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(RESEARCH ARTICLE)

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Norepinephrine corrected shock index as an innovative hemodynamic based prognosticator in critically ill patients

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Abstract

Background: Hemodynamic instability in critically ill patients can be assessed by various hemodynamic valid indicators. One of these approved hemodynamics' prognosticator is the Shock Index (SI), which integrates both the heart rate and systolic blood pressure in one composite indicator. Arbitrarily, higher vasopressor rate indicates poorer prognostic. Whatever, Norepinephrine, the preferred vasopressor in most shock related scenarios, has a tendency to increase heart rate beside its vasoconstriction associated systolic blood pressure augmentation.

Aim: In this study, we primarily aim to investigate the predictive power of a newer proposed composite hemodynamic prognosticator which integrates the average Norepinephrine infusion rates with the assessed patients' Shock Indexes, and to explore its Sensitivity Indices regarding the critically ill patients' major outcomes.

Methods: This study trial was a non-funded, non-sponsored, observational study, which was conducted retrospectively on the Intensive Care Unit (ICU) at King Hussein Medical Center, Royal Medical Services, Amman, Jordan, over 60 months between Jan 2018 and Dec 2022. Exclusion criteria including but not excluded to, admission days less than 24 hours and missing data more than 80%. All eligible investigated critically ill patients were dichotomously divided into 2 comparative NE×SI products' cohorts; lower product's (NE×SI<14.835 µg.bpm/min. mmHg) cohort (Cohort I) versus higher product's (NE×SI≥14.835 µg.bpm/min. mmHg) cohort (Cohort II). A Chi Square test were conducted across these 2 dichotomized cohorts. The Binary Logistic Regression (BLgR) analysis was conducted for the tested patients' prognosticator (NE×SI) against the probability of being allocated to the Non-Survivors State (The Positive State) rather than to the Survivors State (The Negative State). The Receiver Operating Characteristic (ROC) and Sensitivity Analysis were processed to explore the area under the ROC curves (AUROC±SEM), optimal cut-off points, and the other sensitivity indices.

Results: Actually, 2528 and 3217 cases were processed as positive actual states (Positive OI, Non-Survivors) and as negative actual states (Negative OI, Survivors) respectively. The AUC±SEM for the NE×SI was significantly determined at 0.944±0.003 (95% CI; 0.938-0.949). The probability of the positive OI was 66.12% at the optimal operating cutoff point of 14.84 µg.bpm/min. mmHg. In this study, we constructed a BLgR model to prognosticate the admitted ICU patients' mortality and was formulated as [e (-6.986+0.516× NE.SI) /1+ e (-6.986+0.516× NE.SI)].

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Conclusion: Our results revealed that our proposed an innovative hemodynamic composited product had a reasonable constructed area under the curve with an interesting sensitivity index for prognosticating the admitted critically ill patients' mortality rate.

Keywords: Norepinephrine infusion rate; Shock Index; Hemodynamic indicators; Critically patients; Mortality prognosticating

1. Introduction

In contrast to stable patients, a several possible of Intensive Care Unit (ICU) related potential confounder factors, particularly the vasopressors and the corresponding shock statuses, insulin infusion management therapy, and others fewer impacting confounders (e.g., Oxygenation, acid-base, temperature, and hematocrit statuses) or possible interacting drugs (e.g., Vitamin C, mannitol, and paracetamol), may interfere with the BG_Glk reliability in BG monitoring against the reference BG_Lab. Notably, the BG_Glk precision is often considered clinically accepted, even in ICU admitted patients, as long as the gap against the BG_Lab doesn't exceed 15% or drop into the negative gap direction [1-6].

In this study, we primarily aim to investigate the predictive power of a newer proposed composite hemodynamic prognosticator which integrates the average Norepinephrine infusion rates with the assessed patients' Shock Indexes, and to explore its Sensitivity Indices regarding the critically ill patients' major outcomes.

2. Material and methods

This study trial was a non-funded, non-sponsored, observational study, which was conducted retrospectively on the Intensive Care Unit (ICU) at King Hussein Medical Center, Royal Medical Services, Amman, Jordan, over 60 months between Jan 2018 and Dec 2022.

Exclusion criteria including but not excluded to, admission days less than 24 hours and missing data more than 80%. The Age-adjusted Charlson Co-Morbidity Index (AACCI) was used for the co-morbidity burden assessment, and a dichotomized value of 8 was adopted in the comparison analysis across Cohort I-II. All eligible investigated critically ill patients were dichotomously divided into 2 comparative NE×SI products' cohorts; lower product's (NE×SI<14.835 µg.bpm/min. mmHg) cohort (**Cohort I**) versus higher product's (NE×SI≥14.835 µg.bpm/min. mmHg) cohort (**Cohort II**).

A Chi Square test were conducted across these 2 dichotomized cohorts to express the comparison results as Number (Percentages), strength of associations (odd ratios), Pearson chi-square statistic (χ 2), Goodness of Fit (G-Test of independence), and Pearson (r) and Spearman (ρ) correlations.

The admitted ICU patients' mortality statuses were defined in our study as Survivors versus Non-Survivors, Survivors with LOS <3 weeks versus Survivors with LOS ≥ 3 weeks, and Early Mortality if LOS ≤2 weeks versus Late Mortality if LOS >2 weeks. The NE infusion was stocked at concentration of 60 mcg/ml and the infusion rate was labelled in mcg/min. The NE rates were categorized to 3 mcg/min incremental rate from 0-≥18 mcg/min.

The Binary Logistic Regression (BLgR) analysis was conducted for the tested patients' prognosticator (NE×SI) against the probability of being allocated to the Non-Survivors State (The Positive State) rather than to the Survivors State (The Negative State). The BLgR analysis was primarily conducted to abstract the necessary coefficients to present the corresponding logistic model.

The Receiver Operating Characteristic (ROC) and Sensitivity Analysis were processed on a total of 5745 processed cases for the investigated prognosticator against the higher probability of 28-day overall mortality (Positive State and assigned as 1) versus the lower probability (Negative State and assigned as 0) to explore the area under the ROC curves (AUROC±SEM), optimal cut-off points, sensitivities (TPRs), specificities (TNRs), positive and negative predictive values (PPVs and NPVs), positive and negative likelihoods ratios (PLRs and NLRs), and the Youden and accuracy indices (YIs and AIs). For our tested prognosticator, the higher values of the NE× SI indicate stronger evidences for the Positive State (Higher %Prob of mortality). While the lower values of the tested independent variable indicate stronger evidences for the Negative State (lower %Prob of mortality). Statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 23.0. Statistical significance was set at 5%.

3. Results

The probability of critically ill patients' mortality can be mathematically proposed according to their tracked NE×SI products. In this study, we constructed a BLgR model to prognosticate the admitted ICU patients' mortality and was formulated as [e (-6.986+0.516× NE.SI) /1+ e (-6.986+0.516× NE.SI)]. The explained variations in the dependent variable based on the adopted independent investigated composited variable ranged significantly from 49.1%-65.8% depending on whether you reference the Cox & Snell R2 or Nagelkerke R2 methods, respectively, and correctly classified 83.8% of the cases, $\chi^2(8) = 315.67$.

Actually, 2528 and 3217 cases were processed as positive actual states (Positive OI, Non-Survivors) and as negative actual states (Negative OI, Survivors) respectively. The AUC±SEM for the NE×SI was significantly determined at 0.944±0.003 (95% CI; 0.938-0.949). The probability of the positive OI was 66.12% at the optimal operating cutoff point of 14.84 µg.bpm/min. mmHg.

The overall tested gender's ratio (Male: Female ratio, M: F) in this study was assigned to 2.262: 1 with insignificant distributions across the NE×SI <14.835 (Cohort I) vs ≥ 14.835 (Cohort II) [2.245: 1 vs 2.284: 1, respectively, 1.017 (95% CI; 0.909-1.139), 0.004±0.013, χ^2=0.091, p-value=0.763].

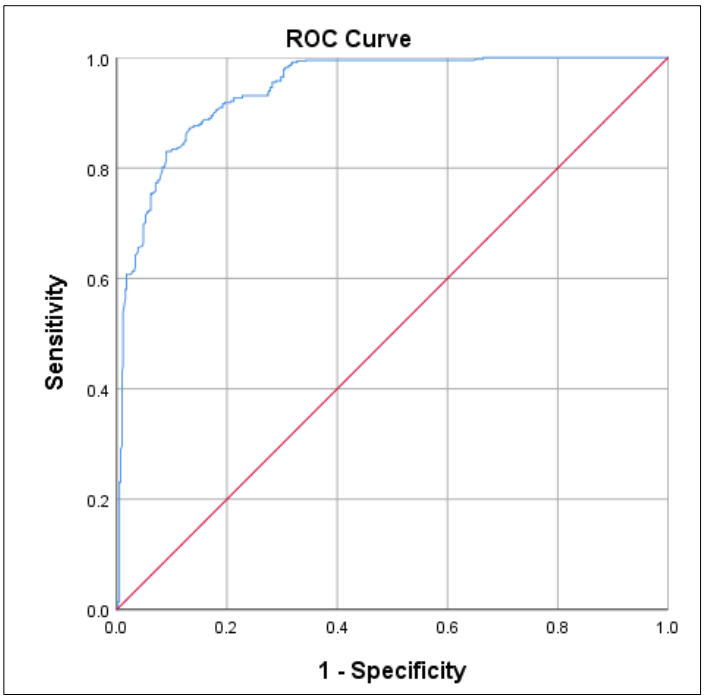
The tested patients who were belonged to Cohort II had significantly higher proportional distributions of Early and Late mortalities compared to Cohort I [623 (23.7%) and 1290 (49.1%) vs 17 (0.5%) and 203 (6.5%), respectively]. Oppositely, the Cohort I had significantly higher proportional distributions of Surviving rates < and ≥3 weeks compared to Cohort II [2049 (65.7%) and 849 (27.2%) vs 23 (0.9%) and 691 (26.3%), respectively], with a significant and strong positive correlation of 0.747±0.006, χ2=3344.913, p-value=0.000].

All the tested patients' analysis results and illustrations were clearly and fully presented in Table 1-3 and Figure 1-3.

Table 1 The Binary Logistic Regression (BLgR) analysis' results for our admitted critically ill patients in the Intensive Care Unit (ICU) at the King Hussein Medical Center (KHMC) between the Jan 2018 and Dec 2022 regarding the tested prognosticator; Norepinephrine Corrected Shock Index (NE.SI), against the probability of mortality

Tested predictors	**B±SEM**	**Wald**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**		**χ2(df)**	**VR**	**%Cases**
					Lower	**Upper**			
Mortality rate	= e (-6.986+0.516× NE.SI) /1+ e (-6.986+0.516× NE.SI)								
NE.SI (µg.bpm/min. mmHg)	0.516±0.015	1113.225	0.000	1.676	1.626	1.727	(8) 315.67	49.1%-65.8%	83.8%
Constant	-6.986±0.231	915.458	0.000	0.001					
The Binary Logistic Regression Test was conducted to explore the degree of correlations, the quality of the prediction, and how range of the total variations (VR) in the investigated dependent variable (the probability of mortality) and % of cases that can be explained by the Norepinephrine Corrected Shock Index (NE.SI). Also, this test was conducted to abstract the necessary coefficients to present the corresponding explored Binary Logistic Regression models.									

NE. SI



Positive OI (Non-Survivors)	2528
Negative OI (Survivors)	3217

AUC±SEM	p-Value
0.944±0.003 (95% CI; 0.938-0.949)	**0.000**

Figure 1 The Receiver Operating Characteristic (ROC) test was conducted to explore the area under the ROC curves (AUROCs) for the tested prognosticator; Norepinephrine Corrected Shock Index (NE.SI), against the probability of mortality, for our admitted critically ill patients in the Intensive Care Unit (ICU) at the King Hussein Medical Center (KHMC) between the Jan 2018 and Dec 2022

Table 2 The optimal cut-off points, TPRs, TNRs, FPRs, YIs, TNRs, PPVs, NPVs, NLRs, PLRs, and AIs for the tested prognosticator; Norepinephrine Corrected Shock Index (NE.SI), against the probability of mortality, for our admitted critically ill patients in the Intensive Care Unit (ICU) at the King Hussein Medical Center (KHMC) between the Jan 2018 and Dec 2022

Prognostic Indicator	**Cutoff**	**TPR**	**FPR**	**YI**	**TNR**	**PPV**	**NPV**	**NLR**	**PLR**	**AI**
NE. SI	14.84	87.2%	13.1%	74.03%	86.85%	83.90%	89.61%	14.76%	663.05%	87.00%

The sensitivity analysis was processed on a total of 5745 processed cases for the investigated prognosticator in the Jordanian investigated patients, against the higher probability of 28-day overall mortality (Positive state and assigned as 1) versus the lower probability (Negative state and assigned as 0) to explore the optimal cut-off points, sensitivities (TPRs), specificities (TNRs), positive and negative predictive values (PPVs and NPVs), positive and negative likelihoods ratios (PLRs and NLRs), and the Youden and accuracy indices (YIs and AIs).

2528 and 3217 cases were processed as positive actual states and as negative actual states, respectively. For our tested prognosticator, the higher values of the NE. SI indicate stronger evidences for the Positive State (Higher %Prob of mortality). While the lower values of the tested independent variable indicate stronger evidences for the Negative State (lower %Prob of mortality).

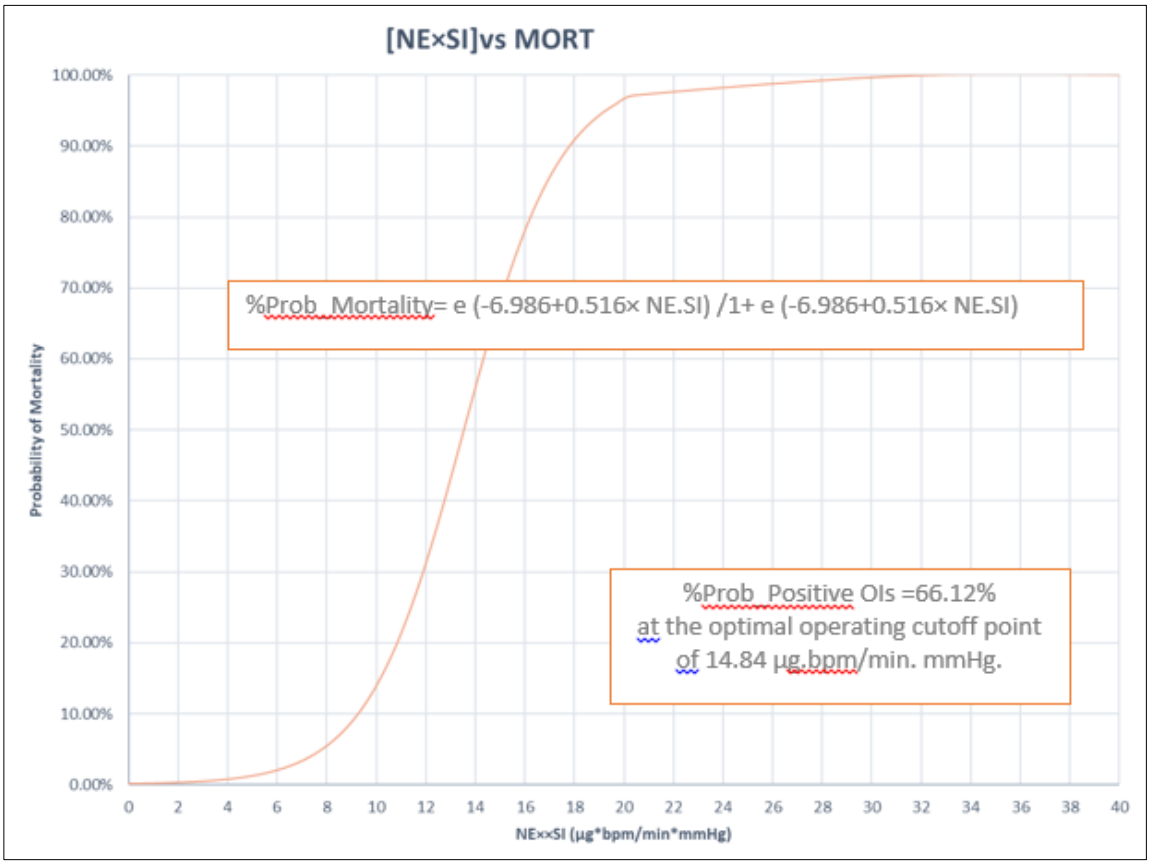


Figure 2 The Binary Logistic Regression (BLgR) analyses' illustration for the investigated; Norepinephrine Corrected Shock Index (NE.SI), against the probability of mortality, for our admitted critically ill patients in the Intensive Care Unit (ICU) at the King Hussein Medical Center (KHMC) between the Jan 2018 and Dec 2022. For our tested prognosticator, the higher values of the NE. SI indicate stronger evidences for the Positive State (Higher %Prob of mortality). While the lower values of the tested independent variable indicate stronger evidences for the Negative State (lower %Prob of mortality)

Table 3 Comparatively studied variables across Cohort I-II; Lower Product (NE×SI<14.835) [Cohort I] versus Higher Product (NE×SI≥14.835) [Cohort II], for the tested Jordanian critically ill patients who were admitted at King Hussein Medical Center between Jan 2018 and Dec 2022

	Lower Product (NE×SI<14.835) (3118, 54.27%)	**Higher Product (NE×SI≥14.835) (2627, 45.73%)**	**Total (5745, 100%)**	**OR**	**R ρ**	**χ^2 G-Test**	**p-Value**
Gender							
Female	961 (30.8%)	800 (30.5%)	1761 (30.7%)	1.017 (95% CI; 0.909-1.139)	0.004±0.013 0.004±0±.013	0.091 0.091	0.763 0.763
Male	2157 (69.2%)	1827 (69.5%)	3984 (69.3%)				
Female: Male	2.245: 1	2.284: 1	2.262: 1				
Age (Yrs)							
18-<30	17 (0.5%)	19 (0.7%)	36 (0.6%)	NA	- 0.173±0.013*	185.36	0.000

30-<40	94 (3.0%)	128 (4.9%)	222 (3.9%)		-0.177±0.013*	188.41	0.000
40-<50	628 (20.1%)	792 (30.1%)	1420 (24.7%)				
50-<60	1237 (39.7%)	1118 (42.6%)	2355 (41.0%)				
60-<70	823 (26.4%)	440 (16.7%)	1263 (22.0%)				
>=70	319 (10.2%)	130 (4.9%)	449 (7.8%)				
AACCI							
<8	2341 (75.1%)	2604 (99.1%)	4945 (86.1%)	0.027 (95% CI; 0.018-0.040)	-0.346±0.008*	687.692	0.000
≥8	777 (24.9%)	23 (0.9%)	800 (13.9%)		-0.346±0.008*	685.688	0.000
MORT							
Survivors	2794 (89.6%)	423 (16.1%)	3217 (56.0%)	44.932 (95% CI; 38.48-52.47)	0.738±0.009*	3126.454	0.000
Non-Survivors	324 (10.4%)	2204 (83.9%)	2528 (44.0%)		0.738±0.009*	3482.231	0.000
MORT.DIS							
Survivors (<3wks LOS)	2049 (65.7%)	23 (0.9%)	2072 (36.1%)	NA	0.747±0.006*	3344.913	0.000
Survivors (≥3wks LOS)	849 (27.2%)	691 (26.3%)	1540 (26.8%)		0.759±0.006*	4206.746	0.000
Late MORT (≥2wks LOS)	203 (6.5%)	1290 (49.1%)	1493 (26.0%)				
Early MORT (<2wks LOS)	17 (0.5%)	623 (23.7%)	640 (11.1%)				
NE rate (μg/min)							
0-3	585 (18.8%)	0 (0.0%)	585 (10.2%)	NA	0.812±0.005*	4194.655	0.000
3-6	1420 (45.5%)	0 (0.0%)	1420 (24.7%)		0.825±0.003*	5662.829	0.000
6-9	305 (9.8%)	0 (0.0%)	305 (5.3%)				
9-12	174 (5.6%)	8 (0.3%)	182 (3.2%)				
12-15	620 (19.9%)	877 (33.4%)	1497 (26.1%)				
15-18	14 (0.4%)	1721 (65.5%)	1735 (30.2%)				
>=18	0 (0.0%)	21 (0.8%)	21 (0.4%)				

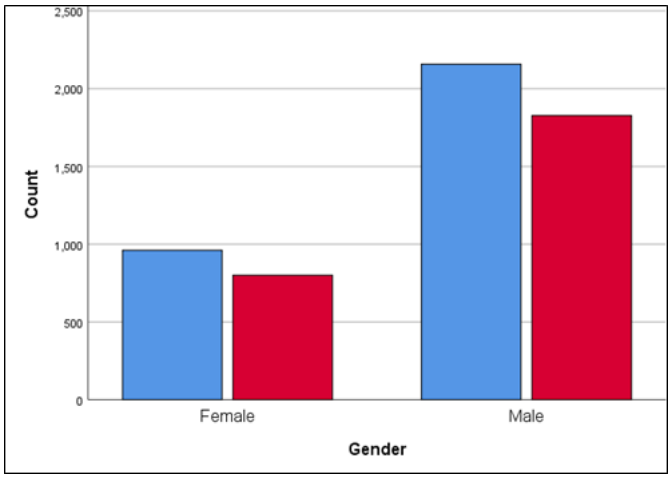
SI (bpm/mmHg)							
0.7-0.9	37 (1.2%)	0 (0.0%)	37 (0.6%)	NA	-0.077±0.012*	84.716	0.000
0.9-1.1	2588 (83.0%)	2362 (89.9%)	4950 (86.2%)		-0.069±0.013*	101.248	0.000
1.1-1.3	406 (13.0%)	242 (9.2%)	648 (11.3%)				
>=1.3	87 (2.8%)	23 (0.9%)	110 (1.9%)				
CrCl (ml/min)							
>40	2589 (83.0%)	554 (21.1%)	3143 (54.7%)	18.313 (95% CI; 16.04-20.91)	0.620±0.010*	2207.960	0.000
≤40	529 (17.0%)	2073 (78.9%)	2602 (45.3%)		0.620±0.010*	2367.208	0.000

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value.

The studied patients were dichotomously categorized into 2 comparatives' NE.SI products' cohorts; lower product's (NE. SI<14.835 µg.bpm/min. mmHg) cohort (Cohort I) versus higher product's (NE. SI≥14.835 µg.bpm/min. mmHg) cohort (Cohort II).

MORT: Overall mortality.
AACCI: Age-adjusted Charlson Co-Morbidity Index.
MORT.DIST: Mortality distributions.
LOS: Length of stay

NE: Norepinephrine infusion rate in ml/hr or µcg/min.
SI: Shock index.
CrCl: Creatinine clearance.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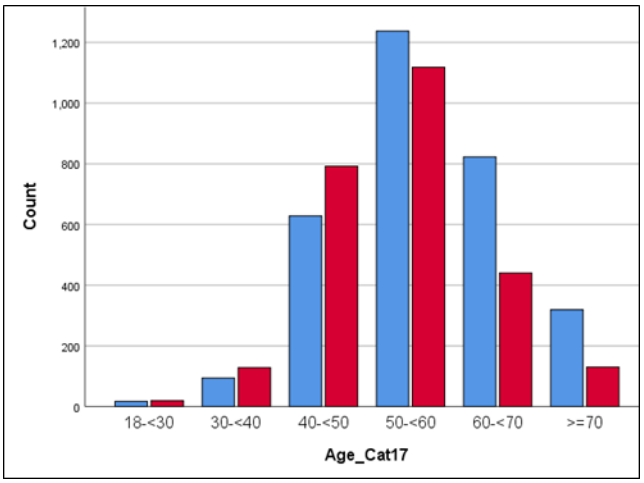
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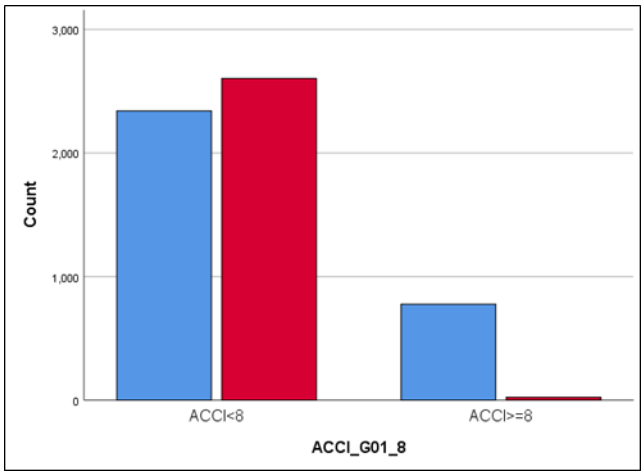
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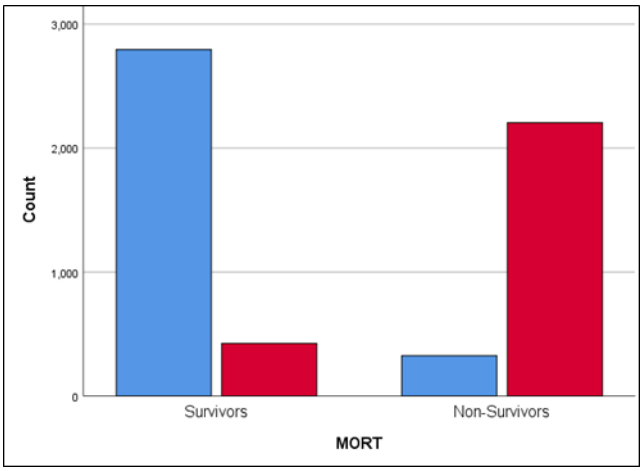
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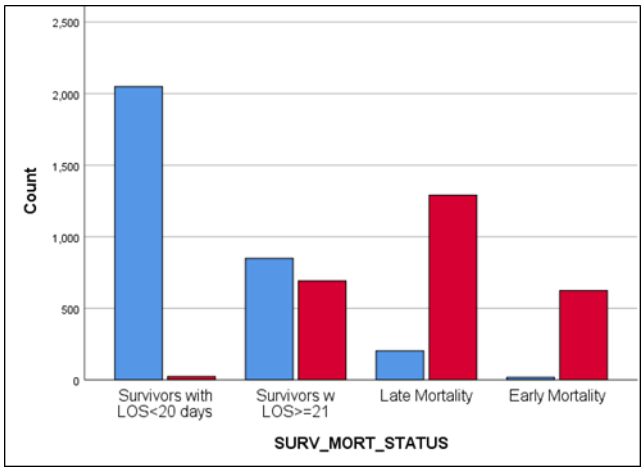
Survivors
Non-Survivors
MORT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Survivors w LOS>=21
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Early Mortality
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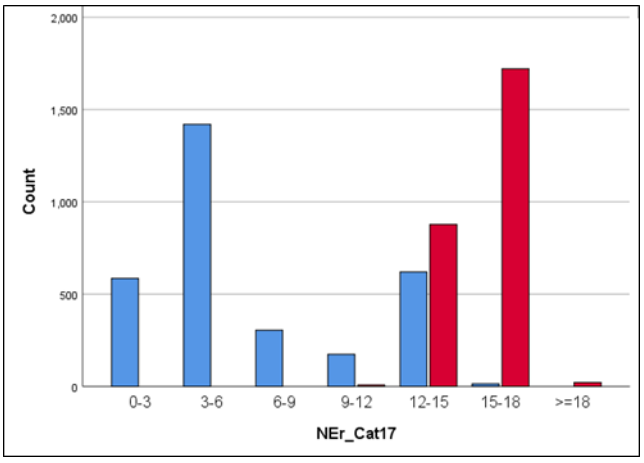
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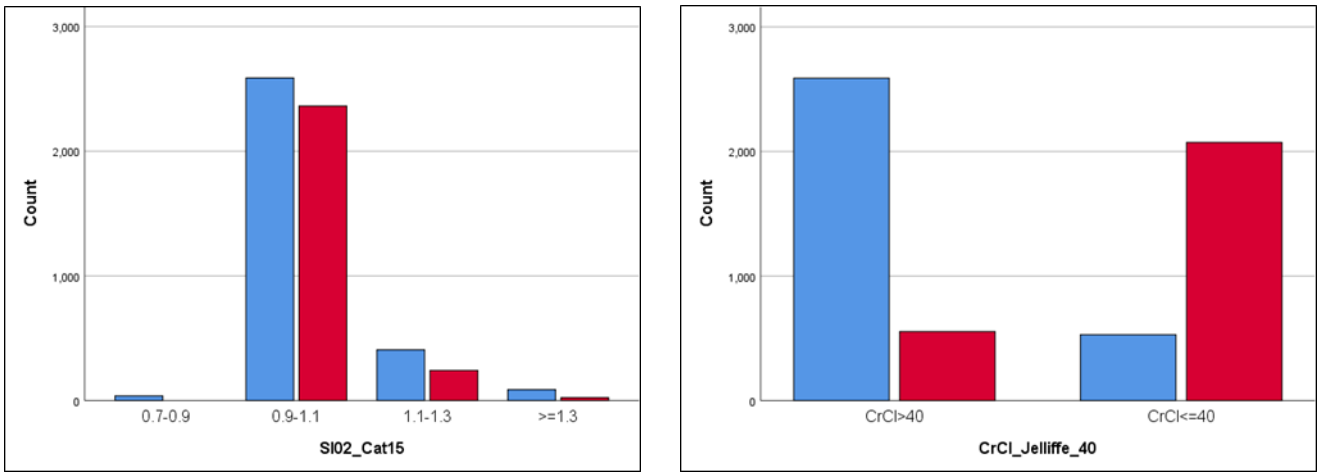

Figure 3 Bar charts' visualizations for the comparatively studied variables across Cohort I-II; Lower Product (NE×SI<14.835) [Cohort I] versus Higher Product (NE×SI≥14.835) [Cohort II], for the tested Jordanian critically ill patients who were admitted at King Hussein Medical Center between Jan 2018 and Dec 2022

4. Discussion

Our observational retrospective study was pursued for Jordanian admitted critically ill patients, including both gender and wide investigated age's ranges, at the King Hussein Medical Center.

An innovative proposed prognosticator was tested in this study to explore its sensitivity utilities in predicting the probability of being on the Non-Survivors' Cohort rather than being on the Survivors' Cohort. This explored mortality predictor integrates dual hemodynamic related independent variables; the Norepinephrine rate in mcg per min (NE) and the shock index (SI) in bpm per mmHg, in one composited tested variable.

A two contrarily cohorts were yielded after we opted the optimal operating point of the NE ×SI (14.835 μg.bpm/min. mmHg) as a dichotomized level. In this study, we compare between the comparative yielded cohorts; the lower composited prognosticator product (Cohort I) versus the higher composited prognosticator product (Cohort II). At this optimal product level, we explored that the probability of mortality for critically ill patients in our critical unit was 66.12%. Also, we determined at this abstracted optimal point that the sensitivity, specificity, accuracy index and positive/negative predictive values were 87.2%, 86.85%, 87.00%, 83.90%, and 89.61%, respectively.

5. Conclusion

Our results revealed that our proposed an innovative hemodynamic composited product had a reasonable constructed area under the curve with an interesting sensitivity index for prognosticating the admitted critically ill patients' mortality rate. This study is limited by its retrospective design, single-center, and relatively small sample size.

Compliance with ethical standards

Acknowledgement

Our appreciation goes to staff of the department of King Hussein Medical Center for their enormous assistance and advice.

Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

Statement of ethical approval

There is no animal/human subject involvement in this manuscript.

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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