

Vital signs monitoring critically ill patients in traditional triage: room for improvement and innovation

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Abstract: **Objective:** In traditional triage, there is often a challenge in accurately assessing the severity of a patient's condition, which can result in under-triage or over-triage. The purpose of this study is to compare traditional and innovative vital signs in predicting possible mortality in critically ill patients.

Methods: This is a cross-sectional study conducted over a three-month period. Patients presenting emergency severity index (ESI) level 1 and 2 triage were divided into two groups: those with and without mortality. Subsequently, the role of traditional triage vital signs [blood pressure, heart rate, oxygen saturation (SpO₂), mean arterial pressure (MAP), pulse pressure (PP)] was compared with that of innovative vital signs [shock index (SI), reverse shock index (RSI), modified shock index (MSI), age-shock index (ASI)] in predicting mortality in two groups.

Results: A total of 360 patients were included in the study. A statistically significant association was observed between all innovative and traditional vital signs (with the exception of heart rate) and mortality. In logistic regression, the univariate model revealed a significant association between age, triage level, innovative and traditional vital signs with the occurrence of mortality. In the multivariate model, only MAP, PP, SI, RSI×SpO₂, and ASI were found to have a significant association with mortality.

Conclusion: The combination of innovative and traditional vital signs, including MAP, PP, SI, MSI, RSI×SpO₂, and ASI in triage may be capable of predicting critically ill patients with a higher probability of mortality.

Keywords: Mortality; Oxygen Saturation; Triage; Vital Signs

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1. Introduction

Upon arrival, patients referred to the emergency department (ED) undergo evaluation in hospital triage, where one of the most widely employed triage systems is the Emergency severity index (ESI). The ESI employs an algorithm to categorize patients from level I, the most critically ill, to level V, the least critically ill and resource intensive. The assignment of ESI is determined by a combination of assessments based on initial vital signs and triage nurse judgment. Consequently, vital signs measurement constitutes a pivotal method for assessing the severity of critical conditions, thereby facilitating the prioritization of patient care (1,2). However, the accuracy of these vital signs can sometimes present a challenge in diagnosing the vital conditions of patients, leading to situations of under-triage or over-triage that can be highly threatening for the patients (3-6). It may be necessary to modify the assessment of patients with newer and more accurate vital signs, particularly in cases of critical illness resulting in cardiac arrest (7-9).

Recent studies have underscored the necessity for further research on the integration of shock indices in clinical practice and their impact on patient outcomes. Investigating the po-

tential improvements in diagnostic accuracy and patient care by incorporating these indices into routine ED protocols is crucial (10,11).

One such innovative vital sign is the shock index (SI), which is derived from the ratio of heart rate to systolic blood pressure. The shock index can predict the outcome of patients in a multitude of scenarios (12,13). This index, which is the ratio of two traditional vital signs, has demonstrated superior prognostic capabilities compared with traditional vital signs in several studies (14-16). Additionally, the reverse shock index (RSI), defined as the inverse of SI, has exhibited even more predictive accuracy in some studies. This index has been investigated across a multitude of conditions, demonstrating superior prognostic capability compared to traditional vital signs (17-20). The modified shock index (MSI), which is the ratio of heart rate to mean arterial pressure (MAP), has also shown effectiveness in expediting patient diagnosis, and its effectiveness has been corroborated (21,22). In elderly patients, the prognostic value of traditional vital signs can be uncertain. However, the age-shock index (ASI), which incorporates age into the SI calculation, may provide a more accurate prediction of critical conditions in elderly pa-

tients. Given the rapid deterioration these patients can experience, an accurate prognostic tool is essential (23,24).

Therefore, integrating innovative vital signs, such as the SI, RSI, MSI, and Age-SI, has the potential to enhance the accuracy of patient prognosis in emergency settings. These indices, through their unique calculations, offer a promising avenue for improving the stratification and prioritization of patient care. Future research and validation of these indices across diverse patient populations will be crucial in solidifying their role in clinical practice (25,26).

It may be beneficial to modify triage vital signs to expedite the identification of critically ill patients, thereby reducing the likelihood of unfavorable outcomes from misdiagnosis. The objective of this study is to focus on comparing traditional [blood pressure, heart rate, oxygen saturation (SpO₂), mean arterial pressure (MAP), pulse pressure (PP)] and innovative vital signs (SI, RSI, MSI, and ASI) as quantitative physiological measures in facilitating the earlier prediction of mortality in critically ill patients at ESI level 1 and 2 triage presenting at the ED. This study aims to address this gap by comparing the performance of innovative vital signs with traditional vital signs in predicting mortality in critically ill patients. This will help determine whether integrating these innovative indices can enhance the accuracy and efficiency of triage, ultimately improving patient outcomes.

2. Methods

2.1. Study design and setting

This is a retrospective, descriptive-analytical cross-sectional study conducted on critically ill patients referred to the emergency department (ED) of Afzalipour academic Hospital, the internal medicine Center, located in the southeast of Iran, Kerman city, over a three-month period from May 1 to August 1, 2024. The hospital has an average annual hospitalization rate of over 12,000 patients.

2.2. Participants and data collection

Following the acquisition of the ethical code, data collection commenced with an examination of the relevant case files. Given the observational nature of the study, obtaining informed consent from patients was not required. However, all patient names and file information were kept confidential by the research team, and the principle of confidentiality and data protection was upheld throughout the research process. The study population included patients who had been triaged as emergency severity index (ESI) level 1 or 2 who were aged 18 years or older over a three-month period. The study excluded individuals under the age of 18, those requiring ESI levels 3, 4, and 5, patients presenting with traumatic injuries, pregnant women, and patients with incomplete or missing data (Figure 1). The sampling method involved consecutive sampling to ensure comprehensive inclusion of patients meeting the ESI criteria during the study period. The sample size was deemed adequate to provide sufficient sta-

tistical power for detecting significant associations between traditional and innovative vital signs and mortality, based on the expected prevalence of such cases in the target population.

The requisite information was obtained from the patients' medical records via a designed checklist that contained demographic data and traditional vital signs upon their arrival at the emergency department. The variables included age, gender, and traditional vital signs [blood pressure, heart rate, oxygen saturation (SpO₂), mean arterial pressure (MAP), pulse pressure (PP)] from the initial assessment. Innovative vital signs (SI, RSI, MSI, and ASI) were also calculated and recorded. After a review of the files, the information from ESI level 1 and 2 patients based on their clinical conditions was documented in the checklist. Subsequently, the patients were classified into two groups: those who experienced mortality and those who did not. Subsequently, the variables were compared between the two groups.

2.3. Sample size

Based on prior studies (14), we assumed a minimum odds ratio (OR) of 2.0 for the association between key predictors (e.g., shock index) and mortality, with an expected mortality prevalence of approximately 20–30% in ESI level 1 and 2 patients in our setting. Using a two-sided alpha of 0.05 and power of 80%, we estimated a required sample size of approximately 300–350 patients for logistic regression analysis, accounting for multiple predictors (up to 10 variables, requiring 10–20 events per variable). To accommodate potential data loss due to incomplete records (estimated at 5–10%), we aimed to include at least 350 patients.

Using a sample size calculator for logistic regression (e.g., G*Power or online tools), the formula for a binary outcome is:

$$n = ((Z_{1-\alpha/2} + Z_{1-\beta})^2 (1 + 1/R_2)) / P(1-p) \ln(OR)^2$$

$$Z_{1-\alpha/2} = 1.96 \quad (\alpha = 0.05)$$

$$Z_{1-\beta} = 0.84 \quad (80\% \text{ power})$$

$$p = 0.25 \quad (\text{midpoint of } 20\text{--}30\% \text{ prevalence})$$

$$OR = 2.0 \quad (\ln(2) \approx 0.693)$$

$$R_2 = 0.2 \quad (\text{assumed correlation among predictors})$$

This yields ~300 patients, adjusted to 350 for attrition.

2.4. Outcome

The objective of this study is to conduct a comparative analysis of the predictive value of traditional vital signs in triage with that of innovative vital signs, which are derived from traditional vital signs through a formulaic process. The aim is to ascertain whether innovative vital signs can predict mortality in critically ill patients at ESI levels 1 and 2 with higher accuracy to identify patients with a high probability of developing cardiac arrest. It is conceivable that the prediction of these critical patients will facilitate the prevention of more serious complications. Furthermore, it may be feasible to identify a superior alternative to the existing vital signs. Patients were followed from triage in the ED until the occurrence of the pri-

mary outcome (in-hospital mortality or survival to discharge) during their hospitalization.

2.5. Ethical considerations

This study was approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (IR.KMU.AH.REC.1403.010).

2.6. Statistical analysis

The data were analyzed using the statistical software package SPSS, version 27.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables were expressed as frequencies (percentages). For data that follows a normal distribution, the mean \pm SD (standard deviation) is presented. For data that does not follow a normal distribution, the median and IQR (interquartile range) are presented. A P-value of less than 0.05 was considered statistically significant. Then, univariate regression analysis was employed to ascertain the strength of the relationship between the variables and the outcome of the study (mortality). The strength of the relationship between the variables and the patient outcome was subsequently assessed by calculating odds ratios (OR) and confidence intervals (CIs). Regarding collinearity problems in the multivariate regression model, variables that had a P-value less than 0.2 and met the conditions for entering the multivariate model were selected. Then, according to the variance inflation factors (VIF) index, only one of the variables that were collinear with each other was entered into the model. For example, among the variables SI \times Age/SPO2 and SI, age, and SPO2, the multiple model was fitted once with only the SI \times age/SPO2 variable with variables that were not collinear with this variable, and the multiple model was fitted once with the SPO2 variable with variables that were not collinear with this variable, and in each time the model was fitted, the coefficient related to the variable that was collinear with the others was reported. Subsequently, the variables that demonstrated a statistically significant relationship were incorporated into the multivariate regression analysis using the backward method. Additionally, the characteristics of the intensity of the relationship were examined using the odds ratio within a 95% confidence interval (95% CI).

3. Results

A total of 3,218 patients were examined over a three-month period, and 360 patients with ESI level 1 and 2 critical conditions were ultimately included in the study, 55% of whom were male. Mortality was observed in 56.1% of patients classified as ESI level 1. A statistically significant correlation was observed between triage level and the occurrence of mortality ($P=0.002$) (Table 1). Subsequently, an investigation was conducted to ascertain the relationship between quantitative variables and the occurrence of mortality in patients. A statistically significant association was observed between all innovative and traditional vital signs (with the exception of heart rate) and mortality (Table 2). A logistic regression

was employed to ascertain the strength of the correlation between variables and mortality. In the univariate regression analysis, a significant relationship was observed between age, triage level, and both innovative and traditional vital signs and the occurrence of mortality. However, this relationship was not significant for the gender variable in patients. At the triage level, the odds ratio was 5.56, indicating that the probability of mortality in individuals with a triage level is approximately fivefold that of the general population. Moreover, the ratio exceeded 12 and 5 times that value for the SI and MSI, respectively. Subsequently, the significant variables were entered into the multivariate regression analysis using the backward method. In this model, the variables of mean arterial pressure, pulse pressure, SI, RSI, MSI, and ASI exhibited a statistically significant correlation with the probability of mortality. Among the variables that were significant in the multivariate model, the strongest relationship with the outcome of the patients was related to the SI, which demonstrated that individuals with a higher SI were more than three times more likely to develop mortality than those with lower shock index (Table 3).

4. Discussion

The ability to rapidly identify patients who are critically ill in the emergency department triage area is of paramount importance. It may therefore be beneficial to consider modifying or incorporating innovative vital signs in the triage process, with a view to facilitating more accurate diagnosis of these patients. The findings of this study indicate that MAP, PP, SI, RSI, MSI, and ASI may prove to be more effective in the prediction of mortality in critically ill patients. While these indices have been studied individually, this research highlights their combined predictive power and innovative application in a triage setting. This research underscores the importance of integrating innovative vital signs with computer-aided tools to facilitate precise triage in high-volume emergency departments.

In the majority of cases, critically ill patients present with unstable hemodynamics, which can affect the perfusion of the body's organs and potentially cause damage to vital organs. One of the factors that indicate an unstable state of hemodynamics and can predict the proper perfusion of organs is MAP. Hou et al. demonstrated in their study that alterations in MAP in critically ill patients can forecast their hospital mortality. Individuals with higher and lower MAP at the time of admission to the ICU exhibited higher mortality rates (27). The MAP can predict the outcome of critically ill patients with higher accuracy than BP alone. A lower MAP value is indicative of a poorer prognosis for the patient (28). Consequently, maintaining the MAP within an optimal range can diminish the mortality rate of critically ill patients (29). This investigation demonstrated that the MAP at the time of hospital admission for triage ESI level 1 and 2 patients can predict the likelihood of mortality in these patients. As Yangchen et al. have previously demonstrated, a reduction

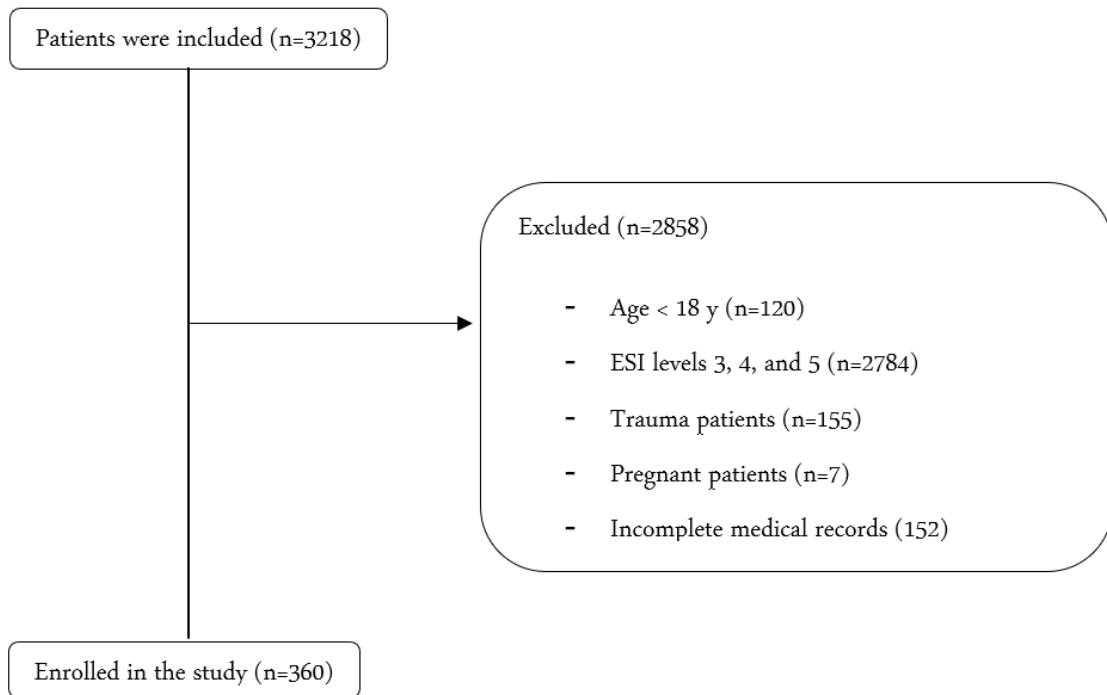


Figure 1 Flow chart showing enrollment of patients

Table 1 Association between qualitative variables with mortality

Variables	Mortality		P-value
	Yes n = 180	No n = 180	
Sex			0.83
Male	98 (54.4%)	100 (55.6%)	
Female	82 (45.6%)	80 (44.4%)	
ESI Triage			0.002
Level 1	101 (56.1%)	85 (44.4%)	
Level 2	79 (43.9%)	95 (52.8%)	

Data are presented as frequency (%); ESI: Emergency severity index

Table 2 Association between quantitative variables with mortality

Variables	Mortality mean ±SD, median [IQR]		P-value	
	Yes	No		
Age	60.34 ±22.09, 65 [30]	43.58 ±19.24, 44[32]	<0.0001	
Traditional Vital Signs	SBP	85.69 ±12.21, 90 [10]	125.63 ±26.01, 120 [30]	<0.0001
	DBP	55.75 ±9.81, 57.50 [10]	77.31 ±17.16, 77 [23]	<0.0001
	HR	97.69 ±27.17, 100 [41]	100.51 ±55.08, 96 [25]	0.72
	SPO2	80.34 ±14.74, 84 [20]	95.31 ±90.48, 92 [16]	<0.0001
	MAP	65.30±9.25, 66.66 [10]	93.95±18.53, 93.33 [24.33]	<0.0001
	PP	29.99±9.66, 30 [12]	48.65±18.66, 45 [25]	<0.0001
	SI	1.15±0.35, 1.14 [0.48]	0.83±0.64, 0.75 [0.29]	<0.0001
Innovative Vital Signs	SI/SPO2	0.014±0.005, 0.013 [0.01]	0.009±0.004, 0.008 [0.001]	<0.0001
	SI× Age/SPO2	0.93±0.43, 0.88[0.57]	0.42±0.28, 0.33 [0.35]	<0.0001
	RSI	0.96±0.39, 0.87[0.40]	1.37±0.45, 1.33 [0.47]	<0.0001
	RSI×SPO2	76.96±34.86, 72[37.41]	128.90±115.51, 119.56 [46.60]	<0.0001
	RSI×SPO2/Age	1.77±4.45, 1.12[0.75]	3.55±2.78, 2.96 [2.91]	<0.0001
	MSI	1.50±0.46, 1.46[0.63]	1.12±0.91, 1[0.33]	<0.0001
ASI	72.28±30.69, 68.17[36.09]	36.38±24.00, 31.96[25.14]	<0.0001	

Data are presented as mean±standard deviation, median (IQR: interquartile range); P value significant at < 0.05; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; SPO2: Oxygen saturation; MAP: Mean arterial pressure; PP: Pulse pressure; SI: Shock index; RSI: Reverse shock index; MSI: Modified shock index; ASI: Age-shock index

Table 3 Univariate/multivariate regression analysis of variables according to their association with mortality

	Variables	Univariate logistic regression Odds ratio (95% CI)	P-value	Multivariate logistic regression Odds ratio (95% CI)	P-value
Age	1.03 (1.02-1.05)	<0.0001	-	-	-
Sex	0.95 (0.63-1.44)	0.83	-	-	-
ESI Triage					
Level 1	5.56 (2.00-15.44)	0.001	-	-	-
Level 2	3.80 (1.36-10.58)	0.01	-	-	-
Traditional Vital Signs					
SBP	1.17 (1.11-1.54)	0.001	0.001	-	-
DBP	1.44 (1.22-1.90)	0.001	0.001	-	-
SPO2	1.02 (0.88-1.43)	0.002	0.002	-	-
MAP	0.83 (0.80-0.87)	<0.0001	0.73 (0.66-0.81)	<0.0001	<0.0001
PP	0.88 (0.85-0.91)	<0.0001	0.91 (0.88-0.95)	<0.0001	<0.0001
SI	12.62 (5.98-26.63)	<0.0001	3.01 (1.42-8.59)	0.005	0.005
Innovative Vital Signs					
SI/SPO2	7.26 (4.06-12.99)	<0.0001	-	-	-
SI/SPO2	7.26 (4.06-12.99)	<0.0001	-	-	-
SI× Age/SPO2	10.48 (6.42-17.10)	<0.0001	-	-	-
RSI	0.05 (0.02-0.12)	<0.0001	-	-	-
RSI×SPO2	0.97 (0.96-0.97)	<0.0001	0.95 (0.91-0.99)	0.02	0.02
RSI×SPO2/Age	0.66 (0.57-0.77)	<0.0001	-	-	-
MSI	5.56 (3.18-9.73)	<0.0001	0.39 (0.16-0.96)	0.04	0.04
ASI	1.04 (1.03-1.05)	<0.0001	1.02 (1.00-1.03)	0.001	0.001

OR: Odds ratio; CI: Confidence interval; P value significant at < 0.05; ESI: Emergency severity index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SPO2: Oxygen saturation; MAP: Mean arterial pressure; PP: Pulse pressure; SI: Shock index; RSI: Reverse shock index; MSI: Modified shock index; ASI: Age-shock index.

in MAP upon arrival can indicate the highest risk of mortality in patients (30).

The prediction of vital conditions in patients by measuring PP has been demonstrated to be of some utility (31). In clinical practice, PP is recognized as a valuable indicator of vascular stiffness. Ferreira et al. have demonstrated that PP is an effective predictor of hospital mortality in patients (32). In their study, Lempiäinen et al. highlighted the role of PP in long-term mortality prediction in heart patients (33). Thus, an elevated pulse pressure is associated with an increased risk of mortality in patients (34). Similarly, this study corroborates the prognostic role of PP in critically ill patients, as previously demonstrated by Gavish et al. (35).

Another index that can predict hemodynamic disorder in critically ill patients is the SI. A higher SI indicates a potential state of shock, where the body is struggling to maintain adequate perfusion to vital organs. SI reflects the balance between cardiac output and systemic vascular resistance. An elevated SI suggests that the heart is compensating for reduced perfusion by increasing heart rate, which may not be sufficient to maintain adequate blood pressure. SI can be an early indicator of various types of shock, including hypovolemic, cardiogenic, and septic shock. It helps in identifying patients who may require immediate intervention to prevent progression to severe shock (36,37). The veracity of this assertion has been corroborated by several meta-analyses conducted in diverse clinical contexts. In a similar vein, Alsagaff et al. have corroborated its capacity to predict mortality in patients infected with the SARS-CoV-2 virus (38). Middleton et al. have discussed the role of the SI in predicting the outcome of sepsis patients (39). Carsetti et al. have demonstrated the pre-

dictive value of this index in the context of the necessity for massive blood transfusion in trauma patients (40). Similarly, this study corroborates the utility of the SI in predicting mortality in critically ill patients at ESI levels 1 and 2. These findings indicate that patients with a high SI have a threefold increased probability of experiencing mortality. In this study, we investigated the ratio of SI/SpO2 and SI×age/SpO2 in the prediction of mortality in patients. Although these indices were significant in the univariate model, they were not in the multivariate model. This may be due to the significant statistical correlation of other variables with the outcome in this model.

The RSI has been demonstrated to possess predictive capabilities in a multitude of clinical scenarios. Among these, its application in conjunction with the Glasgow coma scale (GCS) has been particularly instrumental in forecasting the mortality of trauma patients (41-44). Moreover, Po-Chen Lin et al. demonstrated that this index offers superior predictive capabilities compared to other indices, including the SI, in forecasting the prognosis of patients with traumatic head injury (45). In the context of sepsis, it may serve as an effective predictive tool for the initiation of resuscitation (46). It may be the case that this index is of higher value when considered in conjunction with other parameters. In this study, this index was employed in conjunction with oxygen saturation (SpO2) to predict mortality in critically ill patients. These findings indicate that this index, when utilized alone or as RSI×SpO2/age, is an ineffective predictor. Conversely, when considered alongside oxygen saturation (RSI×SpO2), it may offer a more pronounced prognostic capacity for the early detection of mortality. In a separate study, Hsieh et al.

demonstrated the efficacy of SI×SpO₂ in predicting mortality and the necessity for hospitalization in the ICU. It was highlighted that the combination of these two indices can provide a more effective predictive role, given the role of hypoxia in increasing mortality rates among patients (47).

MSI is a prognostic and predictive marker in various diseases. This index has been demonstrated to predict hospital admission and mortality in patients referred to the emergency department, as observed by Hamade et al. (48). In their study, Sade et al. highlighted the value of this index in elderly individuals aged 65 and above. They demonstrated that elevated scores on this index are associated with an increased mortality rate and prolonged hospitalization in this patient population (49). Furthermore, this index can assist in prognosticating the outcomes of critically ill patients with acute myocardial infarction (50). Moreover, the potential utility of this index in the screening of sepsis patients has been previously discussed (51). In patients with traumatic injuries, this index has been demonstrated to serve as a predictor of mortality and the necessity for blood transfusion (52). The findings of this study indicate that this index has the significant predictive capacity with regard to mortality in critically ill patients. As age increases, so too does the risk of mortality and morbidity in patients. It may therefore be posited that the ASI has the potential to predict the prognosis of the patient. ASI was initially developed to improve prognostication in elderly patients, where age-related physiological changes can obscure traditional vital sign interpretations (23,24). However, ASI's formula inherently treats age as a continuous modifier, making it adaptable for broader adult populations (≥18 years) rather than being strictly limited to the elderly. This allows ASI to account for age-related risk gradients across the lifespan, enhancing its utility in heterogeneous ED settings, where it serves as a simple bedside tool independent of age-specific thresholds. Additional research has used ASI across adult age ranges, highlighting its role in identifying high-risk patients regardless of elderly status, as age integration improves sensitivity for age-dependent hemodynamic instability (53,54). In a study conducted by Demir et al., the prognostic value of the age index in patients with acute stroke was investigated. The findings indicated that the ASI may serve as a predictor of hospital mortality in this patient population (55). Similarly, Costa and colleagues demonstrated that this index plays a comparable role in cardiac patients (56). Moreover, Bondaryan et al. demonstrated that this index can be utilized to identify high-risk patients with decompensated acute heart failure, thus further substantiating its prognostic role (57). Furthermore, this study corroborates the prognostic value of the ASI in predicting the risk of mortality in critically ill patients.

In light of the pivotal role of innovative vital signs in the prediction of critical conditions, it may be an opportune time to consider their implementation in the context of hospital triage. However, a challenge remains in the calculation of these innovative vital signs, particularly in emergency de-

partments with high patient volumes. In light of the predictive value of these innovative vital signs with intricate calculations, it is imperative to employ computer-aided tools to facilitate more precise triage for patients (58). The integration of these advanced vital signs into a contemporary triage system, leveraging computer technology in conjunction with effective human resources, holds promise for expediting and enhancing the accuracy of diagnoses for critically ill patients. This approach has the potential to mitigate issues such as under-triage and over-triage.

5. Limitations

The present study was subject to several limitations. The single-center design of the study was a salient limitation; however, this constraint was mitigated by the fact that the hospital designated as the provincial referral hospital and consequently admitted a high volume of patients. In examining the data from the archive, we encountered issues due to the presence of defects in the files, which we were unable to incorporate as a variable in the study due to the extensive amount of missing data pertaining to body temperature and respiratory rate in the triage. It should be noted that the retrospective nature of this study is also a limitation.

6. Conclusion

The integration of innovative and traditional vital signs, including MAP, PP, SI, RSI×SpO₂, MSI, and ASI, in triage, has the potential to enhance the accuracy of predicting critically ill patients with a higher probability of mortality. It is plausible that the implementation of innovative vital signs in ED triage may prove advantageous in this context. Incorporating these innovative vital signs into triage protocols can significantly improve the early identification of critically ill patients. Future studies can evaluate the impact of such changes on clinical practice and patient outcomes through the implementation of computer-aided tools and new modern triage systems.

7. Declarations

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7.2. Authors' contribution

Study concept, design and supervision: M.T, A.S., MR.K. Acquisition of data: MR.K. Analysis and interpretation of data: M.M, M.T. Drafting of the manuscript, technical and material support: M.T, A.S., MR.K., M.M.

7.3. Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of

this article.

7.4. Funding

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