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Hospital Observation Upon Reversal (HOUR) with Naloxone: A Prospective Clinical Prediction Rule Validation Study

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Running Title: HOUR with Naloxone

Key Words: Naloxone, Drug Overdose, Opioid-Related Disorders, Emergency Medicine
Abstract:

**Objective:** St. Paul’s Early Discharge Rule was derived to determine which patients could be safely discharged from the emergency department after a 1-hour observation period following naloxone administration for opiate overdose. The rule suggested that patients could be safely discharged if they could mobilize as usual; had a normal oxygen saturation, respiratory rate, temperature, heart rate, and Glasgow Coma Scale score. Validation of the St. Paul’s Early Discharge Rule is necessary to ensure that these criteria are appropriate to apply to patients presenting after an unintentional presumed opioid overdose in the context of emerging synthetic opioids and expanded naloxone access. **Methods:** In this prospective, observational validation study, an emergency medicine provider assessed subjects one hour after administration of prehospital naloxone. Unlike in the derivation study the threshold for normal oxygen saturation was set at 95% and subjects were not immediately discharged after a normal one-hour evaluation (1HE). Subjects were judged to have a normal 1HE if all 6 criteria of the rule were met. Patients were judged to have an adverse event (AE) if they were admitted to the hospital or had one of the pre-established adverse events. **Results:** 583 subjects received at least one administration of prehospital naloxone, were transported to the study hospital and had a one hour evaluation performed by a provider. Adverse events occurred in 82 (15.4%) subjects. The rule exhibited a sensitivity of 84.2% (95% CI: 76.2 – 92.1%), specificity of 62.1% (95% CI: 57.6 – 66.5%) and a negative predictive value of 95.6% (95% CI: 93.3 – 97.9%). Only one subject with a normal one hour evaluation subsequently received additional naloxone following a presumed heroin overdose. **Conclusion:** This rule may be used to risk stratify patients for early discharge following naloxone administration for suspected opioid overdose.
Introduction

Opioid related emergency department (ED) visits continue to increase, with the number nearly doubling from 2005 to 2014.\textsuperscript{1} Although opioid use disorder and its associated harms are not a new phenomenon, appropriate patient disposition after naloxone reversal of a presumed opioid overdose remains unclear. Some providers have advocated for a four to six-hour observation period, but a recent systematic review concluded that one hour of observation is sufficient for patients who are able to ambulate as usual, have normal vital signs, and a Glasgow Coma Scale of 15.\textsuperscript{2, 3} This recommendation was based on the St. Paul’s Early Discharge Rule. This clinical predication rule was derived from a single clinical site but was never externally validated nor widely adopted.\textsuperscript{4, 5}

The landscape of opioid use disorder has changed dramatically since 2000, when that derivation study was originally published. Since that time, there has been a rise in opioid related overdose deaths, partly due to increasing heroin use. From 2014-2015, there was a 20.6% increase in heroin-involved deaths in the United States.\textsuperscript{6} The emergence of fentanyl and other synthetic opioid analogues has also played a significant role, resulting in a 72.2% increase in deaths involving synthetic opioids (other than methadone) over the same time period.\textsuperscript{6, 7} These synthetic opioid analogs, like carfentanil, can be significantly more potent than heroin and their pharmacokinetics in humans are still poorly understood.\textsuperscript{8} Finally, while naloxone administration was limited to hospitals and paramedics at the time of the derivation study, access to naloxone has drastically expanded over the last decade. Today, naloxone is also carried and administered by emergency medical technicians, firefighters, police officers and the lay public.\textsuperscript{9}

These factors have complicated the disposition of patients presenting to emergency departments after a presumed opioid overdose. Validation of the St. Paul’s Early Discharge Rule
is necessary to ensure that these criteria are appropriate to apply to patients presenting after an unintentional presumed opioid overdose in the context of emerging synthetic opioids and expanded naloxone access.

Methods

Study Design

This was a prospective observational study to determine if clinical judgment and/or a six component clinical prediction rule applied one hour after prehospital naloxone administration for suspected opioid overdose, could predict which subjects would have an adverse event in the first 24 hours. This study was approved by the University at Buffalo Institutional Review Board.

Study Setting

The study took place at a single urban academic tertiary care center with an annual emergency department census of approximately 65,000 visits. The hospital has specialized services for trauma, psychiatric, and substance abuse care. The city is covered by a single large commercial ambulance provider with advanced life support (ALS) and basic life support (BLS) units. The outlying areas are covered by multiple agencies with a variety of staffing patterns. Advanced life support ambulance crews can administer naloxone via the intravenous (IV), intraosseous (IO), intramuscular (IM) or intranasal (IN) route. BLS providers, firefighters and police officers can provide naloxone via the IN route. Laypersons trained through a community naloxone program can administer naloxone via the IM or IN route.

Subject Enrollment

Adult patients (≥ 18 years of age) who arrived at the emergency department via ambulance after being treated with naloxone by emergency medical services (EMS), firefighters,
police or laypersons were enrolled in the study as a convenience sample. Subjects were excluded if they were prisoners or under arrest, did not receive a one hour evaluation, had an incomplete but otherwise normal one hour evaluation, received in hospital naloxone prior to the one hour evaluation, if their study data could not be linked to their hospital records, or if they requested to be withdrawn from the study. On arrival, hospital triage staff identified potential study subjects, and research associates in the ED helped facilitate enrollment and data collection.

**Patient Care**

All study subjects received usual care at the discretion of the treating emergency medicine provider, regardless of their enrollment in the study or their risk stratification based on the prediction rule. At the time of the study, the typical duration of observation following naloxone administration in the study ED was four hours. All subjects were free to leave the emergency department against medical advice at any time during the study if they had capacity to do so. Subjects were able to be discharged earlier than four hours based on their providers’ clinical judgement.

**One hour Evaluation**

A one-hour evaluation by the emergency medicine provider (attending physician, resident, or advanced practice provider) was planned one hour after the first dose of out of hospital naloxone. At that time, providers were asked to evaluate if the subject had the ability to mobilize as usual, a normal oxygen saturation, a normal respiratory rate, a normal temperature, a normal heart rate, and a normal GCS. Providers were asked to provide a binary “yes” or “no” for each component, with “yes” representing a normal exam finding. The normal criteria for each component of the rule were the same as those utilized in the derivation study, except that the threshold for normal oxygen saturation was increased from > 92% to > 95%. The revised
prediction rule used for this study is shown in Table 1. If all six criteria were noted to be normal, the subject was deemed low risk for adverse events based on the rule. If any one of the criteria was noted to be abnormal, the subject was deemed high risk based on the rule. Independent of the results of the prediction rule, providers were also asked if the patient appeared safe for discharge at that time based on their clinical judgment.

**Adverse Events**

After the subject was discharged, the hospital record was reviewed for the presence of adverse events. Three reviewers (MC, NP, ES) abstracted data from the hospital records. All reviewers were medical students trained by the primary investigator in study procedures. The reviewers were blinded to the results of the recorded one hour evaluation while reviewing the hospital records for adverse events. The reviewers utilized a list of *a priori* clear adverse events and unclear adverse events based on those used in the original derivation study (Table 2). An adverse event was considered to be present if it was noted in any one of the following during the first 24 hours: the nursing note, the provider’s notes or the orders.

All clearly defined adverse events were treated as adverse events without further adjudication. If the subject was found to have one or more unclear adverse events, but no clearly defined adverse events, one of two board certified emergency medicine physicians (BC, MM) reviewed the hospital record. The emergency medicine physicians were blinded to the results of the recorded one hour evaluation while reviewing the records for adverse events. Based on predetermined criteria, the physicians determined if the unclear adverse event met the criteria for an adverse event.

Finally, local county medical examiner records were queried for subject death within 48 hours. All deaths within 48 hours were considered adverse events.
**Sample Size Calculations**

The sample size calculations for this study mirrored those from the derivation study. In order to obtain a lower bound 95% confidence interval of 97%, with up to one failure of the rule, 160 subjects with adverse events would be required. The expected adverse event rate was 30%, making the required sample size 540 subjects.

**Data Analysis**

Statistics regarding subject age, gender, total naloxone dose, time to one hour evaluation, route of naloxone administration and ED length of stay were obtained and compared to that of the derivation study.

A chi square test was utilized to calculate the sensitivity, specificity, positive predictive value and negative predictive value for the prediction rule, clinical judgment, the prediction rule in combination with clinical judgment and each of the 6 components of the prediction rule. Further descriptive analysis was performed for cases where the rule and/or the provider’s clinical judgment failed to predict an adverse event.

**Data Validation**

To ensure agreement among the reviewers, each of the three reviewers independently reviewed a sample of 50 charts to assess for agreement regarding the presence or absence of clearly defined and unclear adverse events. A kappa score was calculated to assess for inter-rater agreement.

To ensure agreement among the board certified emergency physician adjudicators, each of the two adjudicators independently reviewed a sample of 50 charts that had been identified by the reviewers as having a potentially adverse events to assess for agreement regarding the
presence or absence of an adverse event. A kappa score was calculated to assess for inter-rater agreement.

To assess for systematic bias among the cases excluded for absence of a one hour evaluation, a sample of 50 excluded cases were reviewed for the presence of an adverse event from the hospital records. The prevalence of adverse events was compared to the prevalence of adverse events among subjects included in the study.

**Results:**

A convenience sample of subjects was enrolled from May 2016 to September 2017. A total of 690 subjects were screened for inclusion on arrival, 538 (78.0%) subjects met the inclusion/exclusion criteria and were included in the analysis, as shown in Figure 1. Adverse events occurred in 82 (15.4%) subjects. A description of subject characteristics and a comparison to subjects from the deviation study are shown in Table 3. No subjects died within 48 hours.

**Prediction Rule**

The rule and each of its individual components were predictive of adverse events. Among the components of the rule, not having the ability to mobilize as usual had the greatest sensitivity (58.0%), and not having a normal temperature had the greatest specificity (99.1%) to predict adverse events. The rule exhibited a sensitivity of 84.2% (95% CI: 76.2 – 92.1%), specificity of 62.1% (95% CI: 57.6 – 66.5%) and a negative predictive value of 95.6% (95% CI: 93.3 – 97.9%). The rule failed to predict adverse events in 13 (2.4%) out of 538 cases.
Provider Judgments

Provider judgment was predictive of adverse outcomes. Provider judgment exhibited a sensitivity of 85.4% (95% CI: 77.7 – 93.0%), specificity of 60.9% (95% CI: 56.3 – 65.4%) and a negative predictive value of 95.8% (95% CI: 93.4 – 98.1%). Provider judgment that the patient was safe for discharge failed to predict adverse events in 12 (2.3%) out of 529 cases.

Provider Judgment + Prediction Rule

The combination of provider judgment plus the rule exhibited a sensitivity of 87.8% (95% CI: 80.7 – 94.9%), specificity of 53.0% (95% CI: 48.4 – 57.7%) and a negative predictive value of 96.0% (95% CI: 93.5 – 98.4%). When provider judgment and the rule were used together, they failed to predict adverse events in 10 (1.9%) out of 529 subjects.

Prediction Failures

The cases where the clinical prediction rule, provider judgment or both failed to predict an adverse event are shown in Table 5. Among the 10 cases where both provider judgment and the rule failed to predict an adverse event, two subjects received a repeat dose of naloxone after the one hour evaluation and one patient was treated with artificial ventilation (BiPaP). These cases may have led to morbidity or mortality if left untreated. Of the remaining seven cases, six received low flow supplemental oxygen via nasal cannula and one received IVF for hypotension. These final seven cases met the predefined adverse event criteria, but the adverse events were unlikely to have caused morbidity or mortality if left untreated.

Data Validation
Three medical student reviewers reviewed a sample of 50 charts to assess for agreement on study outcomes. Among the 50 charts reviewed, they agreed on the presence or absence of at least one clearly defined adverse event in 50 charts (Kappa = 1.000). They agreed on the presence or absence of at least one potential adverse event in 49 charts (Kappa = 0.987).

Two attending physicians reviewed a sample of 50 charts that had been identified as having a potentially adverse event to assess for agreement. They agreed on the presence or absence of a true adverse event in 47 cases (Kappa = 0.789).

Three medical student reviewers reviewed a sample of 50 charts that were excluded because no one hour evaluation had been performed. Among the charts there were three true adverse events in the hospital. The rate of adverse events was 6%, demonstrating a lower prevalence of adverse events among excluded subjects.

**Discussion**

In this data set, there was only one subject with a normal one hour evaluation per the clinical prediction rule that subsequently received additional naloxone following a presumed heroin overdose. Despite their differences in study design and study population, similar adverse event rates were found in the derivation study and this study. No subjects in either study died following a normal one hour evaluation.

In this validation study, the prediction rule demonstrated inferior sensitivity and negative predictive value, but superior specificity and positive predictive value compared to the derivation study. There are multiple reasons for this both inherent to the prediction rule creation process in general and specific to the study context. The derivation study assessed 31 potential variables and included six (19.3%) in the final rule in an effort to maximize sensitivity.\(^4\) It is not
uncommon for prediction rules to have less favorable results when validated with a different patient population, but this step is critical to establish the generalizability of the rule.\textsuperscript{10} The derivation study also excluded five subjects with adverse outcomes due to “intervening incidents”.\textsuperscript{4} It is unclear how many of these excluded subjects from the derivation study had normal one hour evaluations using the rule. No such exclusions were included in the design of the validation study.

All naloxone in the derivation study was administered parenterally by paramedics or hospital staff, compared to this study where the majority (85.4\%) of the initial doses were delivered IN predominantly by BLS or lay responders. The total dose of naloxone was also considerably higher in this study, due in part to the fact that the standard IN dosing formulation used was 2 mg, which is higher than typical parenteral dosing. Many subjects also received more than one prehospital naloxone administration. This finding is consistent with the increase in the frequency of multi-dose naloxone administrations that was described by Fault et al.\textsuperscript{11} Roberson et al. demonstrated that patients receiving IN naloxone were more likely to receive repeat doses than those receiving parenteral naloxone, likely due to its delayed onset of action.\textsuperscript{12} It is unclear what effect the increased onset time from IN administration,\textsuperscript{12, 13} administration by non-paramedics and the presence of synthetic opioids in the drug supply had on the total dose of naloxone received by patients in this study.

Adverse outcomes were determined based on an \textit{a priori} list adapted from the derivation study’s design. There were multiple cases that met the criteria for adverse events following normal evaluations which were unlikely to have been clinically significant in this observational study. The majority of patients who had predefined adverse events following normal one hour evaluations required supplemental oxygen administered as low flow nasal cannula, but not
additional doses of naloxone. Desaturations can naturally occur while sleeping, and often elicit a response from medical providers even when not clinically important. This effect is likely magnified as length of stay increases. The majority (64.3%) of patients in this study had ED lengths of stays greater than four hours, compared to 28.8% of patients who had hospital stays of greater than four hours in the derivation study. Length of stay may be a confounder, as patients who stay in a medical environment longer may be more likely to receive additional care, some of which may meet the pre-established criteria for adverse events. It is unlikely that the cases of transient mild hypoxia in subjects not requiring additional naloxone or ventilatory support that occurred in this study, would have resulted in a clinically important adverse outcomes if left untreated.

When the prediction rule was used in tandem with the provider impression, it improved overall sensitivity and decreased overall specificity. Utilizing a two-step process of provider impression followed by application of a prediction rule is not uncommon in emergency medicine. Early discharge among patients who the provider feels are at low risk for an adverse event and who pass the clinical prediction rule is a rational approach that in this study population yielded a 96.0% negative predictive value.

Some authors recommend a two hour observation, others recommend a four to six hour period of observation. At the time of the study, the general practice at the study hospital was to observe patients with suspected parenteral opioid overdose for at least four hours following naloxone administration. The one subject who received naloxone following a heroin overdose and had a normal one hour evaluation was given another dose of naloxone five hours and 30 minutes after her first dose in the field. In that case, the repeat naloxone administration occurred beyond the four-hour window we typically observe patients for in our department following
naloxone administration. Also of note, although that subject was bradypneic, her pulse oximetry on room air was normal.

Similar to the original derivation study, this validation study did not include information on the route or type of opioid involved in the exposure when determining the performance characteristics of the rule. This limitation should be taken into consideration by providers when assessing patients with opioid toxicity using the prediction rule. Patients presenting after intravenous injection or insufflation of an opioid likely experience peak drug effect prior to or shortly after arriving in the Emergency Department. In these cases, reemergence of toxicity should occur rapidly as naloxone is metabolized. However, oral overdose of opioids can result in altered absorption with delayed emergence or reemergence of toxicity. Additional data is needed to assess the role of the prediction rule in this patient population.

Patients included in the study population were presumed to have used opioids based on the administration of out of hospital naloxone. Urine testing was not obtained to analytically confirm the presence or type of opioid in these cases. It is unknown if a majority of patients presenting after intravenous opioid use were exposed to heroin, fentanyl, or another synthetic opioid analog. The kinetics of these drugs are still largely unknown, although a window of observation beyond the duration of effect of naloxone would seem reasonable after intravenous or insufflation of an unknown opioid.

Clinical prediction rules are best for answering binary questions, such as can a condition be ruled out or is a patient safe for discharge. However, it is critically important that they only be used for the condition for which they are intended when patients have multiple acute conditions. For example, in this study, one patient with a normal one hour evaluation required incision and drainage, intravenous antibiotics and admission for abscesses. In this case, the provider
appropriately evaluated and treated the infectious condition independent of the outcome of the prediction rule. Finally, the performance of any clinical prediction rule is only as good as the availability of the data and the providers who are applying the rule. In two cases where the prediction rule failed to predict an adverse event, the provider evaluated the subject as normal using the rule, despite the presence of a low SpO2 recorded in the nursing notes.

Patients who are determined to be low risk may still experience complications after discharge. Therefore, discharge instructions and medications are important steps for risk mitigation. Patients should be advised not to use drugs or alcohol following an opioid overdose. Mixing opioid drugs with other drugs like cocaine or benzodiazepines may be particularly problematic. Patients should also be provided with materials outlining local resources for the treatment of opioid use disorder and with a take home naloxone kit when appropriate. These steps may further mitigate potential complications in low risk patients. At home observation by a responsible adult who has naloxone and who is able to summon 911 in the cases of delayed sequelae makes intuitive sense.

Concerns over the legal and social implications of illegal drug use often lead a patient to want to leave the emergency department early. Risk stratifying a patient based on the results of their one hour evaluation may inform shared decision making conversations between providers and patients with decision making capacity. The ideal duration of observation for patients who fail the one hour rule remains unclear.

**Limitations**

Unlike the derivation study, the design of this study did not include patient follow up by phone. This is balanced by the fact that patients did remain in the ED longer than in the
derivation study. Like the derivation study, this study did not categorize overdoses based on the drug used or route of administration. Therefore, it is not possible to specifically determine the performance of the rule among patients following parenteral opioid overdose. Some of the patients treated with naloxone for presumed opioid overdose may not have actually overdosed on opioids.

Unlike the derivation study which based the timing of the one hour evaluation on the last naloxone administration, this study based the timing of the one hour evaluation on the first prehospital naloxone. This difference in design is unlikely to have affected the performance of the rule, because repeat doses of naloxone were frequently clustered together over a short period of time.

The prediction rule and provider impression had similar performance characteristics. The treating provider’s clinical impression was asked immediately after assessing the six components of the rule, and this may have influenced the provider’s gestalt. In our city, EMS transports a disproportionate number of overdose patients to the study hospital, due in part to the availability of specialized substance abuse and psychiatric services at the study hospital. As a result, providers have more frequent exposure to overdose patients which may improve their ability to identify patients at risk for adverse outcomes when compared to providers who see overdose patients less frequently.

Conclusion

Applying the prediction rule for patients for whom providers have a low clinical suspicion for adverse events is a reasonable approach for risk stratifying patients for early discharge following naloxone administration for suspected opioid overdose. The rule should be used with caution in cases of oral or mixed overdose. Further study is needed to determine the
exact performance characteristics of the rule in the context of overdoses of various drugs, drug combinations and routes of administration subgroups.
References


One hour after the administration of naloxone for presumed opioid overdose, patients can be safely discharged from the emergency department if they meet all 6 criteria:

- Can mobilize as usual
- Have a normal $O_2$ saturation (>95%)
- Have a normal respiratory rate (>10 and <20 breath/min)
- Have a normal temperature (>35.0°C and <37.5°C)
- Have a normal heart rate (>50 and <100 beats/min)
- Have a Glasgow Coma Scale score of 15

Note: From “Early discharge of patients with presumed opioid overdose: development of a clinical prediction rule,” by Christenson J, et al., 2000, Academic Emergency Medicine, 7, p. 1116. Copyright 2000 by John Wiley and Sons. Adapted with permission. Adapted with modifications made to the lower limit of acceptable $O_2$ saturation.
### Table 2: Adverse Event Criteria

#### Clearly Defined Adverse Events
- Death
- Repeat naloxone for respiratory rate $\leq 10$ breaths/min or oxygen saturation $\leq 92\%$
- Delivery of supplemental oxygen for a saturation $\leq 92\%$
- Assisted ventilation (including BiPAP)
- Administration of IV inotropic agents
- Administration of antiarrhythmic medications for sustained tachycardia $>130$ beats/min
- Cardioversion
- Administration of mannitol
- Dialysis
- Administration of bicarbonate for $\text{HCO}_3 < 5$ mmol/L in ABG or $\text{CO}_2 < 5$ mmol/L in VBG

#### Criteria for Adjudicating Unclear Adverse Events

<table>
<thead>
<tr>
<th>Unclear Adverse Event</th>
<th>Guidelines for Adverse Event Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Naloxone without recorded respiratory rate or oxygen saturation</td>
<td>Respiratory compromise or hemodynamic compromise</td>
</tr>
<tr>
<td>Oxygen administration without recorded oxygen saturation</td>
<td>Respiratory compromise</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td>Respiratory compromise or hemodynamic compromise or pneumonia, sepsis, or CNS infection or $&gt;24$-hour stay</td>
</tr>
<tr>
<td>Fluid bolus $\geq 1$ liter</td>
<td>Systolic blood pressure of $#80$ mm Hg</td>
</tr>
<tr>
<td>Any unscheduled surgery</td>
<td>Surgery for life or limb threat</td>
</tr>
<tr>
<td>Antiarrhythmic medications without a recorded heart rate of $&gt;130$ beats/min</td>
<td>Hemodynamic compromise</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>Other life-threatening overdose</td>
</tr>
</tbody>
</table>

Table 3: Comparison of Subject Characteristics from Derivation and Validation Study

<table>
<thead>
<tr>
<th></th>
<th>Derivation</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>35.7 (±10.5) year</td>
<td>33.4 (±23.1) years</td>
</tr>
<tr>
<td>% Male</td>
<td>82.4%</td>
<td>69.5%</td>
</tr>
<tr>
<td>Total Naloxone Dose</td>
<td>0.9 (±0.5) mg</td>
<td>3.1 (±1.6) mg</td>
</tr>
<tr>
<td>Adverse Event Rate</td>
<td>16.4%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Time from Naloxone to 1-hour evaluation a</td>
<td>1.1 (±0.4) hours</td>
<td>1.2 (±0.3) hours</td>
</tr>
<tr>
<td>Route of Administration b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>23.2%</td>
<td>10.3%</td>
</tr>
<tr>
<td>IM/SQ</td>
<td>88.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>IV and SQ</td>
<td>12.9%</td>
<td>N/A</td>
</tr>
<tr>
<td>IN</td>
<td>N/A</td>
<td>85.4%</td>
</tr>
<tr>
<td>Length of Stay c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 hours</td>
<td>48.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>2-4 hours</td>
<td>22.7%</td>
<td>29.2%</td>
</tr>
<tr>
<td>&gt;4 hours</td>
<td>28.8%</td>
<td>64.3%</td>
</tr>
</tbody>
</table>

a Time since most recent naloxone reported in derivation study, time since first dose of prehospital naloxone reported by validation study.

b Route of Administration for all dose reported for derivation study, first dose reported for validation study.

c Hospital length of stay reported for derivation study, ED length of stay reported for validation study.

Table 4: Performance of Rule and Provider Impression

<table>
<thead>
<tr>
<th></th>
<th>Normal Evaluation</th>
<th>Abnormal Evaluation</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobilize as Usual</td>
<td>AE (6.3%)</td>
<td>372 (69.3%)</td>
<td>47 (8.8%)</td>
<td>84 (15.6%)</td>
<td>58.0%</td>
<td>81.6%</td>
<td>&lt;0.0001</td>
<td>537</td>
</tr>
<tr>
<td>Normal O₂ Saturation</td>
<td>41 (7.7%)</td>
<td>431 (80.7%)</td>
<td>41 (7.7%)</td>
<td>21 (3.9%)</td>
<td>50.0%</td>
<td>95.4%</td>
<td>0.0001</td>
<td>534</td>
</tr>
<tr>
<td>Breathing Normally</td>
<td>60 (11.2%)</td>
<td>448 (83.3%)</td>
<td>22 (4.1%)</td>
<td>8 (1.5%)</td>
<td>26.8%</td>
<td>98.2%</td>
<td>&lt;0.0001</td>
<td>538</td>
</tr>
<tr>
<td>Normal Temp</td>
<td>76 (14.2%)</td>
<td>451 (84.1%)</td>
<td>5 (0.9%)</td>
<td>4 (0.7%)</td>
<td>6.2%</td>
<td>99.1%</td>
<td>55.6%</td>
<td>0.0032</td>
</tr>
<tr>
<td>Normal HR</td>
<td>38 (7.1%)</td>
<td>354 (65.9%)</td>
<td>44 (8.2%)</td>
<td>101 (18.8%)</td>
<td>53.7%</td>
<td>77.8%</td>
<td>30.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GCS normal</td>
<td>50 (9.3%)</td>
<td>400 (74.5%)</td>
<td>32 (6%)</td>
<td>55 (10.2%)</td>
<td>39.0%</td>
<td>87.9%</td>
<td>36.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 Hour Rule normal</td>
<td>13 (2.4%)</td>
<td>283 (52.6%)</td>
<td>69 (12.8%)</td>
<td>173 (32.2%)</td>
<td>84.1%</td>
<td>62.1%</td>
<td>28.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Provider Impression</td>
<td>12 (2.3%)</td>
<td>272 (51.4%)</td>
<td>70 (13.2%)</td>
<td>175 (33.1%)</td>
<td>85.4%</td>
<td>60.9%</td>
<td>28.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Provider Impression + Rule</td>
<td>10 (1.9%)</td>
<td>237 (44.8%)</td>
<td>72 (13.6%)</td>
<td>210 (39.7%)</td>
<td>87.8%</td>
<td>53.0%</td>
<td>25.5%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 5: Adverse Events Following Normal Evaluations Using Prediction Rule and/or Provider Judgment

<table>
<thead>
<tr>
<th>Overdose</th>
<th>Predefined Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PO Acetaminophen/Hydrocodone and PO Carisoprodol</td>
<td>Repeat naloxone</td>
<td>Multiple repeat doses of naloxone and naloxone drip</td>
</tr>
<tr>
<td>2 PO Clonazepam</td>
<td>Supplemental oxygen</td>
<td>Nasal cannula oxygen for desaturations</td>
</tr>
<tr>
<td>3 PO Oxymorphone and PO benzdiazepines</td>
<td>Supplemental oxygen</td>
<td>Nasal cannula oxygen for desaturations</td>
</tr>
</tbody>
</table>

**Low Risk Based on Provider Judgment only**

| 4 | Heroin | IVF for hypotension | Asymptomatic hypotension, history of low BP at baseline |
| 5 | Inhaled Oxycodone | Bipap, supplemental oxygen | Pulmonary edema |

**Low Risk Based on Prediction Rule + Provider Judgment**

| 6 | Heroin | Repeat naloxone | Naloxone Drip |
| 7 | PO Methadone | Repeat naloxone | Repeat naloxone administered |
| 8 | PO Methadone | Bipap, supplemental oxygen | Pulmonary edema |
| 9 | Heroin and Cocaine | Supplemental oxygen | Pulmonary edema requiring nasal cannula oxygen and admission |
| 10 | Heroin | Supplemental oxygen | Nasal cannula oxygen for desaturations |
| 11 | Heroin | Supplemental oxygen | Nasal cannula oxygen for desaturations while sleeping, morbidly obese, evaluated for CPAP |
| 12 | PO Alprazolam and PO Acetaminophen/Hydrocodone | Supplemental oxygen | Nasal cannula oxygen for desaturations |
| 13 | Heroin and Alcohol | Supplemental oxygen | Nasal cannula oxygen for desaturations |
| 14 | PO Acetaminophen/Hydrocodone | Supplemental oxygen | Nasal cannula oxygen for desaturations |
| 15 | Heroin | IVF for hypotension, antibiotics | Skin abscess requiring antibiotics and admission |

The term “heroin” was used in the describe what patients believed was heroin, and may have contained synthetic opioids or other drugs