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A Clinical Decision Rule to Predict Intracranial Hypertension in Severe Traumatic Brain Injury

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Abstract

Object: While existing guidelines support the treatment of intracranial hypertension in severe traumatic brain injury (TBI), it is unclear when to suspect and initiate treatment for high intracranial pressure (ICP). The objective was to derive a clinical decision rule that accurately predicts intracranial hypertension.

Methods: Using Delphi methods, we identified a set of potential predictors of intracranial hypertension and a clinical decision rule a priori by consensus among a group of 43 neurosurgeons and intensivists who have extensive experience managing severe TBI without ICP monitoring. To validate these predictors, we used data from a Latin American trial (n=150). To report on the performance of the rule, we calculated sensitivity, specificity, positive and negative predictive values with 95% confidence intervals (CIs). In a secondary analysis, the rule was validated using data from a North American trial (n=131).

Results: The final predictors and the clinical decision rule was approved by 97% of participants in the consensus-working group. The predictors are divided into major and minor criteria. High ICP would be considered suspected in the presence of one major or ≥2 minor criteria. Major

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DISCLOSURE

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criteria are: compressed cisterns (CT classification of Marshall DI III), Midline shift >5 mm (Marshall DI IV) or non-evacuated mass lesion. Minor criteria are: Glasgow Coma Scale (GCS) motor ≤ 4, pupillary asymmetry, abnormal pupillary reactivity, or Marshall DI II. The area under the curve for the logistic regression model that contains all the predictors was 0.86. When high ICP is defined as >22mmHg, the decision rule performed with a sensitivity of 93.9% (95%CI: 85.0–98.3%), a specificity of 42.3% (95%CI: 31.7–53.6%), a positive predictive value of 55.5% (95%CI: 50.7–60.2%), and a negative predictive value of 90% (95%CI: 77.1–96.0%). The sensitivity of the clinical decision rule improved with higher ICP cutoffs up to a sensitivity of 100% at a threshold of >30 mm Hg to define intracranial hypertension. Similar results were found in the North American cohort.

Conclusion: A simple clinical decision rule based on a combination of clinical and imaging findings was found to be highly sensitive in distinguishing severe TBI patients who would suffer intracranial hypertension. It could be used to identify patients who require ICP monitoring in high-resource settings or start ICP lowering treatment in environments where resource limitations preclude invasive monitoring.

Keywords

traumatic brain injury; intracranial pressure; clinical decision rule; clinical prediction rule

INTRODUCTION

Traumatic brain injury (TBI) is a pressing public health and medical problem worldwide. It constitutes the leading cause of injury-related deaths and loss of human potential.[18] Recent estimates suggest that more than 50 million people worldwide are affected by TBI every year.[8] The burden of TBI is substantially higher in low- and middle-income countries, which have more prevalent risk factors for TBI and inadequately resourced health systems to address its profound consequences.[11]

Severe TBI accounts for about 10% of all TBIs but it contributes the greatest proportion of death, disability and TBI-related costs.[9,21] Among those who sustain severe TBI, the majority of deaths are associated with raised intracranial pressure (ICP).[16,19] In addition, patients who respond to ICP lowering treatment have better outcomes than those with refractory intracranial hypertension.[7] Therefore, a fundamental focus of acute TBI care continues to be the alleviation of intracranial hypertension.

The most recent update of the Brain Trauma Foundation guidelines offers an array of ICP lowering treatment options.[3] However, it remains unclear when to suspect and initiate treatment for high ICP. The recent update did not carry forward the indications for initiation of ICP monitoring that were suggested by older guidelines.[1,3] Those indications were derived from descriptive studies of patient characteristics associated with risk of raised ICP and were not validated.[1,3,14] Although continuous invasive ICP monitoring may facilitate the diagnosis of raised ICP, its effectiveness in improving outcomes has been questioned by the recently published BEST-TRIP trial.[5] Further, resource limitations may preclude the utilization of ICP monitoring especially in low- and middle-income countries.

In this context, we conducted this study to develop a validated set of indications to start treatment for intracranial hypertension in environments where resource limitations preclude invasive ICP monitoring. The same indications can also be used to select patients for invasive ICP monitoring in high resource settings.

METHODS

Study Design:

The set of potential predictors that we tested arose via a Delphi-based consensus development process.[10] The consensus group involved 43 neurosurgeons and intensivists who have extensive experience managing patients with severe TBI based on clinical examination and CT findings alone without ICP monitoring. They proposed a set of predictors, based on CT and clinical findings at baseline after resuscitation, to identify those patients for whom they would recommend initiating treatment for suspected intracranial hypertension under conditions without ICP monitoring. This process was part of an NIH clinical research study funded through NINDS and the Fogarty International Center (NS080648).[10] The details of the Delphi consensus process were published elsewhere.[10] To validate the clinical decision rule, we used individual patient data from two randomized controlled trials conducted at different settings. This study was determined exempt from review by the Institutional Review Board at the University of Washington, Seattle, Washington.

Data Source:

In the primary analysis, we used data from the BEST TRIP randomized controlled trial (n=324). This trial prospectively compared the treatment of severe TBI patients using a protocol based on invasive ICP monitoring (n=157) versus an alternate protocol based on imaging and clinical examination without monitoring (n=167) in 10 hospitals from low and middle-income countries (LMICs) in Latin America. In a secondary analysis, we also validated the clinical decision rule in a separate dataset from the Citicoline Brain Injury Treatment Trial (COBRIT) to ensure generalizability to populations of high-income countries (HICs). [20] The COBRIT trial was a multicenter, double-blinded, randomized trial among 1,213 patients at 8 level I trauma centers in the US to investigate effects of citicoline versus placebo in patients with complicated mild, moderate, or severe TBI.[20]

Assembly of Validation Cohort

We identified patients enrolled in the trial who were 13 years of age or older with a total Glasgow Coma Scale (GCS) score ≤8 on admission or within 48 hours after injury. Only patients who underwent invasive ICP monitoring were included in the validation cohort. Patients with foreign objects in the brain parenchyma, a GCS of 3 and bilateral fixed and dilated pupils or unsurvivable injuries were excluded from the trials.

Outcome Measures

The outcome of interest is intracranial hypertension. In the primary analysis, we defined intracranial hypertension as an hourly ICP reading of greater than 22 mm Hg in any hour during the ICP monitoring period. In secondary analyses, we defined intracranial

hypertension as an ICP greater than 25 and greater than 30 mm Hg in any hour during the monitoring period.

Statistical Analysis

Descriptive statistics were calculated for all patients included in our validation cohort. We compared the baseline characteristics of patients who had intracranial hypertension with those who did not. We used the $\chi 2$ with continuity correction or Fisher test, as appropriate, to compare proportions, and Wilcoxon rank-sum test to compare distributions.

To assess the discrimination and calibration of the proposed predictors, we created a binary logistic regression model with the dependent variable of intracranial hypertension modeled relative to the predictors. To account for missing values for pupillary asymmetry (3.3%) and reactivity (24.6%), a multiple imputations procedure with 10 iterations was performed using the Markov chain Monte Carlo method.[15] This imputation method is considered less susceptible to bias than performing a complete case analysis by dropping cases with incomplete variables.[17] The model was tested through the construction of receiver operator characteristic (ROC) curves, for each of the imputation iterations. The area under the curve (AUC) is a summary measure of the discriminative ability of the model, with higher values indicative of better predictive discrimination. AUC values from each of the imputation iterations were averaged to create a single value quantifying model discrimination. Calibration was tested using Hosmer-Lemeshow goodness-of-fit test.

To report on the performance of the clinical decision rule, we calculated sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios with 95% confidence intervals (CIs), for the proposed rule (based on clinical and imaging findings at baseline after resuscitation) to predict intracranial hypertension. In secondary analyses, we assessed the performance of the clinical decision rule at definitions of intracranial hypertension using higher ICP thresholds, i.e. above 25 and above 30 mm Hg. Finally, we examined the performance of the rule, using postoperative clinical and imaging variables, in predicting postoperative intracranial hypertension among patients who underwent craniotomy to evacuate a mass lesion or craniectomy. To define postoperative clinical variables, we used the first reported postoperative exam findings as long as they were obtained at least 6 hours after the operation to minimize the potential confounding effect of general anesthetic drugs. The mass lesion was defined as epidural hematoma, subdural hematoma, contusion or intracerebral hematoma. Only postoperative variables (i.e. postoperative clinical findings and CT scans) were used to predict intracranial hypertension in this subgroup of patients.

In sensitivity analyses, we assessed the performance of the clinical decision rule derived from admission variables after excluding patients who underwent cranial surgery from the validation cohort. We also assessed the performance of the rule in predicting postoperative intracranial hypertension at varying ICP thresholds to define intracranial hypertension. Finally, we examined performance of the rule after excluding patients who underwent decompressive craniectomy from the postoperative subgroup.

To ensure the clinical decision rule can be generalized to populations of HICs, we validated the rule using a dataset from the North American COBRIT trial in a secondary analysis using the same methods to define predictors and outcomes.

All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, North Carolina). All tests were two sided and p values less than 0.05 were considered to be significant.

RESULTS

Predictors of Intracranial Hypertension

The consensus working group proposed the following set of predictors to suspect intracranial hypertension. They divided the predictors into major and minor criteria.

Major Criteria are:

1. Compressed cisterns (CT classification of Marshall diffuse injury III)[12]
2. Midline shift > 5 mm (Marshall diffuse injury IV)[12]
3. Non-evacuated mass lesion (larger than 25 cubic centimeters).

Minor Criteria are:

1. GCS motor score of 4 or less
2. Pupillary asymmetry (difference in diameter between the two pupils of more than 1 mm)
3. Abnormal pupillary reactivity (lack of reactivity to light in one or both pupils).
4. CT classification of Marshall diffuse injury II (i.e. basal cisterns are present with midline shift 0–5 mm and/or high- or mixed-density lesion of 25 cm^3 or less).[12]

All predictors are to be obtained at baseline following the resuscitation of severe TBI patients.

Clinical Decision Rule

High ICP would be suspected and ICP monitoring and/or ICP lowering treatment should be initiated in the presence of one major or two or more minor criteria (Table 1). The final rule was approved by 97% of the participants in the consensus development process.

Characteristics of Latin American Validation Cohort

The final cohort with ICP data consisted of 150 patients with a median age of 28 years and median total and motor GCS score of 7 and 5, respectively (Table 2). In contrast to patients without intracranial hypertension, patients who suffered high ICP were younger, and more likely to have abnormal pupillary response to light, or diffuse injury II-IV as measured by Marshall CT classification system (Table 2, Supplementary Appendix Table S1).

Performance of the Predictors

For the logistic model containing the proposed predictors, the area under the curve value averaged across the 10 imputation iterations was 0.86 (0.81 in complete case analysis). P value for the Hosmer-Lemeshow goodness-of-fit test was 0.49 (0.54 in complete case analysis).

Validation of the Clinical Decision Rule in the Latin American Cohort

When high ICP is defined as >22mmHg, the decision rule performed with a sensitivity of 93.9% (95% CI: 85.0–98.3%), a specificity of 42.3% (95%CI: 31.7–53.6%), a positive predictive value of 55.5% (95%CI: 50.7–60.2%), and a negative predictive value of 90% (95%CI: 77.1–96.0%), (Table 3A).

Secondary Analyses

The sensitivity of the clinical decision rule improved with higher ICP cutoffs (Table 3B-C) up to a sensitivity and negative predictive value of 100% at a threshold of >30 mm Hg for intracranial hypertension. Among patients who underwent craniotomy to evacuate a mass lesion or craniectomy (n=69, Table S1, Supplementary Appendix), the clinical decision rule for predicting postoperative intracranial hypertension based on postoperative clinical and imaging findings had a sensitivity of 80% and a specificity of 9.3% (Table 4).

Sensitivity Analyses

Similar results were found after excluding patients who underwent cranial surgery (Table S5, Supplementary Appendix) from the validation cohort. For predicting postoperative intracranial hypertension, the performance of the clinical decision rule did not change significantly with changing the ICP thresholds to 25 or 30 mm Hg (Table S6, Supplementary Appendix), or after excluding decompressive craniectomy patients (Table S7, Supplementary Appendix).

Validation of the Clinical Decision Rule in the North American Cohort

Similar results were found in the North American cohort. When high ICP is defined as >22mmHg, the decision rule performed with a sensitivity of 93.6% (95% CI: 85.7–97.9), and a specificity of 34.0% (95%CI: 21.5–48.3%) (Table S9, Supplementary Appendix). The sensitivity of the rule increased to 95.7% at the higher ICP threshold of >30 mm Hg.

DISCUSSION

Using Delphi consensus method, a large multidisciplinary group of experienced neurosurgeons and intensivists from resource-limited countries identified a set of predictors derived from basic clinical and imaging findings that defined those patients whom they would treat for suspected intracranial hypertension in the absence of ICP monitoring.[10] Based on these predictors, we proposed and validated in two different populations a clinical decision rule that is clinically sensible, easy to apply, and highly sensitive for the prediction of intracranial hypertension events on arrival to the hospital, especially at high thresholds to define raised ICP. However, the performance of the decision rule using postoperative data in

predicting postoperative intracranial hypertension was limited by modest sensitivity and poor specificity.

Management of intracranial hypertension is considered the cornerstone of modern care for severe TBI. Accurate and continuous ICP monitoring via an invasive tool can lead to the prompt recognition of spiking pressure around the injured parts of the brain.[13] Timely recognition would facilitate expedient intervention to control the rising pressure.[16,19] It is unclear, however, how to predict a rise in ICP, and when to start monitoring and treatment. This challenge gets further complicated in environments with limited resources that preclude the utilization of ICP monitors.

The recently updated Brain Trauma Foundation guidelines did not carry forward the traditional indications for ICP monitoring; because they were derived from a descriptive study of patient characteristics associated with risk of high ICP and were never validated.[1,3,14] In addition, the BEST TRIP trial found no outcome differences between a protocol based on ICP monitoring versus an alternate protocol based on imaging and clinical examination without monitoring as applied to the collective group of all patients with severe TBI. Therefore, it can be argued that the imaging and clinical exam protocol is an acceptably effective option especially in low- and middle-income countries. However, the absence of a published protocol for managing severe TBI patients without ICP monitoring necessitates elaborating and validating one. Our study addressed the first step in building such a protocol by providing a tool to predict and initiate treatment for intracranial hypertension.

This clinical decision rule was developed and approved by consensus among a large group of clinicians who have extensive experience in managing severe TBI patients without monitoring.[10] The rule is based on sensible clinical and CT scan variables that can be easily measured by the intended users upon arrival of patients to the hospital. It was designed to achieve a high level of sensitivity and performed at this sensitivity level during the validation part of this study. As with most clinical decision rules that relate to a potentially serious outcome, we believe that the high sensitivity is the most important characteristic of the rule to be sought after, because we are trying to ensure that patients do not have increased morbidity or mortality as the result of a missed intracranial hypertension event.

We do not believe that the relatively modest specificity and positive predictive value of the decision rule would lead to adverse events in cases where the rule is falsely positive. The results of the BEST TRIP trial have suggested that ICP lowering therapy is relatively benign. Although the trial group that were treated without ICP monitoring received more ICP lowering interventions for longer periods of time, they did not suffer higher rates of adverse events and they had similar long-term outcomes.[5]

This clinical decision rule is not intended to limit the individualization of management appropriate for each patient or to impose a particular treatment structure on clinicians. The subsequent ideal step after a patient is identified by this rule might be to monitor ICP invasively in environments where ICP monitoring technology is feasible. In resource-poor environments, one possible subsequent step might be initiating a low-risk treatment as a safe and more practical approach given the lack of invasive ICP monitoring tools. Another

potential option is closer serial clinical assessment and more frequent CT scanning. The ultimate choice of subsequent course of action depends on individual patients' characteristics and clinician's judgment of risk-to-benefit ratio.

Our study has several limitations. The validation cohorts were derived retrospectively from two randomized controlled trials conducted in Latin America and North America, which may not be representative of the entire spectrum of severe TBI population. Consecutive patients, however, were prospectively enrolled in these pragmatic multi-center trials and high-quality data were prospectively collected after extensive training of site personnel and under close monitoring in both trials.[2,5] Another limitation is that clinical exam data including pupillary findings and CT scan data were reported by the treating clinicians. It is possible that individual clinicians interpret pupillary size and reactivity, and CT scans differently. However, a previous study has shown good interobserver reproducibility between neurosurgeons and neuroradiologists in categorizing CT scans according to the Marshall classification system.[6] Further, this decision rule is meant to be a feasible tool that can be used by clinicians caring for TBI patients acutely at the bedside in a timely fashion. A third limitation is the modest sensitivity of the rule in predicting postoperative intracranial hypertension. It is possible that the relatively small sample size of postoperative patients in the trial is not representative of the general postoperative TBI population. Another potential explanation is the difficulty in predicting intracranial hypertension in this patient subgroup without accounting for the details of the surgical procedure and/or more detailed CT scan assessment. Further studies are needed to address this subgroup of TBI patients. The evolution of serial clinical examination and imaging data is another potential variable that might help better predict intracranial hypertension and should be examined in future research.

The sensitivity of the rule was high at the traditional ICP cutoff used to define intracranial hypertension. However, it reached 100% only at a threshold of 30 mm Hg. We believe this is an opportunity to further question the value of a universal fixed threshold for defining intracranial hypertension rather than an actual limitation of the rule. First, the stepwise progressive increase in sensitivity with higher thresholds in two different populations lends further credence the underlying rationale, face validity and clinical sensibility of the rule. Second, the BEST TRIP trial showed no difference in long term efficacy between a protocol based on ICP monitoring and a fixed universal value to define raised ICP and a protocol based on imaging and clinical variables alone similar to the ones included in this decision rule.

The BEST TRIP trial did not address the efficacy of ICP-monitor-based treatment of patients with actual, demonstrated intracranial hypertension (using any threshold).[4] As such, we suggest that the utility of this decision rule in situations where ICP monitoring is available would be to assist in determining whom to monitor rather than whom to treat for suspected intracranial hypertension.

Future studies are needed to validate this rule in other populations. The demographic and injury characteristics of different populations might impact the performance of the rule. In

addition, this rule does not address relevant practical issues, such as when to taper or escalate ICP lowering therapy. Future research should answer these important questions.

CONCLUSION

A simple clinical decision rule based on a combination of clinical and imaging findings was validated in two different populations and found to be highly sensitive in distinguishing severe TBI patients who would suffer intracranial hypertension. It could be used to identify patients who require ICP monitoring in high-resource settings or start ICP lowering treatment in environments where resource limitations preclude invasive monitoring

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Clinical Decision Rule for Prediction of Intracranial Hypertension in Severe Traumatic Brain Injury

High ICP is Suspected and ICP Monitoring and/or ICP lowering Treatment Should be Initiated in the Presence of One Major or Two Minor Criteria
Major Criteria:
1. Compressed cisterns (Marshall diffuse injury III)
2. Midline shift > 5 mm (Marshall diffuse injury IV).
3. Non-evacuated mass lesion (>25 cm^3).
Minor Criteria:
1. GCS motor score of 4 or less
2. Pupillary asymmetry
3. Abnormal pupillary reactivity
4. Marshall diffuse injury II (i.e. basal cisterns are present with midline shift 0–5 mm and/or high- or mixed-density lesion of ≥25 cm^3).

ICP: intracranial pressure; GCS: Glasgow Coma Scale

Table 2:

Baseline Characteristics of the Latin American Validation Cohort

Characteristic	Overall Cohort (n=150)	High ICP Group * (n=65)	Normal ICP Group (N=85)	P Value
Age, median (IQR)	28 (21–44)	25 (20–34)	31 (22–48)	0.009
Female sex, no. (%)	12 (8)	4 (6.2)	8 (9.4)	0.55
Initial GCS Score, median (IQR)	7 (5–9)	7 (6–9)	7 (5–9)	0.69
Initial Motor GCS Score, median (IQR)	5 (3–5)	4 (3–5)	5 (3–5)	0.91
Pupillary symmetry $ on admission, no. (%)				
Normal	109 (72.6)	51 (78.5)	58 (68.2)	0.37
Asymmetrical	36 (24)	12 (18.5)	24 (28.2)	
Unknown	5 (3.3)	2 (3.1)	3 (3.5)	
Pupillary reactivity ^ on admission, no. (%)				
Normal	71 (47.3)	24 (36.9)	47(55.2)	0.05
Abnormal	42 (28)	24 (36.9)	18 (21.2)	
Unknown	37 (24.7)	17 (26.2)	20 (23.5)	
Marshall Classification on initial CT, no. (%)				
Diffuse injury II	21 (14)	13 (20)	8 (9.4)	<0.0001
Diffuse injury III	70 (46.7)	40 (60.5)	30 (35.3)	
Diffuse injury IV	9 (6)	6 (9.2)	3 (3.5)	
Evacuated mass lesion	48 (32)	4 (6.2)	44 (51.8)	
Non-evacuated mass lesion	2 (1.3)	2 (3.1)	0 (0)	

ICP: intracranial pressure; IQR: interquartile range; GCS: Glasgow Coma Scale

* High ICP was defined as Intracranial pressure of >22 mmHg at any point during monitoring prior to any neurosurgical intervention

$ Pupillary asymmetry was defined as a difference in diameter between the two pupils of more than 1 mm

^ Abnormal pupillary response was defined as lack of reactivity to light in one or both pupils.

Table 3:

Performance of the Clinical Decision Rule in the Latin American Cohort

A: When High ICP is defined as >22 mm Hg:

Performance	High ICP	Normal ICP
Rule Positive	61	49
Rule Negative	4	36
Sensitivity	93.9% (95% Confidence Interval [CI]: 85.0–98.3%)	
Specificity	42.4% (95%CI: 31.7–53.6%)	
Positive Predictive Value	55.5% (95%CI: 50.7–60.2%)	
Negative Predictive Value	90.0% (95%CI: 77.1–96.0%)	
Positive Likelihood Ratio	1.6 (95%CI: 1.3–2.0)	
Negative Likelihood Ratio	0.2 (95%CI: 0.1–0.4)	

B: When High ICP is defined as >25 mm Hg:

Performance	High ICP	Normal ICP
Rule Positive	50	60
Rule Negative	1	39
Sensitivity	98.0% (95% CI: 89.6–100.0%)	
Specificity	39.4% (95%CI: 29.7– 49.7%)	
Positive Predictive Value	45.5% (95%CI: 41.4–49.5%)	
Negative Predictive Value	97.5% (95%CI: 84.7% to 99.6%)	
Positive Likelihood Ratio	1.6 (95%CI: 1.4–1.9)	
Negative Likelihood Ratio	0.1 (95%CI: 0.0–0.4)	

C: When High ICP is defined as >30 mm Hg:

Performance	High ICP	Normal ICP
Rule Positive	40	70
Rule Negative	0	40
Sensitivity	100.0% (95% CI: 91.2–100.0%)	
Specificity	36.4% (95%CI: 27.4–46.1%)	
Positive Predictive Value	36.4% (95%CI: 33.2–39.7%)	
Negative Predictive Value	100.0% (95%CI: 89.1% to 100.0%)	
Positive Likelihood Ratio	1.6 (95%CI: 1.4–1.8)	
Negative Likelihood Ratio	0.0 (95%CI: 0.0–0.0)	

The area under the curve (AUC) for the logistic regression model that contains all the predictors is 0.861; P=0.49 for the Hosmer-Lemeshow goodness-of-fit test.

The AUC for the logistic regression model that contains all the predictors is 0.83; P=0.36 for the Hosmer-Lemeshow goodness-of-fit test.

The AUC for the logistic regression model that contains all the predictors is 0.82; P=0.72 for the Hosmer-Lemeshow goodness-of-fit test.

Table 4:

Performance of the Clinical Decision Rule in the Postoperative Subgroup of Latin American Cohort

Performance	High ICP*	Normal ICP
Rule Positive	12	49
Rule Negative	3	5
Sensitivity	80% (95% CI: 51.9–95.7%)	
Specificity	9.3% (95%CI: 3.1–20.3%)	
Positive Predictive Value	19.7% (95%CI: 15.8–24.2%)	
Negative Predictive Value	62.5% (95%CI: 31.0–86.1%)	
Positive Likelihood Ratio	0.9 (95%CI: 0.7–1.2)	
Negative Likelihood Ratio	2.2 (95%CI: 0.6–8.0)	

*High ICP is defined as >22mm Hg

The AUC for the logistic regression model that contains all the predictors is 0.65; P=0.96 for the Hosmer-Lemeshow goodness-of-fit test.