Interaction of admission platelet count with current medications and the risk for chronic subdural recurrence

Shawn R. Eagle, PhD,1 Aditya M. Mittal, BS,1 Ryan T. Kellogg, MD,2 Jan Vargas, MD,3 Enyinna Nwachuku, MD,1 Hansen Deng, MD,1 Thomas J. Buell, MD,1 David O. Okonkwo, MD, PhD,1 and Matthew Pease, MD1

1Department of Neurological Surgery, University of Pittsburgh, Pennsylvania; 2Department of Neurosurgery, University of Virginia, Charlottesville, Virginia; and 3Department of Neuroendovascular Surgery, Prisma Health-Upstate, Greenville, South Carolina

OBJECTIVE Chronic subdural hematoma (cSDH) has a reported 10%-24% rate of recurrence after surgery, and prognostic models for recurrence have produced equivocal results. The objective of this study was to leverage a data mining algorithm, chi-square automatic interaction detection (CHAID), which can incorporate continuous, nominal, and binary data into a decision tree, to identify the most robust predictors of repeat surgery for cSDH patients.

METHODS This was a retrospective cohort study of all patients with SDH from two level 1 trauma centers at a single institution. All patients underwent cSDH evacuation performed by 15 neurosurgeons between 2011 and 2020. The primary outcome was the rate of repeat surgery for recurrent cSDH following the initial evacuation. The authors used CHAID to identify relevant predictors of repeat surgery, including age, sex, comorbidities, postsurgical complications, platelet count prior to the first procedure, midline shift prior to the first procedure, hematoma volume, and preoperative use of anticoagulants, antiplatelets, or statins.

RESULTS Sixty (13.8%) of 435 study-eligible patients (average age 74.0 years) had a cSDH recurrence. These patients had 2.0 times greater odds of having used anticoagulants. The final CHAID model had an overall accuracy of 87.4% and an area under the curve of 0.76. According to the model, the predictor with the strongest association with cSDH recurrence was admission platelet count. Approximately 28% of patients (n = 23/87) with an admission platelet count < 157 × 10^9/L had a cSDH recurrence, whereas none of the 44 patients with admission platelets > 313 × 10^9/L had a recurrence. Approximately 17% of patients in the 157–313 × 10^9/L platelet group who had used preoperative statins required a second procedure, which was associated with a 2.3 times increased risk for repeat surgery compared to those who had not used statins preoperatively. Among those who had not used preoperative statins, a platelet count ≤ 179 × 10^9/L on admission for the first procedure was the strongest differentiator for a second surgery (n = 5/22 [23%]), which increased the risk of recurrence by 4.5 times. Among the patients using preoperative statins, the use of anticoagulants was the strongest differentiator for requiring repeat surgery (n = 11/33 [33%]).

CONCLUSIONS The described model identified platelet count on admission as the most important predictor of repeat cSDH surgery, followed by preoperative statin use and anticoagulant use. Critical cutoffs for platelet count were identified, which future studies should evaluate to determine if they are modifiable or reflective of underlying disease states.

https://thejns.org/doi/abs/10.3171/2023.7.FOCUS23240

KEYWORDS chronic subdural hematoma; recurrence; statins; anticoagulants; platelet count
reoperation for recurrent cSDH. A subsequent operation can increase the risk of mortality and morbidity in this aging population. Understanding the risk factors associated with the need for a second operation for cSDH may reveal viable treatment pathways to avoid repeat surgery.

Prior studies have reported recurrence rates of 10%–24% following cSDH evacuation. Given such a high incidence, a spectrum of prognostic models have been reported in the literature and internally validated. Among the most common predictors retained in the final models are older age, initial hematoma size and density, greater midline shift, and postoperative cavity volume. However, only a few studies have examined the potential role of postsurgical complications, existing comorbidities, or antithrombotic medication use, or platelet count prior to the first evacuation, with equivocal results. Given the longer life expectancy in the US, these variables will be of significant concern for the population moving forward. Moreover, nearly all prior studies have used univariate and/or multivariate logistic regression analyses that have included dichotomous predictors to develop their models. This method is commonly used in logistic regression analyses to enhance the interpretability of the association between predictor and outcome. For example, Suero Molina et al. presented a prognostic model for progression analyses to enhance the interpretability of the midline shift, and postoperative cavity volume.

Institutional Management of cSDH

The majority of neurosurgeons at our institution use a mini craniotomy for the treatment of cSDH. Typically, patients are placed under general anesthesia, and a small incision is made over the cranial convexity. A small, 3- to 4-cm-diameter mini craniotomy is made and copiously irrigated with warmed saline. Some neurosurgeons will use one or two burr holes at their discretion. The standard at our institution, and consistent with randomized controlled trials, is to place a subdural drain that remains in place until postoperative day 2 or 3. Patients are mobilized immediately after surgery and are not confined to the bed. The management of antithrombotic and antiplatelet agents was at the discretion of the managing neurosurgeon but typically followed guidelines from the Neurocritical Care Society. If feasible, the effects of warfarin and direct-acting oral anticoagulants were allowed to wear off through waiting until either normalization of the international normalized ratio or 5 half-lives, respectively. Antiplatelet agents were managed similarly, with a 7-day waiting period for clopidogrel and 4-day waiting period for aspirin. In situations in which the cSDH threatened life or severe neurological injury, antiplatelets and anticoagulants were reversed according to guidelines. Anticoagulants and antiplatelets were restarted, if appropriate, typically after 1 month and a stable head CT scan. Agents were restarted sooner for more serious, life-threatening pathologies such as active pulmonary embolism or drug-eluting cardiac stents.

Data Analysis

We used descriptive statistics for the overall sample, as well as chi-square analyses and odds ratios to identify relevant univariate clinical predictors for cSDH recurrence. The CHAID algorithm is a data mining algorithm that we used to differentiate patients who required retreatment for cSDH from those who did not. The use of CHAID to develop prognostic models has several advantages over multivariable logistic regression. CHAID is a nonparametric statistical analysis that has no requirements to conform to the normal distribution assumptions of logistic regression modeling. CHAID adjusts for multiple comparisons, which is a limitation of logistic regression. Furthermore, CHAID can automatically identify interactions between included predictors in the model, as well as significant relationships within nominal variables, and other included predictors. CHAID can also identify the point in a continuous variable that maximizes the difference in the outcome (i.e., repeat cSDH surgery).
put is produced, showing the identified predictors of the outcome in order of strength from top to bottom. The algorithm proceeds iteratively through the available predictors until the cohort cannot be further subdivided. Each node split is assessed with Bonferroni corrections for statistical significance. These CHAID characteristics are executed automatically by the algorithm based purely on the mathematical information provided in the data set.\(^{21}\) The investigator does not select or control which cut point or combinations for each variable are included in the final model. The risk ratio and 95% confidence intervals are reported for each node split. For our model, we included the following predictors: 1) continuous: age, platelet count on admission, midline shift on admission, midline shift following the index cSDH evacuation, and greatest width of the preoperative hematoma on axial slices (in millimeters); 2) nominal: postsurgical complications after the first surgery (e.g., cerebrovascular accident, pneumonia, sepsis, deep vein thrombosis/pulmonary embolism, urinary tract infection, acute kidney injury), preexisting comorbidities (e.g., hypertension, abnormal liver function, heart failure/atrial fibrillation, chronic kidney disease, coronary artery disease, malignancy); 3) binary: biological sex at birth, statin use, anticoagulant use (i.e., warfarin, rivaroxaban, apixaban, onxaparin), or antiplatelet use (i.e., aspirin or clopidogrel).

Statistical significance was set at \( p < 0.05 \). Statistics were completed using SPSS version 28.0.1 and SPSS Modeler version 18 (IBM Corp.).

### Results

#### Demographics and Odds Ratios

Overall, 60 (13.8%) of 435 study-eligible patients had a cSDH recurrence. These patients had a larger SDH on presentation, lower platelet count, and higher odds of at least one postsurgical complication (Table 1). Patients with a cSDH recurrence also had 2.0 times greater odds of having used preoperative anticoagulants. There was no difference between patients who required a second intervention and those who did not in terms of age, number of males, use of preoperative antiplatelet medication, rate of comorbidities, or rate of postsurgical complications (Tables 1 and 2). One in 4 patients who required retreatment had been taking presurgical warfarin (Table 3). Nearly half of the patients requiring retreatment had been taking aspirin, and almost one-third had not been taking anticoagulants or antiplatelet medications.

#### Differentiating Patients Requiring a Second Surgery for SDH From Those Who Did Not

A CHAID decision tree model was built to differentiate patients with cSDH recurrence (Fig. 1). The model had 13 nodes and 4 split levels. The model had an overall accuracy of 87.4% and an area under the curve of 0.76.

### Split Level 1

The predictor with the strongest association with cSDH recurrence was admission platelet count. Approximately
26% of patients (n = 23/87) with a platelet count < 157 × 10^9/L had a cSDH recurrence, whereas none of the 44 patients with a platelet count > 313 × 10^9/L had a cSDH recurrence. Patients between that range (157–313 × 10^9/L; n = 304) required a second procedure at a 12.2% rate (n = 37). A dose-response relationship was observed between a lower platelet count on first admission and an increased risk of recurrence (Table 4).

### Split Level 2

The next strongest predictor of the risk for a second procedure was preoperative statin use among the patient group with 157–313 × 10^9/L platelet count. Approximately 17% of patients in this category who had used statins required a second procedure, which was associated with a 2.3 times greater risk for repeat surgery compared to patients not using statins preoperatively.

### Split Level 3

Among those who had not used preoperative statins, a platelet count ≤ 179 × 10^9/L on admission for the first procedure was the strongest predictor of a second surgery. Nearly 23% (n = 5/22) of patients in this category required a second procedure, which was associated with a 4.5 times increased risk compared to patients with a platelet count > 179 × 10^9/L and not using statins.

Among those who had used preoperative statins, the use of preoperative anticoagulants was the strongest predictor of repeat surgery. Approximately 33% (n = 11/33) of patients using statins and anticoagulants required a second surgery, which was associated with a 2.7 times greater risk compared to patients using statins but not anticoagulants.

### Split Level 4

The final indicator of patients requiring a second procedure was midline shift. Among patients using preoperative statins and anticoagulants, a midline shift between 3–9 mm required a second surgery at a 75% rate (n = 9/12). This shift was associated with a 6.8 times increased risk for a second surgery compared to patients with a midline shift < 3 mm and a 9.0 times greater risk for a second surgery compared to patients with a midline shift > 9 mm.

### TABLE 2. Prevalence of risk factors for repeated surgical intervention for SDH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Repeat Surgical Intervention</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>Yes</td>
<td>60</td>
<td>375</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>Yes</td>
<td>49</td>
<td>265</td>
<td>1.85</td>
</tr>
<tr>
<td>Preop anticoagulant use</td>
<td>Yes</td>
<td>19</td>
<td>70</td>
<td>2.01</td>
</tr>
<tr>
<td>Preop antiplatelet use</td>
<td>Yes</td>
<td>28</td>
<td>181</td>
<td>0.93</td>
</tr>
<tr>
<td>Preop statin use</td>
<td>Yes</td>
<td>34</td>
<td>169</td>
<td>1.55</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>35</td>
<td>233</td>
<td>0.85</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>Yes</td>
<td>5</td>
<td>14</td>
<td>2.34</td>
</tr>
<tr>
<td>Heart issue/atrial fibrillation</td>
<td>Yes</td>
<td>15</td>
<td>85</td>
<td>1.14</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Yes</td>
<td>12</td>
<td>57</td>
<td>1.40</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Yes</td>
<td>4</td>
<td>34</td>
<td>0.72</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Yes</td>
<td>12</td>
<td>81</td>
<td>0.91</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular accident</td>
<td>Yes</td>
<td>3</td>
<td>9</td>
<td>2.14</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Yes</td>
<td>2</td>
<td>13</td>
<td>0.96</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Yes</td>
<td>1</td>
<td>14</td>
<td>0.44</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Yes</td>
<td>2</td>
<td>16</td>
<td>0.77</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>Yes</td>
<td>6</td>
<td>17</td>
<td>2.34</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Yes</td>
<td>6</td>
<td>23</td>
<td>1.70</td>
</tr>
</tbody>
</table>

**DVT** = deep vein thrombosis; **PE** = pulmonary embolism.

Values are expressed as number (%). Boldface type indicates statistical significance (p < 0.05).

### TABLE 3. Number of patients taking specific anticoagulant and antiplatelets and the rate of retreatment for cSDH

<table>
<thead>
<tr>
<th>Anticoagulant/Antiplatelet Agent</th>
<th>No. of Patients Taking Medication (n = 434)</th>
<th>Rate of Retreatment (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>73 (16.8)</td>
<td>15 (25.0)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>197 (45.4)</td>
<td>27 (45.0)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>35 (8.1)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>4 (0.9)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>3 (0.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>8 (1.8)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Multiple</td>
<td>49 (11.3)</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>None</td>
<td>162 (37.3)</td>
<td>18 (30.0)</td>
</tr>
</tbody>
</table>

Values are expressed as number (%).
Discussion

We used CHAID, a decision tree algorithm, to develop a prognostic model of cSDH recurrence and identified platelet count, statin and/or anticoagulant use, and midline shift as significant predictors. The most important driver of the risk of cSDH recurrence was admission platelet count. Patients with platelets below a $157 \times 10^9$/L threshold had a 26% prevalence for cSDH recurrence, compared to 11% for those above that threshold. None of the 44 patients with a high platelet count ($> 313 \times 10^9$/L) had a cSDH recurrence. The next strongest predictor of cSDH recurrence was preoperative statin use, an agent with known antiplatelet effects. The use of anticoagulants in addition to statins further exacerbated the cSDH recurrence risk by an additional 167% among patients who presented with platelet counts of 157–313 $\times 10^9$/L. Our study extends prior work on prognostic modeling for recurrent cSDH surgery through identifying several, clinically relevant, population-specific cut points that increase the risk of cSDH recurrence.

The major strength of our study is that many of the cutoff points we identified may be clinically modifiable. While previously reported age and preoperative cSDH volumes are known predictors of cSDH recurrence, they are not modifiable clinical characteristics. In contrast, we identified three groups of patients based on preoperative platelet count (group 1: $< 157 \times 10^9$/L, group 2: 157–313 $\times 10^9$/L, group 3: $> 313 \times 10^9$/L) that have large differences in cSDH recurrence (26.4%, 12.2%, and 0%, respectively). Without significant supporting evidence, traditional neurosurgery dogma teaches that patients with $< 100,000$ platelets have an increased risk for postoperative hematoma. Our results suggest that a higher threshold (i.e., 157,000) may be necessary to reduce the risk of cSDH recurrence. Importantly, our work supports only a correlative, not a causative, relationship between admission platelet count and cSDH recurrence. A low platelet count can reflect poor underlying health, such as alcoholic cirrhosis or chronic kidney disease. While we attempted to control for underlying preoperative health conditions (i.e., chronic kidney disease, abnormal liver function), future studies should assess whether higher preoperative platelet goals reduce the postoperative hemorrhage risk.

In a vein similar to the platelets, anticoagulation and antithrombic agents increased the risk of cSDH recurrence.

![FIG. 1. CHAID decision tree model. (number) = node identifier for statistical comparison.](image)

**TABLE 4. Risk ratios between predictor nodes from the CHAID decision tree**

<table>
<thead>
<tr>
<th>Node Comparison</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt;157 vs $&gt;313 \times 10^9$/L</td>
<td>11.90</td>
<td>1.66–85.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelets 157–313 vs $&gt;313 \times 10^9$/L</td>
<td>5.48</td>
<td>0.77–38.94</td>
<td>0.046</td>
</tr>
<tr>
<td>Platelets &lt;157 vs $&gt;313 \times 10^9$/L</td>
<td>2.17</td>
<td>1.35–3.47</td>
<td>0.001</td>
</tr>
<tr>
<td>Statin use vs no statin use</td>
<td>2.28</td>
<td>1.19–4.38</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelets $\leq 179$ vs 179 $\times 10^9$/L</td>
<td>4.45</td>
<td>1.55–12.78</td>
<td>0.004</td>
</tr>
<tr>
<td>Anticoagulant use vs no anticoagulant use</td>
<td>2.67</td>
<td>1.34–5.34</td>
<td>0.01</td>
</tr>
<tr>
<td>Midline shift $3–9$ vs $&lt;$3 mm</td>
<td>6.75</td>
<td>1.03–44.08</td>
<td>0.004</td>
</tr>
<tr>
<td>Midline shift $3–9$ vs $&gt;$9 mm</td>
<td>9.00</td>
<td>1.34–60.46</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Boldface type indicates statistical significance (p < 0.05).
Cerebral hemorrhage (ICH) from stroke. While statins may increase the risk for spontaneous ICH, postoperative hematoma volume. Several other groups have shown that larger hematoma volumes are associated with an increased risk for cSDH recurrence. Our results suggest that chronological and biological age—that is, the difference between evaluating age as a number and evaluating it as the cumulative effect of disease and aging on the body—may have differing effects on the risk of cSDH recurrence.

Study Limitations

Our work has several limitations. Our data set did not include some relevant predictors from prior work, including pre- and postoperative hematoma volume. Some other groups have shown that larger hematoma volumes are associated with an increased risk for cSDH recurrence. While cSDH width, which was used in our study, serves as a proxy for volume, hematoma volume itself may be more predictive. Additionally, our model was developed with data from a single institution. While we included patients from two level I trauma centers covered by 15 different neurosurgeons, external validation is needed before widespread use of our model. We did not document the neurosurgeon who performed each procedure, so a comparison of results across surgeons was not possible. The model presented here has only been internally validated and requires validation in external data sets. Future work should directly compare the performance of the model presented here with other prognostic models reported in the literature. Lastly, we collapsed all complications into one binary variable to simplify modeling efforts. This results in a loss of variance in certain outcomes, such as the difference in severity of some postoperative complications.

Conclusions

We applied a data mining decision tree algorithm to a retrospectively reviewed data set of cSDH patients to uncover novel insights for predicting cSDH recurrence. Our CHAID model identified platelet count as the most important predictor of repeat cSDH surgery, followed by preoperative statin use and anticoagulant use. Notably, the decision tree model identified critical cutoffs for platelet count, which future studies should assess as modifiable or reflective of underlying disease states. Within a cohort that presented to the hospital with a platelet count of 157–313 × 10^9/L, preoperative statin and anticoagulant use further increased the risk for cSDH recurrence.

References


A similar effect has been found in patients with intracerebral hemorrhage (ICH) from stroke. While statins improve functional outcomes if initiated after ICH, pre-ICH use can increase the risk for spontaneous ICH, possibly due to platelet effects. Although postoperative statin use, through its antiinflammatory responses, has been proven beneficial at reducing cSDH volume, little is known about the preoperative risks of statin use. Future studies should evaluate whether preoperative platelet transfusions reduce the risks of cSDH recurrence for patients on statins preoperatively. More evidence will be necessary to understand if the use of statins and/or anticoagulants is a reversible risk factor for cSDH recurrence. Future research should also investigate whether the role of statins and/or anticoagulants is only relevant to recurrence when presenting with a certain platelet count, which evidence from this study would suggest.

One of the most common predictors included in previous prognostic models for recurrent cSDH surgery is older age. Although age was included as a predictor in our models, it was not retained in the final decision tree. This may indicate that older age is a proxy variable for more specific predictors, such as lower platelet count and the use of statins/anticoagulant medications. Platelet count decreases with age, with lower average values observed in males. Similarly, older adults are more likely to be taking statins and anticoagulant medications than younger adults because of the higher risk of comorbidities like stroke, atrial fibrillation, and heart disease. Our results suggest that chronological and biological age—that is, the difference between evaluating age as a number and evaluating it as the cumulative effect of disease and aging on the body—may have differing effects on the risk of cSDH recurrence.

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References


Disclosures
Dr. Vargas reported stock options with Viz.ai; consulting for Imperative Care, Scientia, Q’Apel, Medtronic, Cerenovus; and equity in Synchron and Borvo; all outside the submitted work.

Author Contributions
Conception and design: Eagle. Kellogg. Nwachuku, Okonkwo, Pease. Acquisition of data: Mittal, Nwachuku, Deng, Okonkwo, Pease. Analysis and interpretation of data: Eagle, Mittal, Deng, Okonkwo, Pease. Drafting the article: Eagle. Nwachuku, Deng, Okonkwo, Pease. Reviewed submitted version of manuscript: Eagle, Mittal, Kellogg, Vargas, Buell, Okonkwo, Pease. Reviewed submitted version of manuscript: Eagle, Mittal, Kellogg, Vargas, Buell, Okonkwo, Pease. Approved the final version of the manuscript on behalf of all authors: Eagle. Statistical analysis: Eagle. Study supervision: Okonkwo.

Correspondence
Shawn R. Eagle: University of Pittsburgh, PA. eaglesr2@upmc.edu.