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ORIGINAL RESEARCH

Physiological Factors Associated with Peri-intubation Severe Adverse Events and Derivation of an Exploratory Bedside Risk Score; A Cross-sectional Study

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Abstract: **Introduction:** Endotracheal intubation is a life-saving procedure, but it can result in complications such as hypotension, hypoxia, and cardiac arrest. This study aimed to identify physiological factors associated with difficult intubation in emergency departments (ED), in order to derive an exploratory bedside risk score. **Methods:** This retrospective cohort study included patients aged ≥15 years who underwent endotracheal intubation in the ED. Pre-intubation physiological variables, procedural characteristics, and peri-intubation severe adverse events (severe hypoxemia, hypotension, and cardiac arrest) were extracted from standardized intubation records and electronic medical records. Independent physiological predictors of peri-intubation severe adverse events were extracted using logistic regression analysis, and an exploratory point-based bedside risk score was derived and internally validated. **Results:** Among 720 eligible patients, 137 (19.0%) experienced peri-intubation severe adverse events. Five clinically relevant physiological predictors were retained in the exploratory score: suspected sepsis, pre-intubation hypoxemia, low serum bicarbonate level, vasopressor requirement before intubation, and shock index >0.9. The simplified score ranged from 0 to 11 points and showed modest discrimination, with an optimism-corrected C-statistic of 0.686. At a threshold of ≥5 points, the score had limited sensitivity (32.1%) but high specificity (90.1%), with a positive predictive value of 43.1% (95% confidence interval (CI): 33.4–53.3) and a positive likelihood ratio of 3.23 (95% CI: 2.29–4.56). **Conclusion:** The exploratory physiological difficulty score showed modest discrimination for peri-intubation severe adverse events. A threshold of ≥5 points identified a subgroup of patients who may require more preparation and closer monitoring before intubation. However, the score should not replace comprehensive clinical assessment and requires external validation.

Keywords: Intubation, Intratracheal; Airway Management; Emergency Service, Hospital; Risk Assessment; Hypotension

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1. Introduction

Endotracheal intubation is a lifesaving procedure that facilitates oxygenation and ventilation in emergency situations. However, after endotracheal intubation, critically ill patients are at higher risk of complications, such as aspiration pneumonia, hypotension, hypoxemia, and cardiac arrest (1-3). Anatomical difficulties, defined by the LEMON criteria, were shown to be associated with the need for multiple attempts at intubation, leading to complications in 58% of such cases (1). However, physiological difficulties are also a potential factor leading to severe adverse events after intubation, yet they are relatively overlooked in modern practice (2, 4-9).

Physiological challenges are most commonly occur in critically ill patients. For example, Russotto et al. found that tracheal intubation in critically ill patients led to cardiovascular instability at rates of up to 42.6%, severe hypoxemia in 9.3%, cardiac arrest in 3.1%, and overall mortality of patients in intensive care units of 32.8%. They also found that more than one attempt at tracheal intubation could increase adverse events, up to 58% (1). It is thus crucial to consider the factors that may contribute to complications during intubation. Various risk factors associated with physiologically difficult intubation (PDI) or high-risk rapid sequence intubation (RSI) have been studied, including elevated lactate levels, hypoxemia, hypotension, advanced age, obesity, failure to administer oxygen before intubation, and more than one intubation attempt (1, 3, 9-17).

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In 2020, the American College of Emergency Physicians defined a physiologically difficult airway using the acronym CRASH, which stands for Consumption increase, Right ventricular dysfunction, Acidosis, Desaturation, and Hypotension (18). This acronym is intended to help physicians remember these critical factors, in addition to considering anatomical airway-related difficulties, to prevent post-intubation complications. However, evidence supporting the clinical validity of the CRASH acronym remains limited (11, 19). Therefore, this study aimed to identify physiological factors associated with difficult intubation in emergency departments (ED), in order to derive an exploratory bedside risk score.

2. Methods

2.1. Study design and setting

This retrospective cohort study was conducted at the ED of Ramathibodi Hospital, a tertiary academic center in Thailand. We reviewed consecutive patients who underwent tracheal intubation between January 1, 2019, and December 31, 2023. After data collection, the physiological variables were analyzed to identify factors associated with peri-intubation severe adverse events. An exploratory bedside risk score was then derived from clinically relevant predictors and internally validated to assess its performance within the study cohort.

This study was approved by the Faculty of Medicine, Committee on Human Rights Related to Research Involving Human Subjects, Ramathibodi Hospital, Mahidol University (COA No. MURA2024/401). The ethics committee waived the requirement for informed consent due to the study's retrospective nature. The study was conducted in accordance with the principles of the Declaration of Helsinki and institutional regulations.

2.2. Participants

Patients aged 15 years or older who underwent endotracheal intubation in the ED during the study period were eligible. Patients with cardiac arrest before intubation, crash airways, anatomically distorted airways, or those requiring a surgical airway before intubation were excluded.

2.3. Data collection

Data were extracted from standardized intubation protocol documents and electronic medical records. Eligible cases were reviewed according to predefined inclusion and exclusion criteria. Extracted data included baseline characteristics, pre-intubation physiological variables, procedural characteristics, and clinical outcomes.

Candidate predictors were selected based on clinical plausibility within the CRASH physiological framework. These included suspected sepsis, severe anemia, morbid obesity, right ventricular dysfunction, acidosis, pre-intubation hypoxemia, pre-intubation hypotension or vasopressor requirement, and shock index >0.9.

Pre-intubation vital signs were obtained from standardized intubation records and electronic medical records. For hemodynamic variables, the measurement documented immediately before endotracheal intubation was used when available. Shock index was calculated as heart rate divided by systolic blood pressure using the pre-intubation vital signs closest to intubation. Pre-intubation oxygen saturation was defined as the lowest documented oxygen saturation before intubation despite supplemental oxygen or positive-pressure ventilation. Vasopressor requirement before intubation was defined as ongoing vasopressor infusion or documented vasopressor administration before induction or intubation. Arterial pH and serum bicarbonate levels were obtained from the closest available blood gas measurement documented before intubation. Right ventricular dysfunction was defined by documented previous diagnosis or echocardiographic evidence when available.

Exact clock-time intervals between blood gas measurement and intubation were not consistently available in the retrospective dataset; therefore, laboratory predictors were defined using the closest available pre-intubation values. This limitation was considered when interpreting the results.

Treatment-related components, including intravenous fluid bolus administration and initiation or escalation of vasopressor therapy after intubation, were included to capture clinically significant hemodynamic deterioration when blood pressure documentation was incomplete. These components may partly reflect clinician decision-making and local practice patterns. The use of pre-intubation vasopressor requirement as a predictor and post-intubation vasopressor initiation or escalation as part of the hypotension outcome creates potential overlap. This issue was evaluated in a sensitivity analysis and is discussed as a potential source of treatment-related outcome classification bias.

2.4. Definitions

- Physiologically difficult intubation (PDI)

An abnormal physiological status in patients that may lead to complications and adverse outcomes following the intubation procedure (4).

- CRASH criteria

Five high-risk physiological abnormalities associated with an increased risk of clinical deterioration during or after tracheal intubation. These include increased oxygen Consumption, involving severe anemia (hemoglobin level <8 g/dL), morbid obesity (body mass index [BMI] >35 kg/m²), and suspicion of sepsis; Right ventricular dysfunction (either documented or diagnosed by echocardiography); Acidosis, defined as arterial pH of <7.1 before intubation or serum bicarbonate of <15 mEq/L; Pre-intubation hypoxemia, indicated by oxygen saturation <90% despite supplemental oxygen or positive-pressure ventilation; and Pre-intubation hypotension, characterized by systolic blood pressure (SBP) of <90 mmHg, mean arterial pressure (MAP) of <65 mmHg, or re-

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quiring vasopressor administration prior to intubation.
- Peri-intubation severe adverse events
Peri-intubation severe adverse events were defined as any of the following: severe hypoxemia (defined as oxygen saturation <80%), hypotension (defined as systolic blood pressure <90 mmHg, or mean arterial pressure <65 mmHg, or requirement for intravenous fluid bolus, or initiation or escalation of vasopressor therapy), and cardiac arrest. Patients experiencing any of the mentioned severe adverse events after 30 minutes of intubation were categorized as "PDI" or "high-risk RSI" group.

2.5. Outcomes

The primary outcome was the occurrence of severe adverse events (severe hypoxemia, hypotension, and cardiac arrest) within 30 minutes after endotracheal intubation.

2.6. Efforts to address bias

To reduce selection bias, consecutive eligible patients who underwent endotracheal intubation in the ED during the study period were reviewed. Inclusion and exclusion criteria were predefined. Predictor and outcome definitions were specified before analysis. Data were extracted from standardized intubation records and electronic medical records to reduce information bias. Missing data were assessed for candidate predictors, and complete-case analysis was used for the main model. Bootstrap internal validation was performed to estimate model optimism.
Nevertheless, residual bias may remain because of the retrospective design, incomplete documentation, missing physiological measurements, and possible treatment-related outcome classification.

2.7. Statistical Analysis

According to the study conducted by Downing et al., the rate of severe adverse events around the time of intubation was 0.305, with a 95% confidence interval (CI) of 0.25–0.366. We established that the lower limit of the 95% CI, denoted as P, is 0.25. Additionally, using the CRASH criteria, we assumed 30 outcome events per independent variable, based on the method proposed by Guyatt (20). Consequently, the required sample size was 720.
Baseline characteristics were summarized as numbers and percentages for categorical variables and as mean with standard deviation or median with interquartile range (IQR) for continuous variables, as appropriate. The distribution of continuous variables was assessed visually. Group comparisons were performed using the X^2 test or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables. Statistical significance was defined as a two-sided p-value <0.05. All analyses were conducted using STATA version 18 (StataCorp, College Station, TX, USA).
Continuous variables were initially assessed in their original scale for descriptive analysis. For exploratory score derivation, selected quantitative physiological variables were dichotomized using clinically meaningful thresholds: serum bicarbonate <15 mEq/L, oxygen saturation <90%, shock index >0.9, hemoglobin <8 g/dL, and body mass index >35 kg/m². These thresholds were selected based on the CRASH physiological framework and clinical interpretability. We acknowledge that dichotomization may reduce information and statistical power.

2.8. Model development and exploratory score derivation

Candidate predictors were selected based on clinical plausibility within the CRASH physiological framework and supported by univariate logistic regression. Variables with p<0.10 in univariate analysis were considered eligible for inclusion in the multivariable logistic regression model. Multicollinearity was assessed using variance inflation factors (VIFs) before inclusion in the multivariable model. Complete-case analysis was performed for patients with available data for the variables included in the final analysis. Missing data were summarized for each candidate predictor before model development. After exclusion of patients with incomplete core outcome or procedural data, the analytic cohort included 720 patients. Within this cohort, arterial pH was unavailable in 261 patients (36.3%). Serum bicarbonate was available for all patients. The coded variable for right ventricular dysfunction had no missing values in the analytic dataset; however, because routine pre-intubation echocardiography was not performed in all emergency cases, right ventricular dysfunction may have been under-ascertained. Because of the high proportion of missing arterial pH values, arterial pH was not included in the final exploratory score.
After obtaining the final multivariable logistic regression model, the regression coefficients () for each retained predictor were transformed into a simplified point-based exploratory score. Each coefficient was divided by the smallest absolute coefficient in the final model and rounded to the nearest integer. These integer values were assigned as item scores, and the total score was calculated for each patient.

2.9. Model performance and internal validation

The discrimination of the exploratory score for peri-intubation severe adverse events was evaluated using the area under the receiver operating characteristic curve (AUROC). Calibration, defined as the agreement between predicted and observed event probabilities, was assessed visually using a calibration plot and statistically using the Hosmer–Lemeshow goodness-of-fit test; p<0.05 indicated poor calibration. For clinical interpretability, a threshold of ≥5 points was considered to identify patients with a higher observed risk of peri-intubation severe adverse events. Diagnostic performance metrics, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR), and overall accuracy, were calculated. The score

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was considered exploratory and was not intended to rule out peri-intubation severe adverse events or replace a comprehensive clinical assessment.

Internal validation was performed using bootstrap resampling with 1,000 repetitions. For each bootstrap sample, the logistic regression model was refitted, and performance metrics, including predicted probabilities, C-statistics, and Somers' D correlations, were recalculated. Model optimism was estimated as the mean difference between bootstrap-derived performance and apparent performance in the original sample. An optimism-corrected C-statistic was reported as an estimate of internal model performance.

2.10. Sensitivity analysis

A sensitivity analysis was performed using a more objective definition of peri-intubation severe adverse events that excluded treatment-related components, including intravenous fluid bolus administration and vasopressor initiation or escalation.

3. Results

3.1. Baseline characteristics of studied cases

Over the 5-year study period, 789 patients underwent endotracheal intubation in the ED of Ramathibodi Hospital. After excluding 27 patients with crash airways, 34 with cardiac arrest before intubation, and 8 with incomplete data, 720 patients were included in the final analysis, of whom 373 (51.8%) were male. Of these, 137 (19.0%) patients experienced at least one peri-intubation severe adverse event (severe hypoxemia, hypotension, or cardiac arrest). The study flow diagram is presented in Figure 1. Cardiac arrest occurred in 3 patients (0.4%). The patients' baseline characteristics are presented in Table 1. The mean age was similar between patients with and without peri-intubation severe adverse events (72.99±16.02 vs. 72.79±15.04 years; p=0.893). The proportion of male patients was slightly lower in the severe adverse event group than in the no severe adverse event group; however, this difference was not statistically significant (47.45% vs. 52.83%, p=0.296). There was also no statistically significant difference in the proportion of patients with anatomically difficult airways between the two groups (24.1% vs. 21.3%, p=0.486).

3.2. Associated factors of physiologically difficult intubation

Among CRASH-related physiological variables, pre-intubation hypoxemia (p=0.009), low serum bicarbonate level <15 mEq/L (p=0.003), vasopressor requirement before intubation (p<0.001), suspected sepsis (p=0.002), and shock index >0.9 (p<0.001) were associated with peri-intubation severe adverse events in the univariate analysis. In contrast, morbid obesity (BMI >35 kg/m²), severe anemia (hemoglobin <8 g/dL), and right ventricular dysfunction were not significantly associated with peri-intubation severe adverse events.

In univariate logistic regression, pre-intubation hypoxemia was associated with increased odds of peri-intubation severe adverse events (odds ratio (OR): 3.35, 95% CI: 1.38–8.11), as were low serum bicarbonate level <15 mEq/L (OR: 1.97, 95% CI: 1.28–3.04), vasopressor requirement before intubation (OR: 3.32, 95% CI: 2.03–5.43), suspected sepsis (OR: 1.90, 95% CI: 1.28–2.82), and shock index >0.9 (OR: 3.28, 95% CI: 2.23–4.80). These clinically relevant variables were evaluated in the multivariable model and retained for the derivation of the exploratory physiological difficulty score.

In the multivariable logistic regression model, vasopressor requirement before intubation (adjusted OR: 2.12, 95% CI: 1.25–3.60; p = 0.005) and shock index >0.9 (adjusted OR: 2.63, 95% CI: 1.76–3.93; p <0.001) remained independently associated with peri-intubation severe adverse events. Pre-intubation hypoxemia showed a borderline association (adjusted OR: 2.53, 95% CI: 0.99–6.47; p = 0.053), while low serum bicarbonate level <15 mEq/L (adjusted OR: 1.47, 95% CI: 0.92–2.34; p = 0.105) and suspected sepsis (adjusted OR: 1.32, 95% CI: 0.86–2.02; p = 0.204) were retained based on clinical plausibility and the exploratory score derivation strategy.

3.3. PDI score

A simplified exploratory physiologically difficult intubation (PDI) score was developed from the regression coefficients of the retained predictors. Assigned item scores were as follows: suspected sepsis, 1 point; serum bicarbonate <15 mEq/L, 1 point; oxygen saturation <90% before intubation, 3 points; vasopressor requirement before intubation, 3 points; and shock index >0.9, 3 points. The total score ranged from 0 to 11 points. The full multivariable logistic regression equation was:

logit(p) = 2.2269 + 0.9274 × (oxygen saturation <90%) + 0.2761 × (suspected sepsis) + 0.3844 × (serum bicarbonate <15 mEq/L) + 0.7514 × (vasopressor requirement before intubation) + 0.9661 × (shock index >0.9).

All predictors were coded as binary variables, with 1 indicating the presence of the characteristic and 0 indicating its absence. The apparent calibration intercept was 0.000, the apparent calibration slope was 1.000, and the Brier score was 0.141. These performance measures represent apparent model performance in the derivation cohort.

3.4. Predictive performance of the PDI score

The AUROC for the PDI score was 0.69 (95% CI: 0.642–0.744), indicating modest discrimination for peri-intubation severe adverse events (Figure 2). The calibration plot is shown in Figure 2. The observed-to-expected risk ratio was 1.0, suggesting acceptable apparent agreement between observed and predicted risk in this derivation dataset.

For clinical interpretability, a threshold of ≥5 points was considered to identify patients with higher observed risk (table 3). At this threshold, the score demonstrated limited sensi-

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tivity (32.1%, 95% CI: 24.4–40.6) but high specificity (90.1%, 95% CI: 87.3–92.4), with a positive predictive value of 43.1% (95% CI: 33.4–53.3), negative predictive value of 85.0% (95% CI: 81.9–87.7), positive likelihood ratio of 3.23, negative likelihood ratio of 0.75, and overall accuracy of 0.79 (95% CI: 0.76–0.82).

For internal validation, Somers' D was 0.38 (95% CI: 0.28–0.48). After 1,000 bootstrap repetitions, the mean optimism was 0.008. The optimism-corrected Somers' D was 0.372, corresponding to an optimism-corrected C-statistic of 0.686 (95% CI: 0.634–0.736).

3.5. Sensitivity analysis

In the sensitivity analysis using an alternative objective outcome definition that excluded treatment-related components, 159 patients (22.1%) experienced peri-intubation severe adverse events. This alternative definition overlapped with the original composite outcome in 108 patients, while 29 patients classified as having events in the original outcome were not classified as events in the sensitivity outcome. The model showed lower discrimination than the main analysis, with an AUROC of 0.641.

Pre-intubation hypoxemia and shock index >0.9 remained statistically significant in the sensitivity analysis. Oxygen saturation <90% before intubation showed the strongest association (adjusted OR: 15.03, 95% CI: 4.87–46.37), followed by shock index >0.9 (adjusted OR: 2.31, 95% CI: 1.57–3.42). In contrast, vasopressor requirement before intubation was no longer statistically significant (adjusted OR: 1.47, 95% CI: 0.85–2.55). These findings suggest that treatment-related outcome components may have partly contributed to the association between pre-intubation hemodynamic instability and the original composite outcome.

4. Discussion

In this study, peri-intubation severe adverse events occurred in 19.0% of patients undergoing emergency endotracheal intubation. Vasopressor requirement before intubation and shock index >0.9 were independently associated with these adverse events, while pre-intubation hypoxemia showed a borderline association. An exploratory bedside risk score incorporating suspected sepsis, pre-intubation hypoxemia, low serum bicarbonate level, vasopressor requirement before intubation, and shock index >0.9 demonstrated modest discrimination, with an optimism-corrected C-statistic of 0.686. A score of ≥5 identified a subgroup with a higher observed event rate of 43.1%, however, the score had limited sensitivity and should not be used to rule out peri-intubation severe adverse events.

More specifically, 3.2% of patients experienced severe hypoxemia, while 16.7% developed hypotension requiring additional fluid resuscitation or vasopressor dose escalation; also, 0.4% experienced cardiac arrest. The overall complication rate identified in this study was slightly lower than 30.3% (95% CI: 25%–37%), which was reported by Downing et al. Similar tendencies were found for the rates of hypoxemia and hypotension, while the rate of cardiac arrest in Downing et al.'s study was notably higher (2.0% (95% CI 1%–3.5%)) (21). This difference may be explained by the exclusion of patients with crash airways from this study. Patients with crash airways often experience more severe complications during intubation because they require immediate life-saving airway management, leaving insufficient time for preparation or correction of physiological risk factors before intubation.

In this study, patients with suspected sepsis, had a higher risk of peri-intubation severe adverse events. However, other factors that can lead to elevated oxygen consumption, such as morbid obesity and severe anemia, were not found to cause a statistically significant increase in risk. This finding offers important insights into the concept of "Consumption" in practical applications. Moreover, since sepsis involves a range of physiological abnormalities, lactate levels may also be clinically relevant predictors, as suggested by Yang et al. (16).

Low serum bicarbonate was associated with peri-intubation severe adverse events in univariate analysis, but was not independently significant after adjustment. This finding is consistent with previous evidence suggesting that metabolic acidosis is associated with post-intubation hemodynamic instability (22). In clinical practice, recognition of metabolic acidosis before intubation may prompt clinicians to consider the underlying cause, hemodynamic status, and overall physiological reserve. Although sodium bicarbonate has been studied in severe metabolic acidemia, current evidence does not support a clear benefit (23). Therefore, in the present study, low serum bicarbonate should be interpreted primarily as a marker of metabolic acidosis and reduced physiological reserve rather than as evidence supporting sodium bicarbonate administration or any specific treatment strategy. Further prospective studies are required to determine whether targeted physiological optimization before intubation improves outcomes.

For hypoxemia, patients with pre-intubation oxygen saturation below 90% showed a statistically significant association with severe complications, even after positive-pressure ventilation, which aligns with the findings of De Jong et al. (3). The significant impact of hypoxemia can be understood through the pathophysiology observed in patients with severe respiratory compromise. In these cases, preoxygenation is less effective, leading to a shorter safe apnea time and an increased risk of complications. This contrasts with patients experiencing milder respiratory distress, who can maintain a longer safe apnea time.

Regarding hypotension, vasopressor requirement before intubation and shock index >0.9 remained independently associated with peri-intubation severe adverse events. This finding is consistent with previous studies showing that post-intubation hemodynamic instability is an important risk factor for adverse events during emergency airway management (3, 21). These variables should be interpreted as markers of pre-intubation hemodynamic vulnerability rather than evi-

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dence of a treatment effect. Although recognition of shock or elevated shock index may help clinicians prepare for closer monitoring and physiological optimization before intubation, this observational study cannot determine whether fluid administration, vasopressor adjustment, or any specific pre-intubation intervention directly reduces peri-intubation severe adverse events. Prospective interventional studies are needed to determine whether targeted hemodynamic optimization before intubation improves clinical outcomes.

Lastly, regarding right ventricular dysfunction, this study found no statistically significant difference in the incidence of severe complications during intubation. This result contrasts with the recommendations and findings of Wilcox et al. (24). This discrepancy may stem from the low prevalence of right ventricular dysfunction among the intubated patients, or it might indicate incomplete data, as pre-intubation assessments of right ventricular function are not consistently performed in all emergency cases. In conjunction with the study by Wilcox et al., which notes that right ventricular dysfunction is rarely identified in the emergency department, primarily because definitive confirmation requires right-sided heart catheterization, it remains essential to consider right ventricular dysfunction in patients with underlying risk factors. These risk factors include chronic obstructive pulmonary disease, left-sided heart failure, and connective tissue disorders.

The exploratory physiological difficulty score showed modest discrimination for peri-intubation severe adverse events, with an optimism-corrected C-statistic of 0.686. At the threshold of ≥5 points, the score demonstrated high specificity but limited sensitivity. Therefore, the score should not be used to rule out peri-intubation severe adverse events in patients with lower scores. Rather, its potential value lies in identifying a subgroup of patients with higher observed risk who may require closer preparation, monitoring, and physiological optimization before intubation. In this cohort, the observed event probability increased from 19.0% overall to 43.1% among patients with scores ≥5 points.

5. Limitations

This study has several limitations. First, it employed a retrospective design, relying on patients' characteristics and clinical outcomes that were obtained solely from existing records. These records may contain inaccuracies or inconsistencies, and key variables may not have been evaluated or documented during the course of treatment. For example, the low rate of documented right ventricular dysfunction observed in this study may reflect incomplete assessment rather than true absence of the disease.

Additionally, the approach used in this study faces practical challenges in real-life situations. The score relies on serum bicarbonate levels as an indicator of acidosis, which may not be readily available in all emergency situations. A notable limitation was that arterial pH was not routinely assessed before intubation in all patients. Under these circumstances, low serum bicarbonate levels should be interpreted as a marker of metabolic acidosis and reduced physiological reserve rather than as a definitive independent predictor. Consequently, missing or incomplete physiological data may have reduced statistical power. Finally, only internal validation was conducted in this study; external validation is necessary to assess the generalizability of the model and determine whether it remains accurate and reliable when applied to different populations.

Several additional sources of potential bias and imprecision should be considered. First, residual confounding may persist due to the retrospective design and the inability to fully adjust for illness severity, clinician decision-making, pre-oxygenation quality, induction medication dose, fluid status, and other unmeasured physiological factors. This residual confounding could either overestimate or underestimate the associations between pre-intubation physiological abnormalities and peri-intubation severe adverse events. Second, outcome classification may have been influenced by treatment decisions because hypotension included intravenous fluid bolus administration and vasopressor initiation or escalation. This may have increased the observed event rate and could have biased associations involving pre-intubation shock or vasopressor use away from the null. Third, arterial pH was unavailable in a substantial proportion of patients, and right ventricular dysfunction may have been under-ascertained because routine pre-intubation echocardiography was not performed in all emergency cases. These limitations may have reduced statistical power and may have biased the observed associations toward the null for acidosis and right ventricular dysfunction. Fourth, because this was a single-center study that excluded crash airways and patients with cardiac arrest before intubation, the findings may not be generalizable to all emergency airway populations, particularly patients requiring immediate intubation without time for physiological assessment or optimization.

Another important limitation is that the derived score demonstrated only modest discrimination and limited sensitivity. Although the threshold of ≥5 points identified patients with higher observed risk, lower scores did not reliably exclude peri-intubation severe adverse events. In addition, the score was derived and internally validated within a single-center cohort; therefore, external validation in independent emergency department populations is required before clinical implementation.

6. Conclusions

Several pre-intubation physiological factors were identified as clinically relevant components of the exploratory PDI score, including suspected sepsis, pre-intubation hypoxemia, low serum bicarbonate level, vasopressor requirement before intubation, and elevated shock index. In the multivariable model, vasopressor requirement before intubation and shock index >0.9 remained independently associated with peri-intubation severe adverse events. The exploratory

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score showed modest discrimination. A threshold of ≥5 points identified a subgroup of patients with higher observed risk who may require closer preparation, monitoring, and physiological optimization before intubation. However, because of its limited sensitivity, the score should not be used to rule out peri-intubation severe adverse events and should complement rather than replace comprehensive clinical assessment. External validation in independent emergency department populations is required before broader clinical implementation.

7. Declarations

7.1. Acknowledgments

The authors acknowledge the use of Grammarly® (Grammarly Inc., San Francisco, CA, USA) for language editing and grammar improvement during manuscript preparation.

7.2. Ethics approval and consent to participate

This study was approved by the Faculty of Medicine, Committee on Human Rights Related to Research Involving Human Subjects, Ramathibodi Hospital, Mahidol University (COA No. MURA2024/401). The ethics committee waived the requirement for informed consent due to the study's retrospective nature. The study was conducted in accordance with the principles of the Declaration of Helsinki and institutional regulations.

7.3. Consent for publication

Not applicable.

7.4. Availability of data and materials

The datasets used and analyzed during the current study will be retained securely by the corresponding author and the responsible institution for at least 10 years after publication. De-identified data may be made available from the corresponding author upon reasonable request and subject to institutional regulations and ethical approval requirements.

7.5. Competing interests

The authors declare that they have no competing interests.

7.6. Funding

No funding was received for this study.

7.7. Use of artificial intelligence chatbots

The authors declare that artificial intelligence-assisted tools were used only for language refinement, grammar checking, and manuscript preparation support. The authors reviewed, edited, and verified all content generated or modified with the assistance of these tools. No artificial intelligence tool was used to generate study data, perform statistical analysis, fabricate or falsify data, manipulate images, or make authorship decisions.

7.8. Authors' contributions

PT and TB conceived the study and designed the research. PT and TB collected and managed the data. PT and SS performed the statistical analyses. PT, TB, and PN interpreted the data and drafted the manuscript. PN served as the corresponding author. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work and declare that the manuscript is original, with no data fabrication, data falsification, deceptive manipulation of images, or plagiarism.

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Table 1: Comparing baseline characteristics between patients with and without peri-intubation severe adverse events in emergency department (univariate analysis)

Characteristic	Peri-intubation severe adverse events		P
	Yes (n = 137)	No (n = 583)	
Age (years)			
Mean ± SD	72.99 ± 16.02	72.79 ± 15.04	0.893
Age > 60	110 (80.29)	482 (82.68)	0.511
Sex			
Male	65 (47.45)	308 (52.83)	0.296
Female	72 (52.55)	275 (47.17)	
Body mass index			
Mean ± SD	22.78 ± 5.63	23.39 ± 5.54	0.247
Co-morbidities			
Hypertension	100 (72.99)	405 (69.47)	0.468
Diabetes mellitus (DM)	58 (42.34)	245 (42.02)	1.000
Dyslipidemia	86 (62.77)	357 (61.23)	0.770
Chronic kidney disease	41 (29.93)	169 (28.99)	0.835
Hepatic disease	9 (6.57)	45 (7.72)	0.722
Cardiovascular diseases (CVS)	49 (35.77)	209 (35.85)	1.000
Cerebrovascular disease	31 (22.63)	142 (24.36)	0.739
COPD, respiratory disease	29 (21.17)	155 (26.59)	0.231
Cancer	26 (18.98)	123 (21.10)	0.640
Auto-immune disease	9 (6.57)	58 (9.95)	0.255
Indication for intubation			
Acute respiratory failure			
Type 1	42 (30.66)	168 (28.82)	0.011
Type 2	15 (10.95)	106 (18.18)	
Type 4	62 (45.26)	192 (32.93)	
Coma (TBI)	2 (1.46)	11 (1.89)	1.000
Coma (non-TBI)	18 (13.14)	99 (16.98)	0.305
Respiratory tract infection	62 (45.26)	297 (50.94)	0.255
Suspected sepsis	93 (67.88)	307 (52.66)	0.002
CVS except RV failure	19 (13.87)	77 (13.21)	0.889
RV failure	2 (1.46)	7 (1.20)	0.683
Neuromuscular disease	0	5 (0.86)	0.590
Upper airway obstruction	2 (1.46)	12 (2.06)	1.000
Type of laryngoscope			
Video laryngoscope	103 (75.18)	437 (74.96)	0.797
Direct laryngoscope	34 (24.82)	141 (24.19)	
Fiber optic laryngoscope	0	5 (0.86)	
Sedative agent			
Etomidate	82 (59.85)	408 (69.98)	0.039
Propofol	16 (11.68)	73 (12.52)	
Ketamine	18 (13.14)	56 (9.61)	
Diazepam	1 (0.73)	2 (0.34)	
Midazolam	4 (2.92)	5 (0.86)	
No sedative drug	16 (11.68)	39 (6.69)	
Neuromuscular blocking agent			
Succinylcholine	57 (41.61)	336 (57.63)	0.003
Rocuronium	13 (9.49)	40 (6.86)	
No muscle relaxant	67 (48.91)	207 (35.51)	
Intubation attempts			
One	113 (82.48)	487 (83.53)	0.071
Two	16 (11.68)	70 (12.01)	
Three or more	8 (5.84)	26 (4.46)	
Operator			
Extern	2 (1.46)	12 (2.06)	0.151
Resident	107 (78.10)	406 (69.64)	
Staff	28 (20.44)	165 (28.30)	
Anatomically difficult airway			
Number (%)	33 (24.09)	124 (21.27)	0.491

Data are presented as mean ± standard deviation (SD) or frequency. COPD: chronic obstructive pulmonary disease; RV: right ventricular; TBI: traumatic brain injury.

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Table 2: Associations of retained physiological predictors (pre-intubation factor) with peri-intubation severe adverse events and assigned points for the exploratory score

Predictor	OR	P	AOR	P	B*	Points
O2 saturation						
<90%	3.35 (1.38–8.11)	0.007	2.53 (0.99–6.47)	0.053	0.93	3
Suspected sepsis						
Yes	1.90 (1.28–2.82)	0.001	1.32 (0.86–2.02)	0.204	0.28	1
Serum bicarbonate						
<15 mEq/L	1.97 (1.28–3.04)	0.002	1.47 (0.92–2.34)	0.105	0.38	1
Vasopressor						
Requirement	3.32 (2.03–5.43)	<0.001	2.12 (1.25–3.60)	0.005	0.75	3
Shock index						
>0.9	3.28 (2.23–4.80)	<0.001	2.63 (1.76–3.93)	<0.001	0.97	3

Data are presented with 95% confidence interval. OR: odds ratio; AOR: Adjusted OR. Predictors were retained based on clinical plausibility within the physiological difficulty framework and the exploratory score derivation strategy. *: coefficient.

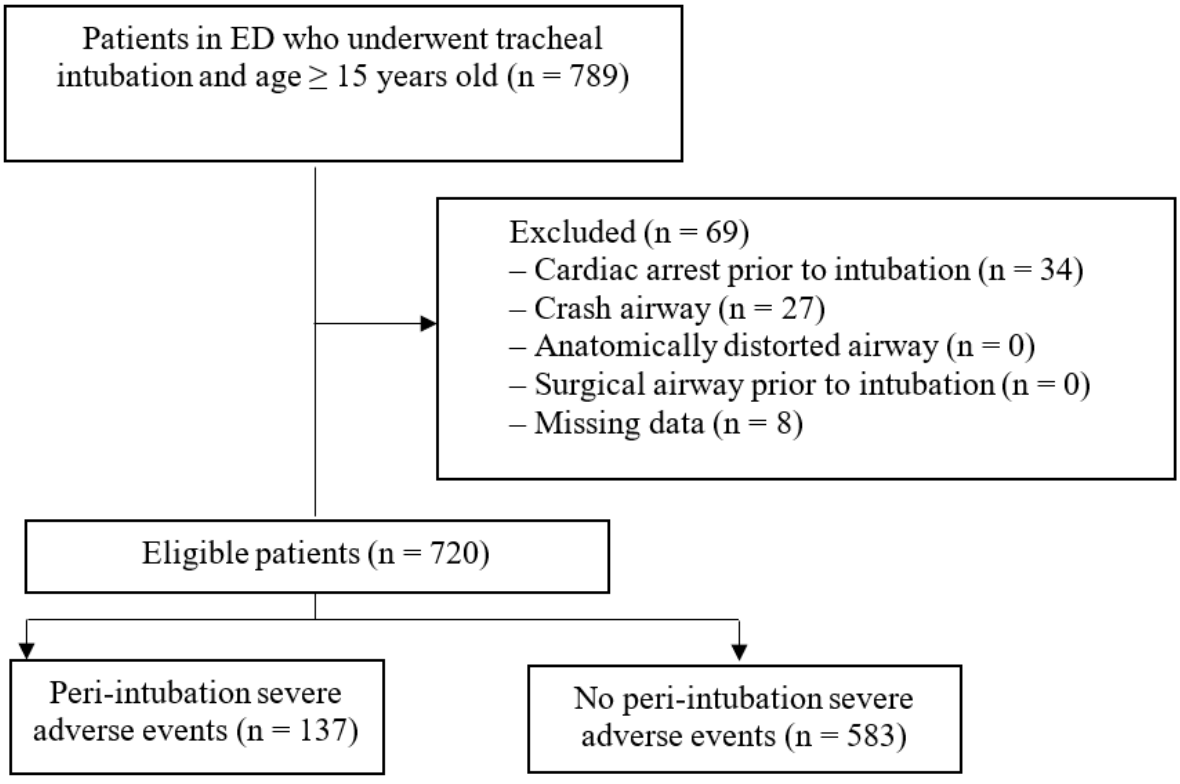

Figure 1: Study flow diagram of patients' inclusion. ED: Emergency department.

Table 3: Observed event distribution and diagnostic performance of the exploratory physiological difficulty score using a threshold of ≥5 points

Score	Total	Peri-intubation severe adverse events	
		Yes	No
<5 points	618	93 (15.0)	525 (85.0)
≥5 points	102	44 (43.1)	58 (56.9)
Overall	720	137 (19.0)	583 (81.0)

Data are presented as number (%).

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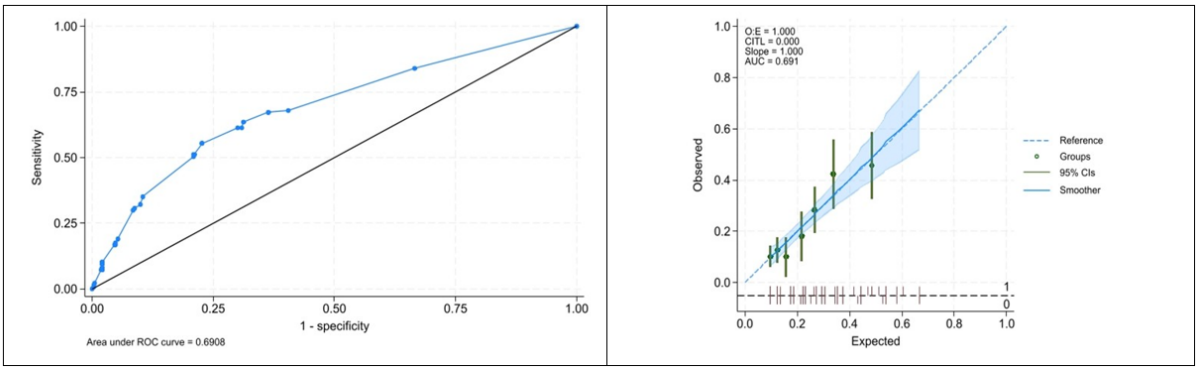

Figure 2: Receiver operating characteristic curve (ROC) of the exploratory physiological difficulty score for peri-intubation severe adverse events (left). Calibration plot of the exploratory physiological difficulty score for peri-intubation severe adverse events (right). CI: confidence interval; AUC: area under the curve.

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