CHRONIC SUBDURAL HEMATOMA: EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS, TREATMENT AND OUTCOME

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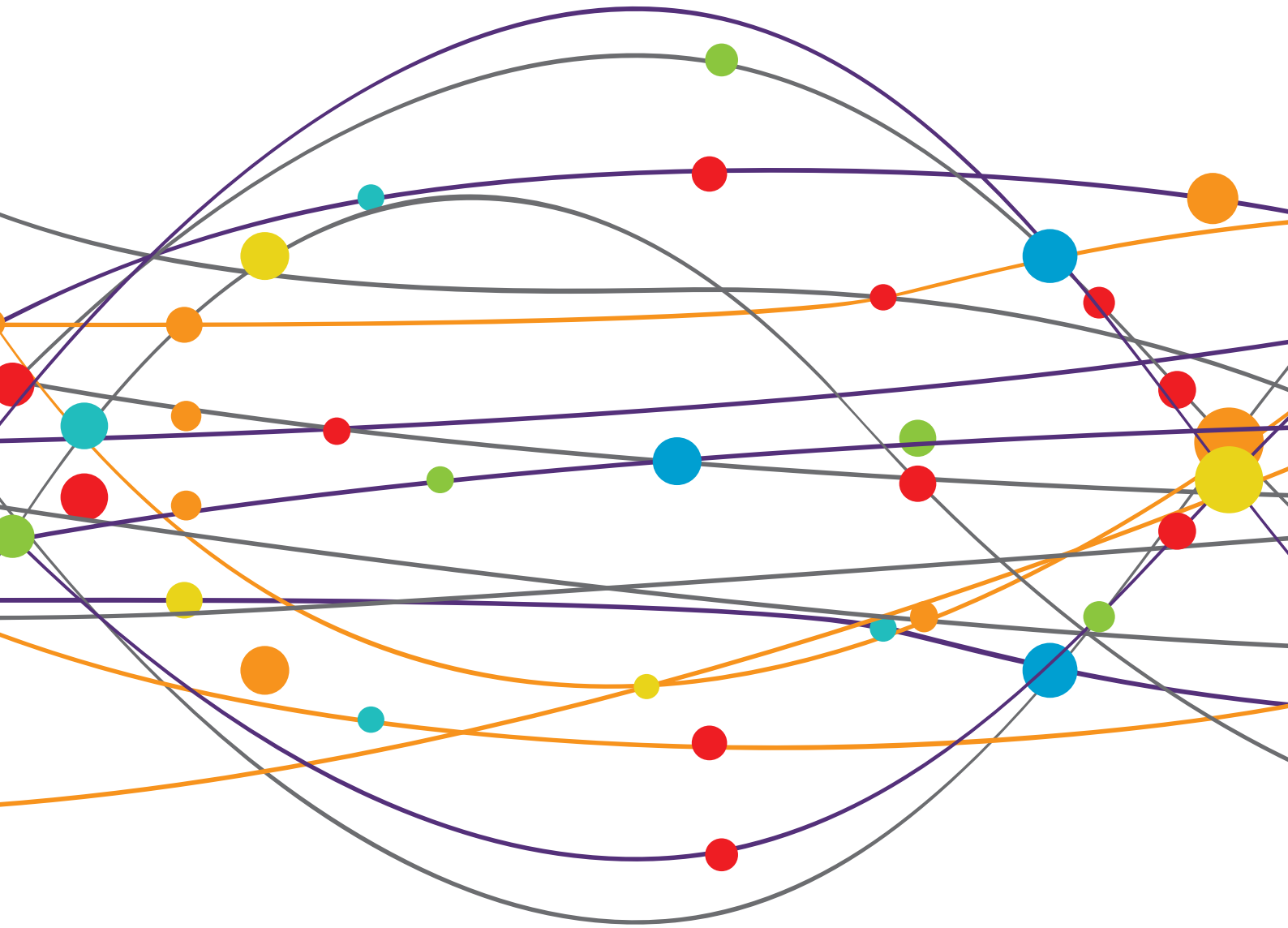

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CHRONIC SUBDURAL HEMATOMA: EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS, TREATMENT AND OUTCOME

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Predicting Chronic Subdural Hematoma Recurrence and Stroke Outcomes While Withholding Antiplatelet and Anticoagulant Agents

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Introduction: The aging of the western population and the increased use of oral anticoagulation (OAC) and antiplatelet drugs (APD) will result in a clinical dilemma on how to balance the recurrence risk of chronic subdural hematoma (cSDH) with the risk of withholding blood thinners.

Objective: To identify features that predicts recurrence, thromboembolism (TEE), hospital stay and mortality. To identify the optimal window for resuming APD or OAC.

Methods: We performed a retrospective multivariate analysis of a prospectively collected database. We then build machine learning models for outcomes prediction.

Results: We identified 596 patients. The rate of recurrence was 22.17%, that of thromboembolism was 0.9% and that of mortality was 14.78%. Smoking, platelet dysfunction, CKD, and alcohol use were independent predictors of higher recurrence, while resolution of the SDH was protective. OAC use had higher odds of developing TEEs. CKD, developing a new neurological deficit or a TEEs were independent predictors of higher mortality. We find the optimal time of resuming OAC to be after 2 days but before 21 days as these patients had the lowest recurrence of bleeding associated with a low risk of stroke. The ML model achieved an accuracy of 93, precision of 0.84 and recall of 0.80 for recurrence prediction. ML models for hospital stay performed poorly (R^2 = 0.33). ML model for stroke was overfitted given the low number of events.

Conclusion: ML modeling is feasible. However, large well-designed prospective multicenter studies are needed for accurate ML so that clinicians can balance the risks of recurrence with the risk of TEEs, especially for high-risk anticoagulated patients.

Keywords: chronic subdural hematoma, recurrence, stroke, antiplatelet, anticoagulation, oral anticoagulation, machine learning

INTRODUCTION

The aging of the western population and the increasing use of oral anticoagulation (OAC) and antiplatelet drugs (APD) will likely result in an increased incidence of chronic subdural hematoma (cSDH) (1). Elderly patients have a 10-fold increase in the risk of developing cSDH, estimated around 58–200 per 100,000 per year, depending on their anticoagulation status (2). Despite technological advances in the neurosurgical field, there has little improvement regarding the surgical technique for cSDH, an entity that has been well-characterized since 1857 (3) and treated with trepanation since prehistoric ages (4).

Although the commonly used techniques are relatively safe and simple (1), cSDH have a mortality rate as high as 42% (5, 6) and a recurrence rate up to 76% (1, 7, 8). Prediction models so far have been inconsistent (9–12) and are not routinely implemented in clinical practice. In addition, questions regarding postoperative OAC and APD management remain unanswered (1).

We aimed to identify features that can predict cSDH recurrence, thromboembolic events (TEE), hospital stay and mortality, using biostatistical analysis and machine learning (ML) models. We then aimed to assess the optimal timing for resuming oral anticoagulation drugs (OADs) or antiplatelet drugs (APDs) by balancing the risk of recurrence with that of thromboembolic events.

METHODS

Patient Characteristics

We performed a retrospective review of patients with cSDH from a single institution between 2007 and 2015 after Institutional Review Board approval. We identified 596 patients, 505 of which had unilateral cSDH (84.7%). Inclusion criteria were age > 40 years and cSDH requiring evacuation by burr-hole drainage. We collected data on age, hypertension, diabetes mellitus status, body mass index (BMI), chronic kidney disease (CKD) (defined as > stage 3), smoking (> 1 pack per day), chronic alcoholism (>3 glasses a day), platelet disorder (pancytopenia), OAC use, aspirin use and dosage, clopidogrel use, history of cerebrovascular accident, history of atrial fibrillation, history of mechanical valve, and history of liver disease. The size of the subdural hematoma on preoperative and postoperative scan was recorded as follows: maximum height on the coronal scan, maximal length on the axial scan and maximal width or thickness on the axial scan. The cortical atrophy grade was measured using Brickman et al. protocol (13), as it has been shown to correlate with a faster decline in cognition in Alzheimer's disease (13). We measured the largest distance between the heads of the caudate and divided it by the width of the skull (from inner table to inner table) on the same slice. Thus, enlarged ventricles increase the value and indicates more atrophy. For time off OAC, patients were classified into the following categories: (1) resumption within the first 2 days post-op, (2) resumption between day 3- and 2-weeks post-op, (3) resumption between 2- and 3-weeks post-op, (4) resumption between 3- and 4-weeks postop, and (5) resumption between 4- and 6-weeks post-op. The same subcategorization was performed for patients on APD. All patients were treated with burr-hole trephination with a closed drainage system. They remained bed rest for 12–24 h post-op and a CT scan was obtained prior to removal of the drain and slow mobilization. During the first 24 h patients were given intravenous fluids unless contra-indicated. Subcutaneous heparin was started after 48 h on all patients who required help with ambulation.

Outcome Assessment

Recurrence was defined as the accumulation of chronic subdural fluid requiring reoperation after at least 48 h from the initial surgery and after discharge. We have chosen 48 h as a cut-off since a postop CT scan is obtained within 24 h. If the surgeon did not properly evacuate the SDH, the patient is taken back to the OR for a re-do surgery during the same hospital stay. Thus, a second surgery performed during the same hospitalization was not considered as a recurrence. Thromboembolic events (TEEs) were defined as transient ischemic attacks or strokes during the follow-up period after surgery. Duration of hospitalization was recorded in days. The size of the postoperative cSDH was measured by the same method as the preoperative cSDH size. The rate of developing post-op neurological deficits and mortality was recorded. New neurological deficit was defined as a neurological deficit that was not present preop. This could be due to seizures, postop bleeding, or stroke (from stopping the anticoagulation or antiplatelets). Death from a neurological injury was defined as death as a result of postoperative stroke, hemorrhage or seizures (which includes withdrawal of care and death from the reasons above). The risk of developing a stroke or a cSDH recurrence in relation to the timing of recommencement of APD or OAC was assessed. Complete resolution of the SDH was defined as the complete disappearance of the cSDH on CT scan on the last follow-up. The mortality was defined as the rate of death from hospitalization to follow-up.

Surgical Method

Patients underwent endotracheal intubation with general anesthesia. For patients who underwent a single burr hole placement, the burr hole was placed at a point that intersects the superior temporal line with a vertical line from the tip of the mastoid (Euryon), which is the area of maximal atrophy. For patients who underwent 2 burr hole placement, a burr hole was placed in the frontal area and one in the parietal area. The exact location was estimated with the help of the CT scan preop. All burr holes were placed with the craniotome. A subgaleal drain (passive system) was always used (it was tunneled from the posterior burr hole when 2 burr holes were placed). The dura was cauterized and opened. Suction irrigation was used to retrieve the clot, and the membrane was open when present. When 2 burr holes were placed, we ensured that irrigating the frontal one lead to drainage of the irrigation solution from the posterior one.

Hemostasis and closure were performed in the usual setting. Of note, a red rubber catheter was used depending on the surgeon's preference. Hemostasis and closure were performed in the standard fashion. The patient remained flat for 24 h duration post surgery. The subgaleal drain was removed at the surgeon's discretion, typically 24 h post surgery.

TABLE 1 | Demographics and characteristics of the study population.

Features	Descriptions
Age	73 ± 13
Unilateral cSDH	84.73%
Male	66.67%
BMI	26.84 ± 5.8
Hypertension	53.68%
Diabetes	24.03%
Chronic Kidney disease	7.56%
Ventriculoperitoneal shunt	4.84%
History of stroke/T.I.As	12.79%
Platelet dysfunction	3.48%
ASA 81	29.45%
ASA 325	15.69%
Clopidogrel	10.07%
Warfarin	20.15%
Smoking	37.21%
Chronic alcohol disease	33.72%
Liver disease	2.91%
Preop	
Height	9.11 ± 1.60 mm
Width	1.98 ± 0.93 mm
Length	12.15 ± 2.22 mm
Cortical atrophy grade	0.16 ± 0.05

Values reported as mean (SD) when appropriate.

TABLE 2 | Outcomes.

Features	Descriptions
Postop	
Height	7.32 ±1.98 mm
Width/Thickness	1.13 ±0.50 mm
Length	8.67 ±2.85 mm
SDH resolution	54.47%
Rebleed	22.17%
TEEs	0.90%
New neurological deficit	6.8%
Death	14.7%

Statistical Analysis

Patients with unavailable data were excluded from the analysis (<1%). Categorical data were transformed to dummy variables. Descriptive statistics was first performed followed by data visualization. Univariate analysis was carried out to test for significance (**Table 1**). Features with $p < 0.20$ were included in the multivariate analysis. A logistic regression model was performed for categorical targets and a multivariate linear regression model was used for numerical targets. A multivariate linear regression model was performed when the data was linear and there was no heteroscedasticity (if not a log transformation or scaling was performed). We tested for autocorrelation through the Durbin-Watson test (accepted values between 1 and 3) and for multicollinearity through the variance inflation factor and excluded features with a factor > 6. Analysis was performed using Python 3.7 in Spyder 3.6 (Anaconda distribution). Stats model library was used for univariate and multivariate analysis.

Machine Learning Modeling

Machine learning modeling was performed to predict hospital stay, recurrence, and stroke risk (see **Supplementals 1**–**3** for details). We excluded patients with unavailable data from the machine learning model. **Supplemental 1** displays our model pipeline. We then standardized all numerical features. For all machine learning models, the features included in the analysis were those with significant F value on the univariate analysis (Scikit learn using F_Classif when the target is categorical and F_regression for numerical target). The target value was defined as the actual value of the independent variable. The predicted value was defined as the predicted value of the independent variable. For numerical values, the residual is defined as the target minus the predicted values. The data was split randomly into 80% for training + validating and 20% for testing, with stratification. A gridsearch with 10-fold cross validation for every model was performed to establish the best hyperparameter and the best score for each model, based on the training/validation data only. The best scores for classifiers were the accuracy score, F1 score, recall and precision. The best model was then chosen and tested on the testing dataset. For regression models, we assessed the linearity by grid search to obtain the best kernel for the SVC model. However, models for both linear and non-linear data were tested and evaluated based on the parameters above. Analysis was performed using Python 3.7 in Spyder 3.6 (Anaconda distribution) using SciKit learn for ML and Yellow brick for data visualization and ML.

RESULTS

Patients Demographics and Outcomes

We identified 596 patients and excluded 10 patients from the inferential analysis and 30 patients from the ML models due to unavailable data on certain features. Patients demographics and characteristics are listed in **Table 1**. The average age was 73 ± 13 years with a range of 40–97 years. Males constituted 66.67% of the population. Chronic kidney disease affected 7% of patients. Twenty percent used OAC (98.83% of which were on warfarin) and 46% used APD. The average BMI was 26.8 ± 5.8. Burr-hole trephination significantly reduced the SDH height by 2 mm ($p < 0.001$) and length by 4 mm ($p < 0.001$) (**Tables 1**, **2**). It did not affect the thickness. The majority of the patients (84.73%) had unilateral cSDH. New neurological deficit occurred in 6.8% of the postoperative patients and included: seizures, stroke, worsening of previous symptoms or post-op hemorrhage. Liver disease affected 1.9% (2.9) of the population and these patients were excluded from the inferential analysis.

Predictors of SDH Recurrence

The rate of recurrence was 22.17%. For patients on blood thinners, the risk of recurrence was significantly higher, and

TABLE 3 | Predictors of recurrence.

	Odds ratio	*P*
Univariate analysis		
SDH resolution	0.627	0.029*
Chronic Kidney Disease	2.690	0.004*
Diabetes	1.13	0.159*
Smoking	1.692	0.104
Alcohol	1.623	0.059
OAC	1.335	0.018*
Preop Height	1.174	0.032*
Postop Height	1.145	0.091
Clopidogrel	1.23	0.03*
Shunt	2.25	0.004*
Platelet disorders	1.76	0.005*
Multivariate analysis		
Smoking	4.867	0.001*
SDH resolution	0.271	0.001*
Platelet disorder	2.74	0.030*
Chronic Kidney Disease	2.332	0.020*

Predictors with p < 0.20 were included in the multivariate analysis.
Predictors with a p < 0.20 on univariate and <0.05 on multivariate analysis were reported.
**Statistically significant.*

TABLE 4 | Predictors of TEEs.

	Odds ratio	*P*
Univariate analysis		
OAC	6.030	0.051*
Diabetes	4.835	0.086
Time off oral anticoagulation	0.5	0.182
Multivariate analysis		
OAC	3.275	0.049*

Predictors with p < 0.20 were included in the multivariate analysis.
Predictors with a p < 0.20 on univariate and <0.05 on multivariate analysis were reported.
**Statistically significant.*

TABLE 5 | Predictors of mortality.

	Odds ratio	*P*
Univariate analysis		
SDH resolution	0.262	0.001*
Smoking	1.95	0.068
Platelet disorder	1.17	0.029*
CKD	2.868	0.005*
DM	1.688	0.052
New neurological deficit	6.755	0.001*
Rebleed	1.795	0.033*
Thrombotic event	9.000	0.017*
Warfarin	1.04	0.20
Multivariate analysis		
New neurological deficit	6.051	0.001*
SDH resolution	0.306	0.001*
Thrombotic event	9.723	0.025*
CKD	2.705	0.019*

Predictors with p < 0.20 were included in the multivariate analysis.
Predictors with a p < 0.20 on univariate and <0.05 on multivariate analysis were reported.
**Statistically significant.*

that of patients with CKD and platelet dysfunction was the highest (**Table 3**). Univariate analysis showed CKD, OAC use, diabetes, smoking, alcohol, platelet dysfunction, having a shunt, pre-operative height, and post-operative height of the SDH were associated with higher odds of recurrence. We found that patients with CKD and those with platelet dysfunction have 2–3 times (platelet disorder OR = 2.74, CKD 2.332) the odds of developing a recurrent bleed on multivariate analysis (**Table 3**). Resolution of the SDH was protective. On multivariate analysis, smoking, platelet dysfunction, CKD, and alcohol use were independent predictors of higher recurrence, while resolution of the SDH remained protective. The number of burr-holes used to treat each cSDH did not affect the outcome, although 2 burr-holes per side were used in 78.5% of the cases (468 patients).

Predictors of Thromboembolic Events

A small number of patients experienced a TEE (0.9%;6/596), all of which were deemed embolic. Univariate analysis showed OAC use, diabetes and a longer time off anticoagulation were associated with higher odds of developing TEEs (**Table 4**). On multivariate analysis, only OAC use had higher odds of developing TEEs, although the low number of TEEs limits this analysis.

Predictors of Mortality

The overall mortality rate was 14.78%. Causes of mortality were the following: neurological injury (6.80%), kidney failure (0.60%), and other causes (10.10%), such as liver disease, cardiac failure, and unknown cause of death in the community. Neurological injury included postoperative complications such as postoperative acute SDH and refractory seizures, ischemic stroke during hospital stay or at follow-up, and development of an acute SDH in a delayed fashion (after discharge) due to blood thinners, fall, or unknown reasons. Direct postoperative complications (acute SDH, refractory seizures) accounted for 2.01% (12 cases) of the population. Univariate analysis showed CKD, diabetes, recurrence of the SDH, developing a TEE or developing a new neurological deficit were associated with higher mortality, while resolution of the SDH was protective (**Table 5**). On multivariate analysis, CKD, developing a new neurological deficit or a TEEs were independent predictors of higher mortality.

Predictors of Duration of Hospitalization

Most frequent hospital length was 3 days. The median and mean were 4 and 6 days respectively. This was due to the range of from 2 to 57 days, making the distribution heavily skewed. Univariate analysis showed use of clopidogrel, higher BMI, and larger SDH were associated with a longer length of stay, while SDH resolution was associated with a shorter hospitalization (**Table 6**).

TABLE 6 | Predictors of longer hospital stay (predictors that increase the length of stay).

	Odds ratio	*P*
Univariate analysis		
Alcohol	1.6	0.073
History of cerebrovascular event	3.678	0.072
Clopidogrel	2.2	0.128
SDH resolution	0.515	0.193
Male	2.36	0.109
Preop average size	2.121	0.035*
Preop height	3.90	0.003*
Preop length	1.96	0.076
Postop height	1.392	0.065
BMI	4.835	0.173
Multivariate analysis		
OAC+APD	3.275	0.049*

Predictors with $p < 0.20$ were included in the multivariate analysis.
Predictors with a $p < 0.20$ on univariate and <0.05 on multivariate analysis were reported.
**Statistically significant.*

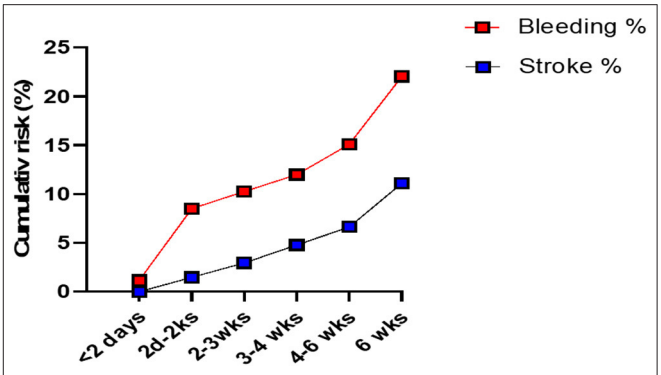

FIGURE 1 | The cumulative risk of recurrence of the chronic SDH ("Bleeding") and that of stroke in patients with cSDH (all patients combined). The cumulative risk of recurrence increases with time. There are 2 periods of higher risk (dramatic increase in the curve) at 2 days to 2 weeks post-op and after 6 weeks post-op. The risk of stroke gradually increases with time.

On multivariate analysis, the combined use of OAC and APD was significantly associated with a longer hospitalization.

Optimal Window for Resuming Blood Thinners

The cumulative risk of recurrence of cSDH appears to increase with time (all patients combined) (**Figure 1**). The risk of stroke appears also to gradually increase with time. The chance of developing a recurrence was highest when APD was resumed 2–14 days post-op (**Figure 2A**). However, this rate is not clinically different from other duration of holding therapy. The low chance of developing a recurrence in patients where the APD was resumed prior to 48 h is biased by the small sample size. The chance of developing a recurrence was highest for OAC when resumed within the first 48 h (**Figure 2B**). It then decreases quickly and stabilizes if the OAC were resumed after 2 days. Thus, the lowest risk of recurrence was the resumption of OAC between 2 and 20 days, with a slight increase after 20 days. The chance of developing TEEs is small and exhibits a small increase with longer time off APD or OAC. We find the optimal time of resuming OAC to be after 2 days but before 21 days as these patients had the lowest recurrence of bleeding associated with a low risk of stroke (**Figure 2**). We did not find the best duration to resume therapy as the risk was always higher than the general population without a specific peak. However, the data suggests a reasonably good safety prole of holding anticoagulation up to day 42.

Machine Learning Models

The optimal classifier to predict recurrence was the RFT with a f1-score of 0.92 and an area under the curve (AUC) of 0.91 based on the 10-fold cross validation using grid search. This model was then tested on the test data and achieved an accuracy of 93%, precision of 0.84 (specificity = 84%) and recall of 0.80 (sensitivity = 80%) for predicting recurrence (**Supplemental 1**).

We could not perform an ML model to predict TEE due to the lack of TEE events (0.09%). Finally, we tested an ML model for the hospital stay. The multivariate linear regression using ML technique had an $R^2 = 0.15$. The RFT model had an $R^2 = 0.33$ outperforming all other models, albeit still having a poor prediction accuracy, as displayed in the residual plots and the difference between predicted and target values plot (**Supplementals 2**, **3**). Thus, the variation in the selected features explain only 33% of the variation in the hospital stay, making our model not useful. This is not surprising giving the heavy skewed distribution in the hospital stay, along with other features that could affect the prediction but were not included in the model (insurance, availability of the rehabilitation facility, etc.). Thus, a ML model for hospital stay may be feasible, but it should be a separate study, and must include insurance and other factors, which will vary according to state, hospital policy, and setting (private vs. academic).

DISCUSSION

Resolution of cSDH is protective against recurrence and is associated with shorter hospitalization, while APD, OAC, CKD, platelet disorders, and alcohol had a higher rate of recurrence. Meanwhile, OAC had a higher risk of stroke likely due to the risks associated with pausing the anticoagulation. CKD patients present complex management issues, as this patient population often have baseline platelet dysfunction due to uremia and often cannot be resuscitated postoperatively with high volume of fluids to help brain expansion. Burr-hole trephination reduced the height and length but did not affect the thickness/width, which is likely related to the brain volume. We have found, similar to Stanišic et al. (12), that large pre- and post-operative SDH volume tend to have a higher recurrence rate, whether the lesion is bilateral or not. Stanišic et al. (12) also showed that bilateral cSDH is not predictive of postoperative recurrence, nor is it a surrogate for the cSDH volume, as the preoperative and postoperative volume of a unilateral CSDH in one patient can have a larger

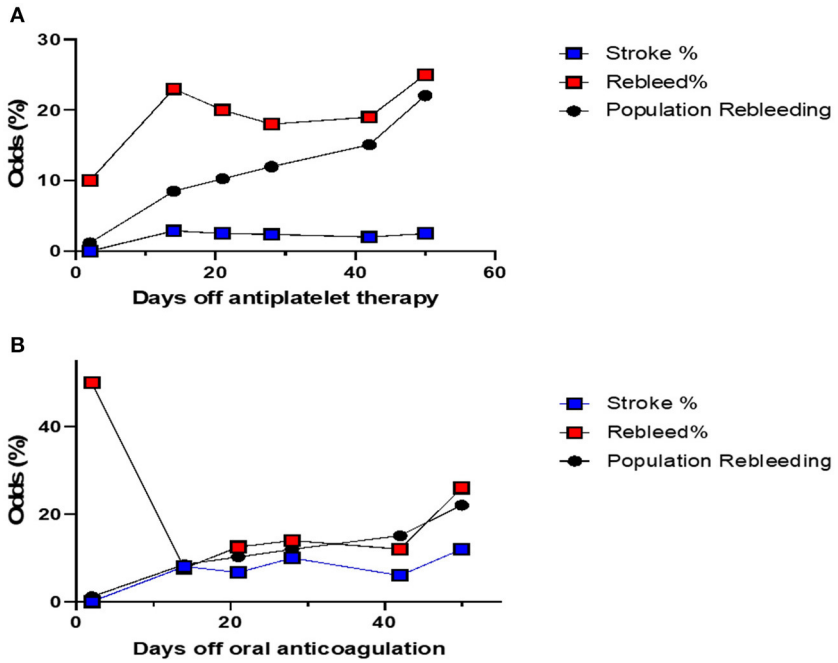

FIGURE 2 | (A) The odds of stroke and recurrence in patients with cSDH on APD, compared with the risk of recurrence in patients not on any blood thinners. This risk is calculated separately for each cohort of patients depending on when their APD were resumed. The risk of recurrence is always higher depending on the duration of withholding therapy. Patients where the APD was resumed between day 2 and week 2 post-op, had the highest risk, although that risk is not significantly different from the rest. Patients who resumed their APD within 48 h had lower odds of recurrence, but this is limited by the small sample size. The odds of stroke are similar. **(B)** The odds of stroke and recurrence in patients with cSDH on OAC, compared with the risk of recurrence in patients not on any blood thinners. This risk is calculated separately for each cohort of patients depending on when their OAC were resumed. The risk of recurrence is highest for patients who resumed their OAC within the first 48 h. The risk of stroke increases with time. The optimal time to restart OAC would be between 2 days and 20 days post-op.

volume than bilateral SDH in a separate patient (14). Similarly, Xu et al. (15) showed that bilateral cSDH were not associated with recurrence; however, with 44 bilateral cases and 10 unilateral cases, the number of patients in that study was small. In contrast, Shen et al. (16), reviewed 102 patients where bilateral cSDH was an independent risk factor for recurrence. The controversy regarding the role of bilateral cSDH in the rate of recurrence may be confounded by the cSDH volume or brain atrophy. We did not find brain atrophy to be related to recurrence unlike Shen et al. (16), but the measurement techniques were different. OACs increase the risk of cSDH 4- to 15-fold (17) depending on the intensity of anticoagulation, (17) patient's age (18); cerebral atrophy may also increase this risk. We did not find age or cortical atrophy grade to be independent predictors for recurrence, although the combined interaction of cortical atrophy with OAC was a predictor of recurrence Similarly, a 5-year retrospective study of 248 patients showed that anticoagulation in addition to headache and preoperative midline shift was an independent predictor for recurrence (9). In that study however, the risk of recurrence was lower than ours (12.6% vs. 22.17%), which may be due to the duration of follow-up.

Interestingly, the risk of recurrence is high when the OAC or APD are started within 48 h post-op. We have also shown that the risk of recurrence increases with time for the first few months. This is likely due to the slow reaccumulation and the time it takes to become symptomatic. Patients that started their OAC between 2 days and 2 weeks post-op had lower rate of rebleeding compared to those who were started within the first 48 h and similar rates to those started after 2 weeks. This is not consistent with a retrospective study of 187 patients where postoperative warfarin resumption within 2–3 days did not affect the recurrence rate (19). In our study, the cohort that resumed the APD or OAC after 2 days post-op, but before 2 weeks, had the same risk of stroke compared to those who resumed their blood thinners within the first 48 h and less than those who did after 2 weeks. The low rate of TEE, however, is a limiting factor for such analysis. In addition, a TEE is associated with a higher mortality on multivariate analysis, while a recurrence by itself is not. In addition, TEEs may result in a poor quality of life compared with cSDH recurrence. This could explain the practice of some neurosurgeons who immediately resume OAC and APD, especially in the setting of a fresh stent or a prosthetic valve, fearing a devastating TEE. Given the results of this study, perhaps patients with high risk of bleeding and low risk of TEEs can resume the anticoagulation at the end of the 2-weeks post-op period, while those with high risk of stroke and low risk of bleeding can resume their blood thinners after 2 days post-op to optimize the balance between risk of recurrence and TEE. Patients with high risk of bleeding and stroke can be followed more closely or referred to the neurosurgeon for routine CT scan

to decide when to resume the blood thinner. It is foreseeable in the future that ML models with accurate predictions will help the discussion between neurologists, cardiologists, hematologist and neurosurgeons to balance the risks of stroke with that of bleeding.

The ML model for recurrence has performed well on the testing data. The 93% accuracy of the model however is misleading; a model that predict no recurrence in all cases will be 78% accurate, as the risk of bleeding is 22%. Thus, our accuracy should be at least >80 for the model to be practical. However, a recall or a precision of a model that predicts no bleeding at all times will be 0. One must carefully evaluate the precision and recall for both recurrence and non-recurrence, and for TEE and non-TEE predictions. The best model would be one that has a higher recall for stroke (minimal false negative and thus highly sensitive, i.e., "sensitivity") and a higher precision for bleeding (minimal false positive and highly specific, i.e., specificity). ML model for recurrence was feasible while that for TEE was not due to the low frequency of these events. More data stratified by stroke risk features (such as prosthetic valve, atrial fibrillation, etc.) will be needed. The sensitivity and specificity of the model limits its use, and call for a multicenter collaboration in order to develop accurate models, available and easy to deploy in referral centers and in the community. Unsurprisingly, hospital stay was unpredictable as it is related to insurance, premorbid status, the availability of physical therapist and social worker, and the occupying state of the rehabilitation or skilled facility chosen by the patients. These data were not available for analysis.

LIMITATIONS

Although there is no consensus on the definition of recurrence, we defined it as symptomatic reaccumulation requiring re-operation. Thus, patients with radiographic recurrence were analyzed with the no recurrence group. In addition, patients are usually followed at 4–6 weeks follow-up, unless their symptoms recur and they return to the hospital. At the follow-up period is the typical diagnosis of recurrence. This may be one confounding factor for having higher recurrence at 4–6 weeks, while in reality the accumulation would have started earlier. In addition, it is hard to tease out a "bad evacuation" requiring a delayed second surgery from a true recurrence, and this may bias the results. However, the period 4–6 weeks reflect practice in the community. In our study, warfarin was the most used OAC, while recently there has been a trend toward using novel agents. Thus, these results may not be generalizable for patients on novel OAC. Another consensus limitation is the definition of mortality in cSDH. We have found mortality to be related to patient's comorbidities, neurological injury, withdrawal of care and old age, making it difficult sometimes to differentiate cSDH-related mortality from other causes. Overall, the cause of mortality in this population is similar to that in the general elderly population. Thus, a ML prediction model for mortality in cSDH will not be useful. However, we have identified that a post-op neurological deficit and TEEs are independent predictors of mortality. For the reasons above, one must be careful before committing high-risk patients for operative management. We did not evaluate the functional disabilities of patients, particularly after reoperation or after experiencing TEEs. The main limitation with TEEs detection is the short observation period. Another important factor in risk decision making for restarting APD is that these commonly are prescribed for cardiac stents; as such information regarding NSTEMI/STEMI while off APD would be useful in this risk stratification process and thus is a limitation. We also did not include other features such as pre-albumin, or neurological status on admission, which could bias the outcome (6). Finally, the heterogeneity of studied predictors, management strategies, and comorbidities do not allow for a comparison between clinical studies (12). A reliable ML model will need more patients, from different centers (to avoid selection bias), in a collaborative prospective well-designed trial. However, the findings from this series are promising.

CONCLUSION

Predictions in cSDH continue to represent a challenging problem. We highlighted features that predict recurrence, higher risk of TEEs and higher mortality. An optimal timing window for OAC is between 2 days and 21 days postop. While a useful ML model for recurrence was feasible, that for TEEs and duration of hospitalization were not. Large well-designed prospective multicenter studies are needed to build prediction models so that clinicians can balance the risks of recurrence with the risk of TEEs, especially for high-risk anticoagulated patients.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB University of Iowa. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KA-I and MZ contributed conception and design of the study. All authors contributed to data analysis, writing, revision, reading and approving final versions of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01401/full#supplementary-material

REFERENCES

1. Mehta V, Harward SC, Sankey EW, Nayar G, Codd PJ. Evidence based diagnosis and management of chronic subdural hematoma: a review of the literature. *J Clin Neurosci*. (2018) 50:7–15. doi: 10.1016/j.jocn.2018.01.050
2. Rust T, Kiemer N, Erasmus A. Chronic subdural haematomas and anticoagulation or anti-thrombotic therapy. *J Clin Neurosci*. (2006) 13:823–7. doi: 10.1016/j.jocn.2004.12.013
3. Weigel R, Krauss JK, Schmiedek P. Concepts of neurosurgical management of chronic subdural haematoma: historical perspectives. *Br J Neurosurg*. (2004) 18:8–18. doi: 10.1080/02688690410001660418
4. Kushner DS, Verano JW, Titelbaum AR. Trepanation procedures/outcomes: comparison of prehistoric peru with other ancient, medieval, and american civil war cranial surgery. *World Neurosurg*. (2018) 114:245–51. doi: 10.1016/j.wneu.2018.03.143
5. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. *Nat Rev Neurol*. (2014) 10:570–8. doi: 10.1038/nrneurol.2014.163
6. Wang S, Ma Y, Zhao X, Yang C, Gu J, Weng W, et al. Risk factors of hospital mortality in chronic subdural hematoma: A retrospective analysis of 1117 patients, a single institute experience. *J Clin Neurosci*. (2019) 10:570–8. doi: 10.1016/j.jocn.2019.06.026
7. Ducruet AF, Grobelny BT, Zacharia BE, Hickman ZL, DeRosa PL, Andersen KN, et al. The surgical management of chronic subdural hematoma. *Neurosurg Rev*. (2012) 35:155–69; discussion 169. doi: 10.1007/s10143-011-0349-y
8. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. *J Neurol Neurosurg Psychiatr*. (2003) 74:937–43. doi: 10.1136/jnnp.74.7.937
9. Kim SU, Lee DH, Kim YI, Yang SH, Sung JH, Cho CB. Predictive factors for recurrence after burr-hole craniostomy of chronic subdural hematoma. *J Korean Neurosurg Soc*. (2017) 60:701–9. doi: 10.3340/jkns.2016.1010.003
10. Oishi M, Toyama M, Tamatani S, Kitazawa T, Saito M. Clinical factors of recurrent chronic subdural hematoma. *Neurol Med Chir*. (2001) 41:382–6. doi: 10.2176/nmc.41.382
11. Stanišic M, Pripp AH. A reliable grading system for prediction of chronic subdural hematoma recurrence requiring reoperation after initial burr-hole surgery. *Neurosurgery*. (2017) 81:752–60. doi: 10.1093/neuros/nyx090
12. Stanišić M, Pripp AH. A reliable grading system for prediction of chronic subdural hematoma recurrence requiring reoperation after initial burr-hole surgery. *Neurosurgery*. (2019) 81:752–60. doi: 10.1093/neuros/nyz224
13. Brickman AM, Honig LS, Scarmeas N, Tatarina O, Sanders L, Albert MS, et al. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Arch Neurol*. (2008) 65:1202–8. doi: 10.1001/archneur.65.9.1202
14. Stanišić M, Hald J, Rasmussen IA, Pripp AH, Ivanović J, Kolstad F, et al. Volume and densities of chronic subdural haematoma obtained from CT imaging as predictors of postoperative recurrence: a prospective study of 107 operated patients. *Acta Neurochir*. (2013) 155:323–33. doi: 10.1007/s00701-012-1565-0
15. Xu F-F, Chen J-H, Leung GKK, Hao S-Y, Xu L, Hou Z-G, et al. Quantitative computer tomography analysis of post-operative subdural fluid volume predicts recurrence of chronic subdural haematoma. *Brain Inj*. (2014) 28:1121–6. doi: 10.3109/02699052.2014.910702
16. Shen J, Gao Y, Li Q, Ge R, Wang Q, Jiang X, et al. Risk factors predicting recurrence of bilateral chronic subdural hematomas after initial bilateral evacuation. *World Neurosurg*. (2019) 130:e133–9. doi: 10.1016/j.wneu.2019.06.016
17. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. *Stroke*. (1995) 26:1471–7. doi: 10.1161/01.STR.26.8.1471
18. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med*. (1994) 120:897–902. doi: 10.7326/0003-4819-120-11-199406010-00001
19. Ryu SM, Yeon JY, Kong D-S, Hong S-C. Risk of recurrent chronic subdural hematoma associated with early warfarin resumption: a matched cohort study. *World Neurosurg*. (2018) 120:e855–62. doi: 10.1016/j.wneu.2018.08.177

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SYSTEMATIC REVIEW
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Type of Drain in Chronic Subdural Hematoma—A Systematic Review and Meta-Analysis

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Background: Chronic subdural hematoma (cSDH) is one of the most common neurosurgical diseases, while burr-hole drainage is the most frequently used surgical treatment. Strong evidence exists that subdural drain (SDD) placement reduces recurrence rates. However, the insertion of a subperiosteal drain (SPD) was shown to lead to similar recurrence rates and less complications than SDD. The aim of this study is to provide a systematic review of the literature and conduct a meta-analysis of studies comparing SPD with SDD after burr-hole drainage of cSDH.

Methods: Pubmed and Embase databases were searched using a systematic search strategy to identify studies on drain location up to December 2019. Two independent researchers assessed the studies for inclusion and quality. Primary outcome measure was recurrence, while secondary outcome measures were drain misplacement, morbidity, mortality, and clinical outcome. Besides randomized controlled trials (RCT), we included non-randomized prospective cohort studies, as well as retrospective cohort studies. A fixed effects model was used if low heterogeneity ($I^2 < 50\%$) was present, otherwise a random effects model was used.

Results: Following removal of duplicates, we screened 1109 articles of which 10 articles were included in our qualitative and quantitative analyses. One study was an RCT, three were non-randomized prospective cohort studies, and the remaining articles were retrospective cohort studies or subgroup analysis. In these 10 articles, 1,553 patients were treated with SPD and 1782 patients with SDD. Comparing the recurrence rate of cSDH a significant difference was found between SPD and SDD insertion (11.9 and 12.3%; RR 0.8, 95% CI 0.67–0.97, $I^2 = 0\%$, $z = -2.27$, $p = 0.02$). SPD had significantly lower rates of drain misplacement and parenchymal injuries (1.2 and 7.8%; RR 0.17, 95% CI 0.07–0.42, $I^2 = 0\%$, $z = -3.4$, $p = 0.0001$), as well as morbidity (6.4 and 8.2%; RR 0.65, 95% CI 0.5–0.84, $I^2 = 44.5\%$, $z = -3.32$, $p = 0.0009$). Mortality rates (5.0 and 4.6%; RR 0.83, 95% CI 0.6–1.14, $I^2 = 0\%$, $z = -1.2$, $p = 0.25$) and favorable clinical outcome (89.6 and 88.9%; RR 1.1, 95% CI 0.89–1.24, $I^2 = 54.2\%$, $t = 0.98$, $p = 0.40$) were comparable in both groups.

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Conclusion: The insertion of SPD after burr-hole drainage of cSDH showed lower rates of recurrence, drain misplacements and parenchymal injuries, as well as overall morbidity, while clinical outcome and mortality were comparable to SDD. Therefore, the insertion of SPD after surgical drainage of cSDH should be encouraged.

Keywords: chronic subdual hematoma (CSDH), subperiosteal drain, subdural drain, meta-analysis, recurrence (MeSH), systematic review

BACKGROUND

Chronic subdural hematoma (cSDH) is one of the most common neurosurgical pathologies. CSDH can lead to substantial morbidity and mortality, which makes optimal treatment paramount (1). The gold standard of treatment remains surgical drainage of the hematoma through burr-hole trepanation and insertion of a drain (2). A randomized controlled trial (RCT) showed that the insertion of a subdural drain (SDD) after burr-hole drainage of cSDH significantly reduces the rate of recurrence and improves outcome (3). However, the insertion of SDD carries a risk of parenchymal injury due to their proximity to the cortex or bridging veins (4–7). Therefore, subperiosteal drains (SPD), which are inserted between the calvarium and the periosteum have been recommended by some surgeons (2, 6). Several studies, amongst others a recently published RCT, were carried out comparing these two different drain types, with regard to outcome and recurrence, with somewhat controversial results (4, 5, 7–14).

The aim of this systematic review and meta-analysis is to compare SPD and SDD with regard to rate of recurrence, morbidity, mortality, and clinical outcome.

METHODS

Search Method and Data Analysis

We used a search string with the keywords "chronic subdural hematoma" and "drain" in the databases Pubmed and Embase (**Figure 1**).

(subdural hematoma[Title/Abstract]	*OR*
subdural hematomas[Title/Abstract]	*OR*
subdural haematoma[Title/Abstract]	*OR*
subdural haematomas[Title/Abstract]	*OR*
Subdural bleed[Title/Abstract])*	*OR*
Subdural haemorrhage[Title/Abstract]	*OR*
subdural hemorrhage[Title/Abstract]	*AND*
(chronic[Title/Abstract]	*OR*
"Hematoma, Subdural, Chronic"[Mesh])	*AND*
(drain[Title/Abstract]*	*OR*
catheter[Title/Abstract]*	*OR*
"catheter" [mh:noexp]	*OR*
"drainage" [mh:noexp])	

FIGURE 1 | Detailed database search parameters used.

All results from Pubmed and Embase published until December 2019 were assessed by two of the authors independently (LG and NH). After removal of duplicates, all remaining articles were analyzed according to their titles. Abstracts were reviewed and a list of references was generated, while the remaining results underwent a full text evaluation and a final list of references was compiled. In case of disagreement concerning the inclusion of a study, the decision to include was made by a third researcher (JS).

Inclusion Criteria and Outcome Measures

Besides randomized controlled trials (RCT), we included non-randomized prospective cohort studies, as well as retrospective cohort studies in our analysis. Technical reports, which described a novel drainage method but lacked to conduct a comparison between two different drainage types, as well as case reports or reviews were excluded from this report. The primary outcome measure was recurrence of cSDH, while secondary outcome measures were drain misplacement and intraparenchymal brain injury rate due to drain misplacement, overall morbidity (including drain misplacement, seizures, and infection), infection rate, mortality, and clinical outcome using modified Ranking Scale (mRS). We included only studies published in English.

Among the included studies, follow-up time points varied; hence, we combined the follow-up reports from 4–12 weeks postoperatively as we did not expect major clinical differences in this time period. Clinical outcomes assessed earlier than 1 month postoperatively were not included in our analysis. There was a heterogeneity of clinical outcome measures in the individual studies with either mRS or Glasgow Outcome Scale. For this analysis, we evaluated solely the mRS results, while favorable outcome was defined as mRS 0–3.

We defined the drains placed above the bone as "subperiosteal" drains rather than "subgaleal" drains. Some authors refer to these drains as subgaleal drains, however, in order to create burr-holes the periosteum needs to be scraped off the bone. Therefore, once the drain is then placed over the frontal and parietal burr-holes, it is automatically placed in a subperiosteal manner. The tunneling of the drain between the two burr-holes can be done subperiosteally or subgaleally, however the technique of tunneling is not essential for the drainage of the hematoma through the drain, but rather where the drains lay above the burr-holes. Therefore, in our opinion, the correct term is "subperiosteal" drain. To note, that not all authors describe the exact method of drain placement, therefore, theoretically some included studies might have used subgaleal drains.

Quality Assessment

Risk of bias of RCTs was assessed by using the revised risk of bias (RoB-2) tool (15). Quality assessment of the non-randomized prospective cohort studies and retrospective cohort studies was carried out using Robins-1, respectively Newcastle Ottawa Scale (16, 17). Quality assessment was carried out individually and thereafter compared by two of the authors (LG, NH).

Statistical Analysis

Risk ratio (RR) was used as an effect measure for the pooled outcomes. In case of low heterogeneity ($I^2 < 50\%$) the fixed-effects method was applied, otherwise the random-effects analysis was used. For the primary outcome measure, the so-called "leave one out" method was carried out, as an additional influence analysis. The results of the meta-analysis were recalculated K-1 times by sequentially leaving one study out to detect the studies which influence the overall effect the most. Finally, forest and funnel plots were generated and are presented for all outcomes.

All analyses were done using the R statistical software (version 3.6.2, 2019) with the help of the dmetar package (18). The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

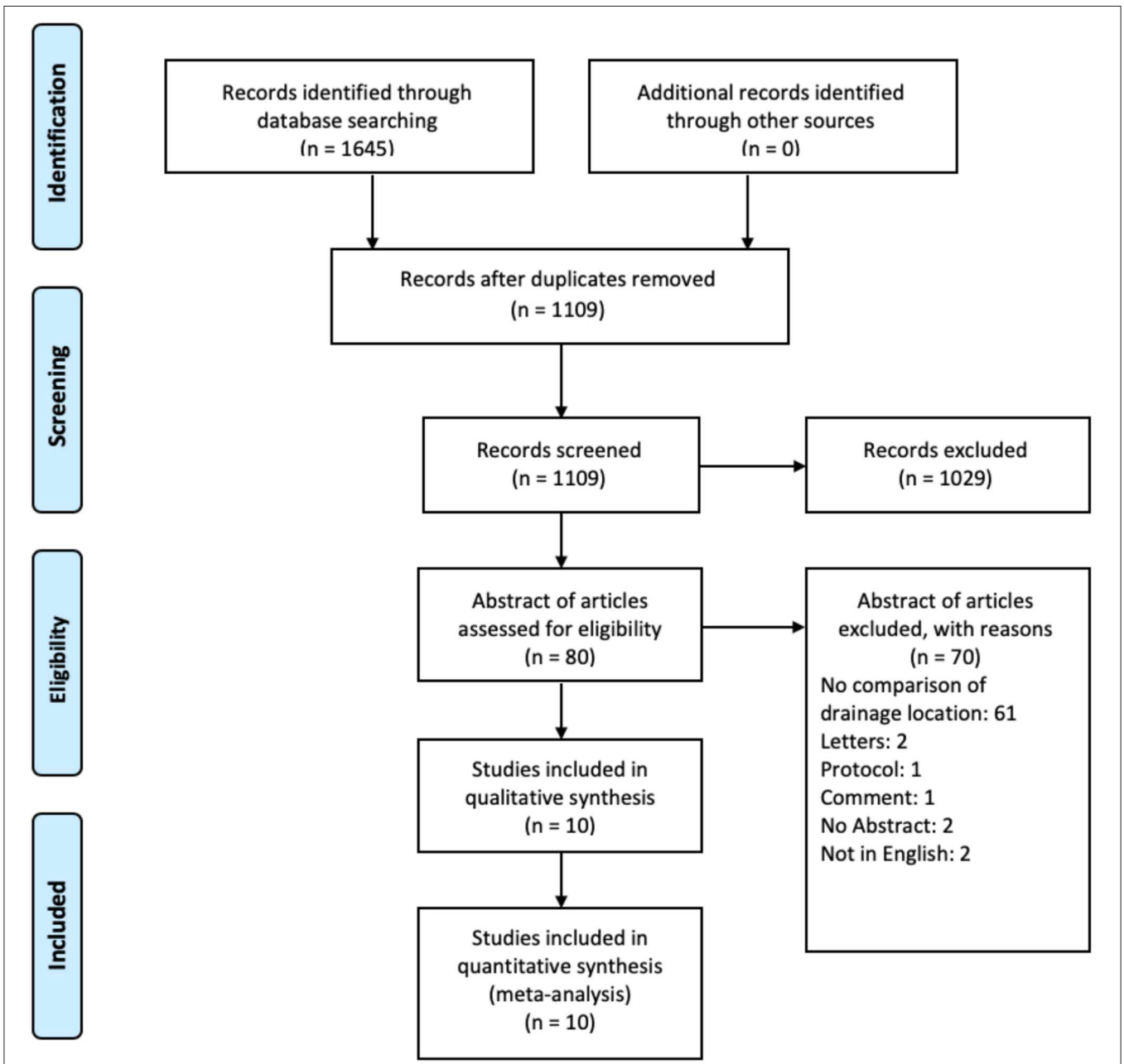

FIGURE 2 | Flow Chart according to the PRISMA guidelines showing study selection.

TABLE 1 | Overview of the included studies showing the number of patients within the subperiosteal drain (SPD) and subdural drain (SDD) group, as well as the primary outcome assessed for each study.

References	Type of study	Primary outcome	Number of SPD	Number of SDD
Häni et al. (8)	*post-hoc* subgroup analysis of single-center RCT	Recurrence	214	135
Zhang et al. (9)	Retrospective cohort study, multicenter	Recurrence, outcome	241	329
Soleman et al. (7)	RCT, multicenter, not blinded	Recurrence	120	100
Glancz et al. (11)	Subgroup analysis of multicenter prospective cohort study	Outcome	44	533
Ishfaq (10)	Prospective, non-randomized trial	Outcome	31	31
Sjavik et al. (13)	Multicenter retrospective comparative cohort study	Recurrence	764	496
Chih et al. (4)	Prospective, non-randomized trial, multicenter	Complications, outcome, mortality	30	30
Oral (5)	Retrospective cohort study, single center	Complications	36	38
Kaliaperumal et al. (12)	Prospective non-randomized trial, single center	Outcome	25	25
Bellut et al. (14)	Retrospective cohort study, single center	Complications	48	65

RESULTS

After screening 1,109 articles, 10 were included in our qualitative systematic review as well as quantitative meta-analysis (**Figure 2**). One study was an RCT (7), three studies were non-randomized prospective cohort studies (4, 10, 12), and six were retrospective cohort studies or sub-group analysis of other studies (**Table 1**) (5, 8, 9, 11, 13, 14). For our analysis 1,553 patients from the SPD group and 1,782 patients from the SDD group were included.

Recurrence

Recurrence rate was reported in all studies. Overall pooled results showed that the use of SPD has a significantly lower recurrence rate than the use of SDD (11.9 and 12.3%, respectively, RR 0.8, 95% CI 0.67–0.97, $I^2 = 0\%$, $z = -2.27$, $p = 0.02$, **Figure 3A**). After applying the "leave-one-out" method, Sjavik et al. (13) was identified as a single influential study. Therefore, the pooled analysis was repeated without Sjavik et al. showing no significant difference in recurrence rates between the groups (12.8 and 10.5%, RR 0.95, 95% CI 0.74–1.23, $I^2 = 0\%$, $z = -0.37$, $p = 0.71$, **Figure 3B**). The distribution of the studies in the funnel plot was homogenous and therefore publication bias was not suspected (**Figure 3C**).

Morbidity

Overall morbidity was described in all included studies. Overall pooled morbidity rate was significantly lower in the SPD group compared to the SDD group (6.4 and 8.2%, respectively, RR 0.65, 95% CI 0.5–84, $I^2 = 44.5\%$, $z = -3.32$, $p = 0.0009$; **Figure 4A**). The corresponding funnel plot showed a homogenous distribution (**Figure 4B**).

Six studies specifically analyzed drain misplacement rate or parenchymal injury rate due to drain misplacement (4, 7, 8, 10, 12, 14). Overall misplacement rate and consecutive parenchymal injury rate was significantly lower in the SPD group compared to the SDD group (1.2 and 7.8%, respectively, RR 0.17, 95% CI 0.07–0.42, $I^2 = 0\%$, $z = -3.4$, $p = 0.0001$, **Figure 4C**), while the funnel plot showed homogenous distribution of the studies (**Figure 4D**).

Eight studies described infection rates (4, 5, 7–9, 11, 14, 19). Overall pooled infection rate was lower in the SPD group, while significance was not seen (1.7% for SPD and 1.9% for SDD; RR 0.71, 95% CI (0.42–1.25), $I^2 = 7.3\%$, $z = -1.29$, $p = 0.20$, **Figure 4E**). The distribution of the studies was homogenous (**Figure 4F**).

Mortality

All studies, except one, reported on mortality rates (4, 7–14). Overall mortality was lower in the SDD group, without showing significance (5.0% for SPD and 4.6% for SDD; RR 0.83, 95% CI 0.6–1.14, $I^2 = 0\%$, $z = -1.2$, $p = 0.25$, **Figure 5A**). The corresponding funnel plot showed homogenous distribution of studies (**Figure 5B**).

Clinical Outcome

Clinical outcome was assessed by six of the studies included (7–9, 11, 12, 14, 19). After analyzing favorable outcome using mRS the heterogeneity (I^2) was 54%, therefore the random-effect analysis was applied, showing similar rates of good clinical outcome between the groups (89.6% for SPD and 88.9% for SDD; RR 1.05, 95% CI (0.90–1.24), $I^2 = 54.2\%$, $t = 0.98$, $p = 0.4$; **Figure 6A**). The corresponding funnel plots showed no bias of publication (**Figure 6B**).

Qualitative Assessment of Studies

Out of the 0 studies included, only Soleman et al. (7) conducted a randomized-controlled trial (RCT). Risk of bias for this study is shown in **Figure 7**. **Table 2** contains the quality assessment of all the other studies included.

DISCUSSION

The aim of this meta-analysis was, to evaluate whether there is a difference in recurrence rate of cSDH following insertion of SPD or SDD. This meta-analysis shows that SPD has a significantly lower risk for recurrence, drain misplacement and intraparenchymal injury, as well as morbidity, when compared to SDD. Concerning mortality and clinical outcome, no significant difference was seen between the drain groups.

Although cSDH remains one of the most common neurosurgical disease entities, there is a paucity of studies on outcome differences in cSDH after insertion of SPD and

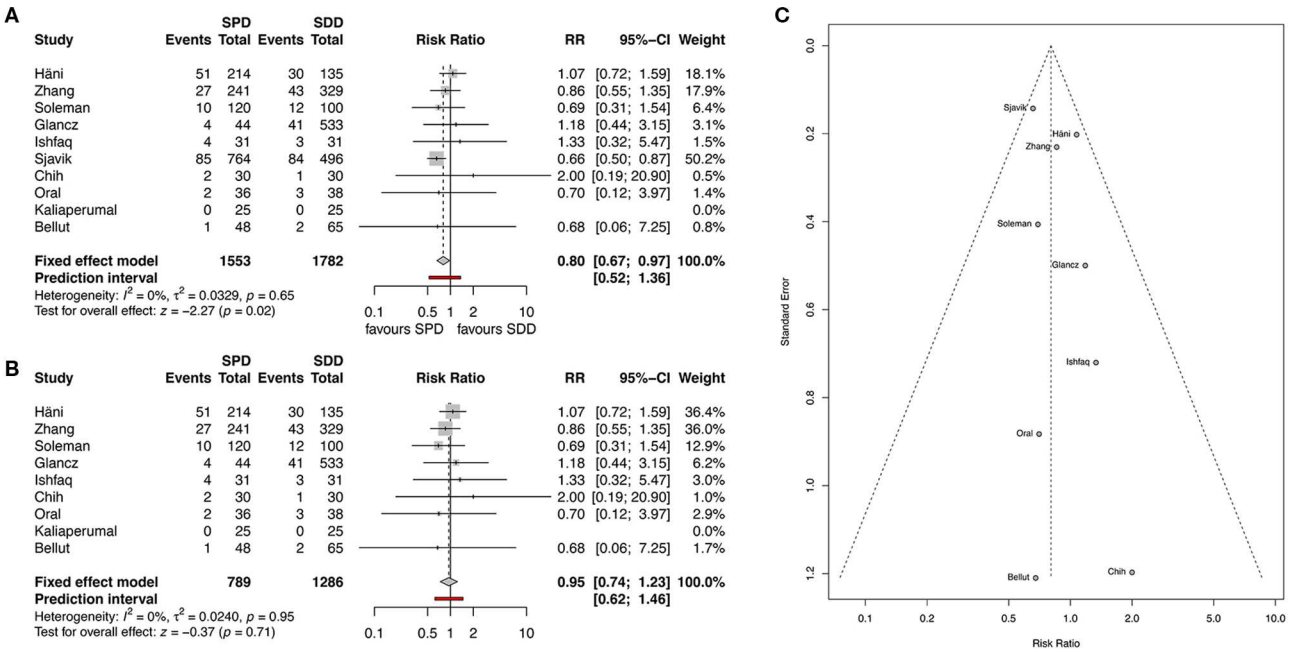

FIGURE 3 | (A) Forest plot of recurrence rates. **(B)** Forest plot of recurrence rate after applying the "leave-one-out" method. **(C)** Funnel plot showing homogenous distribution for recurrence. RR, risk ratio; CI, confidence interval; SPD, subperiosteal drain; SDD, subdural drain.

SDD. Recurrence in cSDH occurs in ∼10% of surgically drained patients and causes higher morbidity in the affected patients (20, 21). It was shown, that the insertion of a drain after burr-hole drainage of cSDH reduces recurrence rates and improves outcome significantly (3). Technical nuances, amongst others, the insertion of a drain, or the localization of the drain (above or under the bone), seem important to achieve better surgical outcome. For this reason, in recent years, some authors compared the outcome of SPD insertion with SDD insertion after burr-hole drainage of cSDH. Unfortunately, to date, only one RCT exists on the matter, while all other series are of retrospective nature, *post-hoc* analysis of prospective cohorts, or consist of rather small cohorts.

To date, the only RCT published comparing SPD and SDD showed no significant difference in recurrence rate between the two groups (11.9 and 12.3%, respectively) (7). Similarly, Zhang et al. (11 and 13%) (9), Chih et al. (7 and 10%) (4), Sjavik et al. (11 and 16%) (13) and Oral et al. (6 and 8%) (5) did not show a significant difference in recurrence rates, while the study by Kaliaperumal et al. showed no recurrences at all (12). Häni et al. (24 and 22%), Glancz et al. (9 and 8%) (11) and Ishfaq (13 and 10%) (10) showed lower recurrence rates in the SDD group compared to the SPD group; however, statistical significance was not observed in any of these studies.

Sjavik et al. (13) compared in their study three different drain techniques: (1) SDD with irrigation, (2) passive SDD, (3) active SPD. For our analyses, both SDD types were included in the SDD group. In Sjavik et al.'s analysis passive SDD showed a higher recurrence rate compared to active SPD. However, the drains with subdural irrigation showed no significant difference in recurrence rate; hence, their results could be due to the active negative pressure within the drain and is most probably less affected by the drain's location. Data on the influence of inserting an active suction drain after surgical drainage of cSDH is sparse, while to our knowledge trials comparing the outcome of active vs. passive drainage do not exist.

Parenchymal hemorrhage due to drain misplacement is a feared complication when inserting an SDD after burr hole drainage of cSDH, potentially increasing perioperative morbidity and mortality (2, 7, 22). All studies reporting misplacement rates showed lower rates in the SPD group (4, 7, 8, 10, 12, 14). The overall misplacement rates in the included studies was 1.2% for SPD and 7.8% for SDD, while only the study by Häni et al. showed a higher misplacement rate in the SPD group. In their *post-hoc* analysis, Häni et al. distinguished between two groups, defined by the year of treatment within their study, namely: "SDD recommended" (n = 214, with a possibility to switch to SPD) and SDD treated (n = 135). All misplacements (n = 6) occurred in the "SDD recommended" group, however, four of these patients ultimately were treated with an SPD since the placement of an SDD was difficult and caused brain injury. These patients were however allocated to the SPD group leading to the above-described overall misplacement rate of 1.2% in the SPD group.

Based on the included studies mortality rate in the SPD group was 5% and in the SDD group 4.6%. Interestingly, although drain misplacement, parenchymal injury, and overall morbidity rate were significantly higher in the SDD group, mortality rate was comparable in both drain groups. This might be because the studies included were not sufficiently powered to show such

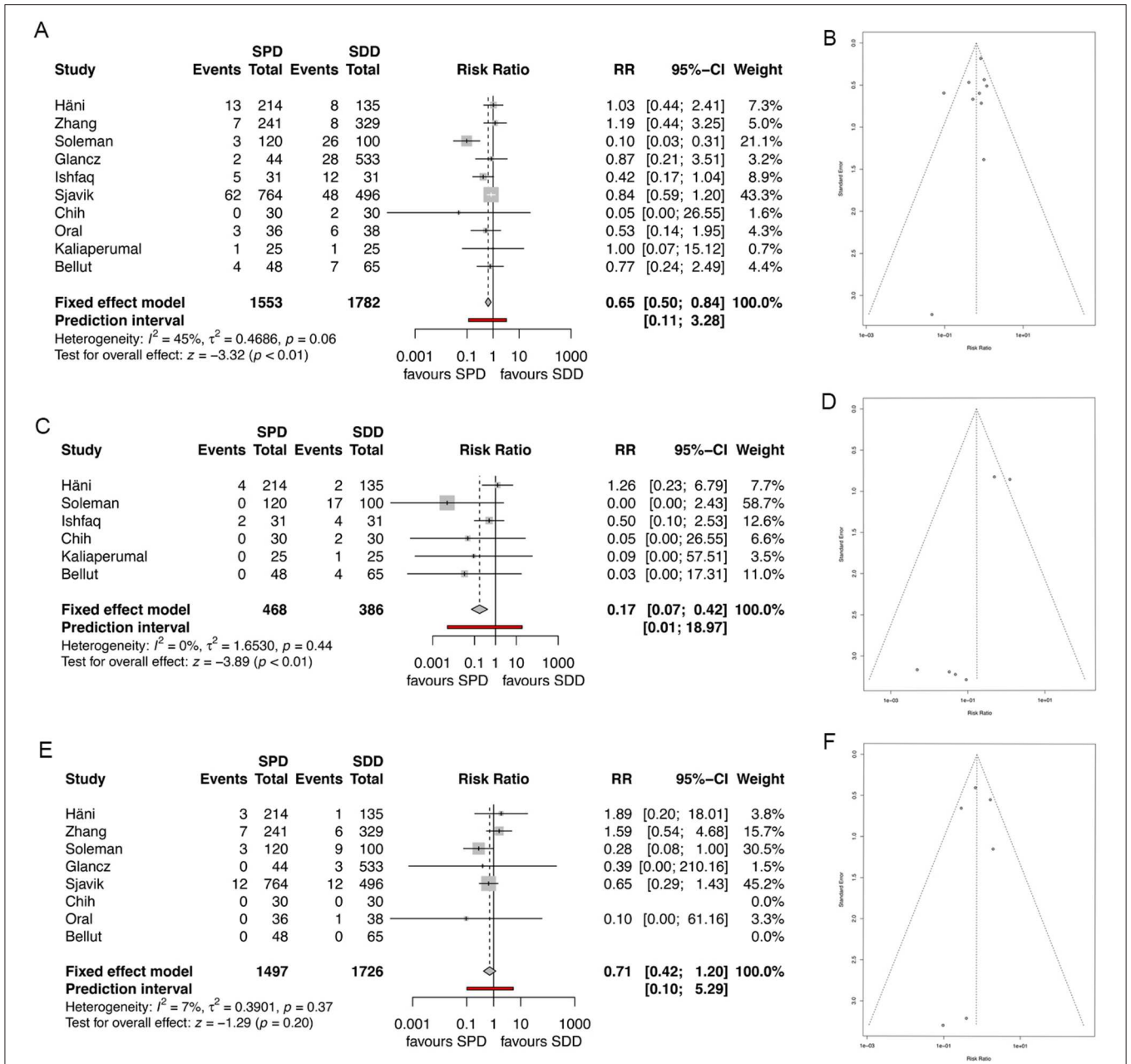

FIGURE 4 | (A) Forest plot of morbidity rates. **(B)** Funnel plot showing homogenous distribution for morbidity. **(C)** Forest plot of drain misplacement rates. **(D)** Funnel plot showing homogenous distribution for drain misplacement rates. **(E)** Forest plot of infection rates. **(F)** Funnel plot showing homogenous distribution for infection rates. RR, risk ratio; CI, confidence interval; SPD, subperiosteal drain; SDD, subdural drain.

an association. Further, most intraparenchymal injuries might lead to transient or permanent morbidity (e.g., hemiparesis or aphasia), however, they are not necessarily fatal.

Our analysis showed no significant difference between the groups concerning infection rate, while SPD showed significant lower rates of overall morbidity. The infection rates in both groups, based on the included studies, were 1.7% for SPD and 1.9% for SDD. The only study showing significantly lower rates of infections in the SPD group (2 vs. 9%) was the RCT by Soleman et al. (7). A possible explanation is that other studies (5, 11), which also showed absolutely lower numbers of infection in the SPD group, were underpowered for such an analysis and therefore statistical significance was not reached (5, 11). Infection rate in cSDH are reported to occur in up to 20% of the cases, while empyema rates are much lower (around 2%) (6). In theory, SPD might lower the risk of subdural empyema or other types of "deep" infections, since no foreign material is placed within the subdural cavity or in proximity to the cortical surface.

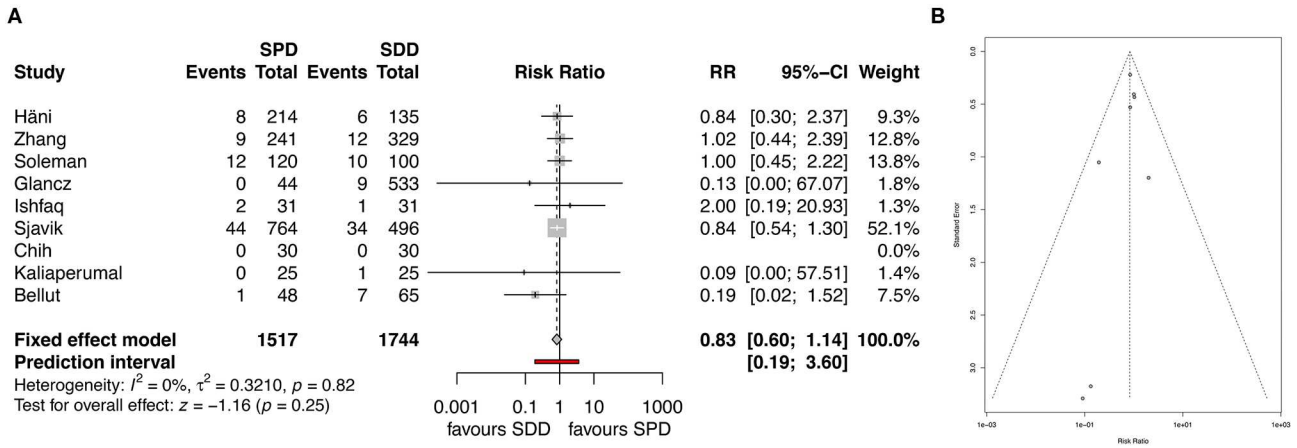

FIGURE 5 | (A) Forest plot of mortality rates. **(B)** Funnel plot showing homogenous distribution for mortality rates. RR, risk ratio; CI, confidence interval; SPD, subperiosteal drain; SDD, subdural drain.

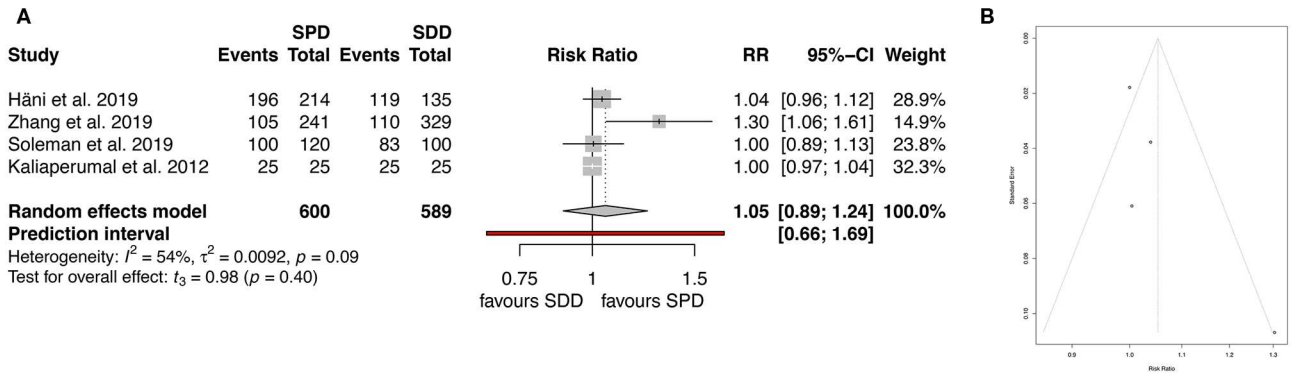

FIGURE 6 | (A) Forest plot of favorable clinical outcome (mRS). **(B)** Funnel plot showing homogenous distribution for clinical outcome (mRS). RR, risk ratio; CI, confidence interval; SPD, subperiosteal drain; SDD, subdural drain.

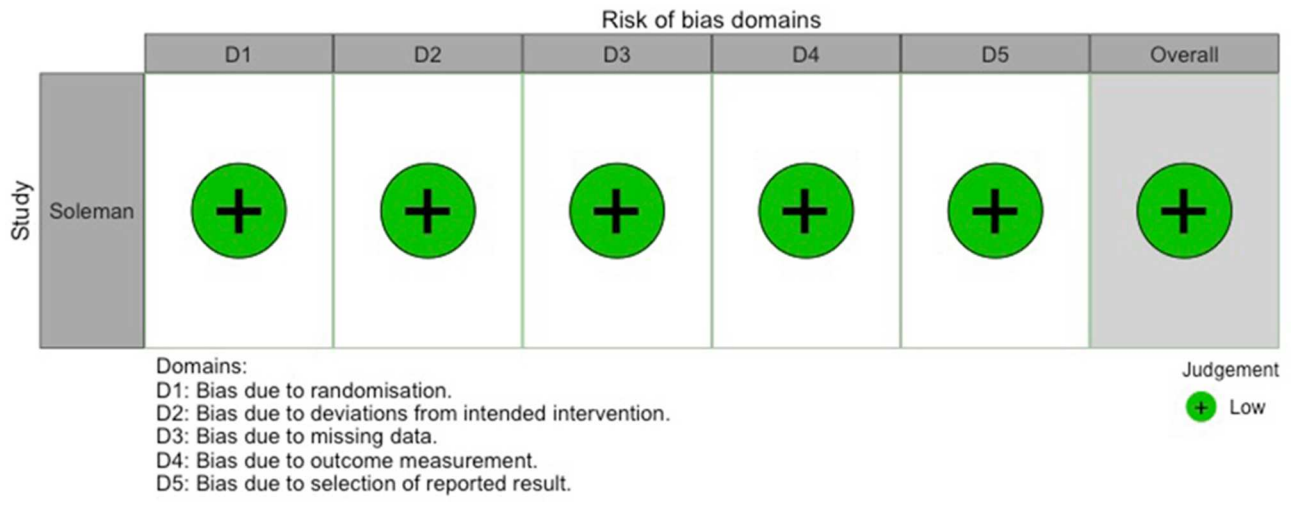

FIGURE 7 | Traffic-light-plot depicting risk of bias for the randomized-controlled trial by Soleman et al. (7).

TABLE 2 | Quality assessment of the retrospective cohort studies using the Newcastle Ottawa Scale (NOS) and of the prospective non-randomized cohort studies using Robins-1.

References	NOS	Robins-1
Häni et al. (8)	8	–
Zhang et al. (9)	9	–
Glancz et al. (11)	7	–
Ishfaq (10)	–	Intermediate
Sjavik et al. (13)	8	–
Chih et al. (4)	–	Intermediate
Oral (5)	6	–
Kaliaperumal et al. (12)	–	Low-intermediate
Bellut et al. (14)	8	–

"–," not applicable.

Santarius et al. showed that the insertion of a drain improves outcome and lowers mortality in cSDH when compared to no drain insertion (3). Based on our pooled analysis the type of drain did not seem to influence clinical outcome. From the included studies, only Kaliaperumal et al. showed significantly better outcome in the SPD group compared to the SDD group (12). All other studies describing outcome showed comparable clinical outcomes in both groups. Interestingly, although recurrence rates, overall morbidity, and intraparenchymal injury rates were significantly lower in the SPD group, clinical outcome was comparable between the groups. One possible explanation might be that the included studies were not powered to detect the true outcome within the groups. Further, morbidity due to misplacement of the drain might be only transient showing an improvement with time. Last, in most studies clinical outcome was assessed in a retrospective manner, with many dropouts or missing information, potentially leading to biased results. Studies focusing and analyzing the outcome after insertion of an SPD compared to SDD in a prospective manner are still needed.

Recently published analysis by Pranata et al., Xie et al., and Ding et al. confirmed our results (23–25). Xie et al. (24), Ding et al. (25), and Pranata et al. (23) also observed significantly lower recurrence rates for SPD as opposed to SDD (Xie et al. and Ding et al.: 12 and 12.7%, Pranata et al.: 12 and 13.2%).

Significantly lower misplacement rates were reported in favor of SPD by Xie et al. (1.% and 2.6%) (24), Ding et al. (0.6 and 2.3%) (25) and Pranata et al. (2.2 and 4.7%) (23). Mortality rates were similar for both groups in all three analysis. Xie et al. (24) reported a mortality rate of 3.7 and 3.8%, in favor of SPD. Ding et al. (25) observed a lower mortality rate for SDD (4.8 and 4.5%) while Pranata et al. (23) published much higher absolute values of 15.7 and 9.4% in favor of SDD.

Comparable outcome rates for both groups were published by Xie et al. (87.4 and 82.1%) (24) Ding et al. (68.1 and 67.5%) (25) and Pranata et al. (percentage not available) (23).

Our assessment and classification of the included studies differed from the meta-analyses by Pranata et al. and Ding et al. while concurred with Pranata et al., Xie et al., Ding et al. (23–25). We considered the study by Soleman et al. (7) the only RCT amongst the included studies, while Pranata et al. and Ding et al. (23, 25) considered Häni et al. (8) and Kaliaperumal et al., respectively, only Kaliaperumal et al. (12), as additional RCTs. We did not consider the study by Kaliaperumal et al. an RCT since the drain type was not randomized (the patients were assigned alternately to SPD and SDD). Similarly, the study by Häni and colleagues was not considered by us as an RCT, since it was not primarily designed to compare the recurrence rate after insertion of SPD or SDD, but rather a *post-hoc* analysis of their RCT initially designed to assess the need for follow up CT after evacuation of cSDH (8). In addition, as opposed to Pranata et al., Xie et al., and Ding et al. (23–25), we combined the two different subdural drain types described by Sjavik et al. into one SDD group (13) and we included the "as treated" rather than the "intention to treat" results from the study by Häni et al. (8) in our analysis. Ding et al. was the only study to report subgroup analysis in their analysis (25). Due these reasons, some of our results differed from the previous reports published.

LIMITATIONS OF THE STUDY

Despite conducting a current systematic review and meta-analysis of the existing literature, our study consists of some limitations. First, we only searched two databases (Pubmed and Embase) and only included English literature, which carries a risk of omitting important data published elsewhere. Second, in our review and analysis we included RCTs, as well as non-randomized prospective cohort studies and retrospective cohort studies. Therefore, the data included was somewhat heterogeneous, potentially influencing the validity of our results. However, to date only one RCT and very few well-designed prospective trials have been published on the matter. Third, even though we assessed for publication bias we cannot exclude a general publication bias, due to unpublished negative studies, which are not included in our meta-analysis. Last, most data included in this meta-analysis derived from retrospective cohorts, inherent to all limitations of such studies, potentially influencing the validity of the results as well.

CONCLUSION

Based on the existing evidence, the insertion of an SPD after burr-hole drainage of cSDH seems superior to SDD, in terms of recurrence, overall morbidity, drain misplacement, and intraparenchymal injury rates, while showing comparable infection rates, mortality, and clinical outcome. Therefore, the insertion of SPD after drainage of cSDH should be encouraged. Further prospective studies on the clinical outcome and mortality after insertion of SPD or SDD should be focus of future research.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material. The R code is available upon request.

AUTHOR CONTRIBUTIONS

LG carried out the database search, review of the literature, data extraction, and analysis as well as drafting of the manuscript. NH was the second researcher who independently reviewed the literature and performed quality and bias assessments. JS the senior author, overviewed the project and took final decisions about inclusion of papers if LG and NH could not reach a conclusion. He critically reviewed the manuscript.

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REFERENCES

1. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. *J Neurology Neurosurg Psychiatry.* (2003) 74:937–43. doi: 10.1136/jnnp.74.7.937
2. Soleman J, Kamenova M, Lutz K, Guzman R, Fandino J, Mariani L. Drain insertion in chronic subdural hematoma: an international survey of practice. *World Neurosurg.* (2017) 104:528–36. doi: 10.1016/j.wneu.2017.04.134
3. Santarius T, Kirkpatrick PJ, Ganesan D, Chia H, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet*. (2009) 374:1067–73. doi: 10.1016/S0140-6736(09)61115-6
4. Chih A, Hieng A, Rahman NA, Abdullah J. Subperiosteal drainage versus subdural drainage in the management of chronic subdural hematoma (a comparative study). *Malays J Medical Sci*. (2017) 24:21–30. doi: 10.21315/mjms2017.24.1.3
5. Oral S. Comparison of subgaleal and subdural closed drainage system in surgical treatment of chronic subdural hematoma. *Northern Clin Istanbul.* (2015) 2:115–21. doi: 10.14744/nci.2015.06977
6. Zumofen D, Regli L, Levivier M, Krayenbühl N. Chronic subdural hematomas treated by burr hole trepanation and a subperiostal drainage system. *Neurosurgery*. (2009) 64:1116–22. doi: 10.1227/01.NEU.0000345633.45961.BB
7. Soleman J, Lutz K, Schaedelin S, Kamenova M, Guzman R, Mariani L, et al. Subperiosteal vs subdural drain after burr-hole drainage of chronic subdural hematoma: a randomized clinical trial (cSDH-Drain-Trial). *Neurosurgery*. (2019) 85:E825–34. doi: 10.1093/neuros/nyz095
8. Häni L, Vulcu S, Branca M, Fung C, Z'Graggen W, Murek M, et al. Subdural versus subgaleal drainage for chronic subdural hematomas: a post hoc analysis of the TOSCAN trial. *J Neurosurg.* (2019). doi: 10.3171/2019.5.JNS19858. [Epub ahead of print].
9. Zhang JJY, Wang S, Foo ASC, Yang M, Quah BL, Sun IS, et al. Outcomes of subdural versus subperiosteal drain after burr-hole evacuation of chronic subdural hematoma: a multicenter cohort study. *World Neurosurg.* (2019) 131:e392–401. doi: 10.1016/j.wneu.2019.07.168
10. Ishfaq A. Outcome in chronic subdural hematoma after subdural vs. subgaleal drain. *J Coll Physicians Surg.* (2017) 27:419–22.
11. Glancz L, Poon M, Coulter I, Hutchinson P, Kolias A, Brennan P, et al. Does drain position and duration influence outcomes in patients undergoing burr-hole evacuation of chronic subdural hematoma? Lessons from a UK multicenter prospective cohort study. *Neurosurgery.* (2018) 85:486–93. doi: 10.1093/neuros/nyy366
12. Kaliaperumal C, Khalil A, Fenton E, Okafo U, Kaar G, O'Sullivan M, et al. A prospective randomised study to compare the utility and outcomes of subdural and subperiosteal drains for the treatment of chronic subdural haematoma. *Acta Neurochir.* (2012) 154:2083–9. doi: 10.1007/s00701-012-1483-1
13. Sjåvik K, Bartek J, Sagberg L, Henriksen M, Gulati S, Ståhl FL, et al. Assessment of drainage techniques for evacuation of chronic subdural hematoma: a consecutive population-based comparative cohort study. *J Neurosurg.* (2017). doi: 10.3171/2016.12.JNS161713. [Epub ahead of print].
14. Bellut D, Woernle C, Burkhardt J-K, Kockro R, Bertalanffy H, Krayenbühl N. Subdural drainage versus subperiosteal drainage in burr-hole trepanation for symptomatic chronic subdural hematomas. *World Neurosurg.* (2012) 77:111–8. doi: 10.1016/j.wneu.2011.05.036
15. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2019]*. The Cochrane Collaboration (2019). Available online at: www.handbook.cochrane.org
16. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2019]*. The Cochrane Collaboration (2019). Available online at: www.handbook.cochrane.org
17. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa, ON (2000).
18. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. *Doing Meta-Analysis in R: A Hands-on Guide*. (2019). doi: 10.5281/zenodo.2551803
19. Kareem H, Adams H. A closed system irrigation & drainage technique for surgical evacuation of chronic subdural haematomas. *F1000research.* (2018) 7:619. doi: 10.12688/f1000research.14932.1
20. Baechli H, Nordmann A, Bucher H, Gratzl O. Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study. *Neurosurg Rev.* (2004) 27:263–6. doi: 10.1007/s10143-004-0337-6
21. Almenawer SA, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, et al. Chronic subdural hematoma management. *Ann Surg.* (2014) 259:449–57. doi: 10.1097/SLA.0000000000000255
22. Alcalá-Cerra G, Young A, Moscote-Salazar L, Paternina-Caicedo Á. Efficacy and safety of subdural drains after burr-hole evacuation of chronic subdural hematomas: systematic review and meta-analysis of randomized controlled trials. *World Neurosurg.* (2014) 82:1148–57. doi: 10.1016/j.wneu.2014.08.012
23. Pranata R, Deka H, July J. Subperiosteal versus subdural drainage after burr hole evacuation of chronic subdural hematoma: systematic review and meta-analysis. *Acta Neurochir.* (2020). doi: 10.1007/s00701-019-04208-5. [Epub ahead of print].
24. Xie Y, Lu Q, Lenahan C, Yang S, Zhou D, Qi X. A comparison of subperiosteal or subgaleal drainage with subdural drainage on the outcome of chronic subdural hematoma: a meta-analysis. *World Neurosurgery.* (2020) 135: e723–30. doi: 10.1016/j.wneu.2019.12.116
25. Ding H, Liu S, Quan X, Liao S, Liu L. Subperiosteal versus subdural drain after burr-hole drainage for chronic subdural hematomas: a systematic review and meta-analysis. *World Neurosurg.* (2020) 136:90–100. doi: 10.1016/j.wneu.2019.12.180

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ORIGINAL RESEARCH
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Neurosurgical and Perioperative Management of Chronic Subdural Hematoma

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Objective: Surgery and specifically burr hole craniostomy is the most common first choice treatment of patients with Chronic Subdural Hematoma (CSDH). However, several aspects of neurosurgical and peri-operative management are still a subject of research, such as how to treat bilateral CSDH and the anesthetic approach. We aim to investigate the effect of the surgical approach to bilateral CSDH and the effect of anesthesia modality on outcome of CSDH patients.

Methods: We retrospectively included surgically treated CSDH patients between 2005 and 2019 in three hospitals in the Netherlands. The effect of the surgical approach to bilateral CSDH (unilateral vs. bilateral decompression) and anesthesia modality (general vs. local anesthesia) on outcome (complications, recurrence, and length of hospital stay over 4 days) was studied with logistic regression adjusting for potentially confounding radiological and clinical characteristics.

Results: Data of 1,029 consecutive patients were analyzed, mean age was 73.5 years (±11) and 75% of patients were male. Bilateral CSDH is independently associated with an increased risk of recurrence within 3 months in logistic regression analysis (aOR 1.7, 95% CI: 1.1–2.5) but recurrence rate did not differ between primary bilateral or unilateral decompression of bilateral CSDH. (15 vs. 17%, $p = 0.775$). Logistic regression analysis showed that general anesthesia was independently associated with an increased risk of complications (aOR 1.8, 95% CI: 1.0–3.3) and with a length of hospital admission of over 4 days (aOR 8.4, 95% CI: 5.6–12.4).

Conclusions: Bilateral CSDH is independently associated with higher recurrence rates. As recurrence rates in bilateral CSDH are similar for different surgical approaches, the optimal choice for primary bilateral decompression of bilateral CSDH could vary per patient. General anesthesia for surgical treatment of CSDH is associated with higher complication rates and longer hospital admission.

Keywords: chronic subdural hematoma, neurosurgery, anesthesia, bilateral chronic subdural hematoma, logistic regression

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INTRODUCTION

Chronic subdural hematoma (CSDH) is one of the most frequent neurosurgical diseases with an incidence of about 17/100,000/year, increasing with age (1). CSDH is often regarded as a benign, easily treatable disorder, but recurrence rates vary between 10 and 15% and mortality can be as high as 27% (2). The most commonly reported risk factors for CSDH are: older age, use of anticoagulants, male sex, alcoholism, and a history of direct or indirect head trauma (3, 4). Although surgical treatment remains first choice, conservative treatment modalities are more and more implemented in daily clinical practice (5). The optimal surgical technique has been studied extensively (6–8), resulting in burr hole craniostomy (BHC) with (subdural) drainage being the preferable method (5, 9–11). Other aspects of neurosurgical and perioperative management of CSDH are less well studied and evidence is still lacking. In this study, we focus on two specific neurosurgical and perioperative aspects of CSDH treatment on which uncertainty exists; the surgical approach to bilateral CSDH and type of anesthesia modality.

There is no consensus about the optimal surgical approach of bilateral CSDH, even though about 25% of CSDH is bilateral at presentation (12, 13). Reports on recurrence rates of bilateral and unilateral decompressed bilateral CSDH vary, and some studies have shown a beneficial effect of primary bilateral decompression in bilateral CSDH (10, 13, 14). However, currently the choice of unilateral or bilateral decompression mainly depends on lateralizing of symptoms and hematoma characteristics (13, 15). Studies that have reported a benefit from primary bilateral decompression suggest that the recurrence is related to a decrease in intracranial pressure after unilateral decompression and subsequent shift of the brain toward the operated side (13). Both factors might lead to an increase of the contralateral subdural space and subsequent expansion of the contralateral hematoma, rather than actual recurrence.

To address the uncertainties concerning the surgical approach of bilateral CSDH, we compare recurrence rates in bilateral and unilateral CSDH, assess the possible beneficial effect of primary bilateral decompression and study the factors associated with choice for side of decompression. We hypothesize that there is a beneficial effect of primary bilateral decompression in reducing the recurrence rate of bilateral CSDH.

The choice of the optimal anesthesia modality is an important aspect of perioperative and neurosurgical management of CSDH. In other conditions primarily affecting elderly patients, the benefits of localized anesthesia (LA) over general anesthesia (GA) has been reported (16). For CSDH only limited studies on this subject exist. Studies that have assessed the differences between LA and GA in CSDH, report beneficial effects of LA (17, 18). Despite this finding, a recent large prospective study showed that 93% of CSDH patients is treated with GA (10).

Abbreviations: ASA, Acetylsalicylic acid; BHC, Burr-hole craniostomy; CCI, Charlson comorbidity index; CSDH, Chronic Subdural Hematoma; DOAC, Direct Oral Anticoagulants; GA, General anesthesia; GCS, Glasgow Coma Scale; LA, Local anesthesia; MGS, Markwalder Grading Scale; VKA, Vitamin- K antagonist.

We hypothesize that there is a beneficial effect of primary bilateral decompression compared to unilateral decompression on recurrence of bilateral CSDH and that LA compared to GA reduces postoperative complication rates and lowers length of hospital stay for patients with CSDH.

METHODS

We retrospectively collected data of all consecutive CSDH patients that were treated in three Neurosurgical centers in the Netherlands between 2005 and 2019. The inclusion period per center varied, based on the availability of patient data caused by transitions from paper to electronical patient files, from eight to thirteen years. We identified patients based on the codes registered for diagnosis, treatment and operation. Exclusion criteria were: Age under 18 years and acute subdural hematomas, defined as a SDH consisting of more than 1/3rd hyperdense components. Furthermore, patients with ventriculo-peritoneal shunts, patients with a history of intracerebral tumor or arteriovenous malformation prior to CSDH diagnosis were excluded as well as all patients who did not receive surgical treatment for their CSDH. The study was approved by the local ethical committees of the three neurosurgical centers. As all the data had been collected for routine clinical care, the necessity of informed consent was waived for this retrospective study.

We recorded side hematoma and of operation, together with anesthesia modality. Specifically we compared unilateral vs. bilateral decompression in patients with bilateral CSDH and general vs. local anesthesia.

Clinical and demographic data that were recorded included age, sex, comorbidity, medication use, hospital of treatment, and length of hospital stay. Additionally, we collected data on clinical severity measured by Markwalder Grading Scale (19) (MGS) and Glasgow Coma Scale (GCS)and on admission. Comorbidities at time of diagnosis were measured with the Charlson Comorbidity Index (CCI) (20).

Preoperative data included CT data comprising hematoma characteristics, such as type [classification of Nakaguchi et al. (21)] side of hematoma, maximal hematoma thickness in the axial plane (in centimetres) and midline shift (in millimetres).

Outcomes were complications, recurrence and length of hospital stay. Recurrence was defined as a return of clinical symptoms and reaccumulation of the CSDH on imaging (CT-scan), requiring retreatment (of the hematoma) within three months from the initial diagnosis. Postoperative complications included delirious state, rebleeding, wound infection, seizures, and systemic infection and were scored to be either present or absent. Due to low numbers of individual postoperative complications, complications were grouped and dichotomized into present or absent. Length of hospital stay was dichotomized at the median of 4 days.

Statistical Analysis

Baseline characteristics and outcomes were compared between intervention groups (unilateral vs. bilateral and local vs. general anesthesia) either with χ^2 tests or Mann-Whitney *U*-test, depending on the type of the variable.

In multivariable binary logistic regression we tested the association of intervention group with outcome, adjusted for the potential confounders (age, sex, CCI, and MGS at presentation). Additionally, since length of stay and complications are correlated, we adjusted for length of hospital stay in the models for complications and for complications in the model for length of hospital stay. Finally for local vs. general anesthesia, we also adjusted for location of treatment (which hospital).

RESULTS

Patient characteristics

We included a total of 1,029 patients, of whom 773 were men (75%). The mean age was 74 years (±11) (**Table 1**). A history of head trauma was present in 571 patients (55%). Most patients had a MGS of 1 or 2 (respectively, 32 and 64%) with a median GCS score of 15 (IQR: 1).

Regarding CSDH characteristics, 772 (75%) of patients had a unilateral hematoma and bilateral CSDH was present in 257 patients (25%). Antiplatelet therapy was used by 247 patients (24%) and 324 patients (32%) used oral anticoagulants. Acetylsalicylic acid (ASA) and Vitamin K Antagonists (VKA) were most often used, in 176 (71%) and 310 (96%), respectively.

Most common hematoma types were hypodense, isodense, and trabecular. As for surgical technique, BHC was applied in 995 patients (96%). Localized anesthesia was performed in 609 patients (66%). The median length of hospital stay was 4 days (IQR 8). A total of 117 postoperative complications occurred in 111 patients (11%). The most often seen complications were delirious state, pneumencephalus, empyema, or wound infection and seizures. Recurrence within 3 months of diagnosis occurred in 115 patients (11 %) and 40 patients died within three months (4%).

Neurosurgical Centers

The data of three neurosurgical centers was used for this study. The majority of patients, 641 (62%) was treated in Center 1 (**Table 2**). The surgical technique used for drainage of CSH was similar in all three centers, i.e., burr-hole drainage in respectively, 99, 94, and 93% of patients with per-operative flushing/ irrigation of the hematoma compartment with saline. Median time of post-surgery drainage was 24 h in center 1 and 48 h in center 2 and 3. In center 2, a relatively high number of patients, 22 (15%) did not receive post-surgery drainage. In center 1, local anesthesia was applied in 587 (92%) of patients, whereas center 2 and 3 applied local anesthesia in, respectively, 2 (3%) and 20 (6%) of their patients.

Bilateral CSDH

The recurrence rate in bilateral CSDH (40 patients, 16%) was significantly higher than in unilateral CSDH (75 patients, 10%) patients ($p = 0.01$). No differences were present in sex ($p = 0.279$), age ($p = 0.555$), MGS at admission ($p = 0.279$), CCI at diagnosis ($p = 0.524$) or three-month mortality rates ($p = 0.139$) (**Table 3**). In multivariable analysis, patients with bilateral CSDH were more likely to develop recurrence than those with unilateral

TABLE 1 | General characteristics of 1,029 surgically treated CSDH patients.

Variables	Patients, *N* (%)	
Sex		
- Male	773 (75)	
- Female	256 (25)	
Age (mean ± SD)	73.5 (± 11)	
Head trauma prior to CSDH	571 (55)	
No/does not recall	256 (45)	
MGS score at presentation:		
MGS 0:	4 (0.4)	
MGS 1:	326 (32)	
MGS 2:	648 (64)	
MGS 3:	31 (3)	
MGS 4:	3 (0.3)	
Unknown	17 (1.7)	
GCS at presentation, median (IQR)	15 (1)	
Side of hematoma		
- Unilateral	772 (75)	
- Bilateral	257 (25)	
Use of Antithrombotic drugs:		
- None	436 (43)	
- Antiplatelet therapy	247 (24)	
- Anticoagulants	324 (32)	
- Other	18 (1)	
- Unknown	4 (0.4)	
Type of antiplatelet therapy		
- Acetylsalicylic acid	176 (71)	
- Clopidogrel	19 (8)	
- Dual therapy	52 (21)	
Type of anticoagulants		
- VKA	310 (96)	
- DOAC	14 (4)	
Hematoma type*	Left (*N* = 681)	Right (*N* = 605)
- Hyperdense	34 (3)	36 (4)
- Isodense	131 (13)	129 (13)
- Separated	58 (6)	54 (5)
- Gradation	43 (4)	41 (4)
- Laminar	40 (4)	32 (3)
- Trabecular	145 (14)	121 (12)
- Hypodense	105 (10)	82 (8)
- Unknown	125 (12)	110 (11)
Hematoma thickness, cm (mean ± SD)	Left: 1.8 (± 0.7)	Right: 1.8 (± 0.7)
Midline shift, mm (mean ± SD)	8.2 (± 4.9)	
Type of surgery		
BHC	995 (97)	
Craniostomy	16 (1.5)	
TDC	6 (0.5)	
Unknown	11 (1)	
Anesthesia modality		
- Local	609 (66)	
- General	314 (34)	
- Unknown	106 (10)	

(Continued)

TABLE 1 | Continued

Variables	Patients, *N* (%)
Length of hospital stay, days median (mean, range)	4 (8, 0–76)
Postoperative complications	117 in 111 patients (11)
Type of postoperative complication	
- Delirious state	34 (29)
- Pneumencephalus	22 (18)
- Empyema/wound infection	15 (13)
- Seizures	14 (12)
- Bleeding of operation wound	11 (9)
- Systemic infection	8 (7)
- Thrombosis /embolism	4 (3)
- Other (e.g., aphasia, CSF leakage, traumatic subarachnoidal hemorrhage resulting from surgery)	9 (8)
Recurrence < 3 months	115 (11)
Mortality < 3 months	40 (4)

**Including bilateral hematomas.*

TABLE 2 | Overview of neurosurgical and perioperative management in the three neurosurgical centers.

	Center 1 *N* (%) Total = 641	Center 2 *N* (%) Total = 69	Center 3 *N* (%) Total = 319
Treated with Burr hole craniostomy *N* (%)	634 (99)	65 (94)	296 (93)
Hours of post-surgery drainage (median)	24	48	48
No post-surgery drainage *N* (%)	14 (2)	15 (22%)	7 (2)
Local Anesthesia applied *N* (%)	587 (92)	2 (3)	20 (6)

CSDH, after adjusting for age, sex, MGS, and CCI at admission. (aOR 1.7, 95% CI: 1.1–2.5)

We found no differences in recurrence rates between bilateral CSDH patients who underwent primary unilateral decompression (18 patients, 17%) and those who underwent bilateral decompression (22 patients, 15%, $p = 0.77$) (**Table 4**). Also, there was no statistically significant difference in hematoma thickness between patients with bilateral (2.9 cm. ± 0.8) and unilateral CSDH (3.0 ± 0.9, $p = 0.057$). Preoperative midline shift was found to be significantly larger in unilaterally treated bilateral CSDH (7.5 vs. 5.6 mm, $p = 0.001$). MGS at presentation did not differ ($p = 0.66$). We did find that in 50% (9 of 18) of the primary unilateral decompressed bCSDH with recurrence, the contralateral side was operated (**Figure 1**).

Local vs. Generalized Anesthesia

Anesthesia modality was known in 923 patients. The number of postoperative complications was significantly higher in general anesthesia (52 cases, 17%) than in local (50 cases, 8%) ($p = 0.000$) (**Table 5**) Median length of hospital stay was significantly longer in general anesthesia (8 days, IQR 8) than in local (3 days, IQR:3)

TABLE 3 | Statistics of differences between unilateral and bilateral CSDH ($N = 1029$).

	Unilateral CSDH N (%) Total = 772	Bilateral CSDH N(%) Total = 257	*p*-value
Sex			*0.279*[1]
- Male	573 (74)	200 (78)	
- Female	199 (26)	57 (22)	
Age (mean + SD)	73 (11.2)	74 (10.3)	*0.555*[2]
Markwalder Grading Scale at admission			*0.279*[1]
MGS 0:	4 (0.5)	0 (0)	
MGS 1:	247 (32)	79 (31)	
MGS 2:	486 (63)	162 (63)	
MGS 3:	21 (3)	10 (4)	
MGS 4:	1 (0.1)	2 (1)	
Missing	13 (2)	4 (1)	
Charlson comorbidity index			*0.524*[1]
CCI : 0	20 (3)	4 (2)	
CCI: 1	42 (5)	10 (4)	
CCI: 2	95 (12)	28 (11)	
CCI: 3	177 (23)	49 (19)	
CCI: 4	191 (25)	69 (27)	
CCI: 5	116 (15)	47 (18)	
CCI: 6 or more	128 (17)	45 (18)	
Missing	3 (0.4)	5 (2)	
Recurrence < 3 months	75 (10)	40 (16)	*0.012*[1]
Mortality < 3 months	26 (3)	14 (5)	*0.139*[1]

[1]analyzed with χ^2 test; [2]analyzed with Mann Whitney U-test.

TABLE 4 | Statistics of differences between unilaterally or bilaterally primary decompression in patients with bilateral CSDH.

	Unilateral Decompression *N* (%) Total = 109	Bilateral Decompression *N* (%) Total = 145	*p*-value
Recurrence < 3 months	18 (17)	22 (15)	*0.771*[1]
Hematoma thickness, cm (mean ± SD)	2.9 ± 0.8	3.0 ± 0.9	*0.057*[2]
MGS score at presentation:			*0.659*[1]
MGS 0:	0 (0)	0 (0)	
MGS 1:	30 (28)	47 (32)	
MGS 2:	73 (67)	88 (61)	
MGS 3:	3 (3)	7 (5)	
MGS 4:	1 (1)	1 (1)	
Missing	2 (2)	2 (1)	
Midline shift, mm (mean ± SD)	7.5 ± 3.8	5.6 ± 3.0	*0.001*[2]

Number of bilateral CSDH patients with known side of primary decompression n = 254.
[1]analyzed with χ^2 test; [2]analyzed with Mann Whitney U test.

($p = 0.000$)and MGS and CCI at admission significantly differed between the groups (respective *p*-values 0.000 and 0.035). Age ($p = 0.468$) and sex ($p = 0.085$) were not significantly different.

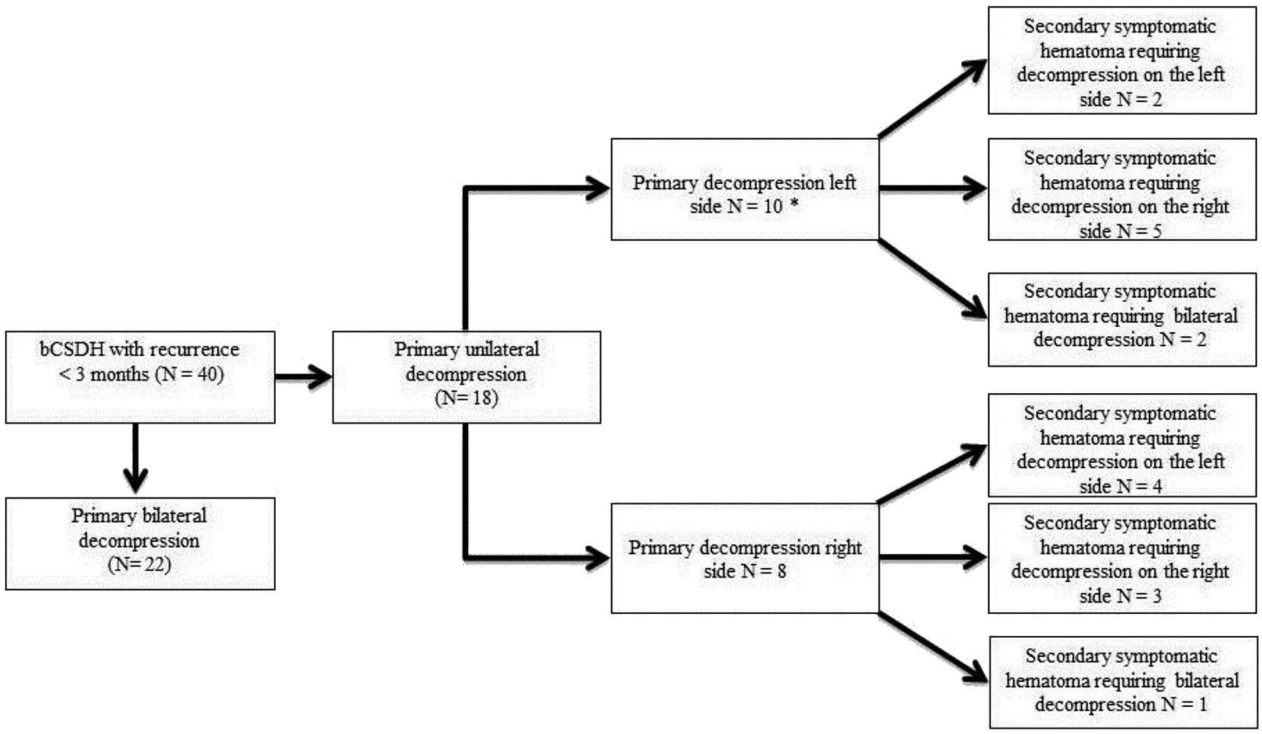

FIGURE 1 | Numbers of contralateral decompression in bilateral CSDH with recurrence. *side of secondary hematoma requiring decompression is unknown in one patient.

Also, no significant differences in three-month recurrence rates (12 vs. 10%, $p = 0.510$) and three-month mortality (4 vs. 3%, $p = 0.324$) between local and general anesthesia were present.

In multivariable analysis, patients who received general anesthesia were 1.8 times more likely to develop postoperative complications than those receiving local anesthesia. (aOR 1.8, 95% CI: 1.0–3.3) (**Table 6**). After adjusting for hospital of treatment, this relationship was no longer present. (aOR 1.7, 95% CI: 0.7–4.0) (**Table 7**).

401 patients (51%) had a length of stay of 4 days or less, and 390 patients (49%) stayed 5 days or more. Patients who received general anesthesia were 8.1 times more likely to have a length of stay of more than four days. (95% CI: 5.6–12.1) (**Table 6**). When adjusted for hospital of treatment, this association was lower, but still present. (aOR 3.0 95% CI: 1.6–5.6) (**Table 7**).

DISCUSSION

In this large retrospective study, one of the largest to date, an independently higher chance of recurrence was found in patients with bilateral CSDH compared to patients with unilateral CSDH. However, a beneficial effect of primary bilateral decompression on reducing recurrence rates in bilateral CSDH, as we hypothesized was not found. Even though no significant differences were present, the number of unilateral treated patients that required secondary contralateral surgery for their recurrence, was high: about half of all patients. This increased chance of recurrence combined with the high number of contralateral treatments for recurrence do suggest that bilateral CSDH requires other treatment strategies, as is proposed by other authors (13).

The contrast of our results with the findings of a recent study stating that there is a beneficial effect of primary bilateral decompression, can be explained by the overall higher incidence of recurrence in their study (13). The authors do not provide an explanation for their high incidence of recurrence, but it could be related to the large number of patients not receiving subdural drainage, which is a risk factor for recurrence (6). In their study, patients that received conservative treatment were also included, opposed to our patients who all underwent surgery. Interestingly, they report a high number of primary craniotomies, which has been related to lower recurrence rates (22). In the literature the consensus is to reserve craniotomy for solid hematomas with multiple recurrences (23). It is debatable whether contralateral recurrence in bilateral CSDH should be considered as secondary hematoma growth rather than recurrence, however we classified it as recurrence in our study. This allowed us to compare our results with other studies, which also consider contralateral growth in bilateral CSDH as "recurrence" (13, 14).

Another important question was the type of anaesthesia that was used. Our study showed that general anesthesia is independently associated with higher odds of postoperative complications and prolonged hospitalization in patients with CSDH. However, this association decreased when adjusted for the hospital in which the surgery was performed. This

TABLE 5 | Statistics of differences between local and general anesthesia.

	Local anesthesia *N* (%) Total = 609	General anesthesia *N* (%) Total = 314	*p*-value
Sex (male)	464 (76)	232 (74)	*0.468*[1]
Age (mean + SD)	74 (10.7)	73 (11.4)	*0.085*[2]
MGS at admission			*0.000*[1]
MGS 0:	2 (0)	2 (0)	
MGS 1:	121 (20)	147 (47)	
MGS 2:	470 (77)	140 (45)	
MGS 3:	15 (3)	15 (5)	
MGS 4:	0 (0)	3 (1)	
Missing	1 (0)	7 (2)	
Charlson comorbidity index			*0.035*[1]
CCI : 0	10 (2)	11 (4)	
CCI: 1	32 (5)	13 (4)	
CCI: 2	68 (11)	42 (13)	
CCI: 3	152 (25)	57 (18)	
CCI: 4	161 (26)	72 (23)	
CCI: 5	96 (16)	53 (17)	
CCI: 6 or more	88 (15)	62 (20)	
Missing	2 (0)	4 (1)	
Length of hospital stay in days median (mean, range)	3 (5, 0-40)	8 (8, 1-76)	*0.000*[2]
Postoperative complication *N* (%)	50 (8)	52 (17)	*0.000*[1]
Recurrence < 3 months *N* (%)	72 (12)	32 (10)	*0.510*[1]
Mortality < 3 months *N* (%)	26 (4)	10 (3)	*0.477*[1]

Number of patients with known anesthesia modality N = 923.
[1]analyzed χ^2 test; [2]analyzed with Mann Whitney U test.

TABLE 6 | Relation between general anesthesia and postoperative complication and chance of hospital admission of five days or more.

	Postoperative complication aOR (95% CI)[1]	Length of hospital stay five days or more aOR (95% CI)[2]
General anesthesia	1.8 (1.0–3.3)	8.1 (5.4–12.1)

[1]Adjusted for age, sex, MGS at admission, Charlson comorbidity index, and length of hospital stay.
[2]Adjusted for age, sex, MGS at admission, Charlson comorbidity index and occurrence of postoperative complication.

TABLE 7 | Relation between general anesthesia and postoperative complication and chance of hospital admission of five days or more.

	Postoperative complication aOR (95% CI)[1]	Length of hospital stay five days or more aOR (95% CI)[2]
General anesthesia	1.7 (0.7–4.0)	3.0 (1.6–5.6)

[1]Adjusted for age, sex, MGS at admission, Charlson comorbidity index, length of hospital stay and treatment hospital.
[2]Adjusted for age, sex, MGS at admission, Charlson comorbidity index, occurrence of postoperative complication and treatment hospital.

is probably related to the fact that the vast majority of patients with local anesthesia (92%) was operated in only one of the three included neurosurgical facilities. There was no difference in (co)morbidity or clinical severity of patients between the hospitals, meaning that the reported differences in hospital stay and postoperative complications are not due to a selection bias. The skewed distribution was caused by the standard procedures of the neurosurgical facilities. For example in center 1, where the vast majority of LA is applied, CSDH patients are always operated under LA unless they are not cooperative or otherwise not having a healthy condition for LA. Contradictory, the other two neurosurgical facilities apply GA as part of their standard procedure and only perform surgery under LA if patient characteristics require so. However, in center 2, a relatively high percentage of patients was treated without application of a subdural drain for post-surgery drainage. This might explain the decreased relationships of anesthesia type with postoperative complications and length of hospital stay, after adjusting for hospital of treatment, where the use of subdural drainage is reported to diminish recurrence and therefore possibly reduces complications (24).

In the current literature, limited numbers of studies have been performed to investigate the difference between LA and GA in CSDH. A recent review article concluded that 'For now, the anesthetist and surgeon, in consultation with the patient, must decide which anesthetic technique to use on an individual basis' (25). However, some remarks can been made regarding the studies that have been cited by these authors. In a retrospective study including 1,000 CSDH patients, of which 919 received LA, no difference in outcome between the types of anesthesia was found (23). However, in this study outcome was only defined as "good vs. bad postoperative results" based on the MGS. Moreover, these LA patients underwent sedation with LA, and not LA alone. Another smaller and retrospective study reported more cardiac complications in the GA group, leading to a longer hospital stay (17). This article is only available in Korean, so the specific methods and possible limitations could not be retrieved. Our number of postoperative complications (without recurrence and death) may be perceived as being high, but is comparable to reported numbers in other CSDH studies (11, 26).

Not all studies share this view on the benefits of LA over GA. Some attribute the increased numbers of postoperative cognitive changes not to GA but to other aspects of surgery, such as an increase in cytokines, and question the supposed benefits of LA (27, 28). Other possible complicating factors of LA, described in the literature comprise discomfort for the patient and movement of patients during surgery, thereby increasing the chance of surgical complications (28, 29). When evaluating the majority of studies including our own results, we would like to conclude that LA, with the possibility to convert to GA in cases where patients are not cooperative, seems to be the better option for treatment of CSDH.

Despite the interesting results, this study comprises strengths and limitations. The strengths of our current study are a high number of patients, with data collected in multiple neurosurgical centers. The retrospective nature of our study may lead to a risk of selection bias, as only those patients who are deemed suitable or even fit for operation are referred to neurosurgical centers. This is partially illustrated by the low number of patients in the MGS 0, 3, and 4 groups. As a result we can mainly analyze the "milder" MGS 1 or 2 groups, possibly leading to lower complication and recurrence rates. The low complication numbers in our study can also be due to the fact that patients are transferred back to their own region quickly after surgery and consequently not all complications are registered in the patient charts of the neurosurgical departments. Finally, due to the observational nature of our study, randomized data was not available, possibly leading to confounding by indication. This is especially difficult seeing that we compared interventions. As a result observed and unobserved patient characteristics, e.g., CT findings, GCS, may drive real-life clinical decisions, confounding the relation between the intervention and the outcome. Statistical approaches can adjust for observed confounders but not for unobserved confounders so findings need to be interpreted with caution.

CONCLUSION

Bilateral CSDH is independently associated with higher recurrence rates, but there is no difference in recurrence between primary bilateral decompression and unilateral decompression.

Our study suggests a beneficial effect of local anesthesia compared to general anesthesia. Therefore, in suitable patients, local anesthesia may be considered over general. Our findings regarding the optimal surgical approach in bilateral CSDH and the benefits of local anesthesia in CSDH should be confirmed in prospective studies.

DATA AVAILABILITY STATEMENT

Requests for access to the anonymized dataset can be send to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Review Board of the University Medical Center Groningen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JB: conception and design, acquisition of data, analysis and interpretation of data and drafting the article, approved the final version of the manuscript on behalf of all authors. BJ, JN, and RG: conception and design, critically revising the article, reviewed submitted version of manuscript, study supervision. HH, NG, KJ, RD, HL, and KK: critically revising the article, reviewed submitted version of manuscript.

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REFERENCES

1. Rauhala M, Luoto TM, Huhtala H, Iverson GL, Niskakangas T, Öhman J, et al. The incidence of chronic subdural hematomas from 1990 to 2015 in a defined Finnish population. *J Neurosurg.* (2019) 22:1–11. doi: 10.3171/2018.12.JNS183035
2. Uno M, Toi Hirai HS. Chronic subdural hematoma in elderly patients: Is this disease benign? *Neurol Med Chir.* (2017) 57:402–9. doi: 10.2176/nmc.ra.2016-0337
3. Sim YW, Min KS, Lee MS, Kim Kim YGDH. Recent Changes in risk factors of chronic subdural hematoma. *J Korean Neurosurg Soc.* (2012) 52:234–9. doi: 10.3340/jkns.2012.52.3.234
4. Adhiyaman V, Asghar M, Ganeshram Bhowmick KNBK. Chronic subdural haematoma in the elderly. *Postgr Med J.* (2002) 78:71–5. doi: 10.1136/pmj.78.916.71
5. Kolias AG, Chari A, Santarius Hutchinson TPJ. Chronic subdural haematoma: Modern management and emerging therapies. *Nat Rev Neurol.* (2014) 10:570–8. doi: 10.1038/nrneurol.2014.163
6. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma : a randomised controlled trial. *Lancet.* (2009) 374:1067–73. doi: 10.1016/S0140-6736(09)61115-6
7. Regan JM, Worley E, Shelburne C, Pullarkat Watson RJC. Burr hole washout versus craniotomy for chronic subdural hematoma: patient outcome and cost analysis. *PLoS ONE.* (2015) 10:e115085. doi: 10.1371/journal.pone.0115085
8. Lega BC, Danish SF, Malhotra NR, Sonnad Stein SSSC. Choosing the best operation for chronic subdural hematoma: A decision analysis - Clinical article. *J Neurosurg.* (2010) 113:615–21. doi: 10.3171/2009.9.JNS08825
9. Santarius T, Lawton R, Kirkpatrick Hutchinson PJPJ. The management of primary chronic subdural haematoma: a questionnaire survey of practice in the United Kingdom and the Republic of Ireland. *Br J Neurosurg.* (2008) 22:529–34. doi: 10.1080/02688690802195381
10. Brennan PM, Kolias AG, Joannides AJ, Shapey J, Marcus HJ, Gregson BA, et al. The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J Neurosurg.* (2017) 127:732–9. doi: 10.3171/2016.8.JNS16134
11. Rovlias A, Theodoropoulos Papoutsakis SD. Chronic subdural hematoma: surgical management and outcome in 986 cases: a classification and regression tree approach. *Surg Neurol Int.* (2015) 6:161788. doi: 10.4103/2152-7806.161788
12. Berghauser Pont LME, Dirven CMF, Dippel DWJ, Verweij BH, Dammers R. The role of corticosteroids in the management of chronic subdural hematoma : a systematic review. *Eur J Neurol.* (2012) 19:1397-403. doi: 10.1111/j.1468-1331.2012.03768.x
13. Andersen-Ranberg NC, Poulsen FR, Bergholt B, Hundsholt Fugleholm TK. Bilateral chronic subdural hematoma: unilateral or bilateral drainage? *J Neurosurg.* (2017) 126:1905–11. doi: 10.3171/2016.4.JNS152642
14. Okano A, Oya S, Fujisawa N, Tsuchiya T, Indo M, Nakamura T, et al. Analysis of risk factors for chronic subdural haematoma recurrence after burr hole surgery: optimal management of patients on antiplatelet therapy. *Br J Neurosurg.* (2014) 28:204–8. doi: 10.3109/02688697.2013.829563

15. Soleman J, Taussky P, Fandino Muroi JC. Evidence-based treatment of chronic subdural hematoma. In: Sadaka F, editors. *Traumatic Brain Injury*. IntechOpen (2014), 249–81. doi: 10.5772/57353
16. Luger TJ, Kammerlander C, Gosch M, Luger MF, Kammerlander-Knauer U, Roth T, et al. Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter? *Osteoporos Int.* (2010) 21(Suppl 4):S555–72. doi: 10.1007/s00198-010-1399-7
17. Kim SO, Jung Il S, Won YS, Choi Yang CSJY. A comparative study of local versus general anesthesia for chronic subdural hematoma in elderly patients over 60 years. *Korean J Neurotrauma.* (2013) 9:47–51. doi: 10.13004/kjnt.2013.9.2.47
18. Mahmood SD, Waqas M, Baig Darbar MZA. Mini-Craniotomy under local anesthesia for chronic subdural hematoma: an effective choice for elderly patients and for patients in a resource-strained environment. *World Neurosurg.* (2017) 106:676–9. doi: 10.1016/j.wneu.2017.07.057
19. Markwalder T, Steinsiepe KF, Rohner M, Reichenbach Markwalder WH. The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. *J Neurosurg.* (1981) 55:390–6. doi: 10.3171/jns.1981.55.3.0390
20. Charlson M, Szatrowski TP, Peterson Gold JJ. Validation of a combined comorbidity index. *J Clin Epidemiol.* (1994) 47:1245–1251. doi: 10.1016/0895-4356(94)90129-5
21. Nakaguchi H, Tanishima Yoshimasu TN. Factors in the natural history of chronic subdural hematomas that influence their postoperative recurrence. *J Neurosurg.* (2001) 95:256–62. doi: 10.3171/jns.2001.95.2.0256
22. Lee KS. How to treat chronic subdural hematoma? Past now. *J Korean Neurosurg Soc.* (2019) 62:144–52. doi: 10.3340/jkns.2018.0156
23. Gelabert-González M, Iglesias-Pais M, García-Allut Martínez-Rumbo AR. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. *Clin Neurol Neurosurg.* (2005) 107:223–9. doi: 10.1016/j.clineuro.2004.09.015
24. Liu W, Bakker N, Groen RJM. Chronic subdural hematoma: a systematic review and meta-analysis of surgical procedures. *J Neurosurg.* (2014) 121:665–73. doi: 10.3171/2014.5.JNS132715
25. Shapey J, Glancz Brennan LJPM. Chronic subdural haematoma in the elderly: is it time for a new paradigm in management? *Curr Geriatr Rep.* (2016) 5:71–7. doi: 10.1007/s13670-016-0166-9
26. Bartek J, Sjåvik K, Kristiansson H, Ståhl F, Fornebo I, Förander P, et al. Predictors of recurrence and complications after chronic subdural hematoma surgery: a population-based study. *World Neurosurg.* (2017) 106:609–14. doi: 10.1016/j.wneu.2017.07.044
27. Shapira-Lichter I, Beilin B, Ofek K, Bessler H, Gruberger M, Shavit Y, et al. Cytokines and cholinergic signals co-modulate surgical stress-induced changes in mood and memory. *Brain Behav Immun.* (2008) 22:388–98. doi: 10.1016/j.bbi.2007.09.006
28. Bodenham AR, Howell SJ. General anaesthesia vs local anaesthesia: an ongoing story. *Br J Anaesth.* (2009) 103:785–9. doi: 10.1093/bja/aep310
29. Kim SE, Kim E. Local anesthesia with monitored anesthesia care for patients undergoing thyroidectomy - a case series. *Korean J Anesthesiol.* (2016) 69:635–9. doi: 10.4097/kjae.2016.69.6.635

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BRIEF RESEARCH REPORT
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Predicting Chronic Subdural Hematoma Resolution and Time to Resolution Following Surgical Evacuation

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Background: Growing evidence suggests that chronic subdural hematoma (CSDH) may have long-term adverse effects even after surgical evacuation. Hematoma recurrence is commonly reported as a short-term, postoperative outcome measure for CSDH, but other measures such as hematoma resolution may provide better insight regarding mechanisms behind longer-term sequelae. This study aims to characterize postoperative resolution times and identify predictors for this relatively unexplored metric.

Methods: Consecutive cases ($N = 122$) of burr hole evacuation for CSDH by a single neurosurgeon at Columbia University Irving Medical Center from 2000 to 2019 were retrospectively identified. Patient characteristics, presenting factors, and date of hematoma resolution were abstracted from the electronic health record. Outcome measures included CSDH resolution at 6 months, surgery-to-resolution time, and inpatient mortality. Univariate and multivariate analyses were performed to determine predictors of outcome measures.

Results: Hematoma resolution at 6 months was observed in 58 patients (47.5%), and median surgery-to-resolution time was 161 days (IQR: 85–367). Heavy drinking was predictive of non-resolution at 6 months and longer surgery-to-resolution time, while increased age was predictive of non-resolution at 6 months. Antiplatelet agent resumption was associated with non-resolution at 6 months and longer surgery-to-resolution time on univariate analysis but was not significant on multivariate analysis.

Conclusion: Postoperative resolution times for most CSDHs are on the order of several months to a year, and delayed resolution is linked to heavy drinking and advanced age. Subsequent prospective studies are needed to directly assess the utility of hematoma resolution as a potential metric for long-term functional and cognitive outcomes of CSDH.

Keywords: chronic subdural hematoma, subdural hematoma, surgical evacuation, hematoma resolution, hematoma recurrence, traumatic brain injury, burr hole, craniotomy

INTRODUCTION

Chronic subdural hematoma (CSDH) has become an increasingly common neurological condition worldwide, with an estimated incidence of up to 20.6 per 100,000 persons per year (1) and 58 per 100,000 per year for those 70 years of age and older (2, 3). While CSDH management varies based on a host of patient characteristics and radiological factors, the mainstay of treatment is neurosurgical evacuation, typically via burr hole drainage (most common), craniotomy, or craniectomy. Very few cases of CSDH resolve spontaneously (4), and even with surgery, hematoma recurrence occurs in 5–30% of reported cases (5–7). Several studies have used hematoma recurrence as a primary outcome variable and investigated predictors for this outcome (3, 7–11). The results of these analyses are quite heterogeneous, due in part to discrepancies in defining CSDH recurrence and variation in surgical and follow-up protocol (12).

In contrast, few studies have investigated predictors of CSDH resolution and CSDH resolution time—though post-operative residual fluid is detected in up to 80% of cases, it often does not precipitate acute symptoms and thus is typically deemed "clinically insignificant" (13). However, there is evidence that residual blood can have adverse effects, such as the prevention of brain re-expansion and prolongation of an inflammatory state (14, 15). While recurrence is a well-documented outcome metric for the acute follow-up period, it may not capture insidious processes that can hinder recovery and lead to poorer long-term functional and cognitive outcomes. In our single-center retrospective study, we aimed to characterize and elucidate potential predictors of CSDH resolution and surgery-to-resolution time.

METHODS

Study Population

The study protocol was approved by the institutional review board (IRB) of Columbia University. Consecutive cases of first-time burr hole evacuation for CSDH performed by a single attending neurosurgeon at Columbia University Irving Medical Center between 2000 and 2019 were retrospectively identified. Patients who had undergone bedside hematoma evacuation procedures prior to surgical evacuation were excluded. Patients who did not have at least 6 months of post-operative follow-up (except in cases of death or where their hematoma had already resolved) were also excluded. Diagnosis of CSDH was confirmed via head computed tomography (CT) or magnetic resonance imaging (MRI). All included patients had already been discharged at the time of study initiation, and informed consent was waived by the IRB.

Surgical Procedure

Of the 122 cases identified, 90 and 32 procedures were performed under general and local anesthesia, respectively. All patients underwent standard single- or double-burr hole craniostomy. Burr holes were created via a high-speed perforator, followed by waxing of the bone edges and opening of the dura in a cruciate fashion. The spaces were copiously irrigated with Tis-U-Sol, and titanium burr hole covers were placed over the durotomies. Closed drainage systems (Hemovac and/or Jackson-Pratt drain) were inserted in all patients and typically removed within 72 h. Antiplatelet agents and anticoagulants were discontinued prior to surgery, and reversal agents (Vitamin K for warfarin, desmopressin for antiplatelet agents) were administered as needed. These medications were re-prescribed at the discretion of the patients' providers, based on individualized consideration of both post-operative status and pre-existing comorbidities.

Variables and Outcome Measures

Patient characteristics data including age, ethnicity, hypertension, diabetes mellitus, heavy alcohol use (>3 drinks per day or >7 drinks per week for women; >4 drinks per day or >14 drinks per week for men), history of prior SDH, recent history of head trauma, recent history of open cranial surgery, antiplatelet agent use (aspirin and/or adenosine-diphosphate receptor inhibitors) at diagnosis, and anticoagulant use (warfarin or direct oral anticoagulants) at diagnosis were collected from the electronic health record (EHR). Radiological factors including laterality and density of CSDH were recorded both at diagnosis and immediately prior to surgery. Number of burr holes, year of surgery (representing attending surgeon experience), month of surgery normalized to the academic year (representing resident experience), diagnosis-to-surgery time, length of hospitalization, and discharge modified Rankin Scale (mRS) were also noted.

Follow-up radiological examinations were conducted routinely within the first 24 h post-operatively as well as prior to discharge. Additional scans were selectively conducted for patients with large residual hematomas, changes in neurological status, and/or as part of outpatient follow-up. The mean number of CT and MRI scans obtained for each patient was 6.2 and 0.3, respectively. Short-term imaging outcomes (i.e., on last CT/MRI prior to discharge) including stability of residual hematoma, ventricular dilation, residual mass effect, and pneumocephalus were recorded, as well as time to last radiological follow-up and hematoma recurrence. Hematoma recurrence was defined as radiologically-confirmed reaccumulation of SDH in the ipsilateral subdural space during the postoperative follow-up period, causing neurological deficits that necessitated repeat surgical evacuation. Primary outcome measures included hematoma resolution at 6 months, surgery-to-resolution time, and mortality prior to discharge. Hematoma resolution was defined as disappearance of CSDH on head CT or MRI by the last follow-up scan.

Statistical Analysis

Statistical analysis was performed via Stata/IC (Version 16, StataCorp), and identifiable personal health information was removed prior to analysis. Data are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. Univariate analyses were conducted via Student's *t*-test (or Welch's *t*-test for heteroscedastic data) for continuous-to-categorical comparisons, Spearman rank correlation for continuous-to-continuous comparisons, and simple logistic regression for categorical-to-categorical

comparisons. Continuous variables with skewed distributions were log-transformed to achieve normality. Factors predictive in univariate analyses ($p < 0.25$) were entered into multivariate analyses (after further culling to minimize multicollinearity), carried out via multiple logistic regression, Firth's logistic regression, or multiple regression as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics and Outcomes

A total of 122 patients were included in this study, and their characteristics and outcomes are detailed in **Table 1**. The mean age was 73.6 ± 11.6 years (range: 36–95 years), and 39 (32.0%) patients were female. Common comorbidities included hypertension (73.0%), diabetes mellitus (28.7%), and history of heavy drinking (7.4%). At the time of CSDH diagnosis, antiplatelet agents were used in 51 (41.8%) patients (86.3% of which were on aspirin) and anticoagulants were used in 20 (16.4%) patients (60.0% of which were on warfarin). Antiplatelet agents were restarted in 12 patients (9.8%) a median of 22.5 days (IQR: 14–70.5) post-operatively, and anticoagulants were restarted in eight patients (6.6%) a median of 28 days (IQR: 8.5–63) post-operatively. Forty-three (35.2%) patients had bilateral hematomas, and 105 (86.1%) had mixed-density hematomas.

Single burr-hole craniostomy was performed in 20 (16.4%) patients and double burr-hole craniostomy in 102 (83.6%) patients. Median diagnosis-to-surgery time was 2 days (IQR: 1–6), median length of hospital stay was 7.5 days (IQR: 5–13), and median discharge mRS was 3 (IQR: 2–4). On the last CT/MRI prior to discharge, stable residual collection was noted in 78 (63.9%) patients, decreasing residual collection in 21 (17.2%), ventricular dilation in 8 (6.6%), residual mass effect in 99 (81.1%), and pneumocephalus in 100 (82.0%). Recurrence occurred in 14 (11.5%) patients, all of whom underwent repeat evacuations. Hematoma resolution was observed in 98 (80.3%) patients.

TABLE 1 | Patient characteristics, presenting factors, procedure types, and outcomes.

Age, mean ± SD	73.6 ± 11.6
Female, *n* (%)	39 (32.0)
Hispanic ethnicity, *n* (%)	50 (41.0)
Comorbidities, *n* (%)	
Prior subdural hematoma	9 (7.4)
Hypertension	89 (73.0)
Diabetes mellitus	35 (28.7)
Heavy drinking	9 (7.4)
Antiplatelet agent use at time of diagnosis	51 (41.8)
Antiplatelet agent use after evacuation	12 (9.8)
Surgery-to-antiplatelet agent resumption time, *d*, median (IQR)	22.5 (14–70.5)
Anticoagulant use at time of diagnosis	20 (16.4)
Anticoagulant use after evacuation	8 (6.6)
Surgery-to-anticoagulant resumption time, *d*, median (IQR)	28 (8.5–63)
Pre-operative factors, *n* (%)	
Recent head trauma	73 (59.8)
Recent open cranial surgery	8 (6.6)
Bilateral SDH	43 (35.2)
Mixed density SDH	105 (86.1)
Procedure type, *n* (%)	
Single burr hole	20 (16.4)
Double burr hole	102 (83.6)
Short-term imaging outcomes (last prior to discharge), *n* (%)	
Stable residual collection	78 (63.9)
Decreasing residual collection	21 (17.2)
Ventricular dilation	8 (6.6)
Residual mass effect	99 (81.1)
Pneumocephalus	100 (82.0)
Diagnosis-to-surgery time, *d*, median (IQR)	2 (1–6)
Length of hospitalization, *d*, median (IQR)	7.5 (5–13)
Surgery-to-last-follow-up time, *d*, median (IQR)	166.5 (79–408)
Discharge modified Rankin Scale, median (IQR)	3 (2–4)
Hematoma recurrence, *n* (%)	14 (11.5)
Hematoma resolution, *n* (%)	98 (80.3)
Hematoma resolution at 6 months, *n* (%)	58 (47.5)
Surgery-to-resolution time, *d*, median (IQR)	161 (85–367)
Mortality prior to discharge, *n* (%)	7 (5.7)

Predictors of Hematoma Resolution at 6 Months and Surgery-to-Resolution Time

Hematoma resolution at 6 months was observed in 58 (47.5%) patients. Predictors of hematoma resolution at 6 months are detailed in **Table 2**. Increased age (OR: 0.95, 95% CI: 0.92–0.99, $p = 0.009$) and history of heavy drinking (OR: 0.18, 95% CI: 0.03–0.94, $p = 0.042$) were both found to be significantly predictive of hematoma non-resolution on multivariate analysis. Antiplatelet agent use after CSDH evacuation was predictive of non-resolution on univariate analysis (OR: 0.22, 95% CI: 0.05–0.95, $p = 0.042$) but did not reach significance on multivariate analysis. Recent head trauma (OR: 0.60, 95% CI: 0.29–1.25, $p = 0.172$) and later month of operation (normalized to the academic year; OR: 1.07, 95% CI: 0.96–1.20, $p = 0.203$) showed modest trends but were not significant on univariate analysis. No significant association was found between hematoma resolution at 6 months and presenting imaging characteristics, number of burr holes, or short-term imaging outcomes.

Of the patients who experienced hematoma resolution, the median surgery-to-resolution time was 161 days (IQR: 85–367 days). A subgroup analysis was performed to elucidate predictors of surgery-to-resolution time (log-transformed to account for non-normality), the results of which are summarized in **Table 3** below. Heavy drinking was independently predictive of longer resolution time, with a 213.64% (95% CI: 33.67–635.93%) increase in surgery-to-resolution time ($p = 0.009$). Antiplatelet agent use was associated with longer surgery-to-resolution time on univariate analysis (ratio of geometric means: 3.15, 95% CI: 1.12–8.86, $p = 0.036$) and trended toward significance on multiple regression ($p = 0.134$). Anticoagulant

TABLE 2 | Predictors of hematoma resolution at 6 months.

	Odds ratio (95% CI)	*P*-value
Univariate analysis		
Age	0.96 (0.93–0.99)	**0.012**
Month of operation (normalized to academic year)	1.07 (0.96–1.20)	0.203
Recent head trauma	0.60 (0.29–1.25)	0.172
Heavy drinking	0.29 (0.06–1.46)	0.134
Antiplatelet agent use after evacuation	0.22 (0.05–0.95)	**0.042**
Multivariate analysis		
Age	0.95 (0.92–0.99)	**0.009**
Heavy drinking	0.18 (0.03–0.94)	**0.042**

Predictors with $p < 0.25$ on univariate analysis and $p < 0.05$ on multivariate analysis are reported. CI, confidence interval. Bold indicates statistical significance.

TABLE 3 | Predictors of longer surgery-to-resolution time.

	Effect size (95% CI)	*P*-value
Univariate analysis		
Year of operation	−0.147 (−0.336–0.052)*	0.147
Decreasing collection	0.67 (0.35–1.27)†	0.226
Heavy drinking	4.67 (2.06–10.60)†	**<0.001**
Antiplatelet agent use after evacuation	3.15 (1.12–8.86)†	**0.036**
Anticoagulant use at time of diagnosis	1.58 (0.80–3.12)†	0.186
Multivariate analysis		
Heavy drinking	213.64 (33.67–635.93)‡	**0.009**

*Predictors with $p < 0.25$ on univariate analysis and $p < 0.05$ on multivariate analysis are reported. CI, confidence interval. *Indicates Spearman's ρ. †Indicates ratio of geometric means. ‡Indicates percent increase in dependent variable (surgery-to-resolution time). Bold indicates statistical significance.*

use at diagnosis was not predictive on univariate or multivariate analysis, and no significant difference in resolution time was found between those who resumed anticoagulation post-operatively and those who did not. Later year of operation showed a modest trend toward shorter surgery-to-resolution time on univariate analysis (Spearman's $\rho = -0.147$, 95% CI:−0.336–0.052, $p = 0.147$) but was not predictive on multivariate analysis. No significant associations were found between surgery-to-resolution time and patient demographics, presenting imaging characteristics, number of burr holes, or short-term imaging outcomes.

Predictors of Inpatient Mortality

Seven (5.7%) patients died prior to discharge, and predictors of inpatient mortality are summarized in **Table 4**. Length of hospitalization was significantly associated with higher mortality (OR: 1.03, 95% CI: 1.00–1.07, $p = 0.047$) on univariate analysis, and anticoagulant use at time of diagnosis strongly trended toward higher mortality (OR: 4.38, 95% CI: 0.99–19.36, $p = 0.052$). None of the variables investigated were found to be independently predictive on multivariate analysis. No significant associations were found between inpatient mortality and patient demographics, presenting imaging characteristics, or number of burr holes.

TABLE 4 | Predictors of inpatient mortality.

	Odds ratio (95% CI)	*P*-value
Univariate analysis		
Length of hospitalization	1.03 (1.00–1.07)	**0.047**
Hispanic ethnicity	0.31 (0.05–1.90)	0.206
Anticoagulant use at time of diagnosis	4.38 (0.99–19.36)	0.052

Predictors with $p < 0.25$ on univariate analysis are reported. CI, confidence interval. Bold indicates statistical significance.

DISCUSSION

Several previous studies have used hematoma recurrence as a variable when assessing CSDH post-surgical outcomes (3, 7–11), but its prognostic utility is limited primarily to the short-term follow-up period. Though given far less attention in the literature given its unclear clinical correlations, characterizing hematoma resolution may provide insight into insidious, longer-term functional and cognitive sequelae of CSDH. In the first study of long-term CSDH outcomes, patients who had undergone surgical evacuation were found to demonstrate poorer long-term functional, cognitive, and mental health outcomes when compared to matched controls, in addition to decreased long-term survival (16). CSDH survivors with dementia have also been reported to experience greater rates of brain volume loss than those without dementia, suggesting that CSDH may be accelerating the effect of brain atrophy in that population (17). None of these studies used hematoma resolution as an outcome variable (and did not report CT or MRI follow-up beyond the immediate postoperative course). Thus, though these long-term effects may be manifestations of poor baseline status (with onset of CSDH being a "sentinel" event), it is entirely possible that unresolved CSDH could contribute to such outcomes through mechanisms such as impairment of brain re-expansion or maintenance of a prolonged state of inflammation in the intracranial environment (14, 15). Brain inflammation, in particular, has been linked to neurodegenerative conditions such as Alzheimer's and Parkinson's disease, suggesting that it may play a role in cognitive dysfunction (18). Though a direct investigation of correlations between hematoma resolution and long-term outcomes is outside the scope of this present study, we believe that characterizing CSDH resolution rates and their predictors serves an important intermediate step toward that end.

In our cohort, 47.5% of patients experienced hematoma resolution by 6 months after burr hole evacuation, of which the median surgery-to-resolution time was 161 days (IQR: 85–367); these metrics are similar to those reported in other recent studies (19, 20). These results suggest that a large proportion of CSDH survivors continue to live with residual hematomas for several months or even years. As we excluded patients without at least 6 months of imaging follow-up, it is possible that a

disproportionate amount of excluded cases resolved sooner than our resolution times may suggest. However, if we use length of follow-up for all consecutive burr hole cases (median: 96.5 days, IQR: 27.5–241 days) as a proxy for a best-case scenario, the time to resolution for a majority of our patients would still be on the order of multiple months or more.

Of the patient demographic factors, medical comorbidities, and presenting characteristics we investigated, history of heavy drinking was found to be predictive of CSDH non-resolution at 6 months and longer surgery-to-resolution time, and advanced age was predictive of non-resolution at 6 months. Cerebral atrophy is a well-described sequela of increased age and excessive alcohol use, which may impede brain re-expansion following CSDH and result in continued vulnerability of bridging veins (21, 22). In contrast, several other frequently reported predictors of hematoma recurrence were not predictive of resolution or resolution time in our cohort, particularly diabetes mellitus (23), bilateral hematoma (22, 24), and loculated-type hematoma (25–28). The discrepancy with regard to presenting radiological features is especially interesting, as it suggests that the nature of the hematoma itself may be of lesser importance for longer-term prognostication, perhaps as adequate surgical evacuation can ameliorate anatomical impediments to resolution posed by complex collections.

Antiplatelet agents were used by 51 (41.8%) of our patients at the time of CSDH diagnosis, of which 12 restarted antiplatelet therapy after a median of 22.5 days post-operatively. Antiplatelet agent resumption was significantly linked to both CSDH non-resolution at 6 months and longer surgery-to-resolution time on univariate analysis, but these associations only trended toward significance on multivariate analysis. Use of anticoagulants has been a well-documented risk factors for CSDH development, and several studies have reported its association with CSDH recurrence as well—however, the association between antiplatelet resumption and rebleeding remains unclear (23, 29). Our relatively small sample size for this subgroup may not have sufficient power to detect this potential effect, and larger studies are needed before a link between antiplatelet resumption to CSDH resolution (or lack thereof) can be established.

Interestingly, no significant differences in outcome were found between those who resumed anticoagulation after surgery and those who did not, though our sample size again limits the statistical power of this assessment. A meta-analysis of three studies of CSDH recurrence vs. thromboembolic risk found that all recurrences and thromboembolic events occurred within the 1st month post-operation (30). As the median time to anticoagulant reinsertion was 28 days in our cohort, there was perhaps a sufficient window of time for adequate clot formation, resulting in an insignificant difference in resolution time between patients who resumed and did not resume anticoagulation. While the feasibility of resuming early antithrombotic treatment in certain patients has been reported, there is yet no consensus on the reinsertion of therapy (30–32). Antithrombotic resumption in post-operative CSDH patients remains at the discretion of the clinician, tailored to individual patients' hemorrhagic and thromboembolic risks. Should CSDH resolution be found as a long-term clinically salient metric in future studies, extra consideration may be warranted when determining the best time interval for restarting antithrombotic therapy in these patients.

No differences in outcomes were found between single burr-hole and double burr-hole evacuation, and recent studies have also not reported any association between type of procedure and hematoma recurrence (22, 25, 33). Discharge mRS and imaging features prior to discharge (e.g., stable/decreasing collection, residual mass effect) also did not yield significance on multivariate analyses, suggesting that such short-term metrics may not be reliable predictors of CSDH resolution. Later year and month (normalized to the academic year) of surgery showed only modest univariate trends toward shorter resolution time and resolution at 6 months with minimal effect sizes. As these temporal variables were not significant on multivariate analysis, attending and resident procedural experience do not appear to be major independent contributors to our outcomes.

Our study has several limitations. All cases of CSDH evacuation were performed by a single neurosurgeon at Columbia University Irving Medical Center, which limits the external validity of our results. The retrospective nature of our study also precluded any predetermined imaging follow-up protocol, which may have introduced selection bias when excluding patients without the requisite 6 months of follow-up (e.g., perhaps the excluded patients tended to recover more quickly). Multi-center prospective, controlled studies with standardized long-term follow-up protocol will be necessary to validate and expand upon our findings.

CONCLUSION

Increasing evidence suggests that CSDH survivors suffer from long-term functional and cognitive outcomes despite successful surgical evacuation. While hematoma recurrence is a commonly used metric for short-term outcomes, we hypothesize that hematoma resolution and surgery-to-resolution time may better capture such adverse effects. Our results suggest that a large proportion of CSDH patients live with residual hematomas for months or even years after surgery, and we found advanced age and history of heavy drinking to be predictive of delayed resolution. Larger prospective, controlled studies are needed to further elucidate the potential effects of antithrombotic resumption on hematoma resolution and will aim to correlate hematoma resolution with functional and cognitive outcomes.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Columbia University Human Research Protection Office Institutional Review Boards. Written

informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CC, JS, and EC contributed to the conception and design of the study. CC, JS, MD, and DR assisted in data acquisition. CC organized the database and performed the statistical analysis. CC, JS, and MD wrote the first draft of the manuscript. CC, JS, and DR contributed to manuscript revision. All authors read and approved the final version of the manuscript.

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REFERENCES

1. Yang W, Huang J. Chronic subdural hematoma: epidemiology and natural history. *Neurosurg Clin N Am.* (2017) 28:205–10. doi: 10.1016/j.nec.2016.11.002
2. Kudo H, Kuwamura K, Izawa I, Sawa H, Tamaki N. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. *Neurol Med Chir.* (1992) 32:207–9. doi: 10.2176/nmc.32.207
3. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet.* (2009) 374:1067–73. doi: 10.1016/S0140-6736(09)61115-6
4. Parlato C, Guarracino A, Moraci A. Spontaneous resolution of chronic subdural hematoma. *Surg Neurol.* (2000) 53:312–7. doi: 10.1016/S0090-3019(00)00200-7
5. Santarius T, Hutchinson PJ. Chronic subdural haematoma: time to rationalize treatment? *Br J Neurosurg.* (2004) 18:328–32. doi: 10.1080/02688690400004845
6. Komotar RJ, Starke RM, Connolly ES. The role of drain placement following chronic subdural hematoma evacuation. *Neurosurgery.* (2010) 66:N15–N6. doi: 10.1227/01.neu.0000367840.82764.3a
7. Carlsen JG, Cortnum S, Sørensen JC. Recurrence of chronic subdural haematomata with and without post-operative drainage. *Br J Neurosurg.* (2011) 25:388–90. doi: 10.3109/02688697.2011.558945
8. Lindvall P, Koskinen LOD. Anticoagulants and antiplatelet agents and the risk of development and recurrence of chronic subdural haematomas. *J Clin Neurosci.* (2009) 16:1287–90. doi: 10.1016/j.jocn.2009.01.001
9. Ramachandran R, Hegde T. Chronic subdural hematomas-causes of morbidity and mortality. *Surg Neurol.* (2007) 67:367–72. doi: 10.1016/j.surneu.2006.07.022
10. Torihashi K, Sadamasa N, Yoshida K, Narumi O, Chin M, Yamagata S. Independent predictors for recurrence of chronic subdural hematoma: a review of 343 consecutive surgical cases. *Neurosurgery.* (2008) 63:1125–9. doi: 10.1227/01.NEU.0000335782.60059.17
11. Yu GJ, Han CZ, Zhang M, Zhuang HT, Jiang YG. Prolonged drainage reduces the recurrence of chronic subdural hematoma. *Br J Neurosurg.* (2009) 23:606–11. doi: 10.3109/02688690903386983
12. Xu CS, Lu M, Liu LY, Yao MY, Cheng GL, Tian XY, et al. Chronic subdural hematoma management: clarifying the definitions of outcome measures to better understand treatment efficacy - a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci.* (2017) 21:809–18. Available online at: https://www.europeanreview.org/article/12246
13. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK. Chronic subdural haematoma in the elderly. *Postgrad Med J.* (2002) 78:71–5. doi: 10.1136/pmj.78.916.71
14. Ernestus RI, Beldzinski P, Lanfermann H, Klug N. Chronic subdural hematoma: surgical treatment and outcome in 104 patients. *Surg Neurol.* (1997) 48:220–5. doi: 10.1016/S0090-3019(97)80031-6
15. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J Neuroinflammation.* (2017) 14:108. doi: 10.1186/s12974-017-0881-y
16. Moffatt CE, Hennessy MJ, Marshman LA, Manickam A. Long-term health outcomes in survivors after chronic subdural haematoma. *J Clin Neurosci.* (2019) 66:133–37. doi: 10.1016/j.jocn.2019.04.039
17. Zahid AB, Balser D, Thomas R, Mahan MY, Hubbard ME, Samadani U. Increase in brain atrophy after subdural hematoma to rates greater than associated with dementia. *J Neurosurg.* (2018) 129:1579–87. doi: 10.3171/2017.8.JNS17477
18. Jarrott B, Williams SJ. Chronic brain inflammation: the neurochemical basis for drugs to reduce inflammation. *Neurochem Res.* (2016) 41:523–33. doi: 10.1007/s11064-015-1661-7
19. Zanaty M, Park BJ, Seaman SC, Cliffton WE, Woodiwiss T, Piscopo A, et al. Predicting chronic subdural hematoma recurrence and stroke outcomes while withholding antiplatelet and anticoagulant agents. *Front Neurol.* (2020) 10:1401. doi: 10.3389/fneur.2019.01401
20. Jang KM, Choi HH, Mun HY, Nam TK, Park YS, Kwon JT. Critical depressed brain volume influences the recurrence of chronic subdural hematoma after surgical evacuation. *Sci Rep.* (2020) 10:1–8. doi: 10.1038/s41598-020-58250-w
21. Schoedel P, Bruendl E, Hochreiter A, Scheitzach J, Bele S, Brawanski A, et al. Restoration of functional integrity after evacuation of chronic subdural hematoma-an age-adjusted analysis of 697 patients. *World Neurosurg.* (2016) 94:465–70. doi: 10.1016/j.wneu.2016.07.027
22. Han MH, Ryu JI, Kim CH, Kim JM, Cheong JH, Yi HJ. Predictive factors for recurrence and clinical outcomes in patients with chronic subdural hematoma. *J Neurosurg.* (2017) 127:1117–25. doi: 10.3171/2016.8.JNS16867
23. Kim SU, Lee DH, Kim YI, Yang SH, Sung JH, Cho CB. Predictive factors for recurrence after burr-hole craniostomy of chronic subdural hematoma. *J Korean Neurosurg Soc.* (2017) 60:701–9. doi: 10.3340/jkns.2016.1010.003
24. Bartek J Jr, Sjåvik K, Kristiansson H, Ståhl F, Fornebo I, Förander P, et al. Predictors of recurrence and complications after chronic subdural hematoma surgery: a population-based study. *World Neurosurg.* (2017) 106:609–14. doi: 10.1016/j.wneu.2017.07.044
25. Motiei-Langroudi R, Stippler M, Shi S, Adeeb N, Gupta R, Griessenauer CJ, et al. Factors predicting reoperation of chronic subdural hematoma following primary surgical evacuation. *J Neurosurg.* (2018) 129:1143–50. doi: 10.3171/2017.6.JNS17130
26. Jack A, O'Kelly C, McDougall C, Findlay JM. Predicting recurrence after chronic subdural haematoma drainage. *Can J Neurol Sci.* (2015) 42:34–9. doi: 10.1017/cjn.2014.122
27. Hammer A, Tregubow A, Kerry G, Schrey M, Hammer C, Steiner HH. Predictors for recurrence of chronic subdural hematoma. *Turk Neurosurg.* (2017) 27:756–62. doi: 10.5137/1019-5149.JTN.17347-16.1
28. Qian Z, Yang D, Sun F, Sun Z. Risk factors for recurrence of chronic subdural hematoma after burr hole surgery: potential protective role of dexamethasone. *Br J Neurosurg.* (2017) 31:84–8. doi: 10.1080/02688697.2016.1260686
29. Nathan S, Goodarzi Z, Jette N, Gallagher C, Holroyd-Leduc J. Anticoagulant and antiplatelet use in seniors with chronic subdural hematoma. *Neurology.* (2017) 88:1889–93. doi: 10.1212/WNL.0000000000003918
30. Nassiri F, Hachem LD, Wang JZ, Badhiwala JH, Zadeh G, Gladstone D, et al. Reinitiation of anticoagulation after surgical evacuation of subdural hematomas. *World Neurosurg.* (2020) 135:e616–e22. doi: 10.1016/j.wneu.2019.12.080

31. Chari A, Morgado TC, Rigamonti D. Recommencement of anticoagulation in chronic subdural haematoma: a systematic review and meta-analysis. *Br J Neurosurg.* (2013) 28:2–7. doi: 10.3109/02688697.2013.812184
32. Phan K, Abi-Hanna D, Kerferd J, Lu VM, Dmytriw AA, Ho YT, et al. Resumption of antithrombotic agents in chronic subdural hematoma: a systematic review and meta-analysis. *World Neurosurg.* (2018) 109:e792–e9. doi: 10.1016/j.wneu.2017.10.091
33. Stavrinou P, Katsigiannis S, Lee JH, Hamisch C, Krischek B, Mpotsaris A, et al. Risk factors for chronic subdural hematoma recurrence identified using quantitative computed tomography analysis of hematoma volume and density. *World Neurosurg.* (2017) 99:465–70. doi: 10.1016/j.wneu.2016.12.058

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Effects of Possible Osteoporotic Conditions on the Recurrence of Chronic Subdural Hematoma

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The recurrence rate of chronic subdural hematoma (CSDH) has been reported to range from 2.3 to 33%. As bridging veins are composed of abundant collagen bundles and bone matrix, we aimed to investigate the possible associations between skull Hounsfield unit (HU) values and the recurrence of CSDH. We retrospectively enrolled patients with CSDH who underwent burr hole surgery. The HU values of the frontal skull were measured on brain CT scans. The cumulative hazard for recurrence was estimated according to predictive factors. To identify the independent predictors associated with the recurrence of CSDH, hazard ratios (HRs) were estimated using multivariate Cox regression analysis. A total of 208 consecutive patients who underwent burr hole trephination for CSDH over a 7-years period at a single institution were enrolled in this study. We found that age, greater midline shift (≥10.5 mm), lower skull HU (<769.5), and diabetes were independent predictors for the recurrence of CSDH (HR 1.06, 95% confidence interval [CI] 1.00–1.12, $p = 0.042$; HR 5.37, 95% CI 1.48–19.46, $p = 0.010$; HR 6.71, 95% CI 1.84–24.45, $p = 0.004$; and HR 3.30, 95% CI 1.05–10.43, $p = 0.042$, respectively). A relationship between possible low bone mineral density (BMD) and CSDH recurrence was observed. In addition, age, greater preoperative midline shift, and diabetes were also identified as predictive factors for recurrence. We expect that our findings may facilitate our understanding of the possible association between CSDH and BMD.

Keywords: chronic subdural hematoma, Hounsfield unit, midline shift, diabetes, osteoporosis

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INTRODUCTION

Chronic subdural hematoma (CSDH) is a common condition in elderly people. The recurrence rate of CSDH has been reported to range from 2.3 to 33% (1). Previous studies have reported many risk factors for CSDH recurrence, including brain atrophy, underexpansion, coagulopathy or anticoagulant use, male sex, hypertension, diabetes, bilateral CSDH, large preoperative hematoma volume, septations, mixed density of hematoma on brain computed tomography (CT) scans, iso- or hypointensity on T1-weighted magnetic resonance images, preoperative midline shift, persistence of a mass effect after burr hole trephination, large postoperative residual hematoma, and postoperative pneumocephalus (2, 3).

To our knowledge, no study has investigated the association between skull Hounsfield unit (HU) values calculated from CT scans and recurrence in patients who have undergone burr hole trephination for CSDH. It is well-accepted that CSDH is caused by the tearing of bridging veins with subsequent bleeding (4). We initiated this study based on the premise that bridging veins are composed of abundant collagen bundles and smooth muscle cells, which are composed of type 1 collagen as well as bone matrix (5, 6). Therefore, we hypothesized that a low bone mineral density (BMD) would negatively influence the integrity of bridging veins and bone. We conjectured that this mechanism may be associated with the recurrence of CSDH after the initial burr hole surgery. We previously reported the significant correlation between skull HU values and BMD (7). Therefore, to assess this hypothesis, frontal skull HU values were measured on brain CT scans of all study patients. Further, we examined the relationship between skull HU values and CSDH recurrence.

MATERIALS AND METHODS

Study Patients

Using the database of the Traumatic Brain Injury Registry of our hospital, we retrospectively investigated all consecutive patients who were diagnosed with CSDH and underwent burr hole surgery from January 1, 2012, to December 31, 2018. We excluded patients (i) with iatrogenic error or surgical complication, (ii) with no initial brain CT scan or with missing data, and (iii) with no measurable intercortical spongy bone in the frontal skull on brain CT. Recurrence was defined as the (i) presence of newly developed CSDH in the ipsilateral subdural space of the initial burr hole surgery on follow-up brain CT scan, (ii) development of neurologic deficits, and (iii) requirement for reoperation.

This study was approved by the Institutional Review Board of Hanyang University Guri Hospital, Korea, and performed in accordance with the tenets of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived. All individual records were anonymized before the analysis.

Surgical Procedures and Management

One- or two-burr hole craniostomy was performed in a standardized manner with or without saline irrigation under general anesthesia. All patients with bilateral CSDH underwent burr hole craniostomy of both sides simultaneously in a single operation. A closed-system drainage was inserted in all patients, and the drain was placed ∼30–50 cm below the patient's head level. The drain was removed within 3 days in most cases. According to our policy and protocol, preoperative dexamethasone was not used in any case. Reoperation was performed with the same procedure in patients with recurrence. Antiplatelet or anticoagulant agents were discontinued before surgery and usually restarted after 1 month from the day of surgery. We usually performed follow-up CT examinations immediately and 1 week after surgery. Patients showing no complications were generally discharged within 10 days.

Abbreviations: CSDH, chronic subdural hematoma; HU, Hounsfield unit; BMD, bone mineral density; PACS, picture archiving and communication system; HR, hazard ratio; CI, confidence interval; AUC, area under the curve.

Clinical and Radiographic Variables

We investigated the factors possibly associated with recurrence in patients with CSDH after burr hole surgery. The demographics, clinical information, and operative information of the enrolled patients were investigated by two trained research members using electronic medical records. Clinical data including sex, age, side of operation, reoperation, hypertension, diabetes, chronic kidney disease, alcohol intake, and history of antithrombotic agent use were collected from medical and operative records.

We analyzed the initial CT scans of all study patients. All radiologic findings were confirmed by two faculty neurosurgeons (I-SB and BH) blinded to the clinical data using the picture archiving and communication system (PACS). Radiographic variables, including the types of the internal architecture of the hematoma, midline shift, and hematoma volume, were evaluated using the initial preoperative CT scans. The internal architecture of the hematoma was classified into four types: homogeneous, laminar, separate, and trabecular (1). The laminar, separate, and trabecular types were also categorized into a heterogeneous group for the analysis. We calculated the hematoma volume using the ABC/2 technique (A = length [in centimeters] between each corner of the subdural crescent, B = width as the maximum thickness [in centimeters] of the hematoma from the inner table of the skull perpendicular to the length, C = depth multiplying the number of slices on which the hematoma was visible by the slice thickness listed on the CT scan) (8). The method and reliability of the ABC/2 technique for subdural hematoma measurement on brain CT scans have been described elsewhere (9).

Measurement of Frontal Skull HU

All CT scans (4.0- to 5.0-mm slice thicknesses) were obtained with CT scanners (Siemens Flash 64, München, Germany) at our hospital. Birnbaum BA et al. described that the variations in HU values are very small (range of 0–20 HU) between five CT scanners, including Siemens (10). The detailed methods for measuring HU values at each of four lines on the frontal skull were previously described precisely (**Figure 1**) (7). The maximum, minimum, and mean HU values were automatically calculated by the PACS based on the values corresponding to the drawn lines, and the mean HU values were recorded for the study. To reduce measurement errors, all brain CT scans were magnified for HU measurement. The frontal skull HU was measured by a faculty neurosurgeon (I-SB) blinded to the clinical data in all study patients.

Statistical Methods

We expressed continuous variables as means ± standard deviations or medians with interquartile ranges. Discrete variables are expressed as counts and percentages. The chi-square test and Student's *t*-test were used to identify differences between the non-recurrence and recurrence groups. The mean frontal

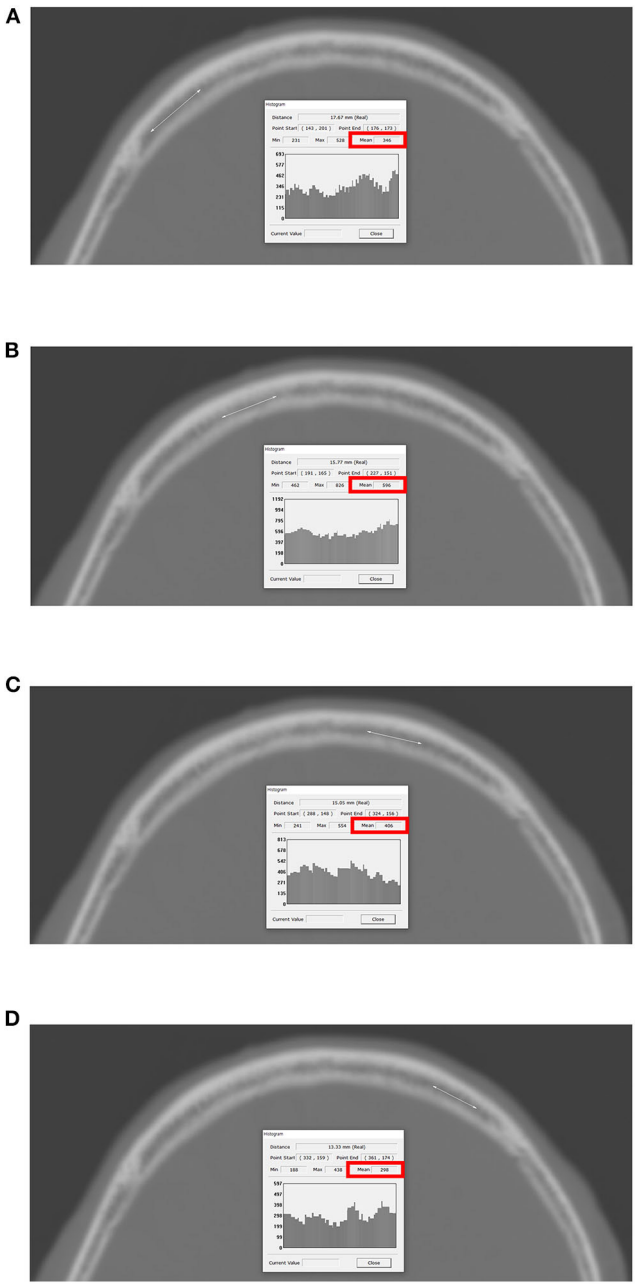

FIGURE 1 | Measurement of HU values at each of four lines on the frontal bone. The PACS automatically calculates the maximum, minimum, and mean HU values according to the values on the drawn lines, and the mean HU value on each of the four lines was recorded. **(A)** Right lateral; **(B)** right medial; **(C)** left medial; **(D)** left lateral. HU, Hounsfield unit; PACS, picture archiving and communication system.

skull HU values used in all analyses were calculated as follows: (mean right lateral HU + mean right medial HU + mean left medial HU + mean left lateral HU)/4.

Box plots were used to show the association among the midline shift, mean frontal skull HU values, and recurrence. Receiver operating characteristic curve analysis was performed to identify whether the midline shift and frontal skull HU can predict recurrence after burr hole surgery for CSDH.

The cumulative hazard for recurrence was evaluated using the Kaplan–Meier method classified based on several predictive factors, with censoring of patients who exhibited no recurrence or recurrence-related symptoms on the last follow-up CT scan or visit during the follow-up period. According to previous studies, we set the end point of the current study at 1 year (365 days) from the first burr hole surgery for CSDH (11, 12). The time interval to recurrence was defined as the number of days between the first burr hole trephination and the recurrence of CSDH requiring reoperation based on brain CT scans. We then calculated hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox regression analyses. These values were used to identify independent predictive factors associated with recurrence after burr hole surgery in patients with CSDH. Values of $p < 0.05$ were considered statistically significant.

All statistical analyses were performed using R version 3.5.2 (https://www.r-project.org/).

RESULTS

Characteristics of the Study Patients

A total of 208 consecutive patients (>18 years old) who underwent burr hole trephination for CSDH over a 7-years period at our hospital were finally enrolled in the study. In total, 19 patients (9.1%) were reoperated for recurrence of CSDH within 1 year from the initial burr hole surgery for CSDH. The mean patient age was 69.9 years, and 63.9% of the patients were men. A total of 26 patients (12.5%) underwent bilateral burr hole trephinations. The mean preoperative midline shift was 10.2 mm, and the mean hematoma volume was 120.5 cm^3. Further descriptive data are shown in **Table 1**.

Skull HU Values According to CSDH Recurrence

Table 2 shows the significant differences in the mean frontal skull HU values according to CSDH recurrence. The overall average mean frontal skull HU value was 763.7 in all study patients and was 772.3 in the non-recurrence group and 677.4 in the recurrence group.

Association Between Preoperative Midline Shift and Skull HU and CSDH Recurrence

Boxplot analysis revealed a significantly higher preoperative midline shift and lower mean frontal skull HU values in the recurrence group than in the non-recurrence group (**Figures 2A,C**). In receiver operating characteristic curve analysis, we identified the preoperative midline shift (area under the curve = 0.676, $p = 0.012$) and mean frontal skull HU (area under the curve = 0.683, $p = 0.009$) as predictive values for CSDH recurrence (**Figures 2B,D**).

Cumulative Hazard of CSDH Recurrence According to Predictive Factors

Figure 3A shows the overall cumulative hazard of CSDH recurrence within 1 year from the initial burr hole trephination

TABLE 1 | Characteristics of patients with chronic subdural hematoma at our hospital.

Characteristics	Non-recurrence	Recurrence	Total	*p*
Number (%)	189 (90.9)	19 (9.1)	208 (100)	
Sex, male, *n* (%)	121 (64.0)	12 (63.2)	133 (63.9)	0.940
Age, mean ± *SD*, years	69.6 ± 12.4	73.2 ± 9.4	69.9 ± 12.2	0.221
Age group, *n* (%)				
≥ 65 years	125 (66.1)	16 (84.2)	141 (67.8)	0.108
Side of operation, *n* (%)				0.585
Right	69 (36.5)	7 (36.8)	76 (36.5)	
Left	95 (50.3)	11 (57.9)	106 (51.0)	
Bilateral	25 (13.2)	1 (5.3)	26 (12.5)	
Internal architecture of the hematoma, *n* (%)				0.221
Homogeneous	66 (34.9)	6 (31.6)	72 (34.6)	
Laminar	26 (13.8)	0 (0)	26 (12.5)	
Separate	56 (29.6)	6 (31.6)	62 (29.8)	
Trabecular	41 (21.7)	7 (36.8)	48 (23.1)	
Preoperative midline shift, mean ± *SD*, mm	10.0 ± 3.8	12.0 ± 3.0	10.2 ± 3.8	0.024
Preoperative midline shift, median (IQR), mm	10.2 (7.1–12.8)	11.5 (10.8–13.9)	10.5 (7.4–12.8)	0.024
Preoperative hematoma volume, mean ± *SD*, cm^3	120.4 ± 47.4	121.3 ± 42.9	120.5 ± 47.0	0.933
Preoperative hematoma volume, median (IQR), cm^3	113.4 (87.6–144.8)	118.7 (92.2–139.9)	113.7 (88.0–144.2)	0.933
Past medical history, *n* (%)				
Hypertension	100 (52.9)	11 (57.9)	111 (53.4)	0.678
Diabetes	43 (22.8)	8 (42.1)	51 (24.5)	0.062
Chronic kidney disease	6 (3.2)	1 (5.3)	7 (3.4)	0.630
Alcohol	73 (38.6)	7 (36.8)	80 (38.5)	0.879
Antithrombotic				0.145
Antiplatelet	52 (27.5)	10 (52.6)	62 (29.8)	
Anticoagulant	3 (1.6)	0 (0)	3 (1.4)	
Both	1 (0.5)	0 (0)	1 (0.5)	

SD, standard deviation; IQR, interquartile range.

TABLE 2 | Descriptive statistics of mean frontal skull HU values according to recurrence in patients with chronic subdural hematoma.

Characteristics	Non-recurrence	Recurrence	Total	*p*
Overall mean frontal skull HU value, median (IQR)	780.5 (667.8–891.3)	723.8 (574.8–768.5)	769.5 (660.9–888.4)	0.009
Overall mean frontal skull HU value, mean ± *SD*	772.3 ± 149.0	677.4 ± 155.4	763.7 ± 151.7	0.009
Mean HU value at each of four sites in the frontal skull, mean ± *SD*				
Right lateral	733.7 ± 148.9	642.6 ± 135.8	725.4 ± 149.8	0.011
Right medial	807.0 ± 172.0	710.7 ± 175.5	798.2 ± 174.1	0.021
Left medial	806.4 ± 147.5	691.3 ± 160.3	795.9 ± 152.0	0.002
Left lateral	742.2 ± 161.1	665.1 ± 164.4	735.2 ± 162.5	0.048
Average, medial	806.7 ± 156.0	701.0 ± 165.4	797.0 ± 159.4	0.006
Average, lateral	738.0 ± 148.9	653.8 ± 149.3	730.3 ± 150.5	0.020

HU, Hounsfield unit; IQR, interquartile range; SD, standard deviation.

for CSDH. We found that patients in the upper median for preoperative midline shift (≥10.5 mm), those in the lower median for skull HU (<769.5), and those with diabetes showed significantly higher recurrence rates of CSDH (**Figures 3B–D**).

Independent Predictive Factors for CSDH Recurrence

Multivariate Cox regression analysis identified age, greater midline shift (≥10.5 mm), lower skull HU (<769.5), and

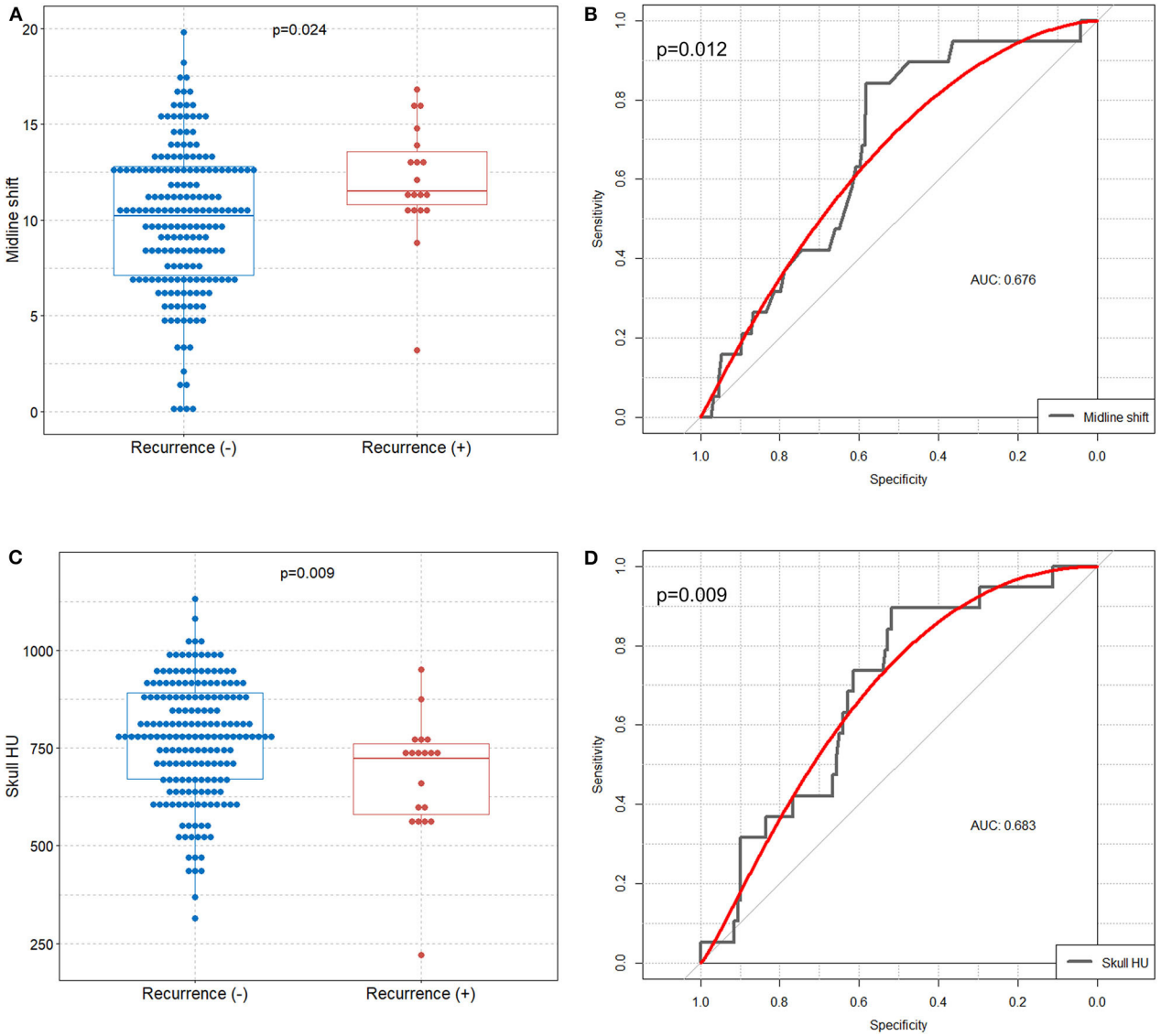

FIGURE 2 | Comparison of preoperative midline shift and mean frontal skull HU values between the recurrence and non-recurrence groups, and identification of the preoperative midline shift and skull HU values for predicting CSDH recurrence. Boxplots with dot plots of **(A)** preoperative midline shift and **(C)** mean frontal skull HU values according to recurrence. Receiver operating characteristic curves to identify the **(B)** preoperative midline shift and **(D)** mean frontal skull HU values for predicting recurrence. HU, Hounsfield unit; CSDH, chronic subdural hematoma; AUC, area under the curve.

diabetes as independent predictors for CSDH recurrence (HR 1.06, 95% CI 1.00–1.12, $p = 0.042$; HR 5.37, 95% CI 1.48–19.46, $p = 0.010$; HR 6.71, 95% CI 1.84–24.45, $p = 0.004$; and HR 3.30, 95% CI 1.05–10.43, $p = 0.042$, respectively) (**Table 3**). Although the study patients showed a relatively narrow age range (most patients were elderly, mean age = 69.9 years), age was negatively associated with BMD. Therefore, we performed multivariate Cox regression with adjustment for age as a continuous variable. In addition, we observed no significant correlation between age and skull HU values in the study patients ($B = 0.678$, $p = 0.434$) (**Supplementary Figure**).

DISCUSSION

We found that the group with a possible lower BMD had an ~6.7-fold higher risk of CSDH recurrence than the possible higher BMD group after adjusting for other predictive factors including age. In addition, older age, greater preoperative midline shift, and diabetes were independent predictors for CSDH recurrence. To our knowledge, this study is the first to suggest a possible relationship between possible lower BMD and recurrence of CSDH.

Previous studies have demonstrated that specific regional cancellous bone HU values from CT scans show a strong

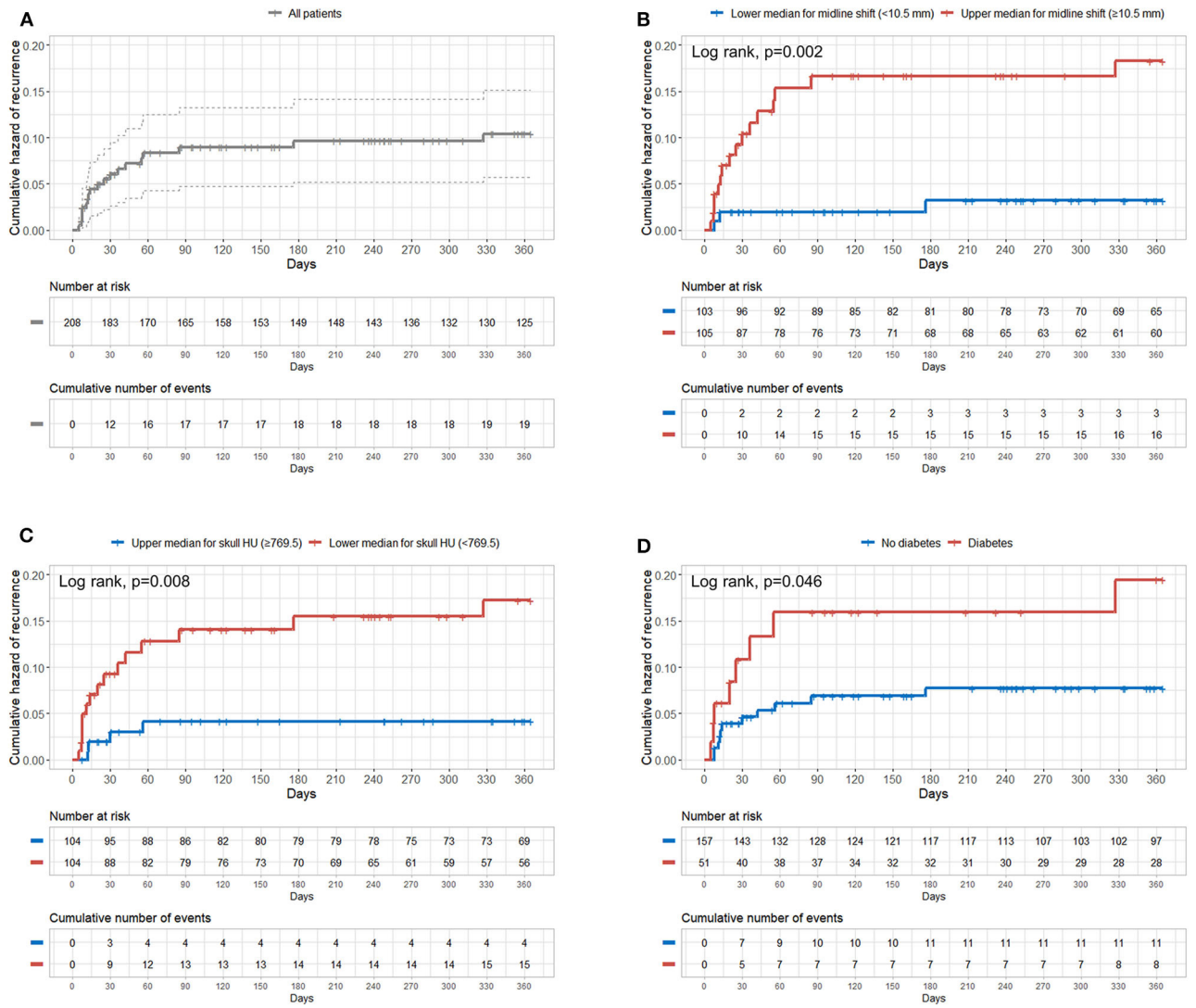

FIGURE 3 | Cumulative hazard of recurrence according to preoperative midline shift, mean frontal skull HU values, and diabetes. **(A)** Overall; **(B)** median of the preoperative midline shift (10.5 mm); **(C)** median of mean frontal skull HU values (769.5); **(D)** diabetes. HU, Hounsfield unit.

correlation with the T-score and may be useful for predicting osteoporotic conditions (13–15). We previously showed a strong correlation between the T-score and frontal skull HU values (7, 16). Because osteoporosis is a systemic disease and is strongly related to genetic components of type 1 collagen (*COL1A1* and *COL1A2),* we propose that osteoporotic conditions may influence cancellous bone of the skull (17).

It is well-known that type 1 collagen is a major bone component. A previous study reported that the bridging vein wall is composed of collagen bundles, with a volume fraction of ∼61% (6). In addition, smooth muscle cells are also associated with cortical bridging veins (5, 18). The smooth muscle cell is also composed of collagen type 1 (19). Therefore, on the basis of the above findings and assumptions, we postulated that an osteoporotic condition, which shows a strong genetic association, leading to systemic disease may also negatively influence the integrity of the bridging veins as well as bone because both bone and bridging veins are associated with type 1 collagen tissues. Weaker bridging veins may be more vulnerable to rupture, and this may naturally lead to a higher chance of recurrence of CSDH. Therefore, we believe that recurrence rate of CSDH may be higher in patients with osteoporotic conditions. In addition, we recently showed an association between osteoporosis and cerebral atrophy (20). Preexisting cerebral atrophy is associated with alteration of brain elasticity and causes cerebral under-expansion after burr hole surgery for CSDH (21, 22). Moreover, this may lead to a persistent cavity in the subdural space and subsequently cause CSDH recurrence (2).

In the present study, patient age, greater preoperative midline shift, and diabetes were also predictors of recurrence. Cerebral atrophy occurs during the normal aging process. Therefore, older patients tend to experience a recurrence of CSDH because

TABLE 3 | Univariate and multivariate Cox regression analyses of the association between recurrence and various variables in patients with chronic subdural hematoma.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex				
Male	Reference		Reference	
Female	1.07 (0.42–2.71)	0.890	2.06 (0.70–6.03)	0.188
Age (per 1-year increase)	1.03 (0.99–1.07)	0.167	1.06 (1.00–1.12)	0.042
Internal Architecture of the Hematoma				
Homogeneous	Reference		Reference	
Heterogeneous	1.23 (0.47–3.24)	0.675	0.62 (0.22–1.75)	0.364
Midline Shift				
Lower median (<10.5 mm)	Reference		Reference	
Upper median (≥10.5 mm)	5.74 (1.68–19.79)	0.005	5.37 (1.48–19.46)	0.010
Mean Frontal Skull HU				
Lower median (<769.5)	4.00 (1.33–12.07)	0.014	6.71 (1.84–24.45)	0.004
Upper median (≥769.5)	Reference		Reference	
Initial hematoma volume (per 1 cm^3 increase)	1.00 (0.99–1.01)	0.943	1.01 (0.99–1.02)	0.404
Side of Operation				
Unilateral	2.79 (0.37–20.88)	0.319	7.71 (0.54–109.84)	0.132
Bilateral	Reference		Reference	
Past Medical History				
Hypertension	1.20 (0.48–2.98)	0.697	0.44 (0.13–1.45)	0.175
Diabetes	2.45 (0.99–6.10)	0.054	3.30 (1.05–10.43)	0.042
Chronic kidney disease	1.88 (0.25–14.11)	0.538	4.41 (0.40–48.42)	0.225
Alcohol	0.87 (0.34–2.20)	0.760	2.44 (0.73–8.14)	0.147
Antithrombotic	2.40 (0.98–5.90)	0.057	2.39 (0.78–7.31)	0.127

HR, hazard ratio; CI, confidence interval; HU, Hounsfield unit.

of the persistent space between the subdural and arachnoid layers resulting from cerebral atrophy (23). The preoperative and postoperative midline shift values have already been considered as predictive factors for CSDH recurrence (3, 22, 24, 25). The sudden decrease in intracranial pressure after trephination may lead to a rapid expansion of the brain parenchyma, which consequently induces stress on the surrounding vessels and a higher risk of acute rebleeding (24). Several previous studies have reported that diabetes is associated with the recurrence of CSDH (22, 26). Exudation due to capillary vasculopathy caused by diabetes or well-developed neovascularization of the neomembrane in diabetes patients may play an important role in the recurrence of CSDH (27). It has also been reported that type 2 diabetes is associated with an increased risk of brain atrophy (28, 29). The cerebral atrophy induced by type 2 diabetes is naturally thought to be associated with the recurrence of CSDH as described above. The association between antithrombotic use and the recurrence of CSDH was slightly short of being significant in this study; however, a previous meta-analysis reported that antithrombotic drugs increased the risk of CSDH recurrence (30). Use of antithrombotic drugs may raise the possibility of micro-bleeding, and this may accelerate the growth of hematoma and recurrence of CSDH.

This study had several limitations. First, our study had a retrospective and single-center design. Our findings may be less accurate than those from a planned prospective study, which limits the generalizability of our results. Second, HU measurement errors may have occurred. However, we magnified all brain CT scans for HU measurement and initially excluded patients with no measurable cancellous bone of the frontal skull on brain CT, as described in the Methods. Third, skull HU is not the actual T-score. The actual T-score was not available because patients with CSDH usually do not undergo BMD testing. However, we have previously shown that the skull HU values have relatively high specificity and sensitivity in predicting the actual T-score (7).

In conclusion, our study suggests the existence of a relationship between possible low BMD and recurrence of CSDH. In addition, our results revealed that age, greater preoperative midline shift, and diabetes are also predictors for recurrence. Our findings may be useful for predicting recurrence in the clinical course of CSDH. Further, we expect that our findings may help enhance the understanding of the underlying mechanism of the association between CSDH and BMD in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Hanyang University Guri Hospital, Korea. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

M-HH: conception, design of the study, analysis of data, and visualization. BH and I-SB: acquisition of data. BH and M-HH: manuscript writing. JK, JC, and JR: study supervision, reexamination, and revision of the paper. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.538257/full#supplementary-material

REFERENCES

1. Ohba S, Kinoshita Y, Nakagawa T, Murakami H. The risk factors for recurrence of chronic subdural hematoma. *Neurosurg Rev.* (2013) 36:145–9. doi: 10.1007/s10143-012-0396-z
2. Jang KM, Choi HH, Mun HY, Nam TK, Park YS, Kwon JT. Critical depressed brain volume influences the recurrence of chronic subdural hematoma after surgical evacuation. *Sci Rep.* (2020) 10:1145. doi: 10.1038/s41598-020-58250-w
3. Motiei-Langroudi R, Stippler M, Shi S, Adeeb N, Gupta R, Griessenauer CJ, et al. Factors predicting reoperation of chronic subdural hematoma following primary surgical evacuation. *J Neurosurg.* (2017) 129:1143–50. doi: 10.3171/2017.6.JNS17130
4. Lee K-S. Chronic subdural hematoma in the aged, trauma or degeneration? *J Korean Neurosurg Soc.* (2016) 59:1–5. doi: 10.3340/jkns.2016.59.1.1
5. Vignes J-R, Dagain A, Guérin J, Liguoro D. A hypothesis of cerebral venous system regulation based on a study of the junction between the cortical bridging veins and the superior sagittal sinus. laboratory investigation. *J Neurosurg.* (2007) 107:1205–10. doi: 10.3171/JNS-07/12/1205
6. Nierenberger M, Wolfram-Gabel R, Decock-Catrin S, Boehm N, Rémond Y, Kahn J-L, et al. Investigation of the human bridging veins structure using optical microscopy. *Surg Radiol Anat.* (2013) 35:331–7. doi: 10.1007/s00276-012-1035-7
7. Han M-H, Won YD, Na MK, Kim CH, Kim JM, Ryu JI, et al. Association between possible osteoporosis and shunt-dependent hydrocephalus after subarachnoid hemorrhage. *Stroke.* (2018) 49:1850–8. doi: 10.1161/STROKEAHA.118.021063
8. Gebel James M, Sila Cathy A, Sloan Michael A, Granger Christopher B, Weisenberger Joseph P, Green Cindy L, et al. Comparison of the ABC/2 estimation technique to computer-assisted volumetric analysis of intraparenchymal and subdural hematomas complicating the GUSTO-1 trial. *Stroke.* (1998) 29:1799–801. doi: 10.1161/01.STR.29.9.1799
9. Won S-Y, Zagorcic A, Dubinski D, Quick-Weller J, Herrmann E, Seifert V, et al. Excellent accuracy of ABC/2 volume formula compared to computer-assisted volumetric analysis of subdural hematomas. *PLoS ONE.* (2018) 13:e0199809. doi: 10.1371/journal.pone.0199809
10. Birnbaum BA, Hindman N, Lee J, Babb JS. Multi-detector row CT attenuation measurements: assessment of intra- and interscanner variability with an anthropomorphic body CT phantom. *Radiology.* (2007) 242:109–19. doi: 10.1148/radiol.2421052066
11. Berhouma M, Krolak-Salmon P. *Brain and Spine Surgery in the Elderly*. Cham: Springer (2017). doi: 10.1007/978-3-319-40232-1
12. Abdelfatah MAR. Recurrence rate of chronic subdural hematoma after evacuating it by two large burr holes, irrigation, and subgaleal low-pressure suction drainage. *Asian J Neurosurg.* (2019) 14:725–9. doi: 10.4103/ajns.AJNS_321_17
13. Choi MK, Kim SM, Lim JK. Diagnostic efficacy of Hounsfield units in spine CT for the assessment of real bone mineral density of degenerative spine: correlation study between T-scores determined by DEXA scan and Hounsfield units from CT. *Acta Neurochir.* (2016) 158:1421–7. doi: 10.1007/s00701-016-2821-5
14. Schreiber JJ, Anderson PA, Rosas HG, Buchholz AL, Au AG. Hounsfield units for assessing bone mineral density and strength: a tool for osteoporosis management. *J Bone Joint Surg Am.* (2011) 93:1057–63. doi: 10.2106/JBJS.J.00160
15. Pickhardt PJ, Pooler BD, Lauder T, del Rio AM, Bruce RJ, Binkley N. Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. *Ann Intern Med.* (2013) 158:588–95. doi: 10.7326/0003-4819-158-8-201304160-00003
16. Na MK, Won YD, Kim CH, Kim JM, Cheong JH, Ryu JI, et al. Opportunistic osteoporosis screening via the measurement of frontal skull hounsfield units derived from brain computed tomography images. *PLoS ONE.* (2018) 13:e0197336. doi: 10.1371/journal.pone.0197336
17. Grant SF, Reid DM, Blake G, Herd R, Fogelman I, Ralston SH. Reduced bone density and osteoporosis associated with a polymorphic Sp1 binding site in the collagen type I alpha 1 gene. *Nat Genet.* (1996) 14:203–5. doi: 10.1038/ng1096-203
18. Yamashima T, Friede RL. Why do bridging veins rupture into the virtual subdural space? *J Neurol Neurosurg Psychiatry.* (1984) 47:121–7. doi: 10.1136/jnnp.47.2.121
19. Ponticos M, Partridge T, Black CM, Abraham DJ, Bou-Gharios G. Regulation of collagen type I in vascular smooth muscle cells by competition between Nkx2.5 and δEF1/ZEB1. *Mol Cell Biol.* (2004) 24:6151–61. doi: 10.1128/MCB.24.14.6151-6161.2004
20. Bae I-S, Kim JM, Cheong JH, Ryu JI, Han M-H. Association between bone mineral density and brain parenchymal atrophy and ventricular enlargement in healthy individuals. *Aging.* (2019) 11:8217–38. doi: 10.18632/aging.102316
21. Sack I, Streitberger K-J, Krefting D, Paul F, Braun J. The influence of physiological aging and atrophy on brain viscoelastic properties in humans. *PLoS ONE.* (2011) 6:e23451. doi: 10.1371/journal.pone.0023451
22. Chon K-H, Lee J-M, Koh E-J, Choi H-Y. Independent predictors for recurrence of chronic subdural hematoma. *Acta Neurochir.* (2012) 154:1541–8. doi: 10.1007/s00701-012-1399-9
23. Motoie R, Karashima S, Otsuji R, Ren N, Nagaoka S, Maeda K, et al. Recurrence in 787 patients with chronic subdural hematoma: retrospective

cohort investigation of associated factors including direct oral anticoagulant use. *World Neurosurg.* (2018) 118:e87–e91. doi: 10.1016/j.wneu.2018.06.124
24. Schwarz F, Loos F, Dünisch P, Sakr Y, Safatli DA, Kalff R, et al. Risk factors for reoperation after initial burr hole trephination in chronic subdural hematomas. *Clin Neurol Neurosurg.* (2015) 138:66–71. doi: 10.1016/j.clineuro.2015.08.002
25. Stanisic M, Lund-Johansen M, Mahesparan R. Treatment of chronic subdural hematoma by burr-hole craniostomy in adults: influence of some factors on postoperative recurrence. *Acta Neurochir.* (2005) 147:1249–56. doi: 10.1007/s00701-005-0616-1
26. Pang CH, Lee SE, Kim CH, Kim JE, Kang H-S, Park C-K, et al. Acute intracranial bleeding and recurrence after bur hole craniostomy for chronic subdural hematoma. *J Neurosurg.* (2015) 123:65–74. doi: 10.3171/2014.12.JNS141189
27. Kim SU, Lee DH, Kim YI, Yang SH, Sung JH, Cho CB. Predictive factors for recurrence after burr-hole craniostomy of chronic subdural hematoma. *J Korean Neurosurg Soc.* (2017) 60:701–9. doi: 10.3340/jkns.2016.1010.003
28. Roberts RO, Knopman DS, Przybelski SA, Mielke MM, Kantarci K, Preboske GM, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology.* (2014) 82:1132–41. doi: 10.1212/WNL.0000000000000269
29. Moran C, Beare R, Wang W, Callisaya M, Srikanth V. Alzheimer's Disease Neuroimaging Initiative (ADNI). type 2 diabetes mellitus, brain atrophy, and cognitive decline. *Neurology*. (2019) 92:e823–30. doi: 10.1212/WNL.0000000000006955
30. Wang H, Zhang M, Zheng H, Xia X, Luo K, Guo F, et al. The effects of antithrombotic drugs on the recurrence and mortality in patients with chronic subdural hematoma: a meta-analysis. *Medicine.* (2019) 98:e13972. doi: 10.1097/MD.0000000000013972

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PERSPECTIVE
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Low-Dose Acetylsalicylic Acid in Chronic Subdural Hematomas: A Neurosurgeon's Sword of Damocles

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Background: The possible influence of different antithrombotic drugs on outcome after neurosurgical treatment of chronic subdural hematoma (CSDH) is still unclear. Nowadays, no randomized clinical trials are available. A metanalysis including 24 studies for a total of 1,812 pooled patients concluded that antiplatelets and anticoagulations present higher risk of recurrences. On the other hand, several studies highlighted that antithrombotic suspension, timing of surgery, and resumption of these drugs are still debated, and patients taking these present higher risk of thromboembolic events with no excess risk of bleed recurrences or worse functional outcome. Our assumption is that the real hemorrhagic risk related to antithrombotic drug continuation in CSDH may be overrated and the thromboembolic risk for discontinuation underestimated, especially in patients with high cardiovascular risk.

Methods: A comprehensive literature review with the search terms "acetylsalicylic acid" and "chronic subdural hematoma" was performed. Clinical status, treatment, time of drug discontinuation, complications (in particular, rebleeding or thromboembolic events), and clinical and radiological outcome at follow-up were evaluated.

Results: Five retrospective studies were selected for the review, three of them reporting specifically low-dose acetylsalicylic intake and two of them general antithrombotic drugs for a total of 1,226 patients. Only two papers reported the thromboembolic rate after surgery; in one paper, it is not even divided from other cardiac complications.

Conclusion: The literature review does not clarify the best management of low-dose acetylsalicylic in CSDH patients, in particular, concerning the balance between thromboembolic event rates and rebleeding risks. We do believe that CSDH precipitates the worsening of comorbidities with a resulting increased mortality. Further studies clearly evaluating the thromboembolic events are strongly needed to clarify this topic.

In this perspective paper, we discuss the difficult choice of low-dose acetylsalicylic acid (LDAA) management in patients suffering from chronic subdural hematoma (CSDH). The balance between hemorrhagic and thromboembolic risks often represents a sword of Damocles for neurosurgeons, especially when dealing with patients with high cardiovascular risk. No guidelines are currently available, and a survey by Kamenova et al.

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showed that most neurosurgeons discontinue LDAA treatment for at least 7 days in the perioperative period of surgical evacuation of CSDH, even though recent studies show that early LDAA resumption might be safe. Thrombosis prophylaxis is administered by only 60%, even though patients with CSDH are at high risk of developing thromboembolic complications. We would like to bring attention to this controversial issue.

Keywords: chronic subdural hematoma, low-dose acetylsalicylic acid, aspirin, antithrombotic drugs, cardiovascular risk, hemorrhagic risk, thromboembolic risk

INTRODUCTION

The possible influence of different antithrombotic strategies on outcomes and recurrences after neurosurgical treatment of chronic subdural hematoma (CSDH) as well as resumption time of such drugs are unclear.

A new ACC/AHA guideline on the primary prevention of cardiovascular disease has recently been published (1).

While aspirin is well-established for secondary prevention of atherosclerotic cardiovascular disease (ASCVD), it should not be used in routine primary prevention due to lack of net benefit. Indeed, for decades, low-dose aspirin has been widely administered for ASCVD prevention increasing the risk of bleeding (1).

Neurosurgeons often face a difficult choice in the management of antithrombotic drugs in patients suffering from CSDHs, in terms of suspension and resumption, trying to balance the risk of hemorrhage vs. thromboembolic events (2).

Phan et al. in 2018 reported that the rate of thromboembolism was statistically lower in patients who resumed antithrombotic drugs after surgical evacuation of CSDH (2.9 vs. 6.8%, $P < 0.001$) (3). However, this paper (as reported by the authors themselves) presents several biases, including inherent patient bias in medication restrictions, selection bias in the directives from different clinicians, and attrition bias in age- and age-related comorbidities of the patients. Furthermore, other confounding factors that could affect the results are the original reason for antithrombotic treatment, the resumption time of antithrombotic agents postoperatively, and preexisting medication regimes, which were not reported in the studies included and, as such, could not be analyzed.

In this complex scenario, the individual risk of thromboembolic events and, most importantly, the kind of antithrombotic drug used needs to be seriously considered (2).

The same analysis should be performed when choosing between antiplatelet and anticoagulant drugs. As a result, an intriguing observation emerged: the disturbance in platelet function (caused almost exclusively by LDAA) correlated with improved neurological outcome at discharge. This could be influenced by the antiphlogistic properties of LDAA as well, as described by Szczygielski et al. (4), even though its effect is correlated with a higher risk to develop chronic subdural hematoma (5).

We, therefore, decided to conduct a narrative review of the literature to analyze the real influence of LDAA on outcomes after neurosurgical treatment of CSDH.

METHODS

A comprehensive review of the current literature regarding "low-dose acetylsalicylic acid" and "chronic subdural hematoma" was performed.

Using PubMed MeSH database (last search was launched in March 2020), all English papers published between the years 2000 and 2020, including the words "acetylsalicylic acid" and "chronic subdural hematoma," were reviewed.

All papers including human participants such as randomized clinical trial, prospective or retrospective studies, as well as case reports were included, whereas articles not involving human subjects were excluded. Other reviews, editorials, and commentaries were excluded as well. Each article was scrutinized in order to select those reporting a detailed description of antiplatelet drug management, drug discontinuation, surgical vs. conservative treatment, complication rate, and a detailed clinical and radiological follow-up.

Papers reporting generic antithrombotic agents without a clear distinction between antiplatelet and anticoagulant medications were not included in the review.

RESULTS

From the first literature search, we retrieved 47 articles. After duplicate removal and title/abstract screening for matching inclusion/exclusion criteria, 40 papers were assessed for eligibility (**Figure 1**). Two papers were further excluded for the following reasons: unclear outcomes and non-elderly population.

The search strategy is reported in **Figure 1**.

Following the aforementioned criteria, five retrospective studies were finally selected for the review. Three studies were specifically on LDAA, while two studies reported on general antiplatelet drugs for a total amount of 1,226 patients (**Table 1**).

LDAA Group

Four hundred thirty-nine patients were collected in this group. Four hundred seven (92.7%) patients discontinued LDAA on admission while 32 patients (7.3%) at least 5 days before surgery due to minor symptom presentation (6–8).

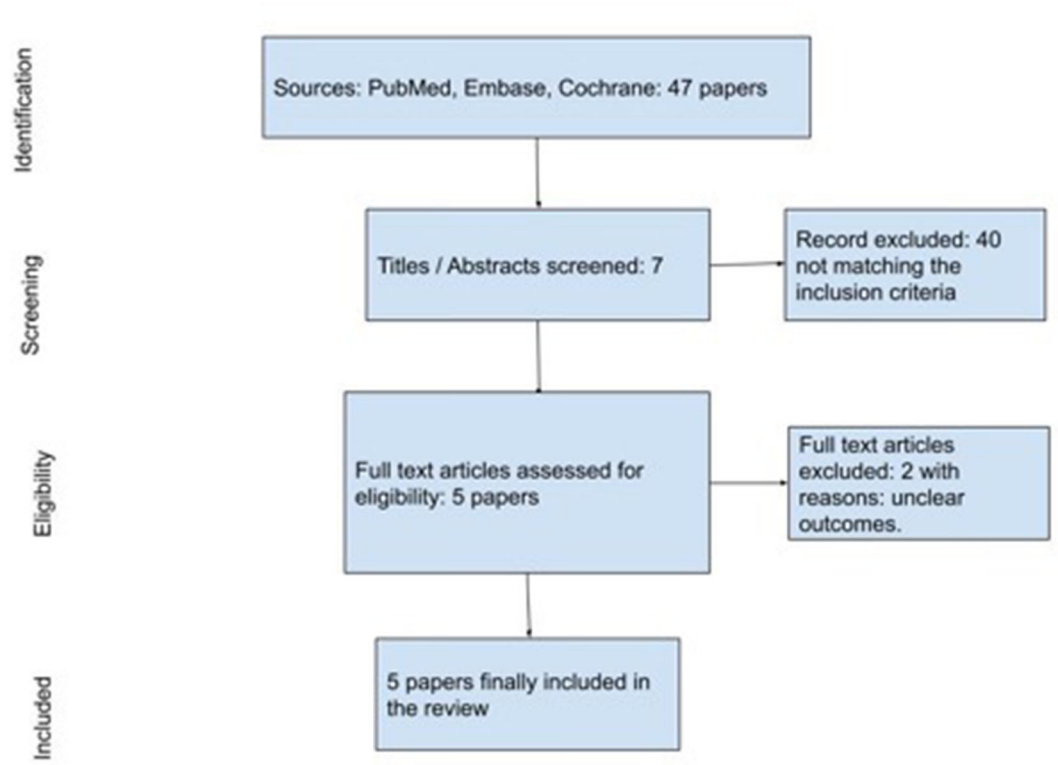

FIGURE 1 | Search strategy.

Only Kamenova et al. reported an LDAA resumption at 1, 7, 14, 21, 28, 35, and 42 days without further information. In 32 patients, the indication for LDAA treatment was not confirmed postoperatively, and the treatment was stopped (6).

All 439 patients underwent surgery: 236 patients (Scerrati et al. and Kamenova et al.) were operated before 5 days from LDAA discontinuation while 68 patients after 5 days (6, 7).

There were no cases of early recurrence (<1 week); Kamenova et al. and Poon et al. reported 28 cases of late recurrence of chronic subdural hematoma and 13 thromboembolic events after surgery. In Kamenova et al., 10 cardiovascular events comprised four myocardial infarction, one occlusion of femoral artery, three pulmonary embolisms, and two cardiac arrhythmia/decompensation, while in Poon et al., the severity of the thromboembolic events was not analyzed (6, 8).

Twenty-one patients died after surgery. Only Kamenova et al. reported the causes of death in five patients: two intraparenchymal hemorrhage after surgery, one subdural empyema, one pulmonary embolism, and one shock due to cardiopulmonary decompensation (6).

General Antiplatelet Drug Group

General antiplatelet drugs evaluated in the abovementioned studies includes LDAA, clopidogrel, and dipyridamole (9, 10).

A total of 797 patients were included, and antiplatelet drug (AD) was discontinued on admission in 539 patients. Fornebo et al. reported that among their 308 patients, 183 were taking specifically LDAA (9).

AD therapy was resumed after >1 week in 220 patients, and after >1 month, 6 in 202 patients were lost at follow-up. Fornebo et al. reintroduced LDAA in 59 patients after 1 week and in 124 after 1 month. In 111 patients, AD therapy was not confirmed after discharge (9).

All of the 797 patients were treated surgically, but timing is not reported. No early recurrences (<1 week) were reported.

Fornebo reported late recurrences, respectively, in 36 patients (11.7%) who reintroduced AD therapy and in 33 patients (10.8%) who did not resume AD therapy. Thromboembolic events were reported on early onset in six patients (2%) and on late onset in 34 patients (11%). Mortality rate was 4.2% among patients who reintroduced the AD therapy and 2.4% in patients who discontinued it (9).

Guha reported 15 (3.1%) recurrences after >1 week in patients who reintroduced AD and 35 recurrences (7.3%) without AD therapy. No thromboembolic events and mortality are described in this series (10).

DISCUSSION

The real influence of different antithrombotic drugs on outcomes after neurosurgical treatment of CSDH is still unclear, especially

TABLE 1 | Collected studies and data characteristics.

Author/year	Scerrati A. 2019	Kamenova 2016	Poon 2019	Fornebo 2017*	Guha 2016*
N° of patients	164 patients	140 patients	135 patients	308 patients	479 patients
LDAA discontination on admission	164 patients	108 (32 patients 5 days before surgery)	135 patients	308 patients (183 were taking LDAA)	231 patients
LLDA early resumption (<48)	At 72 h (in patients at higher risk of thromboembolic complications)	At 1, 7, 14, 21, 28, 35, and 42 days after surgery, 32 patients (22.9%), the indication for LDAA treatment was not confirmed postoperatively	NN	NN	0
LDAA resumption >1 week	At least 15 days (in patients with lower cardiovascular risk)	At 1, 7, 14, 21, 28, 35, and 42 days after surgery, 32 patients (22.9%), the indication for LDAA treatment was not confirmed postoperatively	NN	100 patients (59 were taking LDAA)	120 patients
LDAA resumption >1 month	None	At 1, 7, 14, 21, 28, 35, and 42 days after surgery, 32 patients (22.9%), the indication for LDAA treatment was not confirmed postoperatively	NN	202 patients (124 started again LDAA); 6 missing patients	
Conservative treatment	None	None	None	None	
Surgical treatment	164 patients	140 patients	135 patients	308 patients	479 patients
Early surgery <5	128 patients	108 patients	NN	NN	
Late surgery >5	36 patients	32 patients	NN	NN	
CSDH early recurrence <1 week	In 20 patients, time of recurrence not specified	0 patients	10 (time of recurrence non-specified)		
CSDH late recurrence >1 week	NN	18 patients	NN	11.7% AT vs. 10.8% non-AT, 6.2% in antiaggregation group	AT restarted group, 15 patients AT non-restarted, 35 patients
Thromboembolic events	NN	Cardiovascular events: 9 (in LDAA group) and 1 (no LDAA)	4 patients	2% early group resumption 11% late group resumption ($P < 0.01$)	
Preoperative evaluation (GCS, CCI)	CCI (up to 3), 28 patients (17%) CCI (4–5), 28 patients (17%) CCI (6 or more), 108 patients (66%) The mean CCI values were 4 and 6.	NN	NN	Early group resumption/late group resumption: GCS 3–8, 6 patients (6.2)/6 patients (3.0) GCS 9–12, 9 patients (9.3)/17 patients (8.6) GCS 13–15, 82 patients (84.5)/175 patients (88.4)	
Clinical outcome	At 6 months follow-up: 51 patients (31.1%)—improvement of neurological symptoms, 80 patients (48.8%)—stable, 18 patients (11%)—worsened	NN	- 38 patients—mRS 4–6 at discharge; - 54 patients—no improvement		
Mortality	15 patients	1 (LDAA group) and 4 (no LDAA)	0	4.2% AT vs. 2.4% non-AT	
Quality of the study according to NOS scale	Good	Good	Good	Good	Good

AT, antithrombotic; LDAA, low dose acetilsalicylic acid; GCS, Glasgow coma scale; mRS, modified Rankin scale.

**Unspecified antiaggregation.*

°*Patients were not further classified.*

concerning LDAA, which has widely been administered for ASCVD prevention for decades (2, 3).

In 2019, Wang et al. published a metanalysis of 24 papers with a pool of 1,812 patients on this topic, concluding that antiplatelet and anticoagulation drugs presented higher risk of recurrence in surgically treated CDSH patients (11).

On the other hand, Poon et al. and Szczygielski et al. underlined the lack of clear indication for the management of these drugs, concluding that patients on antithrombotic drugs were at higher risk of thromboembolic events with no excess risk of bleed recurrence or worse functional outcome after CSDH drainage (4, 8).

In 2013, De Bonis et al. demonstrated a significant association between antithrombotic drug intake and an increased risk of developing CSDH (12); the same group in 2018 and 2019 reported that patients on such therapy do not have an increased risk of rebleeding or worsen clinical outcome when compared with other patients (7, 13, 14).

Our literature review highlights the thromboembolic events after LDAA or antithrombotic drug suspension, and the cardiovascular risk of patients are almost always underestimated or not considered. Very few studies reported this kind of information, while most of the studies focused their attention on the rebleeding risk (6–10).

In the LDAA group, among 439 patients, LDAA was discontinued on admission in 407 patients. Only Kamenova et al. reported on LDAA resumption after surgery (6).

There were no cases of early recurrence (<1 week); Kamenova et al. and Poon et al. reported 28 cases of late recurrence and 13 thromboembolic events after surgery, without any statistically significant difference between patients who underwent discontinuation or not (6, 8).

The clinical outcome was reported in only two papers (Scerrati et al.; Poon et al.), and preoperative assessment is available only in the Scerrati et al. series, undermining any possible LDAA management/complication rate/clinical outcome comparison between the groups (7, 8).

The same limitations are present in the general antiplatelet drug group.

In this complex scenario, comorbidities, and presenting neurological conditions seem to play a significant role in the final outcome. The discontinuation of LDAA could not be absolutely necessary prior to CSDH surgery, in particular, in patients with high cardiovascular risk. Indeed, this risk is often underestimated or is not correctly stratified.

We do believe CSDH precipitates the worsening of preexisting comorbidities causing an increased mortality. In particular, in high cardiovascular risk patients, maintaining acetylsalicylic acid treatment to reduce the thromboembolic event rate could have a positive effect on the final clinical outcome.

Furthermore, the real risk of thromboembolic events after LDAA suspension for CSDH patients appears to be not well-analyzed and understood in the current literature, leaving the decision on the experience of the physician. The same issue still remains controversial in other surgery specialties, as reported by a Cochrane Systematic review (15) collecting five RCTs with 666 randomized adults and concluding that they found low-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery may make little or no difference to mortality, bleeding requiring surgical intervention, or ischemic events. They also found moderate-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery probably makes little or no difference in bleeding requiring transfusion.

A new approach of the clinical problem based on pre- and postsurgery clinical evaluation, with a real stratification of indications for LDAA intake and related cardiovascular risk may solve this complex dilemma.

Our perspective is to propose a clinical evaluation scale in order to stratify patient suffering from CSDH in terms of hemorrhagic and ischemic risk. This scale could be built on the basis of already validated scales (16, 17) and should comprehend different parameters. These types of scales have been widely used in general surgery (18) or cardiosurgery (19) for evaluation of the risk of postoperative thromboembolic or hemorrhagic complications (20, 21). A possible scale could be drafted as follows:

High-risk factors for thromboembolic (TE) events	High-risk factors for hemorrhagic events
Previous TE event—*2 points*	Hepatic disease—*2 points*
Hypertension—*1 point*	Alcool abuse—*1 point*
Diabetes—*1 point*	Reduced platelets count or function—*2 points*
CABG grafts or previous cardiac valve surgery—*2 points*	Anemia—*1 point*
Cancer history—*1 point*	Excessive fall risk—*1 point*
Postoperative infection—*1 point*	Consistent residual subdural hematoma—*1 point*
Fibrinogen >3.5 g/L—*1 point*	Renal disease—*1 point*

According to the specific score, patients could be stratified in low, medium, or high risk for thromboembolic or hemorrhagic events, respectively, and drug management planned accordingly. In this way, there would be a numeric and objective estimation of the risks (hemorrhagic vs. thromboembolic), and the surgeon could choose "the lesser of two evils" between them.

These scores could be the first one available for neurosurgical patients, helping in the difficult decision of anticoagulant/antithrombotic management.

LIMITATIONS

Data about the exact dosage and length of period of administration of the drugs in the collected studies are often unclear.

This is a perspective paper and not a systematic review, so we decided not to perform statistical analysis. This could constitute a bias.

One of the major limitations was the poor level of evidence of several collected studies that could represent a bias in the correct evaluation of the extracted data.

Moreover, an expected limitation of including resources with variable qualities, definitions, follow-ups, and diagnostic criteria is the inevitable heterogeneity detected in some outcomes.

CONCLUSIONS

The literature review highlights the underestimation of the importance of thromboembolic events and cardiovascular risk of patients suffering from CSDH who are taking LDAA.

We do believe that CSDH precipitates the worsening of comorbidities causing an increased mortality. In particular, in high cardiovascular risk patients, maintaining acetylsalicylic acid treatment supposedly reduces the thromboembolic event rate and could have a positive effect on the final clinical outcome. Thus, in our opinion, the discontinuation or effect reversal for acetylsalicylic acid could not be absolutely necessary prior to CSDH surgery (particularly in patients with high cardiovascular risk).

Further studies are needed in order to clarify the role of LDAA in the management and clinical course of high cardiovascular risk patients, in particular, collecting data about thromboembolic events. An interesting perspective could be to build specific evaluation scales of risk in order to uniformly stratify this kind of patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conception: AS and PD constructed the idea for research. Design: LM and FD designed and planned the method to achieve the results. Supervision: MC organized the execution of the study, observed the progress, and took responsibility. Data collection: OR, GM, and LR collected all the data. Analysis–interpretation: AS and PD took responsibility for the evaluation and conclusion of the findings. Literature review: OR, GM, and LR took responsibility for the literature review. Writing: LM and FD took responsibility for the writing of the entire work or its noticeable parts. Critical review: AS and MC re-evaluated the study in the scientific sense and prior to the delivery of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.550084/full#supplementary-material

REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. (2019) 140:e596–646. doi: 10.1161/CIR.0000000000000678
2. Soleman J, Kamenova M, Guzman R, Mariani L. The management of patients with chronic subdural hematoma treated with low-dose acetylsalicylic acid: an international survey of practice. *World Neurosurg*. (2017) 107:778–88. doi: 10.1016/j.wneu.2017.08.065
3. Phan K, Abi-Hanna D, Kerferd J, Lu VM, Dmytriw AA, Ho YT, et al. Resumption of antithrombotic agents in chronic subdural hematoma: a systematic review and meta-analysis. *World Neurosurg*. (2018) 109:e792–9. doi: 10.1016/j.wneu.2017.10.091
4. Szczygielski J, Utter K, Oertel J. Response to poon et al. doi: 10.1089/neu.2018.6080 acetylsalicylic acid and chronic subdural hematoma: is it really a bad couple? influence of antiplatelet and anticoagulant drug use on outcomes after chronic subdural hematoma drainage. *J Neurotrauma*. 37:428–29. doi: 10.1089/neu.2019.6528
5. Connolly BJ, Pearce LA, Kurth T, Kase CS, Hart RG. Aspirin therapy and risk of subdural hematoma: meta-analysis of randomized clinical trials. *J Stroke Cerebrovasc Dis*. (2013) 22:444–8. doi: 10.1016/j.jstrokecerebrovasdis.2013.01.007
6. Kamenova M, Lutz K, Schaedelin S, Fandino J. Does early resumption of low-dose aspirin after evacuation of chronic subdural hematoma with burr-hole drainage lead to higher recurrence rates? *Neurosurgery*. (2016) 79:715–21. doi: 10.1227/NEU.0000000000001393
7. Scerrati A, Germano A, Trevisi G, Visani J, Lofrese G. Timing of low-dose aspirin discontinuation and the influence on clinical outcome of patients undergoing surgery for chronic subdural hematoma. *World Neurosurg*. (2019) 129:e695–99. doi: 10.1016/j.wneu.2019.05.252
8. Poon MTC, Rea C, Kolias AG, Brennan PM. Influence of antiplatelet and anticoagulant drug use on outcomes following chronic subdural hematoma drainage. *J Neurotrauma*. (2019). doi: 10.1089/neu.2018.6080. [Epub ahead of print].
9. Fornebo I, Sjåvik K, Alibeck M, Kristiansson H. Role of antithrombotic therapy in the risk of hematoma recurrence and thromboembolism after chronic subdural hematoma evacuation: a population-based consecutive cohort study. *Acta Neurochir*. (2017) 159:2045–52. doi: 10.1007/s00701-017-3330-x
10. Guha D, Coyne S, Loch MacDonald R. Timing of the resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study. *J Neurosurg*. (2015) 124:589–891. doi: 10.1017/cjn.2015.77
11. Wang H, Zhang M, Zheng H, Xia X, Luo K, Guo F, et al. The effects of antithrombotic drugs on the recurrence and mortality in patients with chronic subdural hematoma: A meta-analysis. *Medicine*. (2019) 98:e13972. doi: 10.1097/MD.0000000000013972
12. De Bonis P, Trevisi G, de Waure C, Sferrazza A. Antiplatelet/anticoagulant agents and chronic subdural hematoma in the elderly. *PLoS ONE*. (2013) 8:e68732. doi: 10.1371/journal.pone.0068732
13. Scerrati A, Mangiola A, Rigoni F, Olei S, Santantonio M, Trevisi G, et al. Do antiplatelet and anticoagulant drugs modify outcome of patients treated for chronic subdural hematoma? Still a controversial issue. *J Neurosurg Sci*. (2018). doi: 10.23736/S0390-5616.18.04311-4. [Epub ahead of print].
14. De Bonis P, Olei S, Mongardi L, Cavallo MA. Chronic subdural hematoma in patients aged 80 years and older: A two-centre study. *Clin Neurol Neurosurg*. (2018) 170:88–92. doi: 10.1016/j.clineuro.2018.05.002

15. Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. (2018) 7:CD012584. doi: 10.1002/14651858.CD012584.pub2
16. Butchart EG, Ionescu A, Payne N, Giddings J, Grunkemeier GL, Fraser AG. A new scoring system to determine thromboembolic risk after heart valve replacement. *Circulation*. (2003) 108(Suppl.1):II68–74. doi: 10.1161/01.cir.0000087383.62522.1e
17. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *J Am Coll Cardiol*. (2012) 60:861–7. doi: 10.1016/j.jacc.2012.06.019
18. Fujikawa T, Kawamura Y, Takahashi R, Naito S. Risk of postoperative thromboembolic complication after major digestive surgery in patients receiving antiplatelet therapy: lessons from more than 3,000 operations in a single tertiary referral hospital. *Surgery*. (2020) 167:859–67. doi: 10.1016/j.surg.2020.01.003
19. Reza S, Pinilla N, Belley-Côté EP, Um KJ, Sibilio S, Natarajan MK, et al. Antithrombotic management after transcatheter aortic valve replacement: a survey of Canadian physicians. *Can J Cardiol*. (2019) 35:1596–9. doi: 10.1016/j.cjca.2019.08.017
20. Park BE, Bae MH, Kim HJ, et al. Perioperative outcomes of interrupted anticoagulation in patients with non-valvular atrial fibrillation undergoing non-cardiac surgery. *Yeungnam Univ J Med*. (2020). doi: 10.12701/yujm.2020.00353. [Epub ahead of print].
21. Ziviello F, Pilgrim T, Kroon H, Ooms JF, van Wiechen MP, EI Azzouzi I, et al. HAS-BLED score and actual bleeding in elderly patients undergoing transcatheter aortic valve implantation. *Minerva Med*. (2020) 111:203–12. doi: 10.23736/S0026-4806.19.06154-8

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Middle Meningeal Artery Embolization for Chronic Subdural Hematoma

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Chronic subdural hematoma (cSDH) is a common disease process associated with significant morbidity that occurs most often in elderly patients. Asymptomatic patients are typically treated conservatively, with surgical intervention reserved for patients with symptomatic and/or large hematomas that cause brain compression. However, conservatively managed cSDH cases frequently progress, and surgical evacuation of cSDH is associated with high rates of complication and recurrence. Recently, successful treatment of cSDH via middle meningeal artery (MMA) embolization has been reported in small case series and case reports. This article reviews the existing literature on MMA embolization for cSDH and discusses the need for randomized control trials and/or large prospective studies to establish the efficacy of MMA embolization for this disease.

Keywords: chronic subdural hematoma, cSDH, middle meningeal artery embolization, endovascular cSDH treatment, MMA embolization

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INTRODUCTION

Chronic subdural hematoma (cSDH) is one of the most common neurosurgical pathologies that largely affects elderly patients and is associated with significant morbidity and mortality (1–3). cSDH is thought to evolve from a prior traumatic acute subdural hemorrhage that develops between the dura and arachnoid layer (2, 4, 5). Although this acute hematoma may resolve completely, in many cases the processes of inflammation, fibrinolysis, and/or angiogenesis lead to formation of a vascularized neomembrane that results in fluid exudation and subsequent hemorrhage, ultimately leading to volume expansion and neurological deficits (2, 4, 6). Histologically, the outer neomembrane is composed of friable sinusoidal neovessels that easily rupture spontaneously, which causes recurring hemorrhage (7–9). These neovessels derive their blood supply from the middle meningeal artery (MMA), which transverses the dura to connect to these fragile vessels (7, 8). Evidence in support of this theory comes from imaging studies reporting ipsilateral enlargement of the MMA in patients with cSDH (2, 8).

For symptomatic, refractory, and/or large cSDH causing brain compression, surgical evacuation and placement of a drain are commonly performed (10). On the other hand, asymptomatic and/or small cSDHs without brain compression are typically treated conservatively and followed-up closely with serial imaging. Successful MMA embolization for cSDH has been described in small case reports and series over the past several years (11–18). More recently, Ng et al. (19) in 2020 conducted a randomized controlled trial comparing surgery with and without MMA

embolization in patients with cSDH. The authors reported one recurrence in each group. However, patients who underwent MMA had a higher hematoma reabsorption rate than those with surgical treatment alone (mean difference, 17.5 mL; 95% CI, 3.87–31.16 mL; $p = 0.02$). Embolization of the MMA is hypothesized to occlude the subdural membrane neovessels to inhibit the recurrent rupture of these vessels, thus facilitating reabsorption of the accumulated subdural fluid (20). Postembolization CT suggests that both particles and liquid embolisate can penetrate into the neomembranes, further strengthening this theory (20). Moreover, several systematic reviews and a meta-analysis have shown promising results with MMA embolization, including low rates of complication and recurrence (21, 22).

This review will discuss MMA embolization for cSDHs, focusing on the major literature studies and future directions needed to establish the efficacy of this technique as a stand-alone and/or adjunct alternative to surgical drainage.

DISCUSSION

Demographic Characteristics and Treatment

cSDH typically occurs in elderly patients with or without a recognized preceding traumatic event and can be associated with the use of anticoagulant or antiplatelet medications (1–3, 10, 23–25). The occurrence of cSDHs has been steadily increasing, and with an ever-increasing elderly population, 60,000 new cases are projected each year over the next 10 years (1–3, 12, 24). Clinical manifestations of cSDH are protean; therefore, the diagnosis should be considered in any elderly patient with an altered mental status or new neurological deficit (10).

Conservative management is often reserved for asymptomatic patients without significant brain compression or midline shift (10). Such management includes frequent follow-up imaging, reversal and discontinuation of anticoagulation, and often the administration of corticosteroids (10, 26–34). Steroids are thought to inhibit the formation of the neomembrane and neovessels by suppressing both fibrinolysis and inflammation (35). However, treatment of cSDHs with corticosteroids has yielded mixed results. One systematic review found that 83–97% of patients treated with corticosteroids alone returned to neurological baseline, and only 4–27.8% would need further treatment, defined as a second round of steroids or surgical evacuation (36). A larger meta-analysis of more than 30,000 patients that included both observational studies and randomized control trials found that higher morbidity was associated with the use of corticosteroids to treat cSDHs, with no therapeutic benefit (37). Finally, a small recent randomized control trial comparing corticosteroids to placebo among patients with cSDH found that steroids may decrease the risk of requiring surgical evacuation (38). Larger randomized clinical trials are underway to investigate this therapy (39–41).

Abbreviations: cSDH, chronic subdural hematoma; MMA, middle meningeal artery; mRS, modified Rankin Scale.

Statins are another class of medication that may be considered as conservative treatment of cSDH. This class of medication has demonstrated efficacy in reducing inflammation at the endothelium, which can also help prevent neomembrane formation (42). In addition, the role of statins in enhancing the functionality of endothelial progenitor cells (43) results in vascular protection within the brain (44). One retrospective study observed patients who were found to have a cSDH without an indication for surgery for 3 months. Chan et al. (45) found that those who were receiving atorvastatin had a 16.7% chance of experiencing deteriorating mental status, requiring bur hole drainage, compared with 58.3% of those who were not receiving atorvastatin. Finally, a recent clinical trial that included 200 patients demonstrated that among patients who had cSDH and no indication for surgery, 8 weeks of atorvastatin was associated with a significantly greater reduction in hematoma volume and improvement in neurological outcome, compared with patients who were treated without a statin. Additionally, 11.2% of those receiving atorvastatin required surgical evacuation during the study, compared with 23.5% who were not receiving a statin (46).

For patients with cSDH causing symptoms, significant midline shift, and/or neurological deficits, surgical intervention is often performed via twist drill craniotomy, bur hole craniostomy, or standard or mini craniotomy (10). Although surgical interventions are typically successful and result in clinical improvement in most patients, surgical mortality rates as high as 32% have been reported (4, 10, 24, 47, 48). Furthermore, complications and recurrence following surgical intervention occur in up to 9% and 28% of patients, respectively (10). Although the use of a subdural drain following evacuation has been reported to decrease the risk of recurrence by up to 50%, the rates of complications, recurrences, morbidity, and mortality still remain substantial (10, 49). Recently, Soleman et al. (50) conducted a randomized, controlled trial that found that subperiosteal drains are associated with an 8% rate of recurrence following bur hole drainage and lower rates of iatrogenic morbidity than subdural drain placement. Similarly, Santarius et al. (51) in 2009 conducted a randomized control trial on the use of drains vs. no drain after bur hole evacuation of cSDHs and found a low rate of recurrence of 9% among patients with a drain vs. 24% among those without a drain. Nonetheless, given the substantial risk of recurrence reported across the various surgical techniques, alternative treatment modalities, either in isolation or in combination with surgical intervention, are warranted.

MMA embolization has been shown to be effective, particularly in patients with recurrent cSDH or patients for whom surgical intervention is associated with a particularly high risk (e.g., due to receipt of anticoagulation medication or advanced comorbid conditions), and may significantly reduce the morbidity and mortality associated with cSDH; **Table 1** (11, 16, 18, 22, 52–55) illustrates the major published case series in the current literature (11–18, 22, 52–55). **Figure 1** shows a proposed treatment algorithm for cSDHs with the use of MMA embolization. However, level 1 evidence for the use of MMA embolization is lacking, with the majority of literature consisting of case reports or small case series.

TABLE 1 | Major published studies of middle meningeal artery (MMA) embolization for chronic subdural hematoma (cSDH).

Study	Year	Study type	No. of patients	Embolysate used	Major findings
Ishihara et al. (52)	2007	Case series	7	NBCA	One of the earliest studies in which patients with cSDH were treated with MMA embolization following either a third recurrence or after a second recurrence and major bleeding risk. No recurrences were found in these patients at last follow-up (up to 15 months).
Kim (53)	2017	Prospective cohort	20	PVA	Analyzed 20 patients with recurrent cSDH treated with MMA embolization and found 85% to have a mRS <2 on follow-up; however, found no difference in mRS scores when comparing patients with traditional treatment for recurrent cSDH. Also found a significant increase in brain re-expansion, decreased hematoma recurrence, and similar complication rates to the conventional treatment group.
Ban et al. (11)	2018	Prospective cohort	72	PVA	Largest study to date; reported no complications associated with MMA embolization and found a statistically lower treatment failure rate (1.4%) than 469 conventionally treated patients (28% failure rate).
Farkas et al. (54)	2018	Case series	10	NR	Follow-up CT at 128 days showed a 45% reduction in cSDH size following MMA embolization in 10 patients (5 primary treatment vs. 5 for recurrent treatment).
Matsumoto et al. (18)	2018	Case series	4	NBCA	Four patients underwent combined MMA embolization and bur hole drainage for refractor cSDH, and none required an additional treatment vs. 2 of 10 patients who required another intervention following conventional therapy for a refractory cSDH.
Link et al. (16)	2019	Case series	49	PVA	Total of 60 SDHs embolized in 49 patients (42 primary therapy, 8 recurrences, and 10 prophylaxis prior to surgery). Reported a 91% long-term success rate, measured as either stable or decreased size of cSDH and avoidance of additional surgery.
Waquas et al. (22)	2019	Case series	8	Onyx	Six procedures were for primary therapy and two were after surgical recurrence. No retreatments recorded after embolization with complete resolution in 3 patients. All patients had a mRS <2 with an average follow-up of 3 months.
Okuma et al. (55)	2019	Case series	17	NBCA and microspheres	Nine of 17 patients with mRS ≤2 with average follow-up of 26 months.

CT, computed tomography; mRS, modified Rankin Scale; NBCA, n-butyl cyanoacrylate; NR, not reported; PVA, polyvinyl alcohol.

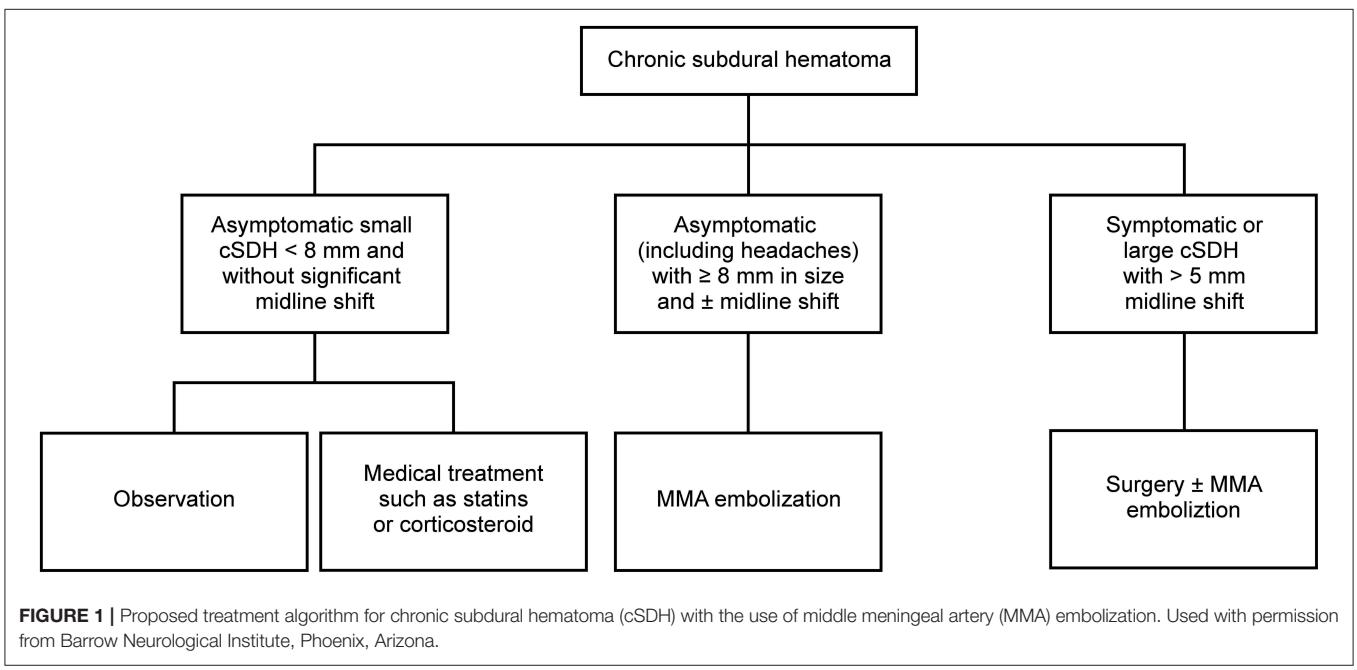

FIGURE 1 | Proposed treatment algorithm for chronic subdural hematoma (cSDH) with the use of middle meningeal artery (MMA) embolization. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.

MMA Embolization Techniques

Descriptions of the technique of MMA embolization remain scarce, with the majority of existing literature reporting the injection of microparticles (11, 16, 17, 22, 56, 57). Some authors have discussed the potential advantages of liquid embolisate for these procedures. These potentially include the depth of penetration, larger volume of embolisate, quicker procedures, increased durability, and improved visualization of the embolic agent (12). To date, no comparative studies have been performed, and further research is warranted to determine the most effective embolic agent for this procedure.

Complications

The reported complication rate among patients who undergo MMA embolization for cSDH is low (12). The two largest series, those of Link et al. (16) ($N = 49$ patients) and Ban et al. (11) ($N = 72$ patients), reported no procedural complications attributable to MMA embolization. The recently published meta-analysis by Srivatsan et al. (21) analyzed three different double-arm studies comparing embolization and conventional surgery. The authors found a complication rate of 2% in the embolization group vs. 4% in the conventional surgical group (21).

Recurrences

With a reported recurrence rate as high as 28% among patients with surgically treated cSDH, one of the main outcome measures analyzed in MMA embolization series is recurrence of the hemorrhage and the need for subsequent intervention. Along these lines, Link et al. (16) found that 9% of a series of 49 patients with 60 cSDHs undergoing MMA embolization required further intervention. This series included 42 hemorrhages treated for the first time, 8 postsurgical recurrences of hemorrhage, and 10 hemorrhages that occurred before surgery (16). In the largest study to date, Ban et al. (11) analyzed 72 patients with cSDH who underwent MMA embolization, including 27 asymptomatic patients who underwent embolization as sole treatment and 45 previously symptomatic patients who had previously undergone hematoma evacuation for symptomatic relief. Ban et al. (11) found a treatment failure rate (remaining or reaccumulated hematoma >1 cm in diameter at 6-month follow-up and/or the need for additional surgical procedures) of only 1.4%. Furthermore, the same authors found the treatment failure rate among 469 conventionally treated patients (402 with initial surgical evacuation and 67 with conservative management) to be significantly higher at 28% (11). Similarly, in the meta-analysis by Srivatsan et al. (21) the authors found a significantly higher hematoma recurrence rate among conventionally treated patients (28%) relative to those undergoing embolization.

Neurological Outcomes

Although the majority of series of patients who underwent MMA embolization used the primary end point of resolution of the hematoma on follow-up imaging, four studies also reported neurological outcomes. In a series of 8 patients, Waqas et al. (22) observed that all patients had a modified Rankin Scale (mRS) score of <2 following a minimum 2-month follow-up (mean follow-up, 3 months). Similarly, Matsumoto et al. (18) published a small series of four patients with refractory cSDH who were treated with MMA embolization and found that all patients exhibited a follow-up mRS of 0. Meanwhile, Okuma et al. (55) reported 9 of 17 patients with an mRS score of ≤ 2 after long-term follow-up of an average of 26 months (only 3 of 17 patients had an mRS score ≤ 2 at admission). Lastly, Kim et al. (53) found that 17 of 20 (85%) patients with a recurrent cSDH treated with MMA embolization had an mRS <2 on follow-up. However, in the same study, 20 of 23 (87%) patients with conventional treatment exhibited similarly low mRS scores (53). Likewise, in the meta-analysis by Srivatsan et al. (21), no significant difference was found between mRS scores among patients treated with embolization embolized vs. patient who received conventional treatment.

Future Direction

Several randomized control trials investigating the efficacy, safety, and utility of MMA embolization for cSDHs are underway (15, 16, 58–63). Additionally, various embolisates for MMA embolization are currently being studied. The SQUID Trial for the Embolization of the Middle Meningeal Artery for Treatment of Chronic Subdural Hematoma (STEM) is a randomized control trial that is investigating the safety and efficacy of SQUID for the management of cSDHS (61). Another embolisate currently being analyzed is Onyx, which is being evaluated in the Embolization of the Middle Meningeal Artery with ONYX Liquid Embolic System for Subacute and Chronic Subdural Hematoma (EMBOLISE) (62). Both of these trials are comparing medical management alone to MMA embolization, and surgical treatment with embolization to surgical treatment alone. Because the literature on MMA embolization of cSDHs includes a large number of patients who also received surgical intervention, randomized control trials will need to be conducted in a manner to also elucidate the appropriate patient selection for either MMA embolization alone or in combination with surgical intervention.

CONCLUSION

MMA embolization for cSDH represents an emerging treatment modality, with a rapidly increasing number of studies analyzing this innovative and largely successful technique. However, many questions remain, including appropriate patient selection, efficacy as a stand-alone procedure, optimal embolization techniques, and timing of embolization with regard to surgical intervention in symptomatic patients. Furthermore, the majority of literature on MMA embolization for cSDH reports cases studies and small case series, whereas several randomized control trials have shown efficacy with surgical interventions. Hence, many randomized clinical trials using MMA as a treatment for cSDH are underway at several centers in the United States and Europe (58–65).

These studies will ultimately provide insight on the safety, efficacy, and use of this novel technique in the treatment of cSDHS.

AUTHOR CONTRIBUTIONS

JC: manuscript writing, editing, and literature review. CN and AW: manuscript writing and literature review. FA: editing. AD: editing and final approval. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Balser D, Farooq S, Mehmood T, Reyes M, Samadani U. Actual and projected incidence rates for chronic subdural hematomas in United States veterans administration and civilian populations. *J Neurosurg.* (2015) 123:1209–15. doi: 10.3171/2014.9.JNS141550
2. Foreman P, Goren O, Griessenauer CJ, Dalal SS, Weiner G, Schirmer CM. Middle meningeal artery embolization for chronic subdural hematomas: cautious optimism for a challenging pathology. *World Neurosurg.* (2019) 126:528–9. doi: 10.1016/j.wneu.2019.03.160
3. Miranda LB, Braxton E, Hobbs J, Quigley MR. Chronic subdural hematoma in the elderly: not a benign disease. *J Neurosurg.* (2011) 114:72–6. doi: 10.3171/2010.8.JNS10298
4. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. *Nat Rev Neurol.* (2014) 10:570–8. doi: 10.1038/nrneurol.2014.163
5. Lee KS. Natural history of chronic subdural haematoma. *Brain Inj.* (2004) 18:351–8. doi: 10.1080/02699050310001645801
6. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J Neuroinflammation.* (2017) 14:108. doi: 10.1186/s12974-017-0881-y
7. Nagahori T, Nishijima M, Takaku A. [Histological study of the outer membrane of chronic subdural hematoma: possible mechanism for expansion of hematoma cavity]. *No Shinkei Geka.* (1993) 21:697–701.
8. Takizawa K, Sorimachi T, Ishizaka H, Osada T, Srivatanakul K, Momose H, et al. Enlargement of the middle meningeal artery on MR angiography in chronic subdural hematoma. *J Neurosurg.* (2016) 124:1679–83. doi: 10.3171/2015.5.JNS1567
9. Tanaka T, Kaimori M. [Histological study of vascular structure between the dura mater and the outer membrane in chronic subdural hematoma in an adult]. *No Shinkei Geka.* (1999) 27:431–6.
10. Mehta V, Harward SC, Sankey EW, Nayar G, Codd PJ. Evidence based diagnosis and management of chronic subdural hematoma: a review of the literature. *J Clin Neurosci.* (2018) 50:7–15. doi: 10.1016/j.jocn.2018.01.050
11. Ban SP, Hwang G, Byoun HS, Kim T, Lee SU, Bang JS, et al. middle meningeal artery embolization for chronic subdural hematoma. *Radiology.* (2018) 286:992–9. doi: 10.1148/radiol.2017170053
12. Fiorella D, Arthur AS. Middle meningeal artery embolization for the management of chronic subdural hematoma. *J Neurointerv Surg.* (2019) 11:912–5. doi: 10.1136/neurintsurg-2019-014730
13. Hashimoto T, Ohashi T, Watanabe D, Koyama S, Namatame H, Izawa H, et al. Usefulness of embolization of the middle meningeal artery for refractory chronic subdural hematomas. *Surg Neurol Int.* (2013) 4:104. doi: 10.4103/2152-7806.116679
14. Kang J, Whang K, Hong SK, Pyen JS, Cho SM, Kim JY, et al. Middle meningeal artery embolization in recurrent chronic subdural hematoma combined with arachnoid cyst. *Korean J Neurotrauma.* (2015) 11:187–90. doi: 10.13004/kjnt.2015.11.2.187
15. Link TW, Boddu S, Marcus J, Rapoport BI, Lavi E, Knopman J. Middle meningeal artery embolization as treatment for chronic subdural hematoma: a case series. *Operat Neurosurg.* (2018) 14:556–62. doi: 10.1093/ons/opx154
16. Link TW, Boddu S, Paine SM, Kamel H, Knopman J. Middle meningeal artery embolization for chronic subdural hematoma: a series of 60 cases. *Neurosurgery.* (2019) 85:801–7. doi: 10.1093/neuros/nyy521
17. Link TW, Rapoport BI, Paine SM, Kamel H, Knopman J. Middle meningeal artery embolization for chronic subdural hematoma: endovascular technique and radiographic findings. *Interv Neuroradiol.* (2018) 24:455–62. doi: 10.1177/1591019918769336
18. Matsumoto H, Hanayama H, Okada T, Sakurai Y, Minami H, Masuda A, et al. Which surgical procedure is effective for refractory chronic subdural hematoma? Analysis of our surgical procedures and literature review. *J Clin Neurosci.* (2018) 49:40–7. doi: 10.1016/j.jocn.2017.11.009
19. Ng S, Derraz I, Boetto J, Dargazanli C, Poulen G, Gascou G, et al. Middle meningeal artery embolization as an adjuvant treatment to surgery for symptomatic chronic subdural hematoma: a pilot study assessing hematoma volume resorption. *J Neurointerv Surg.* (2020) 12:695–9. doi: 10.1136/neurintsurg-2019-015421
20. Saito H, Tanaka M, Hadeishi H. Angiogenesis in the septum and inner membrane of refractory chronic subdural hematomas: consideration of findings after middle meningeal artery embolization with low-concentration n-butyl-2-cyanoacrylate. *NMC Case Rep J.* (2019) 6:105–10. doi: 10.2176/nmccrj.cr.2018-0275
21. Srivatsan A, Mohanty A, Nascimento FA, Hafeez MU, Srinivasan VM, Thomas A, et al. Middle meningeal artery embolization for chronic subdural hematoma: meta-analysis and systematic review. *World Neurosurg.* (2019) 122:613–9. doi: 10.1016/j.wneu.2018.11.167
22. Waqas M, Vakhari K, Weimer PV, Hashmi E, Davies JM, Siddiqui AH. Safety and effectiveness of embolization for chronic subdural hematoma: systematic review and case series. *World Neurosurg.* (2019) 126:228–36. doi: 10.1016/j.wneu.2019.02.208
23. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK. Chronic subdural haematoma in the elderly. *Postgrad Med J.* (2002) 78:71–5. doi: 10.1136/pmj.78.916.71
24. Ducruet AF, Grobelny BT, Zacharia BE, Hickman ZL, DeRosa PL, Andersen KN, et al. The surgical management of chronic subdural hematoma. *Neurosurg Rev.* (2012) 35:155–69. doi: 10.1007/s10143-011-0349-y
25. Foelholm R, Waltimo O. Epidemiology of chronic subdural haematoma. *Acta Neurochir.* (1975) 32:247–50. doi: 10.1007/BF01405457
26. Decaux O, Cador B, Dufour T, Jego P, Cazalets C, Laurat E, et al. [Nonsurgical treatment of chronic subdural hematoma with steroids: two case reports]. *Rev Med Interne.* (2002) 23:788–91. doi: 10.1016/S0248-8663(02)00676-8
27. Delgado-Lopez PD, Martin-Velasco V, Castilla-Diez JM, Rodriguez-Salazar A, Galacho-Harriero AM, Fernandez-Arconada O. Dexamethasone treatment in chronic subdural haematoma. *Neurocirugia.* (2009) 20:346–59. doi: 10.1016/S1130-1473(09)70154-X
28. Dran G, Berthier F, Fontaine D, Rasenrarijao D, Paquis P. [Effectiveness of adjuvant corticosteroid therapy for chronic subdural hematoma: a retrospective study of 198 cases]. *Neurochirurgie.* (2007) 53:477–82. doi: 10.1016/j.neuchi.2007.09.146
29. Sun TF, Boet R, Poon WS. Non-surgical primary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. *Br J Neurosurg.* (2005) 19:327–33. doi: 10.1080/02688690500305332
30. Thotakura AK, Marabathina NR. Nonsurgical treatment of chronic subdural hematoma with steroids. *World Neurosurg.* (2015) 84:1968–72. doi: 10.1016/j.wneu.2015.08.044
31. Inzelberg R, Neufeld MY, Reider I, Gari P. Non surgical treatment of subdural hematoma in a hemodialysis patient. *Clin Neurol Neurosurg.* (1989) 91:85–9. doi: 10.1016/S0303-8467(89)80014-9

32. Rudiger A, Ronsdorf A, Merlo A, Zimmerli W. Dexamethasone treatment of a patient with large bilateral chronic subdural haematomata. *Swiss Med Wkly.* (2001) 131:387.
33. Bender MB, Christoff N. Nonsurgical treatment of subdural hematomas. *Arch Neurol.* (1974) 31:73–9. doi: 10.1001/archneur.1974.00490380021001
34. Pichert G, Henn V. [Conservative therapy of chronic subdural hematomas]. *Schweiz Med Wochenschr.* (1987) 117:1856–62.
35. Thotakura AK, Marabathina NR. The role of medical treatment in chronic subdural hematoma. *Asian J Neurosurg.* (2018) 13:976–83. doi: 10.4103/ajns.AJNS_13_17
36. Berghauser Pont LME, Dirven CMF, Dippel DWJ, Verweij BH, Dammers R. The role of corticosteroids in the management of chronic subdural hematoma: a systematic review. *Eur J Neurol.* (2012) 19:1397–403. doi: 10.1111/j.1468-1331.2012.03768.x
37. Almenawer SA, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. *Ann Surg.* (2014) 259:449–57. doi: 10.1097/SLA.0000000000000255
38. Prud'homme M, Mathieu F, Marcotte N, Cottin S. A pilot placebo controlled randomized trial of dexamethasone for chronic subdural hematoma. *Can J Neurol Sci.* (2016) 43:284–90. doi: 10.1017/cjn.2015.393
39. Allison A, Edlmann E, Kolias AG, Davis-Wilkie C, Mee H, Thelin EP, et al. Statistical analysis plan for the dex-CSDH trial: a randomised, double-blind, placebo-controlled trial of a 2-week course of dexamethasone for adult patients with a symptomatic chronic subdural haematoma. *Trials.* (2019) 20:698. doi: 10.1186/s13063-019-3866-6
40. Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt N, de Laat K, et al. Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial. *Trials.* (2018) 19:575. doi: 10.1186/s13063-018-2945-4
41. Kolias AG, Edlmann E, Thelin EP, Bulters D, Holton P, Suttner N, et al. Dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH) trial: study protocol for a randomised controlled trial. *Trials.* (2018) 19:670. doi: 10.1186/s13063-018-3050-4
42. Buttmann M, Lorenz A, Weishaupt A, Rieckmann P. Atorvastatin partially prevents an inflammatory barrier breakdown of cultured human brain endothelial cells at a pharmacologically relevant concentration. *J Neurochem.* (2007) 102:1001–8. doi: 10.1111/j.1471-4159.2007.04563.x
43. Liu Y, Wei J, Hu L, Hu S. Beneficial effects of statins on endothelial progenitor cells. *Am J Med Sci.* (2012) 344:220–6. doi: 10.1097/MAJ.0b013e31824998f9
44. Potey C, Ouk T, Petrault O, Petrault M, Berezowski V, Salleron J, et al. Early treatment with atorvastatin exerts parenchymal and vascular protective effects in experimental cerebral ischaemia. *Br J Pharmacol.* (2015) 172:5188–98. doi: 10.1111/bph.13285
45. Chan DYC, Chan DTM, Sun TFD, Ng SCP, Wong GKC, Poon WS. The use of atorvastatin for chronic subdural haematoma: a retrospective cohort comparison study. *Br J Neurosurg.* (2017) 31:72–7. doi: 10.1080/02688697.2016.1208806
46. Jiang R, Zhao S, Wang R, Feng H, Zhang J, Li X, et al. Safety and efficacy of atorvastatin for chronic subdural hematoma in chinese patients: a randomized clinicalTrial. *JAMA Neurol.* (2018) 75:1338–46. doi: 10.1001/jamaneurol.2018.2030
47. Ivamoto HS, Lemos HP Jr, Atallah AN. Surgical treatments for chronic subdural hematomas: a comprehensive systematic review. *World Neurosurg.* (2016) 86:399–418. doi: 10.1016/j.wneu.2015.10.025
48. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. *J Neurol Neurosurg Psychiatry.* (2003) 74:937–43. doi: 10.1136/jnnp.74.7.937
49. Peng D, Zhu Y. External drains versus no drains after burr-hole evacuation for the treatment of chronic subdural haematoma in adults. *Cochrane Database Syst Rev.* (2016) 2016:CD011402. doi: 10.1002/14651858.CD011402.pub2
50. Soleman J, Lutz K, Schaedelin S, Kamenova M, Guzman R, Mariani L, et al. Subperiosteal vs subdural drain after burr-hole drainage of chronic subdural hematoma: a randomized clinical trial (cSDH-drain-trial). *Neurosurgery.* (2019) 85:E825–34. doi: 10.1093/neuros/nyz095
51. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet.* (2009) 374:1067–73. doi: 10.1016/S0140-6736(09)61115-6
52. Ishihara H, Ishihara S, Kohyama S, Yamane F, Ogawa M, Sato A, et al. Experience in endovascular treatment of recurrent chronic subdural hematoma. *Int Neuroradiol.* (2007) 13 (Suppl. 1):141–4. doi: 10.1177/15910199070130S121
53. Kim E. Embolization therapy for refractory hemorrhage in patients with chronic subdural hematomas. *World Neurosurg.* (2017) 101:520–7. doi: 10.1016/j.wneu.2017.02.070
54. Farkas N, Bo R, Arcot K, Tiwari A, Rurkel-Parrella D, Selas G, et al. Radiographic efficacy of middle meningeal artery embolization in treatment of chronic subdural hematoma (P6.213). *Neurology*. (2018) 90 (15 Suppl). Available online at: https://n.neurology.org/content/90/15_Supplement/P6.213/tab-article-info
55. Okuma Y, Hirotsune N, Sato Y, Tanabe T, Muraoka K, Nishino S. Midterm follow-up of patients with middle meningeal artery embolization in intractable chronic subdural hematoma. *World Neurosurg.* (2019) 126:e671–8. doi: 10.1016/j.wneu.2019.02.121
56. Catapano JS, Fredrickson VL, Fujii T, Cole TS, Koester SW, Baranoski JF, et al. Complications of femoral versus radial access in neuroendovascular procedures with propensity adjustment. *J Neurointerv Surg.* (2019) 12:611–5. doi: 10.1136/neurintsurg-2019-015569
57. Gore P, Theodore N, Brasiliense L, Kim LJ, Garrett M, Nakaji P, et al. The utility of onyx for preoperative embolization of cranial and spinal tumors. *Neurosurgery.* (2008) 62:1204–11. doi: 10.1227/01.neu.0000333292.74986.ac
58. National Institutes of Health. *Middle Meningeal Artery (MMA) Embolization Compared to Traditional Surgical Strategies to Treat Chronic Subdural Hematomas (cSDH).* (2019). Available online at: https://ClinicalTrials.gov/show/NCT04095819 (accessed October 7, 2020).
59. National Institutes of Health. *Dartmouth Middle Meningeal Embolization Trial (DaMMET).* (2020). Available online at: https://ClinicalTrials.gov/show/NCT04270955 (accessed October 7, 2020).
60. National Institutes of Health. *Embolization of the Middle Meningeal Artery for the Prevention of Chronic Subdural Hematoma Recurrence in High Risk Patients (EMPROTECT).* (2020). Available online at: https://ClinicalTrials.gov/show/NCT04372147 (accessed October 7, 2020).
61. National Institutes of Health. *The SQUID Trial for the Embolization of the Middle Meningeal Artery for Treatment of Chronic Subdural Hematoma (STEM).* (2020). Available online at: https://ClinicalTrials.gov/show/NCT04410146 (accessed October 7, 2020).
62. National Institutes of Health. *Embolization of the Middle Meningeal Artery With ONYX^{TM} Liquid Embolic System for Subacute and Chronic Subdural Hematoma*. (2020). Available online at: https://ClinicalTrials.gov/show/NCT04402632 (accessed October 7, 2020).
63. National Institutes of Health. *Endovascular Embolization for Chronic Subdural Hematomas Following Surgical Evacuation*. (2020). Available online at: https://ClinicalTrials.gov/show/NCT04272996 (accessed October 7, 2020).
64. National Institutes of Health. *Middle Meningeal Artery Embolization for Treatment of Chronic Subdural Hematoma.* (2017). Available online at: https://ClinicalTrials.gov/show/NCT03307395 (accessed October 7, 2020).
65. National Institutes of Health. *Middle Meningeal Artery Embolization for Chronic Subdural Hematoma*. (2019). Available online at: https://ClinicalTrials.gov/show/NCT04065113 (accessed October 7, 2020).

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Endoscope-Assisted Surgery vs. Burr-Hole Craniostomy for the Treatment of Chronic Subdural Hematoma: A Systemic Review and Meta-Analysis

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Objectives: This article aims to evaluate the safety and effectiveness of endoscope-assisted surgery for chronic subdural hematoma (cSDH) in comparison with the burr-hole craniostomy.

Methods: An electronic literature research was performed in MEDLINE, the Cochrane library, and EMBASE from the inception to February 18, 2020. A systematic review with meta-analyses was conducted to compare the efficacy of endoscope-assisted surgery with Burr-hole Craniostomy (BHC) surgery.

Results: This meta-analysis included four studies comprising 441 patients. Endoscope-assisted surgery significantly decreased the risk of recurrence in patients with cSDH [odds ratio, 0.368; 95% confidence interval (CI), 0.178–0.759; $P = 0.007$; $I^2 = 0\%$]. The complication rate was also significantly lower in the endoscope-assisted group (OR, 0.249; 95% CI, 0.07–0.882; $P = 0.031$; $I^2 = 71.87\%$).

Conclusion: We conducted the first meta-analysis of endoscope-assisted surgery for cSDH. The meta-analysis of four studies comprising 441 patients with cSDH suggests a significantly decreased risk of recurrence and postoperative complications after endoscope-assisted surgery. Therefore, endoscope-assisted surgery is effective and safe in treating cSDH.

Keywords: chronic subdural hematoma, cSDH, chronic subdural hemorrhage, endoscope, meta-analysis

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INTRODUCTION

Chronic subdural hematoma (cSDH) is a common disease characterized by abnormal accumulation of blood in subdural space. Most of cSDH patients have traumatic histories, and age, male, and use of antithrombotic drugs are risk factors of cSDH. The incidence of cSDH is 13.5 per 100,000 per year, and it is five times more in people older than 65 years (1). There are several treatment strategies for cSDH, including minimally invasive surgery, such as twist drill craniostomy and burr-hole craniostomy, or relatively highly invasive surgery, craniotomy (2). However, a high recurrence rate is observed in patients undergoing twist drill and burr-hole craniostomy because of inadequate exposure of hematoma cavities during surgery. Craniotomy is more effective in evacuation of hematoma and has a lower reoperation rate than Burr-hole Craniostomy (BHC) and Twist Drill Craniostomy (TDC) (3).

Nevertheless, cSDH patients are often elderly and have various medical comorbidities, which makes it hard to conduct craniotomy.

In recent years, the endoscopic surgery technique has been applied in the treatment of cSDH. The endoscope provides a broader inspection of subdural space and does less harm to patients. Several studies have proven that endoscope-assisted surgery is effective in lessening postoperative complications and recurrence rates (4–8). However, there was no large-scale and controlled study focused on this aspect. Therefore, we conducted a systemic review and meta-analysis of endoscope-assisted surgery in cSDH to explore the efficiency and safety of endoscopic surgery.

MATERIALS AND METHODS

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) criteria (9).

An electronic literature research was performed in MEDLINE, the Cochrane library, and EMBASE from the inception to February 18, 2020. The terms "chronic subdural hematoma," "refractory subdural hematoma," "chronic subdural hemorrhage," "refractory subdural hemorrhage," "endoscope," and "endoscopic" were combined to search for available studies. We also review the bibliographic list of retrieved articles to get additional related studies.

Selection Criteria

Two authors assessed the title and abstract independently to select the eligible studies. The selection criteria were developed based on the following questions:

(1) (patients) adults with cSDH;
(2) (intervention) endoscope-assisted surgery;
(3) (comparator interventions) burr-hole craniostomy;
(4) (outcomes) recurrence, postoperative complications and mortality;
(5) (methods–study design) randomized controlled trials (RCTs) or non-RCT or retrospective or prospective controlled study;
(6) (time or duration) follow-up time longer than 6 months.

The full-text articles were then retrieved to further selection. The following studies were included (a) studies comparing outcomes of endoscopic surgery with conventional surgery, (b) RCT or a non-RCT, or a retrospective or prospective controlled study. The following articles were excluded: (a) single-arm studies that only report endoscopic surgery outcomes; (b) reviews, case reports, abstracts; (c) acute subdural hematoma or infant subdural hematoma studies.

Data Extraction

Two researchers independently extracted the following clinical data from selected studies: basic characteristics of studies (author publication year, study design, sample size, age, and sex), clinical features of the study population (use of anticoagulation or antiplatelet drugs, unilateral or bilateral hematoma, hematoma volume, and midline shift), and clinical outcomes (recurrence rate and postoperative complication rate).

Quality Assessment

Two reviewers conducted the assessment independently using the Newcastle–Ottawa Scale (NOS). The NOS evaluates each study according to three factors: patient selection, the comparability among groups, and the measurement of outcomes. Disagreements were settled through discussion between two researchers. If there was still no consensus, we consulted a third reviewer.

Data Analysis

Statistical analyses were performed using RevMan 5.3 (10) and OpenMeta (11) software. Continuous variables use the mean difference as the indicator of the effect amount, and the binary variables use the odds ratio (OR). Each effect size is expressed as a 95% confidence interval (95% CI). We applied a continuity correction to all four cells if the event rates were zero. Heterogeneity tests were performed on the included studies by the χ^2 test, and the magnitude of heterogeneity was determined by combining the I^2 values. If there was no heterogeneity between the results ($P > 0.10$ and $I^2 \leq 50\%$), then a fixed-effect model was used; otherwise, if there was heterogeneity between the results ($P \leq 0.10$, $I^2 > 50\%$), a random-effects model was used.

Outcome Measure

In this meta-analysis, we studied the recurrence and complications after surgery. Recurrence was defined as a reaccumulation of hematoma seen on a computed tomography scan with symptoms. Any complications or symptoms caused by cSDH surgery were defined as complications. Mortality was defined as death due to cSDH or surgery.

RESULTS

Study Selection

One hundred fifty-six articles were initially generated through search in three databases. Thirty-six duplicated or nonrelated articles were excluded after examination. We then carefully reviewed the title and abstract; 109 studies were not eligible, including studies on acute SDH or infants, case reports, abstracts, and irrelevant studies. Eleven studies have remained, and their full texts were acquired for assessing their eligibility. Finally, seven single-arm studies were excluded, and four studies were eligible and included in meta-analysis (12–15). To our dismay, no RCTs were included. **Figure 1** shows the search process.

Study Characteristics

All four studies were retrospective, and 441 patients were involved, including 187 patients undergoing endoscopic surgery and 254 patients who had a burr-hole treatment. **Table 1** demonstrates the baseline characteristics in both the endoscopic and BHC groups. The study by Yan did not present hematoma volume, and the study by Guan did not involve midline line shift. In each study, no statistically significant difference was found in age, sex, midline shift, hematoma volume, the proportion

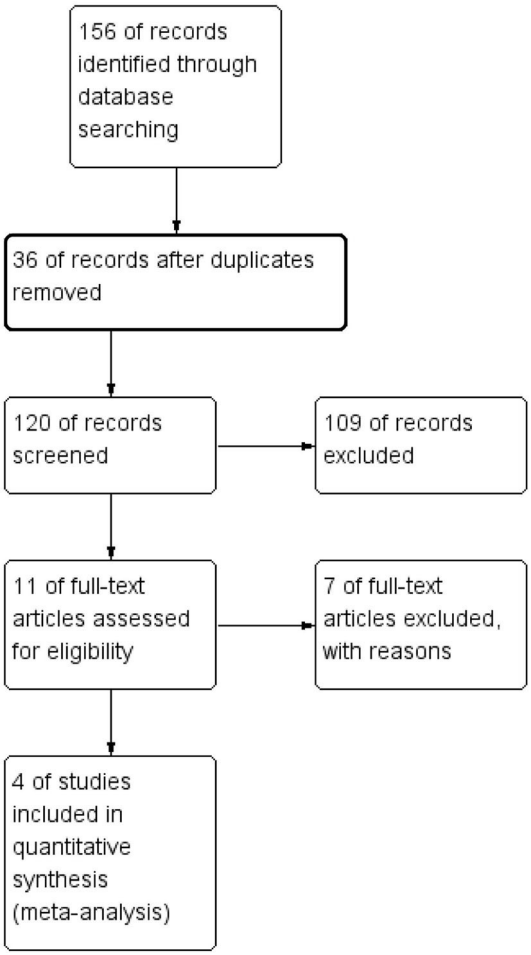

FIGURE 1 | Study flow diagram.

of bilateral hematoma, and antithrombotic drug use between the endoscopic and BHC groups. Three studies used a flexible endoscope, and one study used transparent sheath and hard neuroendoscope. All the surgeries in the four studies were successful. The follow-up time in four studies was quite different. In the studies by Du et al. (12); Zhang et al. (16), the follow-up time was 6 months, and the follow-up time was 12 months in the study by Yan. The results in these three studies are comparable. In Guan's article, the follow-up time was up to 10 years. However, each cohort's recurrence time, which is the main outcome measured in this study, was 12 months. Therefore, we believe it is comparable with the other three studies.

Assessment of Risk of Bias

All four studies had five stars or more in NOS (**Table 2**). Therefore, they were qualified with respect to bias originating from selection, comparability of groups, and outcome evaluation.

Synthesized Findings

One thousand four hundred thirty-three patients from four studies were investigated (188 patients took endoscopic surgery, and 255 patients underwent BHC surgery, respectively). Endoscopic surgery had a significantly lower risk of hematoma recurrence in patients with cSDH (OR of 0.392; 95% CI, 0.190–0.809; $P = 0.011$, $I^2 = 0\%$; **Figure 2**).

Difference in postoperative complications was also significant in the endoscopic surgery and BHC surgery groups for cSDH (OR, 0.249; 95% CI, 0.07–0.882; $P = 0.031$; $I^2 = 71.87\%$) (**Figure 3**). However, heterogeneity was high, indicating the quality of evidence was relatively low.

Mortality did not significantly differ between the endoscope-assisted surgery and BHC groups (OR, 0.539; 95% CI, 0.126–2.304; $P = 0.404$; $I^2 = 0\%$) (**Figure 4**).

DISCUSSION

cSDH is a common disease in neurosurgery, characterized by abnormal accumulation of blood beneath the dural layer. There are several theories that can explain the formation and progression of cSDH. Traumatic theory is the most acceptable one. It revealed that trauma is the key factor in cSDH formation; after trauma, a small and asymptomatic hematoma formed, and because of the fragility of neovasculature, microbleeding occurs and contributes to cSDH progression. In elderly people, especially in those who are older than 65 years old, their brains are naturally in atrophy state. Atrophy brain results in extension of the subarachnoid space, and the subdural veins are stretched and prolonged, which makes veins get easier to be torn and form subdural hematomas. Also, elderly people have a higher chance of falling. As a result, age is the leading risk factor for cSDH (2).

Surgery is the primary treatment for cSDH. However, it needs to be cautious for surgery on elderly patients because most elderly patients have underlying diseases, which is a restriction for highly invasive surgery. Burr-hole craniostomy is now the main method for treating cSDH, whereas many patients experienced recurrent recollection of hematoma after surgery. The postoperative blood recurrence rate has been reported to be 5–33%. It may be attributed to the inadequate clearance of hematoma, and recurrence is particularly likely to occur when there is a separation within the hematoma. The root cause is that the surgical operation is performed in a small bone hole, and the operator cannot remove the hematoma directly. Residual hematoma will impede the recovery of brain tissue, and as a result, the subdural space does not shrink, which leads to subdural gas accumulation. Residual hematomas can also cause recurrence by stimulating the secretion of inflammatory factors. These deficiencies also lead to a series of complications after surgery. The main manifestations lead to cranial hypertension, fresh bleeding, and intracranial infection.

In recent years, the endoscopic surgery technique has been applied in the treatment of cSDH. With the help of neuroendoscopy, operators can observe all corners of the hematoma cavity and confirm if there is residual hematoma. As we have known, there are many mechanisms of subdural hematoma; inflammatory factors produced by hematoma

TABLE 1 | Baseline characteristics of included studies.

Study	Study design	Group	Sample size	Sex (Male/ Female)	Age	Use of anticoagulant/ antiplatelet drugs	Unilateral hematoma	Midline shift	Hematoma volume (mL)
Du et al. (12)	Retrospective	Endoscope	45	29/16	73.2 ± 5.5	23 (51.1%)	38 (84.4%)	9.6 ± 3.1	96.8 ± 19.2
		BHC	49	30/19	70.6 ± 6.1	30 (61.2%)	32 (65.3%)	8.8 ± 3.8	104.3 ± 21.3
Yan et al. (14)	Retrospective	Endoscope	24	10/14	66.00 ± 6.89	7 (29.2%)	18 (75%)	11.75 ± 2.89	N
		BHC	52	37/15	66.38 ± 9.35	12 (23%)	41 (78.9%)	13.00 ± 3.77	N
Zhang et al. (13)	Retrospective	Endoscope	43	32/9	74.3 (67–91)	15 (34.9%)	42 (97.7%)	9.2 (0–19.5)	115.5 (30.3–178.2)
		BHC	27	18/9	69.8 (58–81)	13 (48%)	25 (92.6%)	8.6 (0–23.3)	109.1 (37.6–182.5)
Guan et al. (15)	Retrospective	Endoscope	75	41/34	68.3 (60–81)	N	N	N	117.3 (33.2–170.5)
		BHC	126	75/51	71.4 (61.3–87.5)	N	N	N	114.6 (35.2–157.5)

TABLE 2 | Newcastle-Ottawa Scale for assessing the quality of studies in meta-analysis.

Study	Adequate definition of cases	Representativeness of the cases	Selection of controls	Defnition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Quality score
Du et al. (12)	☆	☆		☆	☆	☆	☆		6
Guan et al. (15)	☆			☆	☆	☆	☆	☆	6
Yan et al. (14)	☆	☆		☆	☆	☆	☆		6
Zhang et al. (13)	☆	☆		☆	☆	☆	☆		6

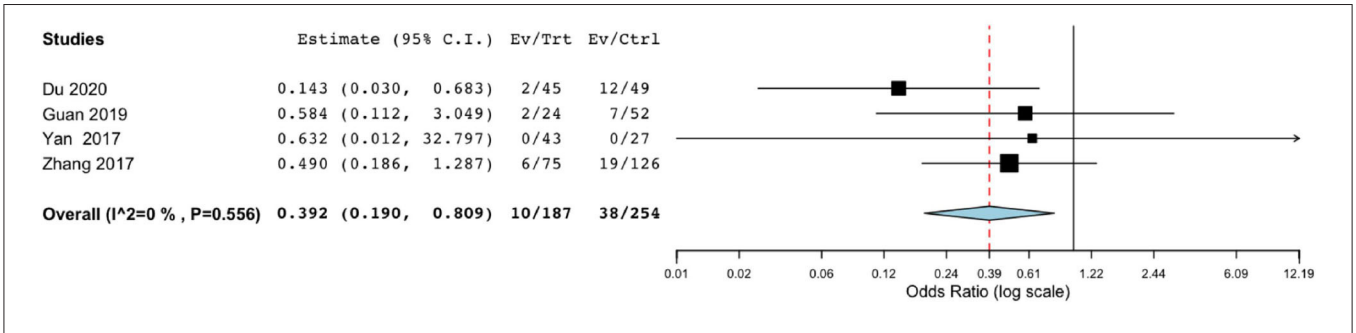

FIGURE 2 | Risk of postoperative recurrence in endoscope-assisted surgery and BHC groups. (OR of 0.392, 95% CI, 0.190–0.809 , $P = 0.011$, $I^2 = 0\%$).

stimulation are the leading reason for the continuous expansion of hematoma (17). It is vital to confirm that there is no residual hematoma under direct observation. Also, subdural hematomas often have septa, and it is hard for BHC to clear all septa and blood during surgery. As a result, residual septa will limit the recovery of the brain and the shrinkage of the subdural space. Endoscopy can fully remove the hematoma and open the septa. Endoscopic surgery has similar or slightly larger incisions and bone holes with BHC, and local anesthesia can be used, which has little damage to the patient and is suitable for elderly patients. Although conventional craniotomy can also provide the operator with sufficient exposure and observation, the trauma caused by surgery is not proper for elderly patients.

In theory, endoscopic surgery combines the advantages of BHC and conventional craniotomy. It has a significant effect on reducing postoperative recurrence and other complications of cSDH, especially for patients who suffer recurrence or patients with septa. Our research provides literature and practical evidence and support for this concept. More

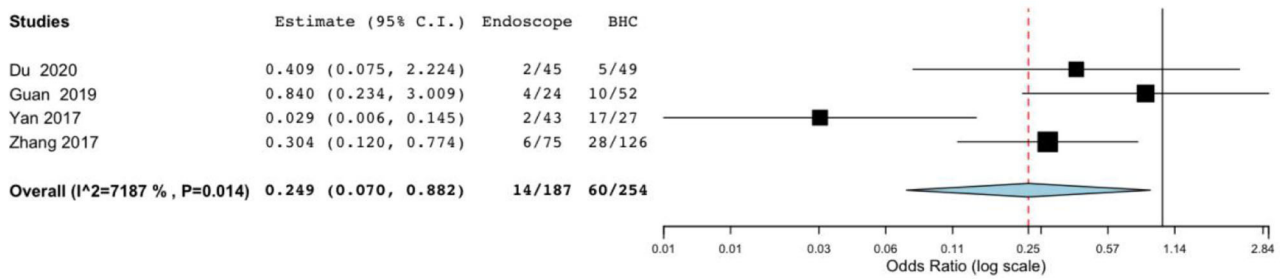

FIGURE 3 | Risk of postoperative complications in endoscope-assisted surgery and BHC groups. (OR of 0.249, 95%CI, 0.07–0.882, $P = 0.031$, $I^2 = 71.87\%$).

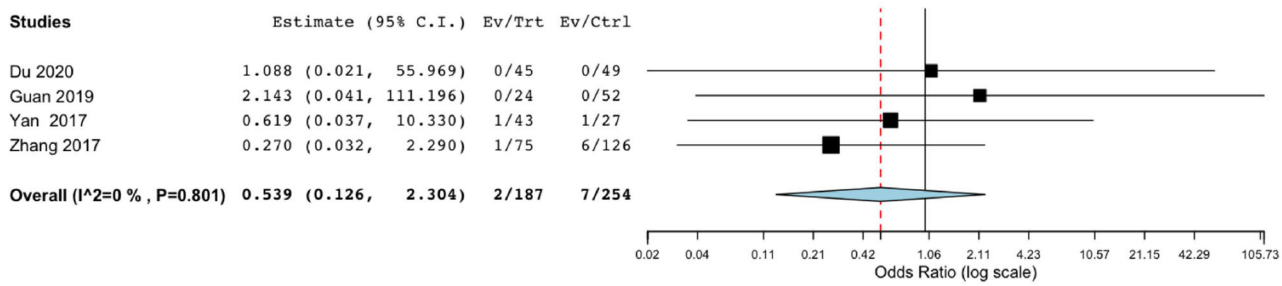

FIGURE 4 | Risk of postoperative mortality in endoscope-assisted surgery and BHC groups. (OR of 0.539, 95%CI, 0.126–2.304, $P = 0.404$, $I^2 = 0\%$).

direct evidence may need to be confirmed by prospective clinical studies.

In this study, we analyzed all studies comparing endoscope-assisted surgery with BHC surgery and conducted the first meta-analysis of endoscope-assisted surgery in cSDH. This article enrolled four studies involving 441 patients in the pooled analysis. All studies collected the baseline characteristics, clinical outcomes, recurrence rate, and postoperative complications of patients. Compared with BHC surgery, endoscope-assisted surgery showed a significantly low recurrence rate and complication rate. Mortality did not show a significant difference between BHC and endoscope.

In addition to the controlled studies, there are single-arm studies that also showed the capacity of endoscope-assisted surgery to improve the prognosis of cSDH patients. Moreover, a large number of studies have attempted to find a solution to decrease the recurrence rate of cSDH. Dexamethasone was used as an adjuvant treatment; however, it is demonstrated that its effect is limited in various studies (16, 18). Atorvastatin had been proved as an efficient therapy to treat cSDH in recent studies. Atorvastatin was effective in reducing the recurrence rate after surgery and promoting the rehabilitation of neurological function (19). Middle meningeal artery embolization combined with craniotomy has arisen as a promising treatment with a significantly lower recurrence rate compared to conventional surgery (20). It is also reported that inserting urokinase into the hematoma can promote clot efflux and show a better outcome.

The leading limitation of this article is the inadequately analyzed studies. No RCTs for the comparison between the endoscope-assisted surgery and the convention surgery were conducted at present. This meta-analysis is based on the double-arm observational studies. None of the evidence originates from conclusions in the gold-standard RCTs. The risk of bias is high owing to the absence of randomized allocation, and historical control groups may have a relatively weak match with the intervention group. In the future, investigators should pay more attention to endoscope-assisted surgery, and more high-quality studies and double-blind, randomized controlled clinical trials are needed to test the effectiveness of endoscope-assisted surgery in treating cSDH patients.

CONCLUSION

We conducted the first meta-analysis of endoscope-assisted surgery for cSDH. The meta-analysis of four studies comprising 441 patients with cSDH suggests a significantly decreased recurrence rate and postoperative complication rate after endoscope-assisted surgery. Therefore, endoscope-assisted surgery is effective and safe in treating cSDH.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

Conception and design: CL and AW. Data collection and analysis: SG, WC, and WG. Critical revision of the article: CL and AW. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Almenawer SA, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. *Ann Surg.* (2014) 259:449–57. doi: 10.1097/SLA.0000000000000255
2. Yang W, Huang J. Chronic subdural hematoma: epidemiology and natural history. *Neurosurg Clin N Am.* (2017) 28:205–10. doi: 10.1016/j.nec.2016.11.002
3. Farhat Neto J, Araujo JL, Ferraz VR, Haddad L, Veiga JC. Chronic subdural hematoma: epidemiological and prognostic analysis of 176 cases. *Rev Col Bras Cir.* (2015) 42:283–7. doi: 10.1590/0100-69912015005003
4. Khongbantabam V, Singh TA, Singh KM, Laifangbam S. Endoscope-assisted single burr hole drainage and irrigation of chronic subdural hematoma (SDH): a retrospective analysis. *J Med Soc.* (2016) 30:103–5. doi: 10.4103/0972-4958.182910
5. Májovský M, Masopust V, Netuka D, Beneš V. Flexible endoscope-assisted evacuation of chronic subdural hematomas. *Acta Neurochir (Wien).* (2016) 158:1987–92. doi: 10.1007/s00701-016-2902-5
6. Masopust V, Netuka D, Häckel M. Chronic subdural haematoma treatment with a rigid endoscope. *Minim Invasive Neurosurg.* (2003) 46:374–9. doi: 10.1055/s-2003-812507
7. Wakuta N, Abe H, Fukuda K, Nonaka M, Morishita T, Arima H, et al. Feasibility and safety of endoscopic procedure in burr-hole surgery for chronic subdural hematoma in patients of very advanced age. *World Neurosurg.* (2020) 134:e1037–e46. doi: 10.1016/j.wneu.2019.11.080
8. Zachariah M, Codd P. Minimally invasive surgery for subdural hematoma. *J Neurotrauma.* (2018) 35:A150. doi: 10.1089/neu.2018.29013.abstracts
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
10. *Review Manager (RevMan) [Computer program]. Version 5.3.* Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration (2014).
11. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw.* (2012) 49:1–15. doi: 10.18637/jss.v049.i05
12. Du B, Xu J, Hu J, Zhong X, Liang J, Lei P, et al. A clinical study of the intra-neuroendoscopic technique for the treatment of subacute-chronic and chronic septal subdural hematoma. *Front Neurol.* (2020) 10:1408. doi: 10.3389/fneur.2019.01408
13. Zhang J, Fan X, Liu X, Chen J, Wang W, Fu K. The optimal treatment options of septated chronic subdural hematoma: a retrospective comparison of craniotomy vs. endoscopic-assisted burr-hole craniostomy. *World Neurosurg.* (2017). doi: 10.1016/j.wneu.2017.11.013. [Epub ahead of print].
14. Yan K, Gao H, Zhou X, Wu W, Xu W, Xu Y, et al. A retrospective analysis of postoperative recurrence of septated chronic subdural haematoma: endoscopic surgery vs. burr hole craniotomy. *Neurol Res.* (2017) 39:803–12. doi: 10.1080/01616412.2017.1321709
15. Guan F, Peng W-C, Huang H, Dai B, Zhu G-T, Xiao Z-Y, et al. Efficacy analysis of flexible neuroendoscopy combined with dry-field techniques in the treatment of chronic subdural hematoma. *Chin Med J (Engl).* (2019) 132:1359–62. doi: 10.1097/CM9.0000000000000249
16. Zhang Y, Chen S, Xiao Y, Tang W. Effects of dexamethasone in the treatment of recurrent chronic subdural hematoma. *World Neurosurg.* (2017) 105:115–21. doi: 10.1016/j.wneu.2017.05.135
17. Frati A, Salvati M, Mainiero F, Ippoliti F, Rocchi G, Raco A, et al. Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: a prospective study. *J Neurosurg.* (2004) 100:24–32. doi: 10.3171/jns.2004.100.1.0024
18. Prud'homme M, Mathieu F, Marcotte N, Cottin S. A pilot placebo controlled randomized trial of dexamethasone for chronic subdural hematoma. *Can J Neurol Sci.* (2016) 43:284–90. doi: 10.1017/cjn.2015.393
19. He C, Xia P, Xu J, Chen L, Zhang Q. Evaluation of the efficacy of atorvastatin in the treatment for chronic subdural hematoma: a meta-analysis. *Neurosurg Rev.* (2020). doi: 10.1007/s10143-019-01218-w. [Epub ahead of print].
20. Srivatsan A, Mohanty A, Nascimento FA, Hafeez MU, Srinivasan VM, Thomas A, et al. Middle meningeal artery embolization for chronic subdural hematoma: meta-analysis and systematic review. *World Neurosurg.* (2019) 122:613–9. doi: 10.1016/j.wneu.2018.11.167

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Risk of Recurrence of Chronic Subdural Hematomas After Surgery: A Multicenter Observational Cohort Study

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Background: Chronic Subdural Hematoma (CSDH) is a common condition in the elderly population. Recurrence rates after surgical evacuation range from 5 to 30%. Factors predicting recurrence remain debated and unclear.

Objective: To identify factors associated with increased risk of recurrence.

Methods: Cases of CSDHs that underwent surgical treatment between 2005 and 2018 in the Neurosurgery Units of two major Italian hospitals were reviewed. Data extracted from a prospectively maintained database included demographics, laterality, antithrombotic therapy, history of trauma, corticosteroid therapy, preoperative and postoperative symptoms, type of surgical intervention, use of surgical drain, and clinical outcomes.

Results: A total of 1313 patients was analyzed. The overall recurrence rate was 10.1%. The risk of recurrence was not significantly different between patients with unilateral or bilateral CSDH (10.4 vs. 8.8%, $p = 0.39$). The risk of recurrence was higher in patients that underwent surgical procedure without postoperative drainage (16.1 vs. 5.4%, $p < 0.01$). No relationship was found between recurrence rates and therapy with antithrombotic drugs ($p = 0.97$). The risk of recurrence was increasingly higher considering craniostomy, craniectomy, and craniotomy (9.3, 11.3, and 18.9%, respectively, $p = 0.013$). Lower recurrence rates following Dexamethasone therapy were recorded ($p = 0.013$).

Conclusion: No association was found between the risk of recurrence of CSDH after surgical evacuation and age, use of antithrombotic medication, or laterality. Burr-hole craniostomy was found to be associated with lower recurrence rates, when compared to other surgical procedures. Placement of surgical drain and Dexamethasone therapy were significantly associated with reduced risk of recurrence of CSDHs.

Keywords: craniostomy, chronic subdural hematoma, corticosteroids, drain, recurrence

INTRODUCTION

Chronic Subdural Hematoma (CSDH) is a common condition affecting the elderly population (>65 years). Its general incidence, estimated between 1.72 and 20.6 per 100,000 persons per year (1), is currently rising due to the increasing age and widespread use of antiplatelet and anticoagulant drugs (2). The appropriate treatment could be conservative or, when symptoms of compression occur, surgical. Burr-hole, twist drill, or craniotomy with or without drain placement are usually considered the surgical treatments of choice (3). Recurrence rates after surgical evacuation range from 5 to 30% (4, 5). Risk factors for recurrence are still debated and there is no universal consensus regarding the best surgical technique or optimal pre- and postoperative management (6, 7). The possible impact of recurrences after surgical treatment of a CSDH on the overall fatality rate is also extensively debated (8), although in most investigations and in the practical clinical situation of extremely old patients suffering from multiple major comorbidities, reliable information concerning the "disease specificity" profile of the fatality rate of CSDH recurrences appear to be still elusive and difficult to collect (8).

The aim of the present investigation is to identify risk factors for recurrence of bleeding, requiring a *repeated* surgical procedure, through the analysis of the clinical, radiological and surgical results of 1,313 surgical cases of CSDH, whose records, including presenting symptoms, hematoma characteristics, type of surgical treatment, corticosteroid treatment, were reviewed retrospectively.

METHODS

Participants and Eligibility

In the present cohort study, we analyzed data of patients suffering from CSDH who underwent surgical treatment between June 2005 and August 2018 in the Neurosurgery Unit of "Città della Salute e della Scienza" of Turin and of the Hospitals of "Sapienza" University of Rome. Clinical management, including surgical and medical treatment, followed a homogenous protocol during the years of the study in the participating centers.

Data were extracted and analyzed retrospectively from our Institutional databases and included: demographic information (age and sex), side of bleeding, antiplatelet and/or anticoagulant therapy at presentation, history of trauma, pre- and/or postoperative corticosteroid therapy, preoperative and postoperative neurological symptoms, type of surgical intervention, use of surgical drain, and neurological outcomes.

Inclusion and Exclusion Criteria

Clinical data belonging to patients who underwent surgery for the management of CSDH were collected. As previously specified, we collected a vast amount of data concerning these patients, in order to investigate the role played by different variables in determining the risk of recurrence and the clinical outcome. All the patients included were operated on for CSDH, this was the main inclusion criteria. Conversely, the absence or unavailability of radiological, clinical, surgical records, and in general, missing information about the follow-up were exclusion criteria. Exception done for all the patients whose radiological, clinical and surgical records presented missing data, the present cohort is a consecutive series.

Data Source

Clinical information was obtained at the time of admission and at follow-up clinic evaluation by fully trained neurosurgeons of the Departments. Patients' age was recorded and analyzed as a continuous variable and was divided subsequently, for statistical purposes, into four groups: <65, 65–74, 75–84, and >85 years. Side of bleeding was categorized into "unilateral" or "bilateral" hematoma. Antithrombotic therapy was considered as a categorical variable: "none," "antiplatelet," "anticoagulant," and "antiplatelet plus anticoagulant." History of trauma was considered as a dichotomous variable (1/0 - "yes" or "no").

Corticosteroid therapy was considered as a categorical dichotomous variable for the preoperative and the postoperative settings; dosage was not investigated, as it usually followed a standardized protocol consisting in an administration of i.m. or i.v. Dexamethasone at the dose of 4 mg twice a day. At admission, presenting symptoms were classified into four groups: "no symptoms," "headache," "focal deficit," or "GCS < 9" (i.e., coma). Type of surgical intervention was categorized into: "craniostomy," "craniectomy," or "craniotomy" (see Treatment Protocol). Use of postoperative surgical drain was considered as a dichotomous variable (1/0 - "yes" or "no"). In general, the use of drainage, the surgical technique, the corticosteroid therapy protocol, and the radiological follow-up program was completely identical in the different centers.

Outcome Variables

Main outcome variables were neurological outcomes and recurrence. The neurological conditions in the preoperative and postoperative period were analyzed with the Markwalder score (9) specifically conceived for the CSDH patients, in order to increase the comparability of our results. The neurological outcomes at last follow-up were furthermore classified into three groups: "improvement," "stable," "worsening"; this was considered as an ordinal variable on the ground of the variation of the Markwalder score between the pre and postoperative period. Neurological outcomes at last follow-up were further classified into four groups: "improvement," "stable," "worsening" or "stable in asymptomatic"; this was considered as a nominal categorical variable. Recurrence was defined as the necessity to repeat the surgical procedure, as determined by a consulting neurosurgeon, according to clinical symptoms (worsening neurological status compared to the first postoperative setting) and radiological findings (dimensional increase of the potentially residual hematoma compared to immediate postoperative and/or increase of midline shift). Variables associated with an increased incidence of recurrence were investigated. The mortality was recorded. In particular, we reported as CSDH related all the fatalities which had a direct or indirect relationship to CSDH, for instance, a myocardial infarction or a pulmonary embolism related the temporary interruption of antiplatelet drugs was considered to be related although involving other organs.

Surgical Indication and Timing

Surgical indication, for patients both at their first surgery or at their surgery for a recurrent CSDH, was reserved for patients presenting 1 cm or more of midline shift on the admission brain CT scan, patients presenting neurological signs or symptoms related to the CSDH (such as cognitive or behavioral slowing, motor or sensory disturbances, seizures), or asymptomatic patients whose maximum thickness of CSDH, independently from the neurological symptoms, was more than 2 cm. Cognitive slowing, a key clinical finding among the CSDH symptoms was defined by an obvious slowing of thought and movement, when the patient is examined, this finding becomes especially clear when the patient dialogs and/or executes motor commands of the examiner.

Surgery was usually performed as early as possible, i.e., within 48 h from admission, according to the clinical presentation of the patient. The procedure was delayed when the results of coagulation studies showed alteration of routine parameters: international normalized ratio (INR) $>$ 1.3, platelet count $<$ 100,000/mL, activated partial thromboplastin time (aPTT) $>$ 45 s. In the aforementioned cases, or when the anamnesis of the patient revealed the use of antiplatelet or anticoagulant drugs, surgery was delayed until after the normalization of parameters and/or the administration of antidotes or blood transfusion.

Surgical Technique

Surgical technique and clinical management were chosen according to radiological findings and surgeon's preference. In most cases a craniostomy with a single parietal or frontal burr-hole was performed. Alternatively, a craniectomy (over 2 $\times$ 2 cm) was executed with an high-speed drill. In selected cases, when acute clots were detected on the CT scan, a craniotomy was preferred. According to the surgeons' preferences through the years, placement of subdural drain was not always performed. The main reason not to leave the drain in the subdural compartment was the evidence of a satisfactory intraoperative decompression of the brain with the absence of enough space between the cortical surface and the dura mater to lay the drainage. When placed, the drainage was removed after approximately 48 h and after a postoperative CT scan, confirming the satisfactory outcome of the procedure.

Clinical Management

The clinical management protocol was homogeneous, identical in the different centers. Whenever possible, according to the other comorbidities (e.g., diabetes, osteoporosis, hypertension, glaucoma) preoperative and/or postoperative corticosteroid taper (lasting up to 2 weeks after the procedure) with Dexamethasone (starting at 4 mg iv bid) was administered. In case of the aforementioned comorbidities, seriously affected by corticosteroid therapy, the dosage and the resulting length of the treatments were halved. The follow-up program included a CT scan and clinical evaluation about 4 weeks after surgery. Management was then individualized according to the clinical and radiological findings after the procedure. The reinstitution of antiplatelet or anticoagulant drugs was planned together with handling cardiologists or primary care physicians. In case of recurrence, the same aforementioned principles for surgical indication and clinical management were followed.

Statistical Analysis and Power of the Study

Descriptive statistics were reported as a median, mean, and standard deviation for continuous variables or frequency and percentage for categorical variables. Comparisons of proportions were performed with Chi^2 test for categorical variables, Risk was stratified according to standard odds radio methods. Multivariate, Repeated Measures and Univariate ANOVA analyses were used for the ordinal and continuous variable, as much as Logistic Regression was used to predict the results concerning the endpoint variable. Statistical significance was defined with a p-value < 0.05. All statistical analyses were performed using SPSS Statistics software (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, New York, USA). In regards to the intrinsically dichotomous nature of prediction/association (1/0 - relapse/no relapse) and in regards to the endpoints selected, the study presents an excellent *post-hoc* statistical estimated power ($1 - \beta = 0.947$ for α 0.05 and effect size "f" as low as $= 0.3$), thus providing extremely reliable conclusions.

Compliance to Ethical Standards

The informed consents were approved by the Institutional Review Board of our Institutions both in regard to the clinical and research purposes. Before surgical procedure, all the patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed. This study is perfectly consistent with Helsinki declaration of Human Rights.

RESULTS

Participants and Descriptive Data

A total of 1,313 patients was analyzed (**Table 1**). Average age was 76.6 years (standard deviation 9.9, median 78); female to male ratio was 0.4/1 (403/910). In 75.8% of cases the CSDH was unilateral. Anticoagulant therapy was reported in 13.6% of cases (179 patients), while antiplatelet in 27.3% (358 patients). Data about past history were reported in 831 cases, with 458 patients reporting a traumatic event having occurred before the diagnosis (55.1%). A neurological deficit was recorded in 1,053 patients (80.5%), while less common presentations were headache (10.1%), history of incidental finding (7.0%), and coma (2.4%). In 1,161 patients (88.4%) surgery consisted in single burr-hole craniostomy. Craniectomy was performed in 4.7% of cases, while craniotomy in 6.9%. A drainage was placed in 537 patients (73.0%, data available for 736 cases).

Outcome Data

Of all treated patients, the vast majority (73.3%) was discharged at home and then followed up in the outpatient services of our institution; 26.7% of patients were transferred to another hospital for neurological rehabilitation after the operation. At follow-up 29 patients were dead because of complications related to the CSDH realizing an overall disease specific mortality

TABLE 1 | Demographics, management, and surgical data.

		No. of patients/No. of patients for whom data are available (%)	
Total no. of patients	1,313		
Mean age in years (SD)	76.6 (9.9)		
Median age in years	78		
Sex	F	403/1,313	(31.7)
	M	910/1,313	(69.3)
	F/M ratio	0.4/1	
Unilateral or bilateral	Unilateral	995/1,313	(75.8)
	Bilateral	318/1,313	(24.2)
Antithrombotic therapy	Anticoagulant	179/1,313	(13.6)
	Antiplatelet	358/1,313	(27.3)
Corticosteroid therapy	Preop	143/719	(19.9)
	Postop	294/719	(40.9)
History of trauma	Yes	458/831	(55.1)
	No	340/831	(40.9)
Surgical drain	Yes	537/736	(73.0)
	No	199/736	(27.0)
Operation	Craniostomy	1,161/1,313	(88.4)
	Craniectomy over 2 × 2 cm	62/1,313	(4.7)
	Craniotomy	90/1,313	(6.9)
Recurrence		132/1,313	(10.1)
Death		29/1,313	(2.2)
Discharge	Home	588/802	(73.3)
	To other hospital	214/802	(26.7)
Preop symptoms	None	92/1,308	(7.0)
	Headache	132/1,308	(10.1)
	Neurological deficit	1053/1,308	(80.5)
	GCS < 9	31/1,308	(2.4)
Neurological outcome	Improvement	1,031/1,266	(81.4)
	Stable	124/1,266	(9.8)
	Worsening	9/1,266	(0.7)
	Stable in asymptomatic	102/1,266	(8.1)

rate of 2.2%. Neurological improvement was recorded in the majority of symptomatic patients (81.4%). A total of 9.8% of patients showed stable postoperative symptoms, while 8.1% of patients were asymptomatic preoperatively and did not worsen. A neurologic worsening was recorded in 0.7% of all cases. In a total of 719 cases the details of the corticosteroid treatment were reported in the clinical records, A total of 401 patients did not undergo any corticosteroid treatment (55.8%), 195 patients underwent preoperative or postoperative corticosteroid treatment (14.9%), whereas 123 patients received pre and postoperative treatment (9.4%).

Risk of Recurrence

Risk factors for recurrence were investigated and summarized in **Table 2**. The overall recurrence rate of the entire cohort was 10.1%. No association was found between patient age group (<65, 65–74, 75–84, and >85 years) and rate of recurrence ($p = 0.93$), but male sex was statistically associated with the risk of relapse ($p = 0.011$, OR 95%IC 1.080–2.550 – **Table 2**) The risk of recurrence was not significantly different between patients with unilateral or bilateral CSDH (10.4 vs. 8.8%, $p = 0.39$).

Recurrence rates were much higher in patients, who underwent surgical procedure without postoperative drainage, namely, positioning of surgical drainage was statistically strongly associated to a reduction of the risk of relapse (16.1 vs. 5.4%, $p < 0.01$ - **Figure 1A**).

No association was found between recurrence rates and therapy with antiplatelet or anticoagulant drugs, or a combination of them ($p = 0.97$). The risk of recurrence was increasingly higher considering craniostomy, craniectomy, and craniotomy (9.3, 11.3, and 18.9%, respectively, $p = 0.013$ - **Figure 1B**).

Considering corticosteroid therapy, lower recurrence rates following Dexamethasone therapy were recorded ($p = 0.013$). Specifically, patients that did not receive Dexamethasone at all, patients receiving therapy only before the procedure, patients that received Dexamethasone only after surgery, and patients

TABLE 2 | Risk of recurrence.

		Risk of recurrence [95% IC]	*p*-value
Age	<65	10.1% [6.2–16 %]	0.93
	65–74	10% [6.7–13.2 %]	
	75–84	10% [9.3–14.9 %]	
	>85	10% [6.5–13.6 %]	
Sex	Male	12.6% [11.3–12.9 %]	0.011
	Female	7.8% [5.7–11.3 %]	
Unilateral or bilateral	Unilateral	10.4% [8.7–12.5 %]	0.39
	Bilateral	8.8% [6.1–12 %]	
Surgical drain	Yes	5.4% [3.8–7.6 %]	< 0.01
	No	16.1% [12–22 %]	
Operation	Craniostomy	9.3% [7.8–11.1 %]	0.013
	Craniectomy over 2 × 2 cm	11.3% [5.5–21.5 %]	
	Craniotomy	18.9% [12.1–28.1 %]	
Antithrombotic therapy	None	10.2% [8.2–12.5 %]	0.97
	Antiplatelet	9.5% [6.8–13 %]	
	Anticoagulant	10.6% [6.8–16.2 %]	
	Antiplatelet + Anticoagulant	10% [1–40 %]	
Corticosteroid therapy	None	11% [8.3–14.4 %]	0.013
	Preop	4.2% [0.7–20.2 %]	
	Postop	6.9% [3.6–11.1 %]	
	Preop + Postop	2.4% [0.8–6.9 %]	
Preop symptoms	None	5.4% [2.3–12.1 %]	0.20
	Headache	6.8% [3.6–12.4 %]	
	Neurological deficit	10.9% [9.2–12.9 %]	
	Cognitive impairment	9.5% [9.4%–30.7%] $p = 0.034$	
	GCS < 9	9.7% [3.3–24.9 %]	
Neurological outcome	Improvement	5% [2–12 %]	0.22
	Stable	10% [8.5–12.9 %]	
	Worsening	11.7% [6.6–20.6 %]	
	Stable in asymptomatic	22.2% [6.3–54.7 %]	

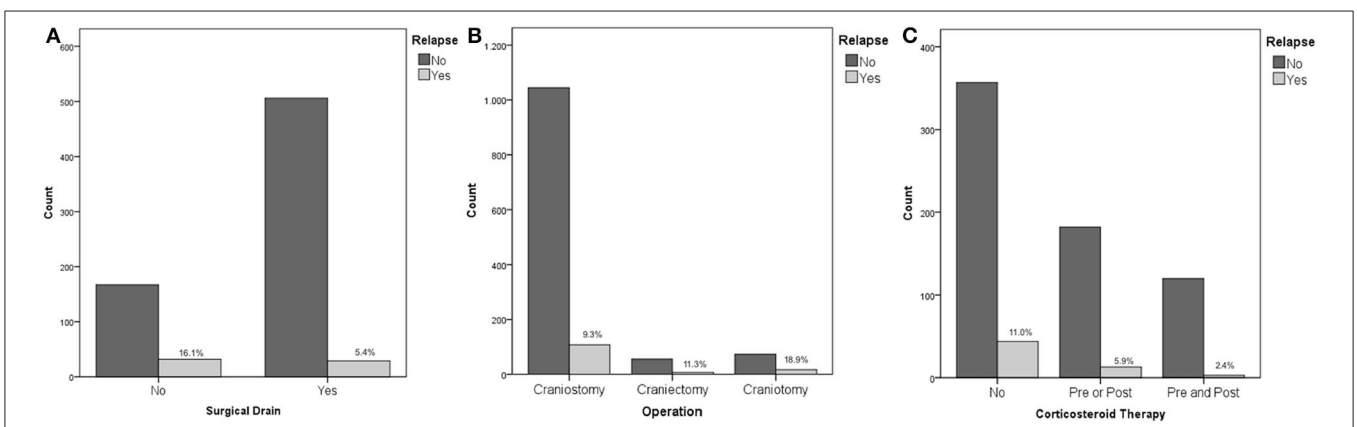

FIGURE 1 | (A) Placement of surgical drain and risk of recurrence; **(B)** Operation type and risk of recurrence; **(C)** Corticosteroid therapy and risk of recurrence.

who received corticosteroid therapy both before and after the procedure had a risk of recurrence of 11, 4.2, 6.9, and 2.4%, respectively (**Figure 1C**). Although pre and postoperative corticosteroid therapy was proven to be associated with a reduced relapse rate, corticosteroid administration, both in the pre and postoperative was not directly associated with a

decreased fatality rate ($p = 0.255$ and $p = 0.221$ pre and post, respectively).

Neurological outcome was not associated with the rate of recurrence ($p = 0.22$) being a repeated surgery no factor predicting a worse outcome. The only clinical feature associated to the incidence of relapses was the cognitive slowing (9.4 vs. 5.5% - $p = 0.034$), being probably the clinical expression of a generalized cortical dysfunction, which was associated to a higher risk of relapses (**Figure 2A**); notably, the risk of fatality was higher in the subgroup of patients who presented a preoperative motor deficit ($p = 0.026$). For what our cohort is concerned, according to our analyses, relapse of a CSDH is, in our cohort, a statistically significant predictor of increased fatality risk ($p = 0.004$, OR 3.939 95% IC 1.689–9.184 – **Figure 2B**).

Other Analyses

Multivariate ANOVA analyses were performed to rule out the possible influence of confounding factors. In particular, we found an interesting statistically significant interaction in patients under anticoagulant therapy with an history of trauma: presurgical corticosteroid treatment was associated to better postoperative functional results as measured with the Markwalder scale ($p = 0.001$). Moreover, presurgical corticosteroid therapy was associated to better Markwalder scores in patients who presented a history of trauma ($p = 0.002$). The better Markwalder outcomes, were, in our cohort, experienced by patients undergoing both a pre and postoperative corticosteroid therapy ($p = 0.043$). ANOVA Repeated Measures analyses investigated the endpoint variables: patients undergoing anticoagulant therapy, experienced averagely statistically significant worse outcomes as measured with Markwalder scores, in respect to patients whose therapy regime did not include anticoagulants, independently from their preoperative conditions ($p = 0.027$ – **Figure 2C**).

Logistic Regression Analyses were added in order to predict the postoperative functional status, concerning the preoperative use of antiplatelet and anticoagulant agents, pre and postoperative use of corticosteroid therapy, surgical drain, laterality of the hematoma and the impact on the functional results of operating a relapse. The results are summarized in **Table 3**. Notably, the number of patients who experience a postoperative improvement, in case of history of anticoagulant or antiplatelet agents intake ranges between 31.5 and 35.3% ($p = 0.23$), and concerning the corticosteroid therapy, a strong statistically significant ($p = 0.036$) prediction of 43.2% of patients experiencing an improvement of their conditions supports the postoperative use of corticosteroids.

DISCUSSION

The present multi-institutional analysis of 1,313 surgical cases of CSDH found then no association between the risk of recurrence and age, use of antithrombotic medication, or whether the hematoma was unilateral or bilateral. Surgical management influenced risk of recurrence, with patients receiving burr-hole craniostomy having the lowest recurrence rate, followed by patients undergoing a wider craniectomy and, lastly, patients receiving a craniotomy. Placement of a surgical drain was associated with a significantly reduced risk of recurrence. Finally, corticosteroid treatment with Dexamethasone was found to be associated with lower recurrence rates. Several papers regarding the treatment of CSDHs have recently been published; for the most part the results from the present study confirm previous findings reported in the literature, providing strengthened evidence in relation to the numerosity of the investigated population.

Chronic subdural hematoma is a common disorder that affects especially elderly people and is associated with substantial morbidity and mortality (5). In the general population its incidence is estimated to be between 1.72 and 20.6 per 100,000 per year, but it is higher for people aged 70 years and older (58 per 100,000 per year) (10–12). Because of the growing proportion of people aged 65 years and older, which is expected to double worldwide between 2000 and 2030 (13), a large rise in the incidence of CSDHs is expected and, consequentially, an increased interest toward the CSDH treatment has been highlighted in the last years (6). Moreover, small differences in surgical or medical treatment can potentially have a great impact on risk of recurrence, making optimization of clinical management of these patients a necessity with extensive repercussions.

Whether age and sex have an influence on the rates of recurrence after surgery for CSDH evacuation is debated, with some reports suggesting older age and male sex to be at higher risk (2) and others with opposite findings (14). In another series, a median age of 78 (interquartile range 70–84) for patients who did not have a recurrence has been highlighted, compared to a median age of 80 (76–87) for patients who did (15). Though such finding was statistically significant, it is arguable that a 2-year difference in age is not clinically relevant. Other authors pointed out in their series that average age was 74 for patients who did not need reoperation, vs. 74.5 for patients that required a second operation (14). This difference was reported not to be statistically significant; it is interesting to point out the difference in average age detailed in different series and different populations.

Use of antiplatelet or anticoagulant medication has consistently been found not to be significantly associated with an increased risk of CSDH recurrence (4, 16). In a Swedish study, preoperative antithrombotic treatment was found not to influence rate of recurrence at 3 months or perioperative mortality; it did, however, increase the risk of perioperative morbidity (17). Some authors have suggested that resumption of anticoagulant therapy is safe 72 h after surgery (4), while antiplatelets should be withheld for at least 7 days following CSDH drainage (7). Results of the present study support the idea that preoperative antithrombotic therapy does not increase the risk of recurrence of CSDH after evacuation; however, treatment should be tailored to each patient, taking specific cardiovascular risks into consideration.

Type of surgical evacuation for CSDHs has been a matter of debate. Though bedside twist-drill craniostomy has been successfully employed (18), a single or double burr-hole craniotomy under local or general anesthesia is usually the procedure of choice. Extended craniectomy or craniotomy

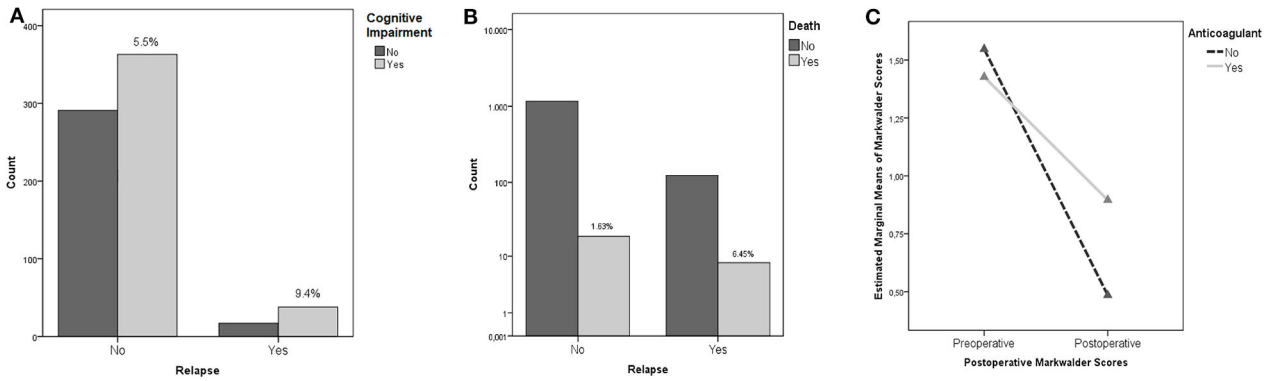

FIGURE 2 | (A) Cognitive Impairment and risk of recurrence (the percentages concern the specific subgroup of patients who presented cognitive impairment in the preoperative period). **(B)** Recurrence and mortality. The percentages, namely the fatality rate, is significantly higher in patients who experienced a recurrence of CSDH. **(C)** ANOVA Repeated Measures analysis demonstrating the better outcomes (as measured with Markwalder scale) of patients with history of anticoagulant intake undergoing a postoperative corticosteroid therapy.

that allow for resection of the capsule or membrane of the hematoma have been shown neither to provide advantages in lowering recurrence rates nor to improve the neurological outcome (19). The results of the present study showed a higher risk of recurrence when extended craniectomy or craniotomy was performed. However, this might depend on the specific characteristics of the hematomas that were chosen to be evacuated with these wider approaches, perhaps hematomas with a subacute component; in other words, these results might be distorted by selection bias. In this series the procedure of choice was single burr-hole craniostomy. It has been reported that a double burr-hole does not provide a significant clinical advantage and leads to higher rates of recurrence (20, 21). The rates of recurrence presented in our series suggest that the less invasive choice of a single burr-hole is adequate for obtaining satisfactory clinical outcomes.

Many studies demonstrated that an important modifiable risk factor for CSDH recurrence is postoperative drainage. Drain placement has been associated with lower recurrence (3.1–10.5% with drain vs. 17–33% without) (17, 22–25). A randomized controlled trial (RCT) reported a reduction of recurrence rates from 24 to 9.3% and no additional complication with the use of a subdural drain (11); the trial was even stopped early because of the clear results. An Indian prospective randomized trial showed similar complications and mortality, but fewer recurrences with drain placement (26 vs. 9%) (26). Other study groups and meta-analyses reached the same conclusions (27–31). An Indian RCT reported a lower rate of recurrence with a single burr-hole with drain placement vs. two burr-holes (1.4 vs. 15.7%) (20). The present study corroborates such literature, providing yet clearer evidence to support the use of postoperative drainage in all cases of surgical evacuation of CSDH.

The position of the drain (subdural vs. subperiosteal) does not appear to modify the outcome (32). Some authors suggested that a subperiosteal drainage could help reduce seizures and infection, avoiding direct contact with the hematoma membranes; in their study re-intervention rate for recurrence was 9.3% with drain placement (33). Although a drain in the subdural space would be the most intuitive solution to allow for complete evacuation of the hematoma, it is arguable that, once a communication between the subdural and subperiosteal spaces is made through a craniostomy, both spaces are suitable for drain placement. Indeed, a recently published RCT demonstrates the non-inferiority of subperiosteal placement in terms of recurrence rates, in the setting of reduced complication rates (18). It has been stated that, when placing a subdural drain, it should not be inserted for more than approximately 4 cm (1). The duration of drainage may matter, but evidence is lacking; a Chinese study reported 6.6% recurrence with drain placement, ranging from 16.3% with drain removal prior to 3 days to 1.3% if removed thereafter (3). However, these results must be interpreted cautiously, as they were obtained retrospectively and timing of removal was decided on an individual non-randomized basis. The present study suggests that 48 h of postoperative drainage is adequate to provide satisfactory outcomes, without significant complications.

The anti-inflammatory and anti-angiogenetic properties of Dexamethasone have repeatedly been shown to be beneficial in treating CSDH, when associated to surgical management (26, 34). In a meta-analysis the adjuvant use of Dexamethasone resulted in a lower recurrence rate if compared with non-Dexametasone therapy (RR, 0.54; 95% CI, 0.33–0.88; $p = 0.01$) (12). Moreover, no additional complications or morbidity appeared to be associated with corticosteroid treatment in this setting (15). The mechanism of action of corticosteroids in CSDH has been associated to the inhibition of the formation granulation tissue, responsible for the creation of a capsule surrounding the hematoma and containing numerous newly formed, permeable capillaries, which could be responsible for recurrent bleeding (22, 35–37). The results of the present study substantiate the hypothesis that Dexamethasone is beneficial as an adjunct treatment to surgery. The lowest of recurrence rates were associated with a combination of preoperative and postoperative administration of corticosteroid therapy; postoperative treatment

TABLE 3 | Multinomial logistic regression predicting the outcomes of patients on the ground of their antiplatelet/anticoagulant and corticosteroid treatments.

Post-corticosteroid therapy	Pre-corticosteroid therapy	Postoperative status (Variation of Markwalder scores)	Frequency			Percentage	
			Observed	Predicted	Pearson residual	Observed	Predicted
No	No	Worsened	4	3.934	0.033	1.0%	1.0%
		Stable	259	260.011	−0.108	66.2%	66.5%
		Improved	128	127.055	0.102	32.7%	32.5%
	Yes	Worsened	1	1.066	−0.065	4.2%	4.4%
		Stable	20	18.989	0.508	83.3%	79.1%
		Improved	3	3.945	−0.521	12.5%	16.4%
Yes	No	Worsened	2	2.066	−0.046	1.2%	1.2%
		Stable	95	93.989	0.157	56.2%	55.6%
		Improved	72	72.945	−0.147	42.6%	43.2%
	Yes	Worsened	7	6.934	0.026	5.8%	5.8%
		Stable	84	85.011	−0.203	70.0%	70.8%
		Improved	29	28.055	0.204	24.2%	23.4%
Antiplatelet	**Anticoagulant**	**Postoperative status (Variation of Markwalder scores)**	**Frequency**			**Percentage**	
			Observed	**Predicted**	**Pearson residual**	**Observed**	**Predicted**
No	No	Worsened	11	11.027	−0.008	2.6%	2.6%
		Stable	276	274.505	0.154	66.2%	65.8%
		Improved	130	131.469	−0.155	31.2%	31.5%
	Yes	Worsened	2	1.973	0.019	1.9%	1.9%
		Stable	67	68.495	−0.309	64.4%	65.9%
		Improved	35	33.531	0.308	33.7%	32.2%
Yes	No	Worsened	1	0.973	0.027	0.5%	0.5%
		Stable	117	118.495	−0.231	63.9%	64.8%
		Improved	65	63.531	0.228	35.5%	34.7%
	Yes	Worsened	0	0.027	−0.163	0%	0.4%
		Stable	6	4.505	1.180	85.7%	64.4%
		Improved	1	2.469	−1.162	14.3%	35.3%

alone was still associated with a significant benefit compared to no corticosteroid therapy.

In the literature, mortality during hospitalization for SCSH ranges from 5 to 13.3% (31, 38, 39). In the present study, perioperative mortality was 2.2% with a fatal outcome in 29 cases.

Limitations and Generalizability

Presented results must be considered in the context of the limitations of this study. The lack of randomization in the design of the study inevitably hinders generalizability of the conclusions that can be drawn. Moreover, the focus on surgical cases only, might not provide a complete depiction of the pathology at hand. However, the large number of the population that was analyzed and the multicenter design allow for suggesting specific indications regarding management of CSDHs. Since small differences in surgical or medical treatment can potentially have a great impact on risk of recurrence, the homogeneous protocol followed by the two centers constitutes a valid support to this study. This study, therefore, substantiates, reassumes, and emphasizes key concepts of CSDHs treatment, in accordance with data reported in the literature.

CONCLUSION

In conclusion, no association was found between the risk of recurrence of CSDH after surgical evacuation and age, use of antithrombotic medication, or laterality. Burr-hole craniostomy was found to be associated with the lowest recurrence rate, when compared to other surgical procedures. Placement of surgical drain and Dexamethasone therapy were significantly associated with reduced risk of recurrence of CSDHs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for

participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FC: study concept, writing, and study analysis. AP: study concept, writing, and data analysis. GV: data analysis. MMa: writing. AM, MMi, GD'A, MP, and CF: data collection. ML, AF, and DG: supervision. FT and FZ: study analysis. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Weng W, Li H, Zhao X, Yang C, Wang S, Hui J, et al. The depth of catheter in chronic subdural haematoma: does it matter? *Brain Inj.* (2019) 33:717–22. doi: 10.1080/02699052.2018.1531312
2. Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt N, de Laat K, et al. Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial. *Trials.* (2018) 19:1–10. doi: 10.1186/s13063-018-2945-4
3. Yu GJ, Han CZ, Zhang M, Zhuang HT, Jiang YG. Prolonged drainage reduces the recurrence of chronic subdural hematoma. *Br J Neurosurg.* (2009) 23:606–11. doi: 10.3109/02688690903386983
4. Ryu SM, Yeon JY, Kong DS, Hong SC. Risk of recurrent chronic subdural hematoma associated with early warfarin resumption: a matched cohort study. *World Neurosurg.* (2018) 120:e855–e62. doi: 10.1016/j.wneu.2018.08.177
5. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. *J Neurol Neurosurg Psychiatry.* (2003) 74:937–43. doi: 10.1136/jnnp.74.7.937
6. Almenawer SA, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. *Ann Surg.* (2014) 259:449–57. doi: 10.1097/SLA.0000000000000255
7. Mehta V, Harward SC, Sankey EW, Nayar G, Codd PJ. Evidence based diagnosis and management of chronic subdural hematoma: a review of the literature. *J Clin Neurosci.* (2018) 50:7–15. doi: 10.1016/j.jocn.2018.01.050
8. Rauhala M, Helén P, Seppä K, Huhtala H, Iverson GL, Niskakangas T, et al. Long-term excess mortality after chronic subdural hematoma. *Acta Neurochir.* (2020) 162:1467–78. doi: 10.1007/s00701-020-04278-w
9. Markwalder TM, Steinsiepe KF, Rohner M, Reichenbach W, Markwalder H. The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. *J Neurosurg.* (1981) 55:390–6. doi: 10.3171/jns.1981.55.3.0390
10. Kudo H, Kuwamura K, Izawa I, Sawa H, Tamaki N. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. *Neurol Med Chir.* (1992) 32:207–9. doi: 10.2176/nmc.32.207
11. Santarius T, Hutchinson PJ. Chronic subdural haematoma: time to rationalise treatment? *Br J Neurosurg.* (2004) 18:328–32. doi: 10.1080/02688690400004845
12. Yang W, Huang J. Chronic subdural hematoma: epidemiology and natural history. *Neurosurg Clin N Am.* (2017) 28:205–10. doi: 10.1016/j.nec.2016.11.002
13. Kinsella K, Velkoff VA. *An Aging World: 2001*. Washington, DC: US Gov Print Off US Census (2001).
14. Bartek J, Sjåvik K, Kristiansson H, Ståhl F, Fornebo I, Förander P, et al. Predictors of recurrence and complications after chronic subdural hematoma surgery: a population-based study. *World Neurosurg.* (2017) 106:609–14. doi: 10.1016/j.wneu.2017.07.044
15. Holl DC, Volovici V, Dirven CMF, van Kooten F, Miah IP, Jellema K, et al. Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis. *Acta Neurochir.* (2019) 161:1231–42. doi: 10.1007/s00701-019-03881-w
16. Fornebo I, Sjåvik K, Alibeck M, Kristiansson H, Ståhl F, Förander P, et al. Role of antithrombotic therapy in the risk of hematoma recurrence and thromboembolism after chronic subdural hematoma evacuation: a population-based consecutive cohort study. *Acta Neurochir.* (2017) 159:2045–52. doi: 10.1007/s00701-017-3330-x
17. Gazzeri R, Galarza M, Neroni M, Canova A, Refice GM, Esposito S. Continuous subgaleal suction drainage for the treatment of chronic subdural haematoma. *Acta Neurochir.* (2007) 149:487–93. doi: 10.1007/s00701-007-1139-8
18. Soleman J, Lutz K, Schaedelin S, Kamenova M, Guzman R, Mariani L, et al. Subperiosteal vs subdural drain after burr-hole drainage of chronic subdural hematoma: a randomized clinical trial (cSDH-Drain-Trial). *Neurosurgery.* (2019) 85:E825–34. doi: 10.1093/neuros/nyz095
19. Lee JY, Ebel H, Ernestus RI, Klug N. Various surgical treatments of chronic subdural hematoma and outcome in 172 patients: is membranectomy necessary? *Surg Neurol.* (2004) 61:523–7. doi: 10.1016/j.surneu.2003.10.026
20. Kutty SA, Johny M. Chronic subdural hematoma: a comparison of recurrence rates following burr-hole craniostomy with and without drains. *Turk Neurosurg.* (2014) 24:494–7.
21. Smith MD, Kishikova L, Norris JM. Surgical management of chronic subdural haematoma: one hole or two? *Int J Surg.* (2012) 10:450–2. doi: 10.1016/j.ijsu.2012.08.005
22. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J Neuroinflammation.* (2017) 14:108. doi: 10.1186/s12974-017-0881-y
23. Gurelik M, Aslan A, Gurelik B, Ozum U, Karadag O, Kars HZ. A safe and effective method for treatment of chronic subdural haematoma. *Can J Neurol Sci.* (2007) 34:84–7 doi: 10.1017/S0317167100005849
24. Tsutsumi K, Maeda K, Iijima A, Usui M, Okada Y, Kirino T. The relationship of preoperative magnetic resonance imaging findings and closed system drainage in the recurrence of chronic subdural hematoma. *J Neurosurg.* (1997) 87:870–5. doi: 10.3171/jns.1997.87.6.0870
25. Wakai S, Hashimoto K, Watanabe N, Inoh S, Ochiai C, Nagai M. Efficacy of closed-system drainage in treating chronic subdural hematoma: a prospective comparative study. *Neurosurgery.* (1990) 26:771–3. doi: 10.1097/00006123-199005000-00006
26. Singh AK, Suryanarayanan B, Choudhary A, Prasad A, Singh S, Gupta LN. A prospective randomized study of use of drain versus no drain after burr-hole evacuation of chronic subdural hematoma. *Neurol India.* (2014) 62:169–74. doi: 10.4103/0028-3886.132364
27. Alcalá-Cerra G, Young AMH, Moscote-Salazar LR, Paternina-Caicedo Á. Efficacy and safety of subdural drains after burr-hole evacuation of chronic subdural hematomas: systematic review and meta-analysis of randomized controlled trials. *World Neurosurg.* (2014) 82:1148–57. doi: 10.1016/j.wneu.2014.08.012
28. Edlmann E, Holl DC, Lingsma HF, Bartek J Jr, Bartley A, Duerinck J, et al. Systematic review of current randomised control trials in chronic subdural haematoma and proposal for an international collaborative approach. *Acta Neurochir.* (2020) 162:763–76. doi: 10.1007/s00701-020-04218-8
29. Guilfoyle MR, Hutchinson PJA, Santarius T. Improved long-term survival with subdural drains following evacuation of chronic subdural haematoma. *Acta Neurochir.* (2017) 159:903–5. doi: 10.1007/s00701-017-3095-2
30. Liu W, Bakker NA, Groen RJM. Chronic subdural hematoma: a systematic review and meta-analysis of surgical procedures. *J Neurosurg.* (2014) 121:665–73. doi: 10.3171/2014.5.JNS132715
31. Ramachandran R, Hegde T. Chronic subdural hematomas–causes of morbidity and mortality. *Surg*

Neurol. (2007) 67:363–7. doi: 10.1016/j.surneu.2006.07.022
32. Glancz LJ, Poon MTC, Coulter IC, Hutchinson PJ, Kolias AG, Brennan PM. Does drain position and duration influence outcomes in patients undergoing burr-hole evacuation of chronic subdural hematoma? Lessons from a UK Multicenter Prospective Cohort Study. *Neurosurgery.* (2018) 85:486–93. doi: 10.1093/neuros/nyy366
33. Zumofen D, Regli L, Levivier M, Krayenbuhl N. Chronic subdural hematomas treated by burr hole trepanation and a subperiostal drainage system. *Neurosurgery.* (2009) 64:1112–6. doi: 10.1227/01.NEU.0000345633.45961.BB
34. Berghauser Pont LME, Dirven CMF, Dippel DWJ, Verweij BH, Dammers R. The role of corticosteroids in the management of chronic subdural hematoma: a systematic review. *Eur J Neurol.* (2012) 19:1397–403. doi: 10.1111/j.1468-1331.2012.03768.x
35. Glover D, Labadie EL. Physiopathogenesis of subdural hematomas. Part 2: inhibition of growth of experimental hematomas with dexamethasone. *J Neurosurg.* (1976) 45:393–7. doi: 10.3171/jns.1976.45.4.0393
36. Hong H-J, Kim Y-J, Yi H-J, Ko Y, Oh S-J, Kim J-M. Role of angiogenic growth factors and inflammatory cytokine on recurrence of chronic subdural hematoma. *Surg Neurol.* (2009) 71:161–6. doi: 10.1016/j.surneu.2008.01.023
37. Moskala M, Goscinski I, Kaluza J, Polak J, Krupa M, Adamek D, et al. Morphological aspects of the traumatic chronic subdural hematoma capsule: SEM studies. *Microsc Microanal.* (2007) 13:211–9. doi: 10.1017/S1431927607070286
38. Rohde V, Graf G, Hassler W. Complications of burr-hole craniostomy and closed-system drainage for chronic subdural hematomas: a retrospective analysis of 376 patients. *Neurosurg Rev.* (2002) 25:89–94 doi: 10.1007/s101430100182
39. Smely C, Madlinger A, Scheremet R. Chronic subdural haematoma–a comparison of two different treatment modalities. *Acta Neurochir.* (1997) 139:818–25. doi: 10.1007/BF01411399

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A Comparative Study of Chronic Subdural Hematoma in Patients With and Without Head Trauma: A Retrospective Cross Sectional Study

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Background: The clinical features of chronic subdural hematomas (CSDHs) in patients with and without a history of head trauma have remained unclear. Here, we investigated differences in clinical characteristics in CSDH patients with and without head trauma.

Methods: We retrospectively collected clinical characteristics of CSDH patients who had undergone exhaustive drainage strategies via burr-hole craniostomies from August 2011 to May 2019. We divided patients into a trauma group (i.e., head trauma) and a no-trauma group. Chi-square tests or *t*-tests were used to analyze differences in clinical characteristics between the two groups. Multiple linear regression analysis was performed to analyze the relationships between the clinical characteristics and either reduction of the hematoma cavity or length of the hospital stay in CSDH patients with trauma.

Results: We collected data from 1,307 CSDH patients, among whom 805 patients had a history of head trauma whereas 502 patients did not. The mean age of patients with head trauma was 64.0 ± 16.1 years, while that of patients without head trauma was significantly younger at 61.5 ± 17.9 years ($p = 0.010$). Furthermore, more patients in the no-trauma group had a history of hypertension compared to those in the trauma group (40.2 vs. 32.9%, $p = 0.007$). Dizziness occurred in 29.2% of patients with trauma and in 23.1% of patients without trauma ($p = 0.016$). A greater number of patients with trauma showed a reduction of hematoma cavity after surgery compared to that of patients without trauma ($p = 0.002$). The length of hospital stay in patients with trauma was 7.9 ± 4.5 days, which was longer than that of patients without trauma (7.3 ± 3.7 days, $p = 0.016$). In contrast, there were no significant different differences between the two groups in terms of the densities of hematomas on computed-tomography scans, complications, mortality rates, recurrence rates, or outcomes.

Conclusion: Our findings indicate that there were some noteworthy differences in the clinical and pathogenic characteristics of CSDH patients with and without head trauma. However, our findings also indicate that if an optimal treatment method is employed, such as our exhaustive drainage strategy, similar treatment outcomes can be achieved between these groups.

Keywords: clinical characteristic, common, chronic subdural hematoma, difference, head trauma

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INTRODUCTION

Chronic subdural hematomas (CSDHs) generally increase with age and are more prevalent in older patients, especial in individuals >65 years old (1). Although many risk factors may contribute to the occurrence of CSDHs, the pathogenic mechanisms underlying CSDH have remained unclear. Head trauma is regarded as a primary cause of CSDH, and 30–75% of CSDH patients have a history of head trauma within 3 months prior to hospital admission (2, 3). However, some patients exhibit CSDH without any known cause. It has been reported that arachnoid cysts, brain surgery, coagulation factors, ventriculoperitoneal shunts, and hypertension may play roles in some spontaneous CSDH patients (4, 5). According to these differences, some reports have found that CSDH patients with a history of head trauma display different clinical and radiological characteristics, as well as different outcomes, compared to those of CSDH patients without a history of head trauma (6–8). However, these conclusions are based on a small number of cases, and these cases have exhibited high recurrence rates. Therefore, further studies with larger sample sizes are needed to more comprehensively analyze outcomes and clinical/radiological characteristics of CSDH patients with or without a history of head trauma in order to guide improved management and treatment of each type of CSDH patient.

In the present study, we retrospectively analyzed 1,307 CSDH patients, and we found that age, a history of hypertension, dizziness symptoms, and the interval from CSDH onset to admission were all significantly different between CSDH patients with and without head trauma. In contrast, there were no significant differences between the two groups in terms of radiological characteristics, outcomes, or recurrence. However, we found that CSDH patients with head trauma exhibited a larger reduction of hematoma cavity after surgery and a longer length of hospital stay compared with those of CSDH patients without a history of head trauma. Therefore, our finding may help to clarify the similarities and differences in the underlying characteristics of CSDH in patients with or without a history of head trauma.

METHODS

Symptomatic CSDH was defined as a predominantly subdural collection with hypodensity, isodensity, or mixed density in computed tomography (CT) scans; and patients with other causes of CSDH identified during operation or subsequent treatment (e.g., empyema, arachnoid cyst) were excluded from further analysis in the present study, and patients taking steroids or atorvastatin for CSDH before operation were also excluded. Following these exclusions, data from 1,307 patients with a primary or recurrent symptomatic CSDH confirmed on cranial imaging were collected from August 2011 to May 2019 at the Department of Neurosurgery in Beijing Tiantan Hospital. Age was not used as an inclusion or exclusion criterion. According to our previous report, an exhaustive drainage strategy via burr-hole craniostomy was carried out in all patients (3). Clinical parameters—such as age, gender, medical history, and history of head trauma events—were collected from each patient. Complications after operations were also recorded, including pneumonia, pulmonary embolism, heart failure, heart attack, stroke, fever, and seizure. A head trauma event was defined as a history of head trauma within 3 months prior to hospital admission. At sixth months after patients were discharged, their CT scans were examined and their corresponding modified Rankin scale (MRS) scores were used by two independent neurosurgeons (via phone correspondence) to analyze each patient's outcome. An MRS score of 0–3 indicated a good outcome, while a score of 4–6 indicated an inferior outcome. The Bender grade was used to analyze the preoperative statuses of patients (9), while a CT grading system by Stanisic et al. was utilized to classify the density of each hematoma (10). The postoperative CSDH recurrence rate was defined as the rate of reoperation to treat recurrent ipsilateral hematoma within 6 months after the original operation. Preoperative and postoperative hematoma volumes were calculated by the Coniglobus formula. Informed consent from patients and ethics approval from the Institutional Research Ethics Committee were obtained (NO. KY 2020-094-02).

Statistical Analyses

For all clinical parameters, means± standard deviations were used for continuous variables, while numbers of patients and percentages were used for categorical variables. Measurement data were tested for normality before statistical analyses, and non- normally distributed data were analyzed via non-parametric tests. Chi-square tests or *t*-tests were used to analyze differences in clinical characteristics in CSDH patients with and without head trauma. Multiple linear regression analysis was performed to analyze relationships between clinical characteristics and either reduction of the hematoma cavity or length of the hospital stay in CSDH patients with head trauma. Statistical analyses were performed by SPSS software version 17.0.0, and a p-value < 0.05 was considered significant.

RESULTS

Relationships Between Clinical Characteristics and Head Trauma

To analyze differences in baseline characteristics of CSDH patients with or without head trauma, we divided patients into a trauma group (i.e., head trauma) and no-trauma group. Among all CSDH patients, 805 cases had a history of head trauma from which they had each since recovered. As shown in **Table 1**, the male:female ratio was 4.6:1.0 (661:144 patients) in patients with head trauma, and 5.0:1.0 (419:83 patients) in patients without head trauma ($p = 0.530$). The mean age of patients with head trauma was 64.0 ± 16.1 years, while that of patients without head trauma was significantly younger at 61.5 ± 17.9 years ($p = 0.010$). In contrast, we did not find any significant differences in terms of a history of smoking, drinking, diabetes, cardiac disease, brain infarction, or antithrombosis between CSDH patients with and without head trauma. However, more patients exhibited hypertension in the no-head trauma group than in the trauma group (40.2 vs. 32.9%, $p = 0.007$).

TABLE 1 | Relationship between clinical characteristics and trauma in patients with chronic subdural hematoma.

Characteristics analyzed	Trauma (*n*)		*p*
	Yes (805)	No (502)	
Gender (Male: Female)	661:144	419:83	0.530
Age	64.0 ± 16.1	61.5 ± 17.9	0.010
Personal/Past history			<0.001
Smoking	216 (26.8)	133 (26.5)	0.893
Drinking	155 (19.3)	94 (18.7)	0.813
Hypertension	265 (32.9)	202 (40.2)	0.007
Diabetes	160 (19.9)	97 (19.3)	0.807
Cardiac diseases	29 (3.6)	20 (4.0)	0.724
Brain infarction	93 (11.6)	50 (10.0)	0.370
History of antithrombotic	92 (11.4)	52 (10.4)	0.548
AC/V-P shunt *n* (%)	68 (8.4)	47 (9.4)	0.570
Symptoms			
Headache *n* (%)	479 (59.5)	279 (55.6)	0.162
Dizziness *n* (%)	235 (29.2)	116 (23.1)	0.016
Limb weakness *n* (%)	457 (56.8)	260 (51.8)	0.079
Dysphasia *n* (%)	80 (9.9)	42 (8.4)	0.342
Disturbance of consciousness *n* (%)	35 (4.3)	25 (5.0)	0.595
Interval from onset to admission	8.5 ± 6.3	11.5 ± 19.3	0.001
Bender grades			<0.001
0	31 (3.9)	35 (7.0)	
I	307 (38.1)	249 (49.6)	
II	431 (53.5)	198 (39.4)	
III	36 (4.5)	20 (4.0)	
Unilateral/bilateral hematoma			0.068
Left	314 (39.0)	227 (45.2)	
Right	266 (33.0)	156 (31.1)	
Bilateral	225 (28.0)	119 (23.7)	
Types of hematoma			0.461
A	108 (13.4)	71 (14.1)	
B	234 (29.1)	148 (29.5)	
C	177 (22.0)	88 (17.5)	
D	65 (8.1)	48 (9.6)	
E	33 (4.1)	26 (5.2)	
F	34 (4.2)	27 (5.4)	
G	154 (19.1)	94 (18.7)	
Preoperative volume (ML)	99.6 ± 28.9	99.2 ± 31.5	0.805

TABLE 2 | Relationship between clinical characteristics and trauma after surgery in CSDH patients.

Characteristics analyzed	Trauma *n* (%)		*p*
	Yes (805)	No (502)	
Reduction of hematoma cavity (%)	58.9 ± 21.4	55.2 ± 22.2	0.002
Symptom disappeared or alleviated (day)	2.5 ± 1.9	2.7 ± 2.2	0.162
Duration of drainage catheter (day)	3.5 ± 1.8	3.4 ± 2.1	0.651
Length of hospital stay (days)	7.9 ± 4.5	7.3 ± 3.7	0.016
Use of urokinase	434 (53.9)	271 (54.0)	0.980
Frequency of urokinase used	1.7 ± 0.9	1.6 ± 0.9	0.678
Recurrence requiring reoperation	13 (1.6)	11 (2.2)	0.183
Complications	55 (6.8)	32 (6.4)	0.747
Death (hospital stay)	4 (0.5)	4 (0.8)	0.490
Death (in 6 month)	12 (1.5)	6 (1.2)	0.656
Outcome (MRS)			0.233
0–3	778 (96.6)	488 (97.2)	
4–6	19 (2.4)	13 (2.6)	

Headache was the most common symptom in each of the two groups (59.5, 55.6%, respectively), whereas a disturbance of consciousness was the least common symptom in each group (4.3, 5.0%, respectively). We found that dizziness occurred in 29.2% (235/805) of patients with head trauma, which was significantly higher than the 23.1% (116/502) of patients without head trauma that experienced dizziness ($p = 0.016$). In contrast, no significant differences were found between the two groups in terms of other symptoms, such as limb weakness or dysphasia. Furthermore, according to Bender grades, more CSDH patients with head trauma exhibited a Bender grade II while more CSDH patients without head trauma exhibited a Bender grade I ($p < 0.001$), suggesting that patients with head trauma suffered from more severe conditions. The average interval from CSDH onset to admission was 8.5 ± 6.3 days in patients with head trauma, which was significantly shorter than the 11.5 ± 19.3 days in patients without head trauma ($p = 0.001$).

The hematomas in CSDH patients displayed different densities on CT scans, in terms of hypodensities, isodensities, or mixed densities. We further analyzed differences in hematoma densities according to the CT grading system of Stanisic et al. (10), and found that they were not significantly different between patients with and without head trauma. Furthermore, there was no significant difference in the anatomical side at which the hematomas were located in either of the two groups. Finally, the average preoperative volume of hematomas was 99.6 ± 28.9 mL in the trauma group, and 99.2 ± 31.5 mL in the no-trauma group ($p = 0.805$).

Relationships Between Clinical Characteristics and Head Trauma After Surgery

According to our previous report (3), an exhaustive drainage strategy via burr-hole craniostomy was carried out foreach CSDH patient after they were admitted to our hospital. As shown in **Table 2**, the reduction of hematoma cavity after surgery was 58.9 ± 21.4% in the head trauma group, and 55.2 ± 22.2% in the no-trauma group ($p = 0.002$), suggesting that brain plasticity in CSDH patients without head trauma may have been worse than that of patients with head trauma. After the operation, the length of hospital stay in patients with head trauma was 7.9 ± 4.5 days, which was longer than that of patients without trauma (7.3 ± 3.7 days, $p = 0.016$).

During our exhaustive drainage strategy, each hematoma was drained by the catheter, which was then removed when drainage ceased. We found that the duration of the drainage catheter in the

TABLE 3 | Multiple linear regression analyses of characteristics related to reduction of hematoma cavity after surgery in CSDH patients with trauma.

Characteristics analyzed	B	Beta	P
AC/V-P shunt	0.080	0.103	0.003
Interval from onset to admission	−0.005	−0.133	<0.001
Cardiac diseases	−0.085	−0.074	0.031
Duration of drainage catheter	−0.011	−0.090	0.009
Unilateral/bilateral hematoma	0.068	0.143	<0.001

TABLE 4 | Multiple linear regression analyses of characteristics related to length of hospital stay after surgery in CSDH patients with trauma.

Characteristics analyzed	B	Beta	P
Brain infarction	1.591	0.114	<0.001
Duration of drainage catheter	0.709	0.287	<0.001
Complications	5.764	0.326	<0.001

trauma group was 3.5 ± 1.8 days, while it was 3.4 ± 2.1 days in patients without head trauma ($p = 0.651$). Otherwise, urokinase was used to promote hematoma drainage during execution of our strategy. There were no differences in the use of urokinase or the frequency of urokinase use between patients with and without head trauma.

A low recurrence requiring reoperation is one of the most important issues to consider before choosing a suitable treatment for patients with CSDH. We found that the recurrence requiring reoperation in patients with head trauma was 1.6% (13/805), and was 2.2% (11/502) in patients with head trauma. Interestingly, we did not find a significant difference between the two groups in terms of this recurrence rate. Additionally, patients with CSDH can experience complications after operation, such as pneumonia, pulmonary embolism, heart failure, heart attack, stroke, fever, and/or seizure. We found that 6.8% (55/805) of CSDH patients with head trauma exhibited complications, and 6.4% (32/502) of CSDH patients without head trauma exhibited complications. We did not identify any significant differences between the two groups in terms of post-operation complications. Furthermore, no significant differences were found between on the two groups in terms of mortality rates during their hospital stays or at sixth months after being discharged. The outcomes in patients with head trauma were excellent, as 96.6% of these patients obtained MRS scores of 0–3. Meanwhile, patients without head trauma also had favorable outcomes, such that 97.2% of them obtained MRS scores of 0–3, revealing that there was no significant difference between the two groups based on this parameter.

According to the above analyses, reduction of hematoma cavity after surgery in CSDH patients without head trauma was less than that of CSDH patients with head trauma, and we further analyzed which clinical parameters contributed to this differential phenotype via multiple linear regression analyses. As shown in **Table 3**, among CSDH patients with trauma, cases with an AC/V-P shunt (B = 0.080, Beta = 0.103, $p = 0.003$) or unilateral hematoma (B = 0.068, Beta = 0.143, $p < 0.001$) were correlated with a greater reduction of hematoma cavity after surgery. Interestingly, patients with an AC/V-P shunt or unilateral hematoma were also significantly younger ($p < 0.01$, respectively). Patients with a long interval from CSDH onset to admission (B = −0.005, Beta = −0.133, $p < 0.001$), long duration of their drainage catheter (B = −0.011, Beta = −0.090, $p = 0.009$), or a history of cardiac disease (B = −0.085, Beta = −0.074, $p = 0.031$) were correlated with less reduction of the hematoma cavity after surgery. Patients with cardiac disease were older than those without cardiac disease ($p < 0.001$), while a long duration of their drainage catheter was also more common in older patients ($p = 0.014$).

Finally, we further analyzed the influencing factors of the length of hospital stay in patients with head trauma (**Table 4**). We found that patients with brain infarction (B = 1.591, Beta = 0.114, $p < 0.001$) or a longer duration of their drainage catheter (B = 0.709, Beta = 0.287, $p < 0.001$) had a longer length of hospital stay, and complications in patients were also correlated with a longer length of hospital stay (B = 5.764, Beta = 0.326, $p < 0.001$).

DISCUSSION

Few previous studies have investigated similarities and differences in characteristics of CSDH patients with or without head trauma, and the results of these studies have remained controversial due to their low sample sizes. Here, we analyzed the clinical characteristics of 1,307 CSDH patients with or without head trauma, which currently represents the largest sample size of any such study. Although CSDH can be identified via an abnormal subdural collection of liquefied blood, the pathogenic mechanism of CSDH has remained unclear. At present, one of the most commonly posited mechanisms of CSDH is that it derives from bridging veins, cortical arteries, and/or cortical veins tearing after mild head injury with subsequent bleeding and induction of hematoma (11). Therefore, head trauma has been considered as one of the most common risk factors for the occurrence of CSDH. To identify differential clinical characteristics, recurrence rates, and outcomes of CSDH patients with and without head trauma, we divided 1,307 CSDH patients into a trauma group (i.e., head trauma) and no-trauma group. We found that 61.6% of our CSDH patients has a history of head trauma. Furthermore, we found that older patients were more likely to have a history of head trauma, which is not consistent with the findings of several previous reports (6, 12, 13). This disparity between studies may be due to some elderly patients not noticing or remembering that they may have had a history of mild head trauma in these previous studies. Additionally, we found that the reduction of hematoma cavity after surgery in CSDH patients with head trauma was greater than that in CSDH patients without head trauma. Among CSDH patients with head trauma, those with an AC/V-P shunt or unilateral hematoma had a greater reduction of the hematoma cavity and were younger; patients with a long duration of their drainage catheter or a history of cardiac disease exhibited less of a reduction of the hematoma cavity, and these patients were also more likely to be

older patients. All of these results suggest that age is an important factor in the reduction of hematoma cavity in patients with head trauma. This phenomenon may be due to age-related brain atrophy, such that the brain gradually loses its plasticity and does not show good re-expansion after removal of a hematoma.

According to our previous reports and other studies (3, 7), only 50–70% of CSDH patients have a history of head trauma, suggesting that other risk factors may also contribute to CSDH. Indeed, in addition to head trauma, many other risk factors have been identified in the process of CSDH, such as alcoholism, coagulopathies, and cerebrospinal fluid shunts (5, 14, 15). In the no-trauma group in our present study, we found that 40.2% of patients had a history of hypertension, which was significantly different compared with that of the trauma group. This result suggests that hypertension may play an important role in the process of CSDH in patients without head trauma. The reason for this phenomenon may be attributed to a fluctuation in blood pressure, which makes bridging veins, cortical arteries, and/or cortical veins more easily torn, suggesting that controlling hypertension may be important for the prevention of CSDH.

Headache is the most common symptom in patients with CSDH (3). However, patients with or without head trauma may exhibit differential symptoms. It has been reported that patients without head trauma have a higher rate of muscle weakness (6). However, we did not find any difference in muscle weakness between the two groups in our present study and found that patients with head trauma displayed a higher rate of dizziness. Furthermore, we did not find any other differences between the two groups in terms of any other symptoms. Moreover, according to the Bender grade system, we found that patients with head trauma exhibited more severe conditions, which is consistent with a previous report (6).

Hematoma densities on CT scans display different densities, such as homogeneous, separated, mixed-density, and high-density features. It has been reported that hematoma density is correlated with different clinical characteristics, and patients with high-density CT areas show the largest incidence of recurrence (16, 17). Jun et al. found that homogeneous density mainly occurred in patients with head trauma, while mixed density was mostly found in patients without head trauma (6). In our present study, we classified hematomas into seven subtypes according to the different densities of hematomas on CT scans (10) and found that there were no significant differences between CSDH patients with and without head trauma.

Complications, mortality rates, recurrence rates, and outcomes are important indexes for evaluating effects of different kinds of treatments. It has been shown that CSDH patients without head trauma exhibit a higher mortality rate than that of CSDH patients with head trauma (6). However, in our present report, we found that 0.5% of CSDH patients with head trauma died during their hospital stay, whereas 0.8% of CSDH patients without head trauma died during their hospital stay. Furthermore, 1.5% of patients died during follow-up in the trauma group, while 1.2% of patients died during follow-up in the no-trauma group. None of these results were significantly different between the two groups, suggesting that mortality rates over short-term or long-term periods are not different in CSDH patients with or without trauma. A history of head trauma is correlated with a poor outcome at long-term follow-ups in CSDH patients (8). However, Jun et al. found that CSDH patients without head trauma had poor outcomes (6). In our present study, the length of the hospital stay in patients with head trauma was longer than that of patients without head trauma, and further analyses revealed that brain infarction, duration of drainage catheter, and complications were correlated with the length of the hospital stay. Furthermore, complication was the most significant factor among these parameters, suggesting that a longer length of hospital stay may cause a poor outcome or more complications. However, we found that there were no significant differences between the two groups in terms of complications or outcomes. The reason for this lack of any differences between groups may be due to the fact that we performed an exhaustive drainage strategy via burr-hole craniostomy in all patients in the present study (3), which may have helped to maximally reduce hematomas, minimize recurrence rates, and yield favorable outcomes. Finally, our present study had some limitations in terms of it being a retrospective single-center study with a relatively small sample size. Therefore, in the future, we plan to conduct a multi-center prospective study and/or randomized-controlled trial to verify or refute our present results.

CONCLUSIONS

In conclusion, hypertension may be a risk factor in CSDH patients without head trauma. In our present study, we found that there were no significant differences in terms of densities of hematomas on CT scans, complications, mortality rates, recurrence rates, or outcomes between CSDH patients with and without head trauma. Taken together, our findings suggest that if an optimal treatment method is employed, such as our exhaustive drainage strategy, similar treatment outcomes can be achieved between these groups.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Tiantan Hospital, Capital Medical University, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YO and WL designed the research. XY, XL, and QJ collected data. YO drafted the manuscript and takes the responsibility for the integrity of the data and the accuracy of the data analysis. BL supervised the project. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Christopher E, Poon MT, Glancz LJ, Hutchinson PJ, Kolias AG, Brennan PM, et al. Outcomes following surgery in subgroups of comatose and very elderly patients with chronic subdural hematoma. *Neurosurg Rev.* (2019) 42:427–31. doi: 10.1007/s10143-018-0979-4
2. Sundström N, Djerf L, Olivecrona Z, Koskinen LO. Postural stability in patients with chronic subdural hematoma. *Acta Neurochir.* (2016) 158:1479–85. doi: 10.1007/s00701-016-2862-9
3. Ou Y, Dong J, Wu L, Xu L, Wang L, Liu B, et al. An exhaustive drainage strategy in burr-hole craniostomy for chronic subdural hematoma. *World Neurosurg.* (2019) 126:e1412–20. doi: 10.1016/j.wneu.2019.03.111
4. Ou Y, Dong J, Wu L, Xu L, Wang L, Liu B, et al. The clinical characteristics, treatment, and outcomes of chronic subdural hematoma in young patients. *World Neurosurg.* (2019) 125:e1241–6. doi: 10.1016/j.wneu.2019.02.017
5. De Bonis P, Trevisi G, De Waure C, Sferrazza A, Volpe M, Pompucci A, et al. Antiplatelet/anticoagulant agents and chronic subdural hematoma in the elderly. *PLoS ONE.* (2013) 8:e68732. doi: 10.1371/journal.pone.0068732
6. Shen J, Shao X, Wang Q, Ge R, Zhang J. Comparison of clinical and radiologic characteristics and prognosis of patients with chronic subdural hematoma with and without a history of head trauma. *World Neurosurg.* (2019) 132:e391–8. doi: 10.1016/j.wneu.2019.08.142
7. Lee KS. Chronic subdural hematoma in the aged, trauma or degeneration? *J Korean Neurosurg Soc.* (2016) 59:1–5. doi: 10.3340/jkns.2016.59.1.1
8. Kim DH, Park ES, Kim MS, Park SH, Park JB, Kwon SC, et al. Correlation between head trauma and outcome of chronic subdural hematoma. *Korean J Neurotrauma.* (2016) 12:94–100. doi: 10.13004/kjnt.2016.12.2.94
9. Robinson RG. Chronic subdural hematoma: surgical management in 133 patients. *J Neurosurg.* (1984) 61:263–8. doi: 10.3171/jns.1984.61.2.0263
10. Stanisic M, Pripp AH. A reliable grading system for prediction of chronic subdural hematoma recurrence requiring reoperation after initial burr-hole surgery. *Neurosurgery.* (2017) 81:752–60. doi: 10.1093/neuros/nyx090
11. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. *Nat Rev Neurol.* (2014) 10:570–8. doi: 10.1038/nrneurol.2014.163
12. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK. Chronic subdural haematoma in the elderly. *Postgrad Med J.* (2002) 78:71–5. doi: 10.1136/pmj.78.916.71
13. Sim YW, Min KS, Lee MS, Kim YG, Kim DH. Recent changes in risk factors of chronic subdural hematoma. *J Korean Neurosurg Soc.* (2012) 52:234–9. doi: 10.3340/jkns.2012.52.3.234
14. Almenawer SA, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. *Ann Surg.* (2014) 259:449–57. doi: 10.1097/SLA.0000000000000255
15. Toi H, Kinoshita K, Hirai S, Takai H, Hara K, Matsushita N, et al. Present epidemiology of chronic subdural hematoma in Japan: analysis of 63,358 cases recorded in a national administrative database. *J Neurosurg.* (2018) 128:222–8. doi: 10.3171/2016.9.JNS16623
16. Ko BS, Lee JK, Seo BR, Moon SJ, Kim JH, Kim SH. Clinical analysis of risk factors related to recurrent chronic subdural hematoma. *J Korean Neurosurg Soc.* (2008) 43:11–5. doi: 10.3340/jkns.2008.43.1.11
17. Oishi M, Toyama M, Tamatani S, Kitazawa T, Saito M. Clinical factors of recurrent chronic subdural hematoma. *Neurol Med Chir.* (2001) 41:382–6. doi: 10.2176/nmc.41.382

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