanism is exhausted, after which CO shows a stair-wise drop [11]. Hence, CO is not a reliable indicator of hemorrhage during development.

The Compensatory Reserve Index (CRI) has been proposed as a noninvasive measure of a patient's ability to compensate for reduced blood volume. It analyzes the waveform of a patient's photoplethysmography (PPG) signal and returns a numerical value. A low CRI indicates that the patient's compensatory mechanisms are exhausted, and that the patient may be at risk of decompensation. A high CRI indicates that the patient has a good compensatory reserve to sustain momentary stress, and may even enable increase in cardiac output if metabolic needs grow. CRI repeatability enables dynamic monitoring of the patient's status. Previous studies have reported promising results in the detection of bleeding [12,13].

The cardiovascular reserve hypothesis was first proposed in 2012 [14,15]. Thereafter, the cardiovascular reserve index (CVRI), was proposed as its estimate. CVRI was derived by a well-known measure of control engineering known as the Open Loop Gain (OLG), which indicates the momentary robustness of the feedback mechanism [16].

A low CVRI indicates that the patient's momentary cardiovascular reserve has been exhausted. A high CVRI indicates that the cardiovascular reserve may enable increase in cardiac output if metabolic needs grow. Previous studies had support CVRI as an estimate to the momentary cardiovascular reserve; One study had reported a strong association between CVRI and diverse morbidities across the entire hemodynamic spectrum [16]. A second study demonstrated CVRI dynamic changes during physical exercise, in which the higher CVRI

was at rest, which decreased to a minimum at peak exercise, and immediately regained with recovery [17]. A third study found CVRI decreased during hemorrhage simulation in an animal model [18]. A fourth study found that CVRI was a better predictor of early trauma death than shock index [19].

This study aimed to evaluate whether the cardiovascular reserve index (CVRI) on arrival detects massive hemorrhage and predicts hemorrhage development in trauma casualties.

METHODS

In an observational prospective cohort study, we recruited a sample of trauma casualties on arrival to a level-1 trauma center in a single tertiary hospital (recruited between 1.1.2021-31.7.2021). The cohort included adult casualties that were brought seemingly with considerable trauma to the emergency department (ED) trauma unit and enrolled on arrival. The patients were selected consecutively but depended on the availability of a research investigator to enroll and to observe each casualty on arrival, which we were unable to pose 24/7. The study population was followed from arrival until discharge. The exclusion criteria were as follows: age < 18 years, pregnant women, acute head injury with GCS score <8, patients who were undergoing cardiopulmonary resuscitation on arrival, patients who were eventually defined as non-injury, and casualties in which considerable bleeding was most unlikely present on arrival but eventually bleed.

Patients were closely observed and documented during their trauma unit stay. Each participant was clinically evaluated, monitored, and underwent diagnostic tests according to ATLS guidelines, institutional protocols, and routine trauma care practices unrelated to study participation.

An investigator, who was not part of the active care team, recruited each participant, documented the study data and measurements on arrival, and escorted him until leaving the

ED (discharged home, admitted for hospitalization, or ED death). The data were collected with arrival in the trauma resuscitation room. Vital signs were continuously monitored through a standalone monitor included measurements of BP, HR, RR, $etCO_2$ and SaO_2 on arrival. The research investigator, who observed each casualty, had snapshot the measurements every 3 minutes. The evaluated value (of each variable) was the average of three consecutive values in order to control biological fluctuations. Laboratory tests included hemoglobin and lactate levels. Most patients underwent chest radiography, Focused Assessment with sonography in Trauma (FAST), total-body CT, and injury-related specific imaging.

CVRI and SI were calculated retrospectively based on vital signs on arrival. Hence, the calculated values are inevitably identical whether done retrospectively or in real time. Moreover it enabled keeping CVRI blinded during treatment which prevents any influence on clinical decisions.

Collected data included the mechanism and setting of trauma, underlying diagnosis, affected organ, referral target from the ED (either discharged home or admitted to a specific ward), ED discharge diagnosis, ward's admission diagnosis, and interpretation of imaging.

Patients were followed-up during their entire hospital stay and additional relevant data was retrieved from the electronic medical records.

Trauma and emergency medicine experts retrospectively determined the severity of the injury and eventual hemorrhage classification after discharge according the algorithm presented in figure 1.

Massive hemorrhage on arrival (MHOA) was defined as treatment with massive transfusion on arrival of ≥6 (O+) packed cells units [20]. Developing hemorrhage (DH) defined for those who had shown a decrease in hemoglobin >1g/dL in consecutive tests [21]. No significant

hemorrhage (NSH) was defined when no hemorrhage was noted throughout the hospital stay. Casualties discharged home directly from the ED were classified by definition as NSH. Casualties who were admitted were defined NSH as neither having received a blood transfusion nor having undergone a bleeding control procedure. As for this study, hemorrhage caused by surgery was not considered to be attributed to trauma.

Calculated measurements

Shock index (SI) was calculated by HR and SBP (6). Body surface area (BSA) was calculated using Mosteller formula (22).

Cardiovascular reserve index CVRI was calculated as (16):

CVRI=18*MAP / (RR*HR*BSA)

Where MAP is the mean arterial pressure, RR is the respiratory rate, and BSA is the body surface area)

The study hypotheses:

Hypothesis 1: "CVRI can successfully identify patients presenting with trauma who suffer massive hemorrhage on arrival (AUC≥0.8)."

Hypothesis 2: "CVRI can successfully identify patients presenting with trauma who are at risk for hemodynamic deterioration (AUC≥0.8)."

Testing hypothesis 1 evaluated the detectability of MHOA of the entire casualties population using C-statistics.

$$\langle \boldsymbol{MHOA \mid entire\ casualties\ population} \rangle$$

Testing hypothesis 2 evaluated the predictability of DH (of the remaining casualties given that MHOA had already been detected and treated with massive blood transfusions) using C-statistics .

$$\langle \boldsymbol{DH} \mid \boldsymbol{DH} + \boldsymbol{NSH} \rangle$$

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, Version 26.0, IBM Corp. Armonk NY, USA. The sample size was calculated according to the following assumptions: single-sided, level of significance=0.05, power=0.8, estimated CVRI difference between groups =0.2, estimated SD of CVRI=0.4, ratio of reference to study group (NSH to DH) = 4:1, which resulted with sample size ≥63.

Nominal scale variables were analyzed by comparing means by hemorrhage category using the analysis of variance (ANOVA). Frequencies were evaluated using Fisher's exact test or the Chi-square test.

We evaluated the detective capability and predictive capability using the C-statistic (also known as "concordance" statistic or C-index) which is a measure of goodness of fit for binary outcomes in a logistic regression model through their risk level. The Receiver Operating Characteristic curve (ROC) represents the association between true positives (sensitivity) on the Y-axis and false positives ' (1-specificity) on the X-axis. Area Under the Curve (AUC) gives a general indication about the strength of the model. AUC above 0.8 is considered strong predictive model, indicating good discriminatory power in distinguishing between patients with and without the outcome of interest (in our study MHOA in hypothesis 1, and DH in hypothesis 2) through their risk level (in our study CVRI).

This study was in line with the STROCSS criteria (23).

RESULTS

The study included 75 casualties, 71 after exclusion (one due to severe isolated head injury, two were eventually defined as non-injury, and one in which considerable bleeding was unlikely to be present on arrival but eventually bleed).

The casualties had a relatively young average age of 37.7, and men predominated the population (58/71, 82%). The leading trauma mechanisms included road accidents (43, 61%) and falls (13, 18%). Road accidents included collision between vehicle 24 (56%), motorcycles and electric bicycles 15 (35%), vehicle rollover 2 (5%) and pedestrians 2 (5%). The mean lactate level was not significantly different between the sexes, but the mean hemoglobin level was significantly lower in women than in women by 1.7g/dL.

Thirty-nine (54%) were admitted to diverse surgical wards, and 14 were operated within 24h (20%), among which the majority of procedures were not necessarily life-saving, but were immediately performed for optimal outcomes, for example, orthopedic procedure of bone fracture fixation or improving wound healing odds.

Casualties distributions by hemorrhage group found five (7%) MHOA, 5 (7%) DH, and the remaining 61 (86%) were NSH.

Table 1 shows the demographic and general characteristics by each hemorrhage group. The admission rates were 100% 5/5 in MHOA, 100% 5/5 in DH, and 28/61 (46%) in NSH.

Blood transfusion was given in 5/5 in MHOA (6-28 packed cells units), 4/5 in DH, and 2/59 in NSH (both of which were due to bleeding caused by surgery).

The mean decrease in hemoglobin in consecutive tests in the DH group was 2.5g/dL (range 1.1-4.5g/dL).

Table 2 presents the variables median with interquartile range (IQR) (25th, 75th percentile) by hemorrhage group. Most variables in MHOA were statistically significant different than both other hemorrhage categories (namely DH and NSH) e.g. lactate, RR, etCO2, HR, SBP, DBP, MAP, CVRI, SI but not in hemoglobin and SaO2.

CVRI (as most other variables) revealed a strong and statistically significant detective model of MHOA out of the entire population of casualties: lactate (AUC=0.97, $p<0.01$), RR (AUC=0.89, $p<0.01$), etCO2 (AUC=0.85, $p<0.01$), HR (AUC=0.95, $p<0.01$), SBP (AUC=0.98, $p<0.01$), DBP (AUC=0.92, $p<0.01$), MAP (AUC=0.96, $p<0.01$), CVRI (AUC=0.98, $p<0.01$), and SI (AUC=1.0, $p<0.01$).

Table 3 shows that only five variables were statistically significant different in between DH and NSH: lactate, RR, SBP, CVRI, and SI. All other variables were not statistically significant different in between the two groups.

Lactate and CVRI were the only variables that revealed a strong and statistically significant predictive model of DH (AUC 0.88, 0.82 respectively). Fig. 2 shows ROC curves of DH prediction upon arrival (given those with MHOA had already been detected and treated).

RR AUC was below 0.8 yet statistically significant predictor of DH (AUC=0.73, p=0.02). SBP AUC was below 0.8 but not statistically significant predictor of DH (AUC=0.74, p=0.13). SI AUC was far below 0.8 and not statistically significant predictor of DH (AUC=0.63, p=0.43).

DISCUSSION

This study prospectively followed 71 trauma casualties with diverse types of injuries from arrival until discharge and eventually assigned each casualty to one of three hemorrhage

classification groups: massive hemorrhage on arrival (MHOA), developing hemorrhage (DH) on arrival, and no significant hemorrhage (NSH).

We followed an accepted definition of massive hemorrhage through massive transfusion [20]. The main challenge was in the definition of developing hemorrhage, as patients were not expected to be left untreated until hemorrhagic shock were evident. We defined developing hemorrhage as a decrease in hemoglobin level > 1 g% in consecutive tests not otherwise explained [21]. The group of no significant hemorrhage throughout hospital stay included two different subpopulations: 1) Those that were discharged home directly from the ED. 2) Patients who were admitted for hospitalization during which they were followed and a considerable decrease in hemoglobin level was not evident; they had also neither received blood transfusion nor undergone a bleeding control procedure.

The results showed that detection of MHOA by CVRI had a high AUC (as did most other variables) hence hypothesis 1 is accepted.

The results showed that the prediction of DH (given that MHOA had already been detected and treated) by CVRI had a high AUC (0.82) (along with serum lactate with even slightly higher AUC 0.88), hence hypothesis 2 is accepted. None of all other variables were found statistically significant predictive of DH. It is interesting to note that neither RR nor SBP nor HR (which are routinely used in practice to detect deterioration) nor SI, were found strong and statistically significant predictors of DH. Moreover, HR was not even found statistically significant different in between DH and NSH (Table 3).

CVRI showed slightly lower predictive capability of DH than Lactate but has an advantage over lactate in that it is feasible even in pre-hospital setting and mass casualty arena where neither experienced experts nor laboratory tests are available. Moreover, Repeated CVRI measurements may enable detection of deteriorating trends.

Our current study is in line with already mentioned previous study evaluated CVRI changes during hemorrhage simulation in an animal model while showed a linear monotonic decrease in CVRI in accordance with cumulative blood loss toward shock, whereas CO in the same study showed a stable level despite considerable bleeding until it dropped in a stair-wise pattern [18].

We are aware that our study represents a single level-1 trauma center; hence, we may be criticized for generalizing the results. However, all casualties were given care according to the same guidelines, protocols, and practice, which may reduce variability. We may be criticized for the small study size in general, and the number of MHOA and DH groups in particular. However the sample size was determined through power analysis which ensures the study has appropriate statistical power to detect significant effects if they exist. We may be criticized that some of the casualties that were discharged home directly from ED may have reflected 'Clinical false negative suspicion'. This may be true but; first, this was an observational study - you have what you see, second, in such case, we would expect to discover post-discharge re-visit, admission, or even death. We are aware of possible concern regarding the lack of a separate validation cohort but suggest to refer our current study as seemingly a prospective "derivation set," wherein a previously proposed formula of CVRI was evaluated as a detector of massive hemorrhage and as a predictor of developing hemorrhage (in comparison with other routinely used predicting variables on arrival).

We believe that the study has met its hypotheses, provided valid findings and may raise further research ideas.

CONCLUSIONS

CVRI was found as a strong detector of MHOA (hypothesis1) and a strong predictor of DH (hypothesis 2). We conclude that CVRI may be a useful additional tool in the assessment of trauma casualties or as a useful guide in trauma management. We suggest considering CVRI monitoring on arrival as an addition to other routinely measured variables. Further studies are warranted to further validate our findings.

Data Access Statement: Research data supporting this publication are not available owing to hospital regulations.

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Figure 1: The eventual hemorrhage classification algorithm

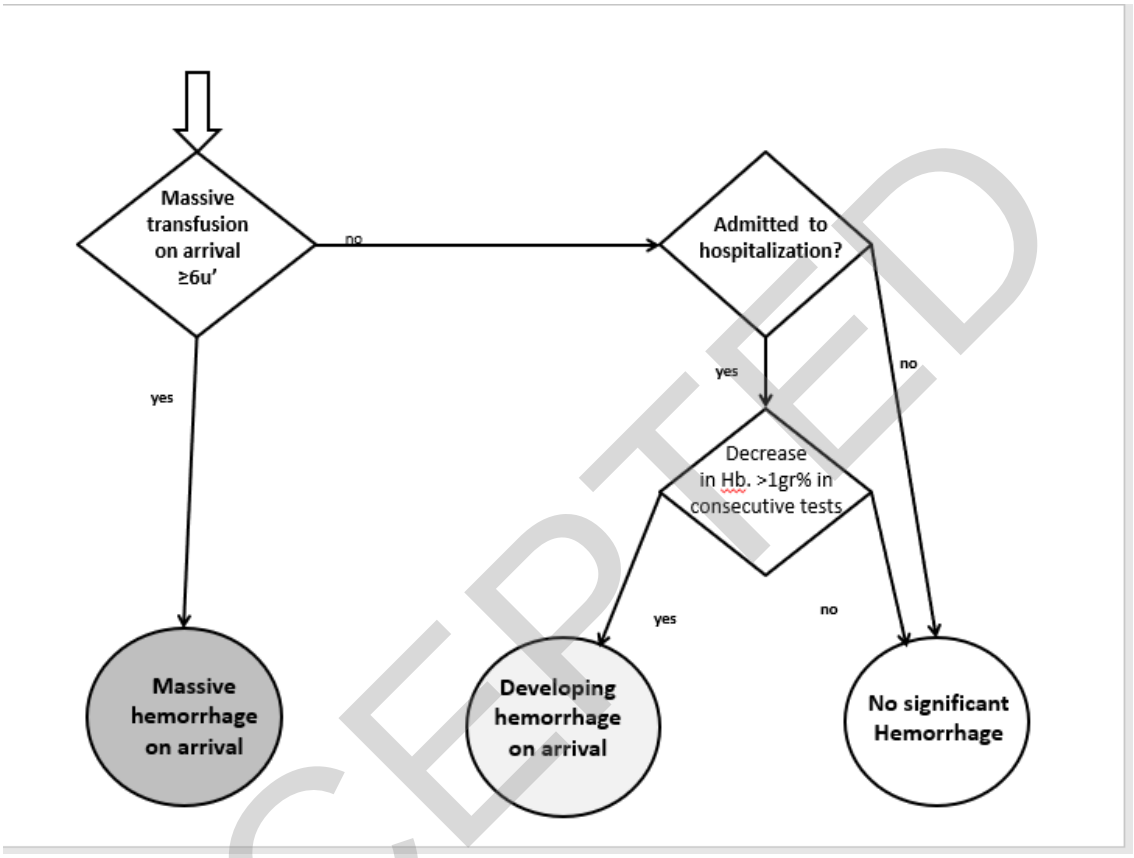

Figure 2: Prediction of developing hemorrhage by lactate and CVRI

Footnote:

Lactate AUC=0.88, p<0.01

CVRI AUC=0.82, p<0.01

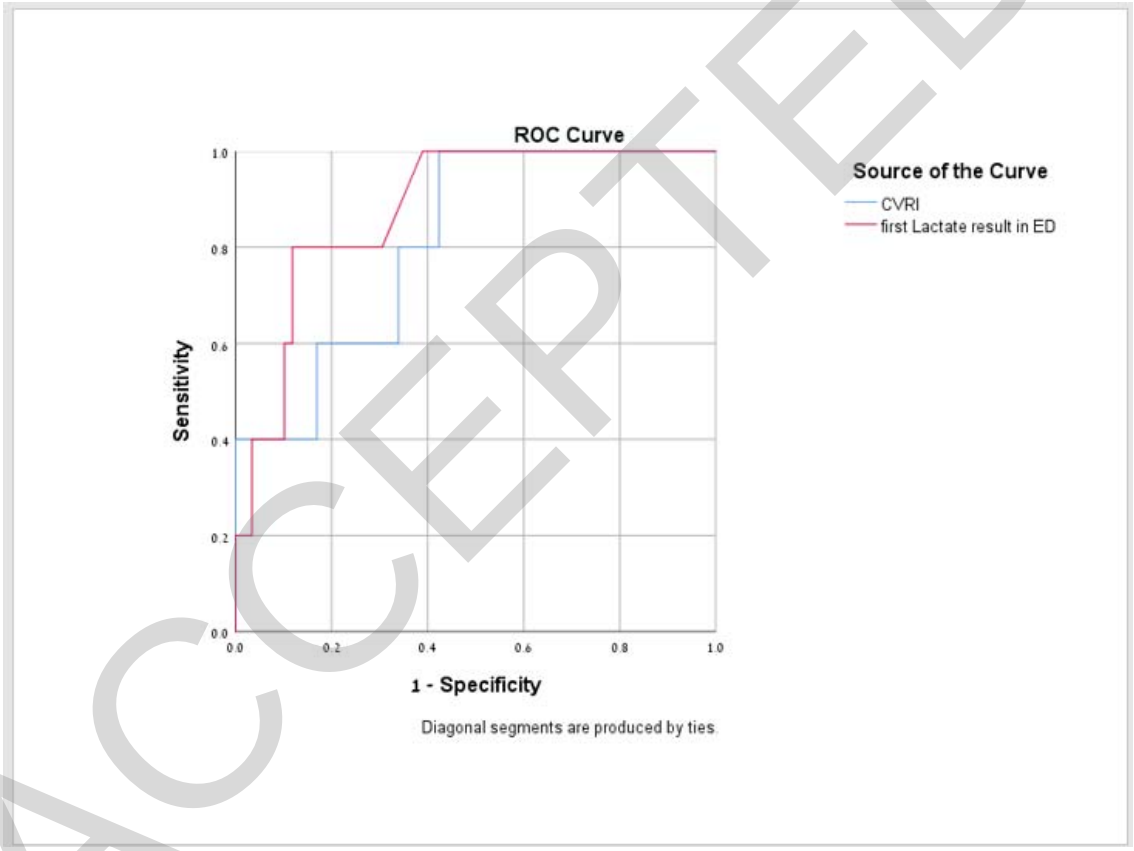

Table 1.

Demography and anthropometric variables median and interquarantile range (IQR) by hemorrhage group

Variable	Hemorrhage group		
	MHOA	DH	NSH
Age (years)	36 (32-47)	32 (22-32)	36 (24-50)
Male (%)	60%	80%	82%
BSA (m^2)	1.74 (1.68-2.33)	1.94 (1.68-1.95)	1.91 (1.79-1.78)
GCS	13 (10-15)	15 (14-15)	15 (15-15)
FAST (+)	60%	20%	10%
Injury severity distribution Mild Moderate Severe	 0% 0% 100%	 0% 60% 40%	 67% 25% 8%

	Median (IQR)			p-value
Variable	Massive hemorrhage on arrival	Developing hemorrhage on arrival	No significant hemorrhage	
Lactate	108 (48-153)	42 (37-57)	21 (15-26)	P<0.01
Hemoglobin	13.4 (-)	13.5 (12.0-14.2)	15.0 (13.9-15.7)	P=0.41
Respiratory rate (RR)	31 (23-35)	22 (19-23)	17 (15-22)	P<0.01
etCO2	14.0 (13-18)	23.3 (21-27)	22.3 (20-26)	P=0.02
Heart rate (HR)	124 (114-137)	84 (80-108)	85 (76-95)	P<0.01
Systolic blood pressure (SBP)	108 (88-116)	126 (117-130)	141 (130-152)	P<0.01
Diastolic blood pressure (DBP)	59 (44-62)	69 (68-71)	79 (71-85)	P<0.01
Mean arterial blood pressure (MAP)	78 (59-82)	89 (85-89)	99 (94-107)	P<0.01
Saturation (SaO2)	95 (91-97)	95 (95-98)	97 (96-99)	P=0.11
Cardiovascular reserve index (CVRI)	0.21 (0.14-0.21)	0.44 (0.29-0.53)	0.66 (0.46-0.85)	P<0.01
Shock index (SI)	1.1 (0.98-1.26)	0.71 (0.55-0.86)	0.62 (0.52-0.70)	P<0.01

Table 2Median and interquarantile range of each variable on arrival by hemorrhage group

	Median (IQR)		p-value
Variable	Developing hemorrhage on arrival	No significant hemorrhage	
Lactate	42 (37-57)	21 (15-26)	P<0.01
Hemoglobin	13.5 (12.0-14.2)	15.0 (13.9-15.7)	P=0.24
Respiratory rate (RR)	22 (19-23)	17 (15-22)	P=0.02
etCO2	23.3 (21-27)	22.3 (20-26)	P=0.63
Heart rate (HR)	84 (80-108)	85 (76-95)	P=0.57
Systolic blood pressure (SBP)	126 (117-130)	141 (130-152)	P=0.04
Diastolic blood pressure (DBP)	69 (68-71)	79 (71-85)	P=0.20
Mean arterial blood pressure (MAP)	89 (85-89)	99 (94-107)	P=0.07
Saturation (SaO2)	95 (95-98)	97 (96-99)	P=0.13
Cardiovascular reserve index (CVRI)	0.44 (0.29-0.53)	0.66 (0.46-0.85)	P=0.02
Shock index (SI)	0.71	0.62	P=0.05

	(0.55-0.86)	(0.52-0.70)	

Table 3

Median and interquarantile range of each variable on arrival by hemorrhage group

(Given massive hemorrhage on arrival had already detected and treated hence not included)