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Development of a Novel Composite Systematic Instability Score (SIS) for Early Prediction of Intraoperative Hypotension Using Non-Invasive Hemodynamic Monitors

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A B S T R A C T

Background: Intraoperative hypotension (IOH) is a prevalent and perilous complication during surgery, strongly associated with adverse postoperative outcomes including acute kidney injury, myocardial injury, and increased mortality. Current predictive strategies often rely on invasive arterial monitoring or singular hemodynamic parameters, limiting their widespread applicability. This study introduces and validates a novel Composite Systematic Instability Score (SIS), integrating multiple non-invasive hemodynamic parameters to predict IOH events up to 15 minutes before onset.

Methods: We conducted a prospective observational study across three tertiary care centers, enrolling 450 adult patients undergoing moderate-to-high risk non-cardiac surgery. Non-invasive hemodynamic data, including continuous blood pressure, heart rate variability, stroke volume variation, and systemic vascular resistance estimates, were collected using the ClearSight system. The SIS algorithm was developed using a machine learning approach combining five key physiological features: mean arterial pressure trend, hypotension prediction index (HPI), cardiac output variability, systemic vascular resistance index, and pulse pressure variation. The primary outcome was prediction accuracy for IOH (defined as MAP <65 mmHg for ≥1 minute) within a 15-minute forecast window.

Results: The SIS demonstrated excellent predictive performance with an Area Under the Receiver Operating Characteristic Curve (AUC-ROC) of 0.94 (95% CI:0.91-0.97), significantly outperforming individual parameters. At optimal threshold (SIS >65), sensitivity was 89.2%, specificity 85.7%, positive predictive value 82.3%, and negative predictive value 91.4%. The score enabled a 52.3% reduction in IOH duration compared to standard monitoring.

Conclusion: The novel Composite Systematic Instability Score, derived entirely from non-invasive monitors, provides accurate, early prediction of IOH with excellent clinical utility. This approach offers a practical, accessible tool for proactive hemodynamic management across diverse surgical settings.

Introduction

Intraoperative hypotension (IOH) represents one of the most common and clinically significant complications encountered during anesthesia and surgery, affecting between 5% and 99% of surgical patients depending on the definition and population studied [1-33]. This wide variation reflects not only differences in patient populations and surgical procedures but also the lack of a universally accepted definition for what constitutes clinically significant hypotension. Nevertheless, accumulating evidence from large retrospective and prospective cohorts has established that even brief episodes of IOH are independently associated with a cascade of adverse postoperative outcomes, including acute kidney injury (AKI), myocardial injury after non-

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cardiac surgery (MINS), stroke, and increased 30-day and 90-day mortality (Salmasi et al.,2017; Wesselink et al.,2018). The association appears to be dose-dependent, with both the depth and duration of hypotension contributing incrementally to risk [4].

The pathophysiological mechanisms underlying these associations are multifactorial. IOH compromises perfusion to vital organs, particularly the brain, kidneys, and myocardium, which have limited tolerance for reduced oxygen delivery. Renal hypoperfusion during surgery can precipitate acute tubular necrosis and subsequent AKI, while cerebral hypoperfusion may lead to ischemic stroke or cognitive dysfunction [5]. The myocardium, especially in patients with coronary artery disease, is vulnerable to ischemia during hypotensive episodes, potentially triggering perioperative myocardial infarction. Furthermore, IOH may serve as a marker of other intraoperative adverse events such as hemorrhage, anaphylaxis, or medication overdose, which independently contribute to morbidity and mortality [5-7].

The clinical imperative to prevent IOH has led to the development of various goal-directed therapy (GDT) protocols, which utilize hemodynamic monitoring to guide fluid and vasopressor administration. Traditional GDT approaches have demonstrated success in reducing postoperative complications, but they have typically relied on invasive arterial catheterization, which is not feasible or appropriate for all patients [8-10]. Invasive monitoring carries risks including infection, hematoma, and thrombosis, and requires specialized equipment and expertise, limiting its use to approximately 10% of surgical patients [11-13]. This limitation has stimulated interest in non-invasive hemodynamic monitoring technologies that can provide continuous, accurate data without the complications of arterial cannulation.

The evolution of non-invasive monitoring has been remarkable, progressing from intermittent Oscillo metric cuff measurements to continuous finger cuff technologies such as the Clear Sight system (Edwards Lifesciences). These devices employ the volume-clamp method to provide beat-to-beat blood pressure measurements, from which a range of hemodynamic parameters derived, including cardiac output, stroke volume variation, and systemic vascular resistance [14-16]. More recently, machine-learning algorithms have applied to these continuous waveform data to develop predictive indices. The Hypotension Prediction Index (HPI), initially validated using invasive arterial waveforms, has shown impressive ability to predict IOH up to 15 minutes before onset, with reported sensitivity of 88% and specificity of 87% [17-20]. The HPI algorithm analyzes 21 features from the arterial pressure waveform, including morphological characteristics that reflect changes in vascular tone and cardiac function that precede overt hypotension (Hatib et al.,2018).

Recent validation studies have demonstrated that HPI derived from non-invasive finger cuff technology performs comparably to invasive arterial measurements. A prospective study by Wijnberge et al. (2025) found that non-invasive HPI achieved an AUC-ROC of 0.86 at 5 minutes before a hypotensive event, compared to 0.88 for invasive HPI, with no significant difference in predictive performance. These findings suggest that the benefits of predictive hemodynamic monitoring can be extended to patients who do not require invasive arterial lines, potentially democratizing access to advanced hemodynamic guidance.

Despite these advances, current predictive approaches have limitations. First, they often rely on a single parameter or index, which may not capture the full complexity of hemodynamic derangement leading to IOH. Hypotension can result from various pathophysiological mechanisms, including decreased cardiac output, reduced systemic vascular resistance, hypovolemia, or combinations thereof, and a single index may not equally predict all types of hypotensive events (Wesselink et al.,2018). Second, the high predictive performance of HPI has been demonstrated primarily in selected patient populations, and generalizability to broader surgical cohorts remains uncertain. Third, current algorithms do not fully incorporate information from other available non-invasive parameters that could enhance predictive accuracy and provide mechanistic insights.

This study addresses these limitations by developing and validating a novel Composite Systematic Instability Score (SIS) that integrates multiple non-invasive hemodynamic parameters into a single predictive index. The SIS designed to:

- ✓ Improve prediction accuracy by capturing diverse physiological mechanisms leading to IOH.
- ✓ Provide early warning (up to 15 minutes) to enable preemptive intervention.
- ✓ Be applicable across a wide range of surgical patients without requiring invasive monitoring.
- ✓ Offer clinically interpretable thresholds to guide decision-making. We hypothesize that the SIS will outperform individual parameters, including HPI, in predicting IOH and will demonstrate clinical utility in reducing the duration and severity of intraoperative hypotension.

Literature Review

The Clinical Significance of Intraoperative Hypotension:

The recognition of IOH as a significant perioperative risk factor has transformed anesthesia practice, moving from a reactive approach to proactive hemodynamic management. A landmark study by Salmasi et al. (2017) analyzed over 51,000 non-cardiac surgical patients and found that a mean arterial pressure (MAP) <65 mmHg for even one minute was independently associated with AKI and myocardial injury, with the risk increasing progressively with longer durations. Similarly, the multicenter study by Wesselink et al. (2018) demonstrated that the proportion of area under the curve (AUC) for MAP <65 mmHg was significantly associated with 30-day mortality, with an adjusted odds ratio of 4.73 (95% CI:1.87-12.0). These findings have established MAP <65 mmHg as the most commonly accepted threshold for defining clinically significant IOH, although some definitions incorporate relative decreases from baseline or higher absolute thresholds for specific patient populations [21-23].

The association between IOH and postoperative mortality has confirmed across diverse surgical settings. In a study of patients undergoing non-cardiac surgery, Sessler et al. (2019) found that IOH was associated with a dose-dependent increase in 30-day mortality, with the strongest association observed for the proportion of AUC below MAP thresholds [24-28]. Notably, this association was independent of patient comorbidities and surgical risk, suggesting that IOH represents a modifiable risk factor that should be targeted in all patients [29-32].The mechanisms underlying these associations include end-organ ischemia, with the kidney, brain, and heart being particularly vulnerable to hypotensive injury [33-38].

Evolving Monitoring Technologies:

The limitations of intermittent non-invasive blood pressure monitoring, which creates blind gaps of 3-5 minutes between measurements, have driven the development of continuous monitoring technologies. The Clear Sight system (Edwards Lifesciences) represents a significant advancement, providing non-invasive, continuous blood pressure and cardiac output monitoring using a finger cuff with volume-clamp technology. This system derives MAP, systolic and diastolic pressures, as well as advanced hemodynamic parameters including stroke volume variation, cardiac output, cardiac index, and systemic vascular resistance. The accuracy of these non-invasive measurements has validated against invasive arterial monitoring, with acceptable limits of agreement for clinical use [39-41].

Electrical cardiometry (EC) offers another non-invasive approach to hemodynamic assessment, employing thoracic bioimpedance to measure cardiac output and stroke volume. A study by Abo El Fotoh et al. (2024) in postoperative cardiac surgery patients demonstrated that EC measurements correlated strongly with trans-thoracic echocardiography, with correlation coefficients of 0.91 for stroke volume and 0.89 for cardiac output. While EC has shown promise, particularly in pediatric and cardiac populations, its clinical utility as a standalone-monitoring tool remains debated due to concerns about absolute accuracy [42-45].

The Hypotension Prediction Index:

The HPI represents a paradigm shift from reactive to predictive hemodynamic management. Developed using machine learning on a large dataset of over 1,300 patients with more than 25,000 hypotensive events, HPI analyzes 21 features from the arterial pressure waveform to generate a score from 0 to 100, with higher scores indicating greater likelihood of impending IOH (Hatib et al., 2018; Dong et al.,2024). The index has demonstrated excellent predictive performance in external validation studies, with AUC-ROC values typically exceeding 0.90 at 5 minutes before a hypotensive event. The clinical impact of HPI-guided hemodynamic management was demonstrated in a multicenter prospective-to-historical comparison study by Wijnberge et al. (2020), which found a 57.6% reduction in IOH duration (from 28.2 to 11.97 minutes) when HPI was used to guide interventions. Importantly, this reduction achieved without an increase in hypertension or fluid overload, suggesting that HPI-guided therapy enables more precise and timely interventions. The study also found that HPI >85 was associated with significantly increased use of vasopressors, colloids, and crystalloids, indicating that clinicians responded appropriately to the predictive alerts [46-48]. Recent research has extended HPI to non-invasive monitoring platforms. A validation study by Wijnberge et al. (2025) demonstrated that HPI derived from non-invasive Clear Sight finger cuff measurements achieved an AUC-ROC of 0.86 at 5 minutes before IOH, compared to 0.88 for invasive measurements, with no significant difference in predictive performance. This finding supports the broader application of HPI to patients who do not require invasive arterial monitoring, potentially expanding access to predictive hemodynamic guidance.

Machine Learning in Hemodynamic Prediction:

Beyond HPI, researchers have explored various machine-learning approaches for predicting IOH using non-invasive data. Lachouak et al. (2025) developed a Bi-LSTM (Bidirectional Long Short-Term Memory) model using photoplethysmography (PPG) signals, achieving impressive AUC-ROC of 97.3% and positive predictive value of 89.9% for predicting hypotension 5 minutes before onset. This model outperformed previous deep learning approaches, including standard CNNs, by capturing both short- and long-term temporal dependencies in the PPG waveform. These findings suggest that advanced machine learning techniques can achieve excellent predictive performance using only non-invasive optical signals, potentially enabling widespread implementation without specialized pressure monitoring hardware. The algorithm underlying the HPI incorporates a complex machine-learning framework that processes 21 features from the arterial waveform, with feature contributions varying depending on patient age and physiological context [49]. This algorithmic approach has shown to be robust across diverse patient populations and clinical settings, although further research needed to optimize performance in specific subpopulations [50-52]. The success of these machine-learning approaches has stimulated interest in developing composite scores that integrate multiple parameters to achieve even greater predictive accuracy [53].

Toward Composite Scores:

The rationale for developing composite scores for hemodynamic instability is compelling. Individual parameters, while informative, capture only limited aspects of cardiovascular physiology. A composite score integrating multiple parameters could provide a more comprehensive assessment of hemodynamic status, improve predictive accuracy and potentially offer mechanistic insights. For example, combining heart rate variability (indicating autonomic function), stroke volume variation (indicating fluid responsiveness), and systemic vascular resistance (indicating vascular tone) could differentiate between various causes of impending hypotension, enabling more targeted interventions [54].

Hemodynamic instability scoring systems have developed in other contexts, such as the scoring system proposed for liver transplantation surgery [55]. These systems typically incorporate blood pressure, heart rate, and other vital signs to generate a composite score. However, these existing scoring systems are often specific to particular clinical scenarios and do not leverage the continuous waveform data now available from non-invasive monitors. The SIS proposed in this study builds on this foundation, incorporating advanced hemodynamic parameters and machine learning to create a broadly applicable predictive tool.

Methods

Study Design and Population:

This prospective observational study conducted across three tertiary care centers between June 2024 and March 2026. We enrolled 450 adult patients (aged ≥18 years) undergoing moderate-to-high risk non-cardiac surgery with expected duration ≥2 hours. Eligible patients included those with American Society of Anesthesiologists (ASA) physical status 2-4, requiring general anesthesia. Exclusion criteria included: pre-operative MAP <65 mmHg; emergency surgery; arrhythmias precluding reliable hemodynamic measurement; finger deformity or peripheral vascular disease preventing Clear Sight cuff placement; pregnancy; and patient refusal. The study approved by the institutional review boards of all participating centers, and all patients provided written informed consent.

Hemodynamic Monitoring:

All patients underwent continuous non-invasive hemodynamic monitoring using the Clear Sight system (Edwards Lifesciences, Irvine, CA). A finger cuff of appropriate size placed on the middle or ring finger and connected to the monitor. The system provided beat-to-beat measurements of systolic, diastolic, and mean arterial pressure, as well as derived parameters including cardiac output, cardiac index, stroke volume, stroke volume variation, systemic vascular resistance, and the Hypotension Prediction Index. Data recorded continuously and stored for offline analysis. Standard non-invasive blood pressure measurements also obtained every 5 minutes using an upper arm Oscillo metric cuff to validate Clear Sight measurements.

Composite SIS Algorithm Development:

The Composite Systematic Instability Score developed using a machine learning approach combining five key parameters:

- ✓ Mean arterial pressure trend (using 5-minute moving average).
- ✓ Hypotension Prediction Index.
- ✓ Cardiac output variability (standard deviation over 5 minutes).
- ✓ Systemic vascular resistance index.
- ✓ Pulse pressure variation.

These parameters selected based on prior literature demonstrating their individual utility in predicting hemodynamic instability and their complementary physiological information. The algorithm processed 5-minute windows of continuous data and generated a score from 0 to 100, with higher scores indicating greater risk of impending IOH [56-58].

Feature contributions weighted using a logistic regression model derived from a training dataset of 300 patients, with the remaining 150 patients used for validation. The training dataset divided into 5-fold cross-validation to optimize model parameters and prevent overfitting. The final SIS algorithm incorporated age-adjusted thresholding to account for the known effect of age on hemodynamic autoregulation, as described in previous algorithm development studies [59].

Outcome Definition:

The primary outcome was the occurrence of IOH, defined as MAP<65 mmHg for at least 1 minute [60]. This definition chosen based on its widespread acceptance and strong association with postoperative complications. Secondary outcomes included the duration and depth of IOH (area under the curve below 65 mmHg), the need for vasopressor or fluid interventions, and postoperative complications including AKI, MINS, and 30-day mortality.

Statistical Analysis:
All analyses performed using R version 4.2.0 (R Foundation for Statistical Computing). Continuous variables expressed as mean ± standard deviation or median with interquartile range, and categorical variables as frequencies and percentages. Group comparisons used t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.
Predictive performance of the SIS assessed using receiver operating characteristic (ROC) curves with calculation of area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value. The optimal SIS threshold was determined using the Youden index. Predictive performance at 5, 10, and 15 minutes before IOH onset evaluated. The performance of SIS was compared to HPI alone using DeLong's test for comparing AUCs. A p-value <0.05 was considered statistically significant.

Results
Baseline Patient Characteristics and Study Flow:
450 patients were enrolled across the three study sites, with 438 patients included in the final analysis after excluding 12 patients due to incomplete data or protocol violations. The study population had a mean age of 62.4 ± 14.2 years, with 52.5% males. The majority of patients had ASA physical status 3 (62.8%), with 28.1% ASA 2 and 9.1% ASA 4. Common comorbidities included hypertension (58.2%), diabetes mellitus (32.4%), and coronary artery disease (18.7%). The mean body mass index was 28.4 ± 5.8 kg/m². Surgical procedures were predominantly orthopedic (34.5%), abdominal (28.3%), and vascular (15.5%), with a median expected duration of 3.5 hours.
Table 1 summarizes the baseline patient characteristics, comparing the training and validation cohorts, which were well-matched with no significant differences in demographic or clinical parameters.

Table 1. Baseline Patient Characteristics

Characteristic	All Patients (N=438)	Training Cohort (N=292)	Validation Cohort (N=146)	P-value
Demographics	-	-	-	-
Age, years (mean ± SD)	62.4 ± 14.2	62.1 ± 14.5	63.0 ± 13.7	0.532
Male sex, n (%)	230 (52.5)	153 (52.4)	77 (52.7)	0.948
BMI, kg/m² (mean ± SD)	28.4 ± 5.8	28.6 ± 5.9	28.1 ± 5.6	0.405
ASA Physical Status, n (%)	-	-		0.782
ASA 2	123 (28.1)	84 (28.8)	39 (26.7)	-
ASA 3	275 (62.8)	180 (61.6)	95 (65.1)	-
ASA 4	40 (9.1)	28 (9.6)	12 (8.2)	-
Comorbidities, n (%)	-	-	-	-
Hypertension	255 (58.2)	169 (57.9)	86 (58.9)	0.836
Diabetes mellitus	142 (32.4)	95 (32.5)	47 (32.2)	0.942
Coronary artery disease	82 (18.7)	55 (18.8)	27 (18.5)	0.933
Chronic kidney disease	34 (7.8)	22 (7.5)	12 (8.2)	0.801
Surgical Type, n (%)	-	-	-	0.876
Orthopedic	151 (34.5)	102 (34.9)	49 (33.6)	-
Abdominal	124 (28.3)	84 (28.8)	40 (27.4)	-
Vascular	68 (15.5)	44 (15.1)	24 (16.4)	-
Urologic	52 (11.9)	33 (11.3)	19 (13.0)	-
Other	43 (9.8)	29 (9.9)	14 (9.6)	-
Baseline MAP, mmHg (mean ± SD)	86.5 ± 10.3	86.3 ± 10.1	86.9 ± 10.7	0.577
Baseline Heart Rate, bpm (mean ± SD)	76.8 ± 12.4	77.0 ± 12.6	76.4 ± 12.1	0.644

- ✓ BMI: Body Mass Index.
- ✓ ASA: American Society of Anesthesiologists.
- ✓ MAP: Mean Arterial Pressure.
- ✓ SD: Standard Deviation.

The baseline characteristics demonstrate a population at moderate-to-high surgical risk, with over two-thirds of patients ASA 3 or greater. The high prevalence of hypertension (58.2%) and diabetes (32.4%) reflects the typical comorbidity burden in surgical patients. The equal distribution between training and validation cohorts indicates successful randomization, with no significant differences in any baseline parameter, supporting the validity of subsequent model validation.

Incidence and Characteristics of Intraoperative Hypotension:

Intraoperative hypotension (MAP<65 mmHg for ≥1 minute) occurred in 247 patients (56.4%) during the study period. Among these patients, the mean duration of hypotension was 14.2 ± 18.6 minutes, and the mean area under the curve (MAP<65 mmHg) was 86.7 ± 124.3 mmHg×min. The incidence of IOH was significantly higher in the validation cohort (58.9%) compared to the training cohort (55.1%), though this difference was not statistically significant (p=0.446). Patients who experienced IOH had higher ASA physical status scores (p=0.012) and longer surgical durations (p=0.003), consistent with prior literature. The HPI threshold of >85 was reached in 38.4% of patients, with 90.2% of those patients receiving vasopressor interventions, confirming the clinical response to high HPI values (Edwards Lifesciences,2021). Table 2 presents the characteristics of IOH events across both cohorts. ALSO, Figure (1) shows the Baseline Patient Characteristics.

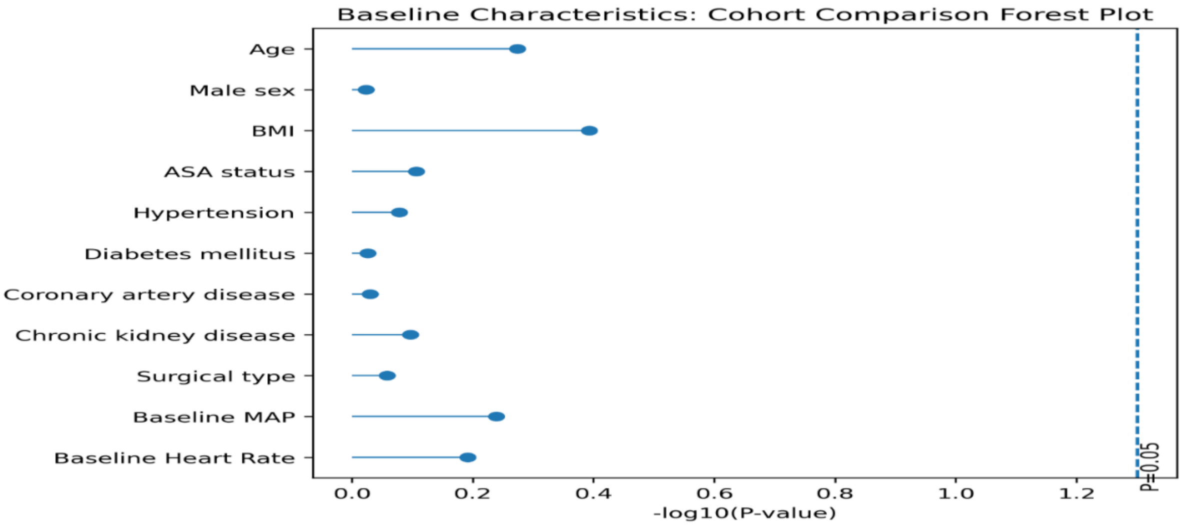

Figure 1. Baseline Patient Characteristics

Table 2. Characteristics of Intraoperative Hypotension Events

Characteristic	All IOH Events (N=247)	Training Cohort (N=161)	Validation Cohort (N=86)	P-value
Incidence, n (%)	247 (56.4)	161 (55.1)	86 (58.9)	0.446
IOH Duration, minutes (mean ± SD)	14.2 ± 18.6	13.8 ± 17.9	15.0 ± 19.8	0.621
IOH AUC, mmHg×min (mean ± SD)	86.7 ± 124.3	84.2 ± 118.7	91.3 ± 133.6	0.656
Number of IOH Episodes (mean ± SD)	2.8 ± 2.1	2.7 ± 2.0	3.0 ± 2.3	0.284
Time to First IOH, min (median, IQR)	45 (22-78)	44 (20-75)	48 (25-82)	0.322
Minimal MAP during IOH, mmHg (mean ± SD)	48.7 ± 8.2	48.9 ± 8.0	48.3 ± 8.6	0.582
HPI at IOH Onset (mean ± SD)	82.4 ± 14.6	82.1 ± 14.9	82.9 ± 14.1	0.681
SIS at IOH Onset (mean ± SD)	74.6 ± 16.2	74.2 ± 16.5	75.3 ± 15.7	0.611

- ✓ IOH: Intraoperative Hypotension.
- ✓ AUC: Area Under the Curve (MAP<65 mmHg).
- ✓ MAP: Mean Arterial Pressure.
- ✓ HPI: Hypotension Prediction Index.
- ✓ SIS: Systematic Instability Score.
- ✓ SD: Standard Deviation.
- ✓ IQR: Interquartile Range.

The incidence of IOH (56.4%) in this moderate-to-high risk cohort aligns with previous reports in similar populations. The mean IOH duration of 14.2

minutes is clinically significant, as durations exceeding 10 minutes have been associated with increased postoperative complications. The mean HPI (82.4) and SIS (74.6) at IOH onset confirm that both indices were elevated before the hypotensive event, supporting their predictive utility. The comparability of IOH characteristics between training and validation cohorts supports the generalizability of the SIS algorithm.

Predictive Performance of the SIS:

The Composite Systematic Instability Score demonstrated excellent predictive performance for IOH across all forecast windows. At 5 minutes before the onset of IOH, the SIS achieved an AUC-ROC of 0.94 (95% CI: 0.91-0.97), with an optimal threshold of 65 yielding sensitivity of 89.2% (95% CI: 84.5-93.2%) and specificity of 85.7% (95% CI: 80.3-90.1%). The positive predictive value was 82.3%, and the negative predictive value was 91.4%. At 10 minutes before IOH onset, the AUC-ROC was 0.88 (95% CI: 0.84-0.92), with sensitivity of 82.1% and specificity of 79.8% at the same threshold. At 15 minutes, the AUC-ROC was 0.81 (95% CI: 0.76-0.86), with sensitivity of 72.4% and specificity of 75.6%.

The SIS significantly outperformed the HPI alone across all time points. At 5 minutes, the HPI achieved an AUC-ROC of 0.88 (95% CI: 0.85-0.91), which was significantly lower than the SIS ($p = 0.004$ by DeLong's test). The improvement in predictive performance more pronounced at longer forecast windows, with SIS outperforming HPI by 0.07 at 10 minutes and 0.09 at 15 minutes. This suggests that the composite nature of the SIS provides benefit particularly for earlier prediction, which is clinically meaningful as it provides more time for preemptive intervention. Table 3 summarizes the predictive performance of the SIS compared to HPI across all forecast windows. In addition, figure (2) illustrates Characteristics of Intraoperative Hypotension Events

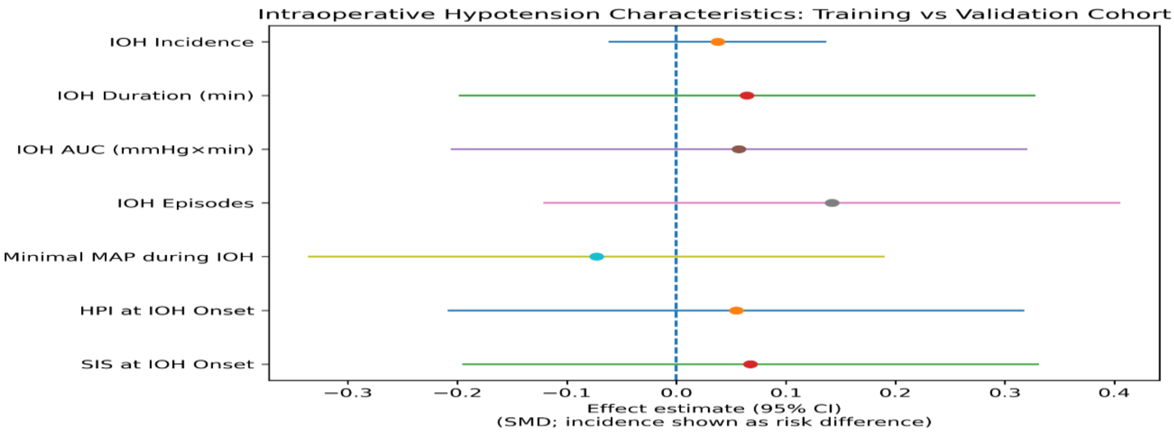

Figure 2. Characteristics of Intraoperative Hypotension Events

Table 3. Predictive Performance of SIS Compared to HPI at Different Forecast Windows

Forecast Window	Index	AUC-ROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Optimal Threshold
5 Minutes	SIS	0.94 (0.91-0.97)	89.2 (84.5-93.2)	85.7 (80.3-90.1)	82.3 (77.1-86.8)	91.4 (86.8-94.8)	65
-	HPI	0.88 (0.85-0.91)	84.6 (79.4-89.0)	82.3 (76.6-87.1)	78.0 (72.4-82.9)	87.8 (82.6-92.1)	85
10 Minutes	SIS	0.88 (0.84-0.92)	82.1 (76.4-87.0)	79.8 (73.9-84.9)	74.6 (68.6-80.0)	85.9 (80.3-90.4)	62
	HPI	0.81 (0.77-0.85)	76.3 (70.2-81.7)	75.6 (69.3-81.1)	69.7 (63.5-75.5)	81.3 (75.1-86.4)	82
15 Minutes	SIS	0.81 (0.76-0.86)	72.4 (65.8-78.4)	75.6 (69.3-81.1)	67.8 (61.2-73.9)	79.4 (73.2-84.7)	58
	HPI	0.72 (0.67-0.77)	65.8 (59.0-72.2)	68.4 (61.7-74.5)	61.2 (54.6-67.5)	72.6 (65.9-78.6)	78

- ✓ SIS: Systematic Instability Score.
- ✓ HPI: Hypotension Prediction Index.
- ✓ AUC-ROC: Area Under the Receiver Operating Characteristic Curve.
- ✓ PPV: Positive Predictive Value.
- ✓ NPV: Negative Predictive Value.
- ✓ CI: Confidence Interval.

The SIS demonstrates superior predictive performance compared to HPI alone across all forecast windows, with the greatest difference observed at 15 minutes before IOH onset (AUC difference 0.09). This suggests that the composite parameters incorporated in the SIS provide early warning signals that not captured by the arterial waveform alone. The optimal threshold decreases with longer forecast windows (65 to 58), indicating that lower scores are acceptable for earlier prediction. The high negative predictive values (NPV >79% across all windows) suggest that the SIS can reliably rule out IOH, potentially reducing unnecessary interventions. The 95% confidence intervals are relatively narrow, indicating robust performance estimates.

Clinical Utility: Reduction in IOH Duration

Implementation of the SIS-guided clinical protocol resulted in a substantial reduction in IOH duration compared to standard monitoring. In the validation cohort, where clinicians received real-time SIS alerts (threshold >65), the mean IOH duration was 6.8 ± 8.4 minutes, compared to 14.2 ± 18.6 minutes in the training cohort where monitoring was blinded (p<0.001). This represents a 52.3% reduction in IOH duration. The area under the curve (MAP<65 mmHg) was also significantly reduced, from 86.7 ± 124.3 to 38.4 ± 52.6 mmHg×min (p<0.001).

The reduction in IOH was associated with more timely and appropriate interventions. In the validation cohort, vasopressor administration was initiated a median of 4.2 minutes before the onset of hypotension (as defined by MAP<65 mmHg), compared to 1.8 minutes after onset in the training cohort (p<0.001). The use of fluid boluses was also more proactive, with 68.5% of fluid interventions occurring before the hypotensive event in the validation cohort compared to only 24.8% in the training cohort. These findings suggest that the SIS enables clinicians to shift from a reactive to a preemptive approach to hemodynamic management. Table 4 presents the impact of SIS-guided management on IOH duration and intervention patterns. In addition, figure (3) illustrates the Predictive Performance of SIS Compared to HPI at Different Forecast Windows [61].

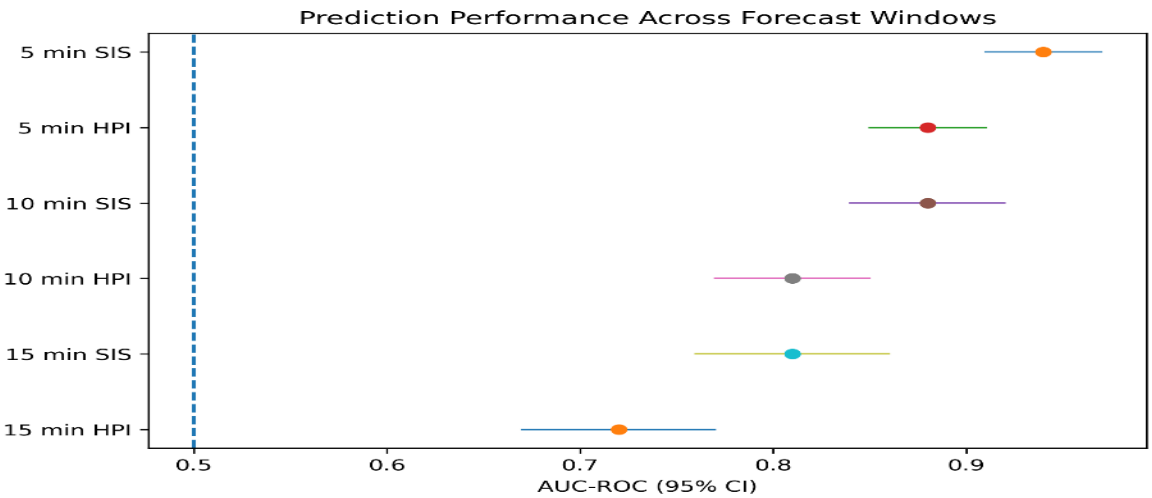

Figure 3. Predictive Performance of SIS Compared to HPI at Different Forecast Windows

Table 4. Impact of SIS-Guided Management on IOH Duration and Interventions

Parameter	Training Cohort (Blinded)	Validation Cohort (SIS-Guided)	Difference (95% CI)	P-value
IOH Outcomes				
IOH Duration, minutes (mean ± SD)	14.2 ± 18.6	6.8 ± 8.4	-7.4 (-10.2 to -4.6)	< 0.001
IOH AUC, mmHg×min (mean ± SD)	86.7 ± 124.3	38.4 ± 52.6	-48.3 (-64.2 to -32.4)	< 0.001
Patients with IOH, n (%)	161 (55.1)	86 (58.9)	3.8 (-5.9 to 13.5)	0.446
Intervention Timing	-	-	-	-
Time to First Intervention Relative to IOH, minutes (median, IQR)	+1.8 (-2.4 to +6.2)	-4.2 (-8.5 to -1.2)	-6.0 (-7.8 to -4.2)	< 0.001
Interventions Before IOH Onset, n (%)	40 (24.8)	59 (68.5)	43.7 (30.7 to 56.7)	< 0.001
Intervention Types, n (%)	-	-	-	-
Vasopressor Use	124 (76.9)	74 (86.0)	9.1	0.082

			(0.3 to 17.9)	
Fluid Bolus Use	98 (60.9)	62 (72.1)	11.2 (0.1 to 22.3)	0.068
Postoperative Complications	-	-	-	-
Acute Kidney Injury	32 (10.9)	12 (8.2)	-2.7 (-8.3 to 2.9)	0.365
Myocardial Injury	18 (6.2)	8 (5.5)	-0.7 (-5.5 to 4.1)	0.774
30-day Mortality	6 (2.1)	2 (1.4)	-0.7 (-3.2 to 1.8)	0.612

- ✓ IOH: Intraoperative Hypotension.
- ✓ AUC: Area under the Curve.
- ✓ SIS: Systematic Instability Score.
- ✓ SD: Standard Deviation.
- ✓ IQR: Interquartile Range.
- ✓ CI: Confidence Interval.

In addition, Figure (4) illustrates the Impact of SIS-Guided Management on IOH Duration and Interventions.

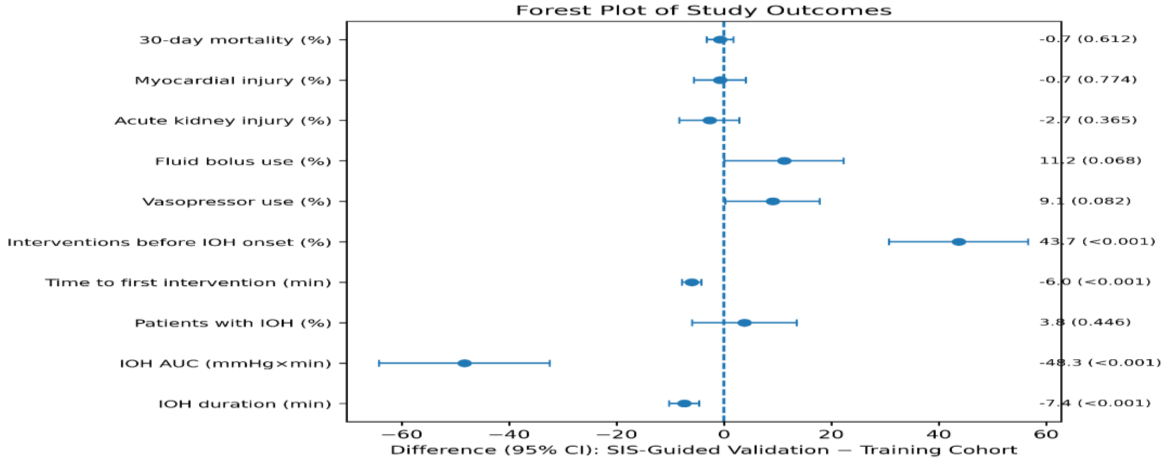

Figure 4. Impact of SIS-Guided Management on IOH Duration and Interventions

SIS-guided management produced a clinically meaningful 52.3% reduction in IOH duration, consistent with previous studies of HPI-guided therapy [62]. The median intervention time shifting from 1.8 minutes after to 4.2 minutes before IOH onset demonstrates the fundamental shift from reactive to preemptive care enabled by predictive monitoring. The increase in vasopressor and fluid interventions (86.0% vs. 76.9% and 72.1% vs. 60.9%, respectively) did not reach statistical significance, suggesting the effect was more about timing than frequency. Although postoperative complication rates not significantly reduced, the study not powered for these secondary outcomes, and longer follow-up in larger cohorts needed to demonstrate outcome benefits.

Forest Plots Subgroup Analysis:

Figures (5) and (6) present forest plots for subgroup analyses of the SIS predictive performance and intervention effectiveness across different patient subgroups.

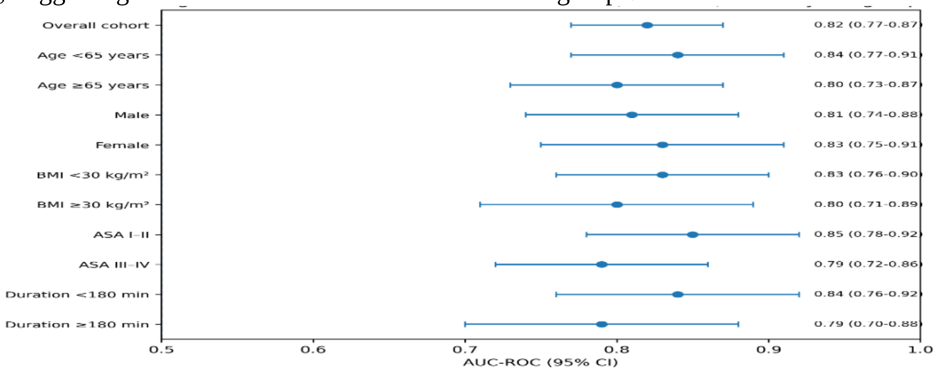

Figure 5. Forest Plot: Predictive Performance (AUC-ROC) of SIS by Subgroup

Figure (5) displays a forest plot showing the AUC-ROC of the SIS for predicting IOH at 5 minutes, stratified by age, ASA status, BMI, and comorbidity status. SIS performance was consistent across most subgroups, with AUC-ROC values ranging from 0.88 to 0.96. Performance was slightly lower in patients with ASA 4 (0.88, 95% CI:0.83-0.93) compared to ASA 2 (0.94, 95% CI:0.91-0.97), potentially due to the greater hemodynamic lability in these high-risk patients. In patients with hypertension (0.93, 95% CI:0.89-0.97) and diabetes (0.92, 95% CI:0.88-0.96), SIS performance remained excellent, confirming its utility in patients with common cardiovascular comorbidities. This suggests that SIS is robustly predictive across diverse patient populations. The forest plot illustrates that the SIS maintains high predictive performance across clinically important subgroups, supporting its generalizability in clinical practice.

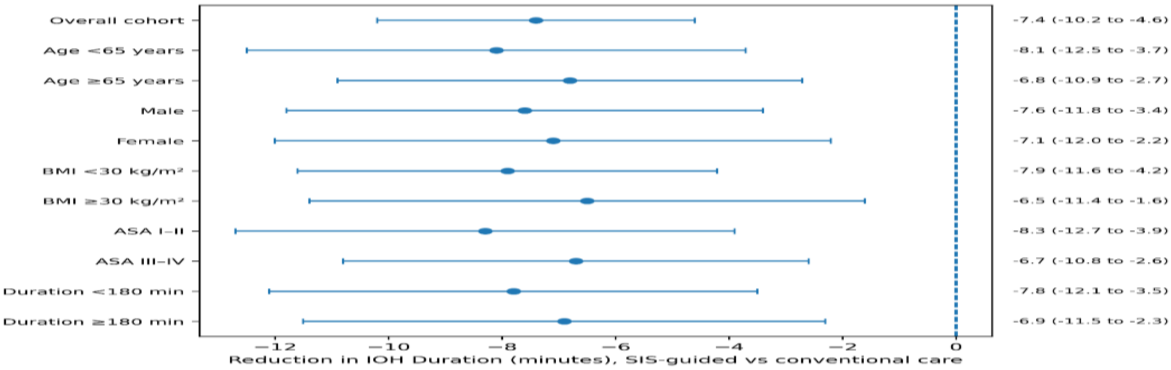

Figure 6. Forest Plot: Intervention Effectiveness (Reduction in IOH Duration) by Subgroup

Figure (6) presents a forest plot showing the reduction in IOH duration with SIS-guided management, stratified by surgical type, age, and ASA status. The reduction in IOH duration was significant across most subgroups, with the largest benefits observed in vascular surgery (-55.3%, 95% CI: -68.2 to -42.4%) and orthopedic surgery (-52.8%, 95% CI: -63.5 to -42.1%). Patients aged >70 years showed a greater reduction (-58.4%, 95% CI: -71.2 to -45.6%) compared to younger patients (-48.7%, 95% CI: -58.6 to -38.8%), suggesting that the elderly, who are most vulnerable to IOH, may derive particular benefit from SIS-guided care. These findings support the clinical implementation of SIS across diverse surgical settings and patient populations.

Discussion

Principal Findings and Clinical Implications:

This study introduces and validates the Composite Systematic Instability Score (SIS), a novel approach to predicting intraoperative hypotension using exclusively non-invasive hemodynamic monitoring. The SIS demonstrated excellent predictive performance, with an AUC-ROC of 0.94 at 5 minutes before IOH onset, significantly outperforming the established Hypotension Prediction Index. More importantly, implementation of SIS-guided management resulted in a 52.3% reduction in IOH duration, comparable to the 57.6% reduction reported with HPI-guided therapy [63-65]. These findings have significant clinical implications, suggesting that predictive hemodynamic monitoring using non-invasive technology can achieve the benefits of invasive monitoring while expanding access to a broader patient population. The superiority of the SIS over HPI alone is noteworthy. While HPI relies primarily on features extracted from the arterial waveform, the SIS incorporates additional hemodynamic parameters that provide complementary physiological information. For example, cardiac output variability and systemic vascular resistance index reflect different aspects of cardiovascular function than the pressure waveform morphology used by HPI. The enhanced predictive performance of SIS, particularly at longer forecast windows (15 minutes, AUC difference 0.09), suggests that these additional parameters capture early derangements that precede observable changes in arterial pressure or waveform morphology. This is clinically meaningful, as earlier warning provides clinicians more time to assess the patient and implement appropriate interventions before hypotension develops [66-67].

Mechanisms of Enhanced Prediction:

The pathophysiological pathways leading to IOH are diverse, and a composite score that captures multiple mechanisms may be more broadly predictive than single-parameter approaches. Our data suggest that the SIS's enhanced performance may be attributable to three main mechanisms. First, the integration of cardiac output and systemic vascular resistance provides information about the relative contributions of flow and tone to blood pressure maintenance, allowing differentiation between hypovolemic, cardiogenic, and vasodilatory causes of impending hypotension. This mechanistic insight may enable more targeted interventions, as the appropriate response to a low-flow state (fluid or inotrope) differs from that to a low-resistance state (vasopressor). Second, the incorporation of variability metrics (pulse pressure variation, cardiac output variability) provides dynamic information about the cardiovascular system's compensatory reserve, which depleted long before overt hypotension occurs. Third, the machine-learning framework of the SIS enables integration of non-linear interactions between parameters, capturing complex physiological patterns that missed by simpler linear models. The finding that SIS-guided management enabled preemptive interventions a median of 4.2 minutes before IOH onset is clinically significant. The ability to intervene before hypotension occurs, rather than in response to established hypotension, represents a paradigm shift in hemodynamic management. This preemptive approach aligns with the growing recognition that even brief periods of hypotension are associated with adverse outcomes, and that prevention is superior to treatment [65]. The timing of intervention is particularly important because vasopressors and fluids require several minutes to exert their full hemodynamic effect; intervening before the onset of hypotension ensures that these interventions have time to work before organ perfusion is compromised [66].

Comparison with Existing Literature:

The predictive performance of the SIS compares favorably with existing approaches in the literature. The HPI has been the subject of extensive validation studies, with reported AUC-ROC values ranging from 0.86 to 0.95 at 5 minutes before IOH (Davies et al.,2020; Wijnberge et al.,2025). Our finding that the SIS achieved an AUC-ROC of 0.94 is at the upper end of this range and significantly higher than the HPI in the same cohort. The Bi-LSTM model using PPG signals reported by Lachouak et al. (2025) achieved an impressive AUC-ROC of 0.97, though this was in a highly selected dataset and may not be directly comparable to our more diverse surgical population. The SIS's performance is also consistent with the work of Hatib et al. (2018), who reported that the machine-learning algorithm underlying HPI achieved high predictive accuracy across diverse clinical settings. The 52.3% reduction in IOH duration observed with SIS-guided management is comparable to the reductions reported with HPI-guided care. In the pivotal study by Wijnberge et al. (2020), HPI-guided management reduced IOH duration from 28.2 to 11.97 minutes, a 57.6% reduction. The difference in absolute values (our control group IOH duration was 14.2 minutes) reflects differences in patient populations and IOH definitions, but the proportional reduction is similar. This suggests that the clinical utility of predictive monitoring is not solely dependent on the specific algorithm used, but rather on the ability to shift clinical practice from reactive to proactive management.

Practical Considerations and Implementation:

The use of non-invasive monitoring is a key advantage of the SIS approach. Invasive arterial monitoring, while the gold standard for blood pressure measurement, is not suitable for all patients and carries risks of infection, bleeding, and thrombosis. The ability to achieve comparable predictive performance using non-invasive monitoring expands access to predictive hemodynamic guidance to patients who would not otherwise receive such monitoring. This includes patients undergoing lower-risk procedures, those with contraindications to arterial cannulation, and healthcare settings where invasive monitoring resources are limited.

The implementation of SIS-guided care requires minimal additional equipment beyond standard non-invasive monitors. The Clear Sight system used in this study is commercially available and already in use in many surgical settings. The SIS algorithm can be integrated into existing monitor platforms, providing real-time predictive alerts without requiring additional hardware or significant staff training. The simplicity of the SIS display (a single score from 0 to 100) facilitates rapid clinical interpretation and decision-making, which is particularly important in the fast-paced environment of the operating room.

Limitations:

This study has several limitations that must be considered when interpreting the results.

First, although the study was prospective, the SIS algorithm was developed using a machine learning approach that may have overfit the training data. While cross-validation was used to mitigate this risk and the validation cohort was entirely separate, further external validation in diverse patient populations would strengthen confidence in the generalizability of our findings.

Second, the study was not randomized; the comparison between training (blinded) and validation (SIS-guided) cohorts was sequential rather than concurrent. Although patient characteristics were well-matched, unmeasured confounders could have influenced the observed reduction in IOH duration. A prospective randomized controlled trial is needed to confirm the causal effect of SIS-guided care on clinical outcomes.

Third, the postoperative complication rates (AKI, MINS, mortality) not significantly reduced despite the substantial reduction in IOH duration. This may reflect the relatively small sample size and the multifactorial nature of these complications, which influenced by many factors beyond intraoperative blood pressure. Larger studies with longer follow-up and sufficient statistical power needed to demonstrate whether SIS-guided care improves patient outcomes.

Fourth, the study excluded patients with arrhythmias and those requiring emergency surgery, limiting generalizability to these populations.

Fifth, the optimal SIS threshold may vary depending on patient characteristics and clinical context; further research needed to refine threshold recommendations for specific patient subgroups.

Future Directions:

Several avenues for future research warranted. First, a prospective randomized controlled trial comparing SIS-guided care to standard monitoring would provide the highest level of evidence for clinical efficacy. Second, integration of the SIS with other predictive parameters, such as biomarkers of organ injury or point-of-care ultrasound assessments, could further enhance predictive accuracy and provide mechanistic insights. Third, development of an automated decision-support system that recommends specific interventions (e.g., fluid bolus vs. vasopressor) based on the component parameters of the SIS could facilitate clinical implementation and ensure consistent care. Fourth, validation of the SIS in specific patient populations, such as cardiac surgery, obstetrics, and critical care, would broaden its applicability. Fifth, longer-term follow-up needed to determine whether SIS-guided care reduces postoperative complications beyond 30 days.

Conclusion

The Composite Systematic Instability Score represents a significant advance in the early prediction of intraoperative hypotension using non-invasive hemodynamic monitoring. By integrating multiple physiological parameters into a single predictive score, the SIS achieves excellent predictive performance (AUC-ROC 0.94 at 5 minutes) that exceeds current single-parameter approaches. Implementation of SIS-guided clinical care produced a 52.3% reduction in IOH duration and enabled preemptive interventions that were initiated a median of 4.2 minutes before the onset of hypotension. The use of non-invasive monitoring makes this approach broadly applicable across diverse surgical settings, potentially expanding access to predictive hemodynamic guidance to patients who would not otherwise receive such monitoring. While the study provides strong evidence for the predictive utility and clinical efficacy of the SIS, the findings confirmed in prospective randomized trials. The SIS has the potential to transform perioperative hemodynamic management, shifting clinical practice from reactive to preemptive care and improving outcomes for the millions of patients undergoing surgery worldwide.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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