Medicina Intensiva 48 (2024) 309–316

medicina intensiva

http://www.medintensiva.org/

ORIGINAL ARTICLE

Shock Index and Physiological Stress Index for reestratifying patients with intermediate-high risk pulmonary embolism

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Received 3 July 2023; accepted 23 October 2023

KEYWORDS
Pulmonary embolism;
Shock Index;
Physiological Stress Index;
Reperfusion treatment;
Risk assessment

Abstract
Objective: Study and Evaluation of Two Scores: Shock Index (SI) and Physiological Stress Index (PSI) as discriminators for proactive treatment (reperfusion before decompensated shock) in a population of intermediate-high risk pulmonary embolism (PE).
Design: Using a database from a retrospective cohort with clinical variables and the outcome variable of ''proactive treatment'', a comparison of the populations was conducted. Optimal cut-off for ''proactive treatment'' points were obtained according to the SI and PSI. Comparisons were carried out based on the cut-off points of both indices.
Setting: Patients admitted to a mixed ICU for PE.
Participants: Patients >18 years old admitted to the ICU with intermediate-high risk PE recruited from January 2015 to October 2022.
Interventions: None.
Main variables of interest: Population comparison and metrics regarding predictive capacity when determining proactive treatment.
Results: SI and PSI independently have a substandard predictive capacity for discriminating patients who may benefit from an early reperfusion therapy. However, their combined use improves detection of sicker intermediate-high risk PE patients (Sensitivity = 0.66) in whom an early reperfusion therapy may improve outcomes (Specificity = 0.9).
Conclusions: The use of the SI and PSI in patients with intermediate-high risk PE could be useful for selecting patients who would benefit from proactive treatment.

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https://doi.org/10.1016/j.medin.2023.10.011
0210-5691/

PALABRAS CLAVE
Embolia de pulmón;
Shock Index;
Physiological Stress Index;
Tratamiento reperfusion;
Evaluación del riesgo

Índice de shock e índice de stress fisiológico para la re-estratificación de pacientes con tromboembolismo pulmonar de riesgo intermedio-alto

Resumen:
Objetivo: Valoración de dos scores: Shock Index (SI) y Physiological Stress Index (PSI) como discriminantes de haber recibido tratamiento proactivo (Fibrinolisis o trombectomía) en una población de tromboembolismo pulmonar (TEP) de riesgo intermedio – alto.
Diseño: Sobre una base de datos de una cohorte retrospectiva con variables clínicas se estudió la variable resultado ''tratamiento proactivo'' en función de los scores SI y PSI. Se obtuvieron los puntos de corte óptimos de haber recibido tratamiento proactivo según el SI y el PSI. Se realizaron comparaciones en función de los puntos de corte de ambos índices.
Ámbito: Pacientes que son ingresados en UCI mixta por TEP.
Pacientes: Pacientes >18 años ingresados en UCI por TEP de riesgo intermedio-alto. Desde enero de 2015 hasta octubre de 2022.
Intervenciones: Ninguna.
Variables de interés principales: Comparación poblacional y métricas en relación a la capacidad predictiva de los scores cuando se determina tratamiento proactivo.
Resultados: Los predictores SI y PSI tienen una capacidad predictiva regular para discriminar los pacientes sometidos a tratamientos proactivos de reperfusión. Su uso combinado mejoran la capacidad de detección de los pacientes más graves (Sensibilidad = 0.66) y que podrían requerir tratamiento (Especificidad = 0.9).
Conclusiones: El uso del SI y del PSI en los pacientes con TEP de riesgo intermedio-alto puede ser útil para seleccionar a pacientes que se beneficiarían de tratamiento proactivo.

Introduction

Pulmonary embolism (PE) is one of the main causes of hospital mortality.[1] Therefore, timely identification, stratification and treatment is mandatory.[2] The prognosis of patients with shock depends on early detection and treatment; therefore, recognizing patients in the initial stages of shock (i.e., compensated shock) is pivotal. The detection of compensated shock in patients with PE may aid in re-stratifying patients which may benefit with reperfusion therapies. Recent publications ''advocate'' for a more ''aggressive'' role when treating intermediate-high risk PE patients, posing an added management difficulty to this challenging group.[3,4]

Patients presenting with both RV dysfunction (on echocardiography or computed tomography) and elevated cardiac biomarkers levels are classified into the intermediate-high-risk category and according to guidelines. They are treated with anticoagulation, and if they deteriorate, with reperfusion therapy.[5]

Adjusting PE treatment is difficult, especially when patients are older or have multiple comorbidities. The use of different reperfusion strategies, such as systemic thrombolysis, extracorporeal support, and mechanical thrombectomy, is becoming standard for these complex cases.[6,7] A simple clinical predictor to rapidly identify early-stage shock in PE patients could be valuable, enabling prompt consideration of various reperfusion options before physiological decline occurs.

To aid in identifying sicker intermediate-high risk PE patients, we considered that the Shock Index (SI) and the Physiological Stress Index (PSI) may be useful. The shock index (SI) is equal to the heart rate (HR) divided by the systolic blood pressure (HR/SBP). This is a well-known parameter used in several scenarios, including PE.[8–12] The PSI is novel, equal to the (oxygen saturation/inspired oxygen fraction) divided by the Shock Index [SaFi/SI]. This index can assess respiratory function, as well as shock state. As PE is a cardiopulmonary condition, we hypothesized that it may be useful in patients with PE. Both indices are simple and easy to implement in clinical practice.

This study aims to identify the optimal cut-off points for SI and PSI to predict the need for 'proactive reperfusion' in intermediate-high risk PE patients.

'Proactive treatment' refers to reperfusion methods, such as fibrinolysis or mechanical thrombectomy, applied proactively (before decompensated shock) rather than reactively (rescue treatment). The focus is on patients with compensated shock.

Additionally, populations differentiated by these cut-off points are analyzed.

Methods

This is a retrospective study (since 2018 the patients were included consecutively), conducted in a tertiary hospital that comprises patients admitted to a mixed Intensive Care Unit (ICU) with PE as main diagnosis (n = 356), 115 of whom were categorized as intermediate-high risk meeting the inclusion criteria: >18 years-old, admitted in the ICU from January 2015 to October 2022. The registry was approved by

the Institutional Review Board. Exclusion criteria: patients with cardiopulmonary arrest (these indices cannot be calculated in them), patients with intermediate-low risk (they do not present hemodynamic or physiological deterioration) or high risk (as they already in a decomcompensated shock state).

Patient management was carried out by intensivists. The assessment, stratification and treatment was carried out according to the recommendations of the different clinical guidelines over time[13] and an adapted hospital protocol.

These scores are not included in either the hospital protocol or clinical guidelines for assessing patients with PE.

Demographic variables were collected such as age and sex, prognostic scores (SAPS3), time of symptom presentation before hospital admission, ICU and hospital admission times, and vital signs (heart rate HR, systolic SBP and diastolic arterial pressures DBP, respiratory rate RR, and saturation by pulse oximetry $SatO_2$). These last variables were the core subject of the study. Due to the hetorogenous origins of patients admitted to the ICU—prehospital transfer, emergency room (ER), or hospital ward—the initial vital signs from prehospital settings and ER were analyzed. For inpatients who developed PE during hospitalization, vital signs recorded after the onset of PE symptoms were considered.

Other variables collected were: analytical (pH, lactic acid, TnT-Hs T, D-dimers, NT-proBNP), electrocardiographic (presence of right branch block), alterations in the echocardiogram (dilation and/or dysfunction of the right ventricle) and radiographic (type of PE according to its location on the computed tomography: central or non-central).

Finally, treatment variables such as: need for vasopressors, invasive mechanical ventilation, fibrinolysis, thrombectomy, time to ICU discharge, the incidence complications (hemorrhagic stroke) and the outcome variable ''proactive treatment'' was also collected.

The 'proactive treatment' variable indicates the use of reperfusion strategies as part of the initial treatment upon ICU admission, rather than as rescue measures (reactive). The indication was determined by the clinical judgment of the attending physician, taking into account hemodynamic and respiratory criteria, laboratory tests, imaging studies, comorbidities, and the physician's own subjective assessment.

Calculations were made to determine the SI (HR/SBP) and the PSI ($(SatO_2/FiO_2)$/Shock Index). Lastly, the medical report on discharge was reviewed to assess hospital length of stay (LOS) and mortality. For the analysis of qualitative variables, proportion was used as a frequency measure. For quantitative variables, the median (interquartile range [IQR]) was used. To estimate the relationship between 2 categorical variables, the χ^2 and Fisher's exact tests were used. For the comparison between 2 means, the Student's t-test was used (previous assumption of normality —Saphiro–Wilk test— and homogeneity of variances —Levene's test—); if the assumptions are violated, the Wilcoxon T test was applied (significance level 0.05). For time variables, a Poisson regression was used.

For each index, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, Positive likelihood ratio (LR+), Negative likelihood ratio (LR−) and Kappa were calculated. The receiver operating characteristics (ROC) curves were obtained and the area under the curve (AUROC) was calculated with their respective 95% confidence intervals. The results of the different indices were compared using the DeLong test. All analyses were performed with the statistical program R (R-4.3.0) and Rstudio (Version: 2023.03.1+446).

Results

A total of 115 patients were included. 40% were women (46), with a median age of 60 (49–71) years of age and a median SAPS 3 of 39 (32–44). The prevalence of ''proactive treatment'' was 53.4% (61). In the proactive treatment group 95,2% of patients received thrombolysis and 4.8% alternative treatments.

Median value for TnT-Hs was 80 (42–140), and for NT-proBNP it was 1559 (525—3000). In CT scans, 25% of patients showed central thrombus. Echocardiography revealed right ventricular (RV) dilation in 95.3% of patients and RV dysfunction in 89.8%.

The median LOS in the ICU was 2 (1–3), and the median hospital LOS was 8 (7–11) days. The mortality rate was 1.75%.

Global variables are detailed in the Supplementary material.

The predictive capacity for discriminating whether proactive treatment was administered was for the SI: AUROC of 0.64 (95% CI: 0.54–0.75), with an optimal cut-off point of 1; accuracy: 0.61 (0.51–0.70); sensitivity: 0.42; specificity: 0.83; PPV: 0.74; NPV: 0.55; Kappa: 0.24. As for the PSI: AUROC of 0.61 (95% CI: 0.51–0.72), with an optimal cut-off point of 317; accuracy: 0.61 (0.51–0.70); sensitivity: 0.54; specificity: 0.70; PPV: 0.67; NPV: 0.56; LR(+): 1.76, LR(−):0.67, Kappa: 0.23.

No significant differences were found between both variables according to the AUROC metric using the DeLong test (P 0.60) (Fig. 1).

A post-hoc analysis was conducted with the established cut-off points and different variables were contrasted, significant differences where found in the SBP, DBP, HR, and $SatO_2$ based on the presence of a SI greater or lesser than 1. Patients with SI > 1 received ''proactive treatment'' (mainly thrombolysis) significantly more often than PE patients with SI < 1.

As for the PSI, significant differences were found in the variables: SBP, DBP, HR, $SatO_2$ (previously found in the SI), respiratory rate (RR) and pH. Patients with PSI < 317 had received ''proactive treatment'' more often, with statistically significant differences. The PSI is close to statistical significance in detecting differences related to systemic thrombolysis and in prognostic severity indices (SAPS 3) (Table 1).

The use of both indices favors sensitivity (0.66) and accuracy (0.64). When patients present with a SI > 1 and also a PSI < 317, the specificity (0.90) and positive predictive value (0.78) of receiving ''proactive treatment'' also increases.

In this intermediate-high risk group, 31% (35/113) presented with hidden shock (SI > 1) and 41.6% (45/108) with cardiorespiratory compromise (PSI < 317). A total of 53.2% (58/109) were found to have either hemodynamic deterioration or cardiorespiratory deterioration. Only 19.6% (22/112) had both SI > 1 and PSI < 317 simultaneously (Table 2).

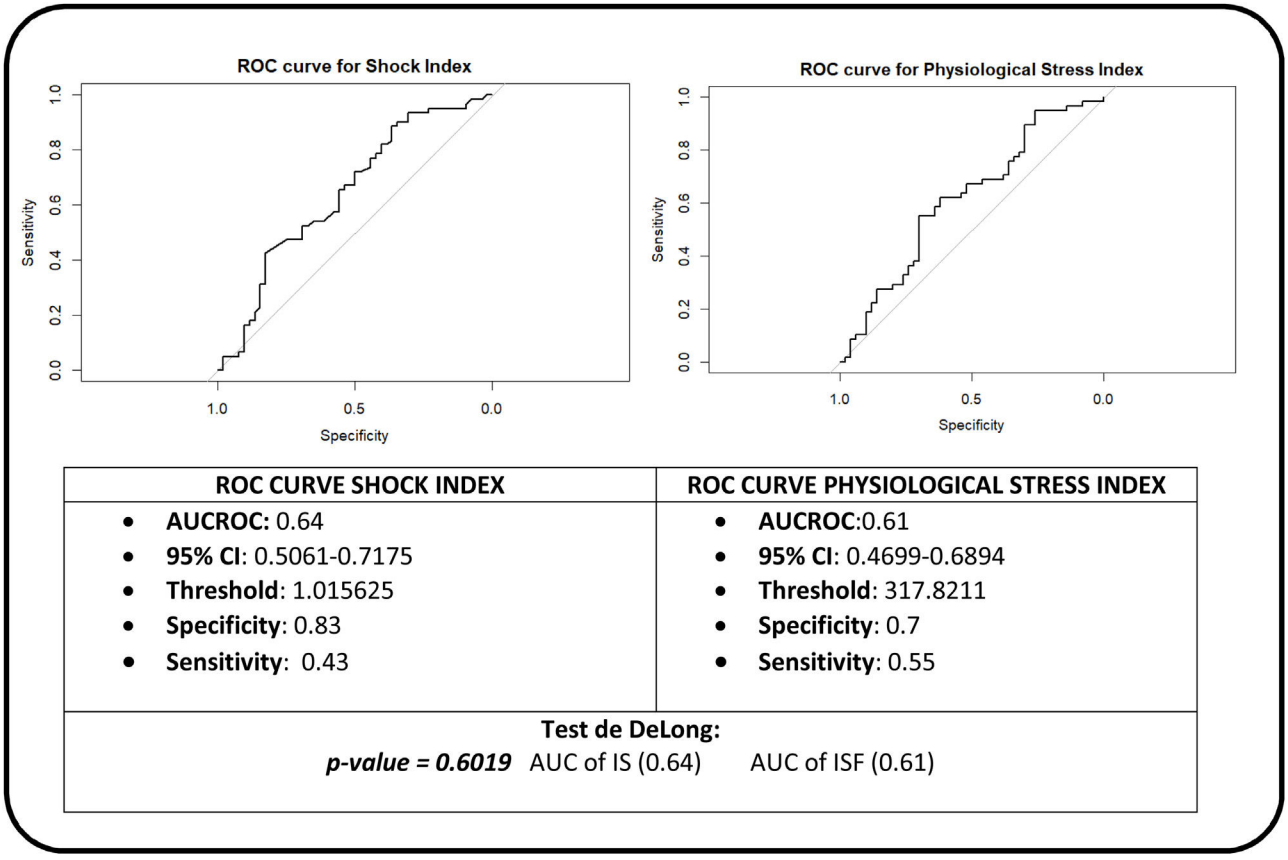

Figure 1 Overview of the metrics of the Shock Index and Physiological Stress Index.

Discussion

PE is a disease that requires early stratification and planning of primary and rescue treatments particularly crucial.[13,14] Studying this group is especially complex[15] due to the relatively low mortality rates and the need for a large sample size in order to demonstrate statistical significance. Hence, the ''proactive treatment'' variable was chosen, as it reflects an active reperfusion strategy. In this study, the concept of ''proactive treatment'' was for the most part, thrombolysis. However, the main focus was not the type of reperfusion strategy (whether it was full-dose fibrinolysis, intermediate-dose fibrinolysis, mechanical thrombectomy, or catheter-directed fibrinolysis) as this decision depends on hospital protocols and logistics of each center. The aim was rather the intention of the treatment, (proactive vs. reactive). In the case of this study, a subgroup of patients classified as intermediate-high risk was identified by intensivists as more critically ill, and the decision to administer reperfusion therapy was based on weighing the benefits and risks.

The scientific literature shows that reperfusion is used less than expected in the high-risk group, and PERT (Pulmonary Embolism Response Teams) use it more frequently in the intermediate-high risk group compared to other teams.[16,17] Current clinical scoring systems are limited in accurately predicting bleeding risk among pulmonary embolism patients. While effective at identifying low-risk patients, they fall short in detecting those at significant risk of hemorrhage.[18,19]

The Shock Index (SI) has validation studies in PE and other scenarios such as: trauma, sepsis and cardiogenic shock.[20,21] SI's lower AUROC values may derive from this study focusing solely on intermediate-high risk PE patients. In this center, proactive treatments as thrombolysis were commonly used, even for patients with respiratory failure—an aspect not accounted for by SI.[22,23,24,25] It was found to be a acceptably specific index (0.70), to identify patients who received proactive treatment.

The possibility of using an index as a 'screening tool' was slightly improved with the PSI, revealing to be a more sensitive index and tending to detect sicker patients (SAPS 42, $P = 0.06$, which would be possibly significant with a larger sample size).

SI and PSI scores combined, identified patients with $SI > 1$ and $PSI < 317$ who are likely to benefit from proactive treatment (specificity = 0.9). Those lacking these criteria were less likely to benefit. These indices serve as tools for refining risk stratification within the intermediate-high risk group.

No significant differences were found in laboratory parameters (TnT Hs and NT-ProBNP) or imaging tests (CT or echocardiography), which may be attributed to the small sample size.

Although these findings should be validated in other cohorts, the study poses a clinically relevant question: ''early assessment of potentially deteriorating

Table 1 Comparative table of the different populations according to the predictors (Shock Index, Physiological Stress Index, union and intersection).

Variable	Shock Index			Physiological Stress Index			Combined index (union)			Combined index (intersection)		
	IS > 1 n = 35	IS < 1 n = 78	P	ISF < 317 n = 45	ISF > 317 n = 63	P	ISF o IS n = 58	Ni ISF ni IS n = 51	P	ISF e IS n = 22	No (ISF e IS) n = 90	P
Age	56 (41–69)	60 (49–72)	0.08	59 (47—71)	60 (49—72)	0.99	58 (42—71)	61 (42—71)	0.15	63 (50—70)	60 (48—72)	0.87
Sex (Female)	48%	37%	0.35	46%	36%	0.39	46.5%	33.3%	0.23	50%	38.8%	0.48
Duration of symptons	2 (1—5)	2 (1—4)	0.63	2 (1—6)	2 (1—4)	0.46	2 (1—6)	2 (1—4)	0.54	2 (1—5)	2 (1—4)	0.52
Time in ICU	2 (1—3)	2 (2—3)	0.78	2 (1—3)	2 (1—2)	0.66	2 (1—3)	2 (1—2)	0.75	2 (1—3)	2 (1—3)	0.67
Time in hospital	8 (7—12)	8 (7—11)	0.24	9 (7—12)	7 (6—10)	0.71	9 (7—12)	7 (6—10)	0.37	8 (6—12)	8 (7—11)	0.59
Syncope	29%	31%	0.99	24%	35%	0.34	27%	33%	0.66	23%	32%	0.54
Right bundle branch block	17%	24%	0.54	26%	16%	0.26	24%	18%	0.55	18%	22%	0.90
Saddle PE	29%	23%	0.72	26%	24%	0.91	26%	24%	0.95	32%	24%	0.60
Interventricular shift	94%	84%	0.36	90%	85%	0.70	93%	83%	0.25	91%	86%	0.91
Right ventricular dilation	97%	94%	0.93	96%	96%	1	96%	94%	1	95%	95%	1
Right ventricular dysfunction	91%	90%	0.4	93%	88%	0.58	93%	87%	0.53	90%	91%	1
SBP in ER	104 (97–121)	130 (117—140)	<0.01*	110 (100–130)	122 (115—140)	<0.01*	110 (100—130)	130 (117—140)	<0.01*	100 (96—110)	126 (115—140)	<0.01*
DBP in ER	70 (60—80)	80 (70—85)	<0.01*	70 (60—80)	80 (70—85)	<0.01*	70 (60–80)	80 (75—86)	<0.01*	70 (60—79)	80 (70—85)	<0.01*
HR in ER	120 (118—134)	100 (86—110)	<0.01*	115 (105—120)	102 (87—116)	<0.01*	120 (110—128)	100 (83–110)	<0.01*	120 (120—138)	105 (90—115)	<0.01*
RR in ER	25 (21—30)	24 (18—27)	0.12	28 (25—30)	22 (18—25)	<0.01*	25 (24—30)	22 (18—25)	<0.01*	25 (25—30)	24 (18—26)	<0.01*
$SatO_2$ in ER	89 (83–94)	92 (88—94)	0.03*	88 (80—92)	93 (89—95)	<0.01*	89 (82–93)	93 (91—95)	<0.01*	85 (80—91)	92 (89—94)	<0.01*
pH	7.4 (7.34—7.46)	7.42 (7.38—7.45)	0.68	7.40 (7.34—7.45)	7.43 (7.4—7.46)	0.02*	7.4 (7.34—7.45)	7.43 (7.4—7.46)	0.02*	7.4 (7.34—7.46)	7.42 (7.39—7.45)	0.34
Lactic	1 (1–3)	2 (1—3)	0.6	2 (1—3)	2 (1—2)	0.17	2 (1—3)	2 (1—2)	0.92	2 (1—3.5)	2 (1—2)	0.34
Troponin	95 (52–168)	78 (41—129)	0.4	83 (54—130)	80 (38—157)	0.81	91 (58—144)	77 (36—125)	0.28	82 (31—140)	84 (49—141)	0.56
D-dímers	7.3 (5.4–21.1)	7.1 (4.3–16.4)	0.32	7.1 (5.4—17.3)	7.1 (4.3—17.4)	0.61	7.5 (5.3—17.2)	6.8 (4.2—17.5)	0.54	6.5 (5.4—23.2)	7.1 (4.2—16.4)	0.36
Pro BNP	1400 (676–2347)	1800 (503—3086)	0.26	1985 (782—3450)	1300 (500—2453)	0.11	2000 (760–3400)	1192 (460–2426)	0.08	1367 (664–2213)	1833 (506—3008)	0.75
Vasoactive drugs	3%	6%	0.72	7%	3%	0.72	5%	4%	1	6%	5%	1
Intubation	0%	4%	0.57	4.5%	0%	0.35	4%	0%	0.55	0%	4%	1
Fibrinolisis	71%	44%	0.01*	64%	44%	0.12	66%	39%	0.01*	73%	43%	0.06
Thrombectomy	3%	3%	0.1	5%	2%	0.76	3%	2%	1	2.2%	4.5%	1
Active treatment	74%	45%	0.01*	67%	44%	0.02*	67%	39%	<0.01*	78%	47%	0.01*
Hemorrhagic stroke	0%	1.3%	1							0%	1%	1
SAPS3	39 (31–43)	40 (32—45)	0.32	42 (34—46)	38 (31—44)	0.06	40 (32—45)	39 (32—45)	0.82	42 (36—45)	39 (41—44)	0.35
ICU discharge	100%	97%	0.85	97%	100%	0.87	98%	100%	1	100%	98%	1

* Statistically significant difference.

Table 2 Confusion matrix.

	Proactive treatment NO	Proactive treatment YES
PSI > 317	35	27
PSI < 317	15	31

Accuracy: 0.61 (0.51—0.70)
Sensitivity: 0.53/specificity: 0.70
Predictive positive value: 0.67/predictive negative value: 0.56
Positive likelihood ratio (LR+): 1.76/negative likelihood ratio (LR—): 0.67
Kappa: 0.23

	Proactive treatment NO	Proactive treatment YES
SI < 1	43	35
SI > 1	9	26

Accuracy: 0.61 (0.51–0.70)
Sensitivity: 0.43/specificity: 0.83
Predictive positive value: 0.74/predictive negative value: 0.55
Positive likelihood ratio (LR+): 2.53/negative likelihood ratio (LR—): 0.69
Kappa: 0.24

	Proactive treatment NO	Proactive treatment YES
Nor SI > 1 Nor PSI < 317	31	20
Union Score (ISF < 317 or IS > 1)	19	39

Accuracy: 0.64 (0.54—0.73)
Sensitivity: 0.66/specificity: 0.62
Predictive positive value: 0.67/predictive negative value: 0.62
Positive likelihood ratio (LR+): 1.74/negative likelihood ratio (LR—): 0.54
Kappa: 0.28

	Proactive treatment NO	Proactive treatment YES
No (PSI < 317 & SI > 1)	47	42
Intersection Score (PSI < 317 & SI > 1)	5	18

Accuracy: 0.58 (0.48—0.67)
Sensitivity: 0.30/specificity: 0.90
Predictive positive value: 0.78/valor predictivo negativo: 0.53
Positive likelihood ratio (LR+): 3/negative likelihood ratio (LR—): 0.77
Kappa: 0.19

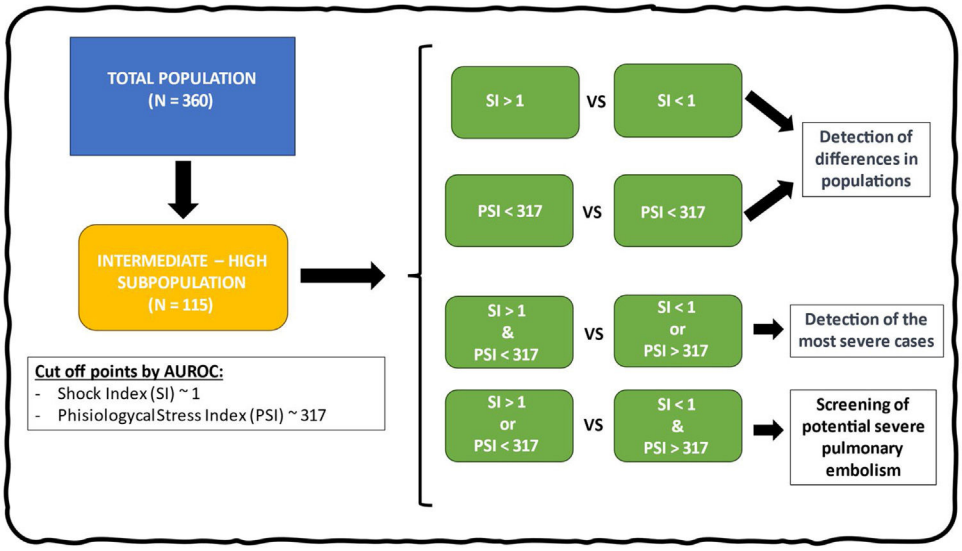

Figure 2 Overview of the work conducted and the main results obtained.

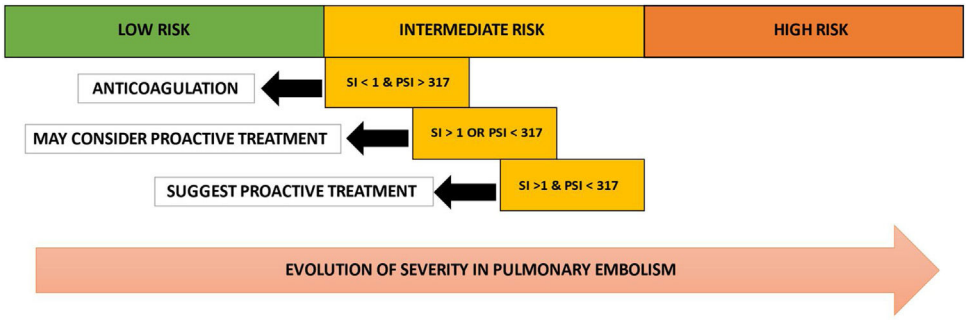

Figure 3 Main practical applications that these predictors could have in the evaluation of pulmonary embolism patients.

intermediate-high risk PE patients'', where current guidelines seem to fail to provide the necessary tools to correctly asses this subgroup. Existing evidence suggests that this subgroup could benefit from more aggressive treatment. This study highlights potential clinical markers (SI > 1 and/or PSI < 317) that may help identify patients within this diverse group, who are experiencing greater physiological decline and therefore would most benefit from reperfusion treatment, especially if they fulfill both SI > 1 and PSI < 317 (Figs. 2 and 3).

Limitations of our study that diminishes the strength of the conclusions

1. Factors as chest pain, other respiratory failure causes, comorbidities (arrhythmias, pacemakers), and medication (e.g. beta blockers) could affect physiology and consequently impact predictive accuracy of SI and PSI.
2. These indices may not initially capture the risk of cardiorespiratory failure in patients with significant clot burden, especially those with deep vein thrombosis.
3. Dynamic data on how these indices change from initial measurement to ICU admission was not evaluated.
4. This is a retrospective study, facilitating bias (information bias, misclassification bias, temporal bias) and the possibility of patient loss due to the fact that patients were treated in different ICUs in the hospital.
5. Due to the study's retrospective nature, it should be noted that the following assumptions have been made to obtain the PSI: without oxygen therapy FiO_2 0.21, oxygen therapy with nasal cannulas FiO_2 0.28, oxygen therapy with venturi mask FiO_2 0.5, oxygen therapy with reservoir mask FiO_2 0.8, oxygen therapy with mechanical ventilation FiO_2 1.
6. Sample size may be insufficient to reveal noteworthy differences between groups.
7. Echocardiography was not standardized in protocol.
8. 'Proactive treatment' variable was influenced by factors like contraindications to thrombolysis, availability of mechanical thrombectomy, and hospital culture.
9. Two secondary transfer patients lacked initial vital signs, this was thought to have minimal impact over the results.

Conclusions

This study found that the combination of a SI > 1 and PSI < 317 aids in detecting sicker intermediate-high risk patients who may benefit from reperfusion therapy. When used separately, the SI and PSI were suboptimal. Further studies including a large number of patients are needed to confirm our findings

Generative AI

During the preparation of this work the author(s) used GPT-4 in order to translate to English. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Funding

No.

Conflict of interest

No conflict of interest disclosures of any of the authors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medin.2023.10.011.

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