frontiers | Research Topics

Chronic subdural hematoma (CSDH) - a well-known unknown

Edited by
Milan Lepić and Hiroki Sato

Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-5301-5
DOI 10.3389/978-2-8325-5301-5

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Chronic subdural hematoma (CSDH) - a well-known unknown

Topic editors

Milan Lepić — Clinic for Neurosurgery, Military Medical Academy, Serbia

Hiroki Sato — Saitama Medical University International Medical Center, Japan

Citation

Lepić, M., Sato, H., eds. (2024). *Chronic subdural hematoma (CSDH) - a well-known unknown*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5301-5

Table of contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 30 July 2024
DOI 10.3389/fneur.2024.1461117

OPEN ACCESS

EDITED AND REVIEWED BY
Jean-Claude Baron,
University of Cambridge, United Kingdom

*CORRESPONDENCE
Milan Lepić
milanlepic@gmail.com

RECEIVED 07 July 2024
ACCEPTED 16 July 2024
PUBLISHED 30 July 2024

CITATION
Lepić M and Sato H (2024) Editorial: Chronic subdural hematoma (CSDH) - a well-known unknown. *Front. Neurol.* 15:1461117. doi: 10.3389/fneur.2024.1461117

Editorial: Chronic subdural hematoma (CSDH) - a well-known unknown

Milan Lepić[1,2]* and Hiroki Sato[3]

[1]Medical Faculty of the Military Medical Academy, University of Defence, Belgrade, Serbia, [2]Clinic for Neurosurgery, Military Medical Academy, Belgrade, Serbia, [3]Department of Neurosurgery, Teikyo University Mizonokuchi Hospital, Kawasaki, Japan

KEYWORDS

chronic subdural hematoma (CSDH), management, surgical treatment, endovascular treatment, adjuvant treatment options, reoccurrence, outcome

Editorial on the Research Topic
Chronic subdural hematoma (CSDH) - a well-known unknown

Chronic subdural hematoma (CSDH) is a common neurosurgical condition that primarily affects the elderly population, characterized by the accumulation of fluid between the dura mater and the arachnoid membrane of the brain. Despite being a well-known entity, CSDH remains a subject of controversy, from its name and origin to advanced therapeutic approaches. Unlike acute subdural hematomas, which typically result from significant head injury, CSDHs can develop insidiously, making their diagnosis and treatment challenging (1).

This condition is increasingly prevalent among the frail and elderly populations due to their common use of anticoagulant and antiplatelet therapy, and age-related vascular fragility. Additionally, the aging population is more prone to underlying chronic diseases that may exacerbate the formation of subdural hematomas. As the global population continues to age, the incidence of CSDH is expected to double over the next decade, presenting a growing public health concern (2).

Understanding the multifaceted nature of CSDH and its growing incidence in the elderly is crucial for developing effective management strategies and improving patient outcomes. Recent research has expanded our understanding of the factors influencing the recurrence, treatment, and outcomes of CSDH, offering new insights that can shape future clinical practices. This Research Topic presents 12 pivotal studies that delve into the nuances of CSDH understanding and management, each contributing valuable evidence and perspectives to the field, focusing on the current state of CSDH management and proposing innovative strategies for improving patient outcomes.

The study titled "*Effectiveness of tranexamic acid on chronic subdural hematoma recurrence: a meta-analysis and systematic review*" by Pan et al. conducted a meta-analysis comparing the effectiveness of tranexamic acid (TXA) in reducing CSDH recurrence rates. Their findings suggest that TXA, an antifibrinolytic agent, can significantly lower postoperative recurrence rates by 67% compared to standard neurosurgical treatment alone. Furthermore, the study found no significant differences in the incidence of thrombosis or mortality between TXA and control groups, with myocardial infarction being less frequent in the TXA group. These results highlight the potential of TXA as an adjuvant therapy for CSDH, providing high-level evidence to support its clinical use (Pan et al.).

In "*Preservation of the middle meningeal artery during unruptured aneurysm surgery: an independent risk factor for postoperative chronic subdural hematoma*," by Kim investigated the association between the preservation of the anterior branch of the middle meningeal artery (MMA) during unruptured and surgery and the development of postoperative CSDH. The study revealed that MMA preservation, advanced age, and male sex are independent risk factors for CSDH following unruptured aneurysm clipping. These findings underscore the importance of considering MMA management during neurosurgical procedures and may guide surgical planning to mitigate postoperative CSDH risk (Kim).

The "*Advances in chronic subrural hematoma and membrane imaging*" by Chen et al. provided a comprehensive review of the current landscape of CSDH diagnosis and treatment, with a focus on advanced imaging techniques for assessing hematomas and subdural membranes. The authors discussed the potential role of MR and dual-energy CT imaging in predicting CSDH recurrence, surgical planning, and patient selection for MMA embolization treatment. As CSDH recurrence remains a significant challenge despite conventional management, the development of novel radiographic biomarkers to guide treatment decisions is a promising avenue for future research (Chen et al.).

A systematic review and meta-analysis titled "*Intraoperative irrigation of artificial cerebrospinal fluid and temperature of irrigation fluid for chronic subdural hematoma: a systematic review and meta-analysis*" by Huang et al. conducted comparing the efficacy of artificial cerebrospinal fluid (ACF) and normal saline (NS) as irrigation fluids during CSDH surgery. Their findings suggest that ACF may reduce postoperative recurrence rates by 47% compared to NS. Furthermore, they discovered that using irrigation fluid at body temperature could decrease recurrence rates by 64% compared to room temperature fluid. These results highlight the importance of optimizing intraoperative techniques to minimize CSDH recurrence (Huang et al.).

A "*Classification of subdural hematomas: proposal for a new system improving the ICD coding tools*" by Langlois et al. proposed a new classification system for subdural hematomas that captures the chronicity and etiology of the condition, factors that significantly impact management and prognosis. The current ICD coding system fails to adequately distinguish between acute and chronic subdural hematomas, hindering administrative, statistical, and research applications. The authors' proposed classification system offers a more comprehensive approach to categorizing subdural hematomas, which could lead to improved patient care and research outcomes (Langlois et al.).

Yang W. et al. investigated the correlation between skull density and CSDH progression in the study titled "*Predicting the progression of chronic subdural hematoma based on skull density*". Their study revealed that lower minimum skull density, higher maximum skull density, and higher skull density difference were significantly associated with CSDH progression. The authors developed and validated a predictive model incorporating these factors, which could aid in early assessment of CSDH progression and guide treatment decisions (Yang W. et al.).

The study titled "*Case report: concurrent low-volume subdural hematoma and ipsilateral ischemic stroke presenting as capsular warning syndrome: a complex case with anticoagulation dilemma and dual pathology*" by Strahnen et al. presented a complex case report of a patient with concurrent low-volume subdural hematoma and ipsilateral ischemic stroke, highlighting the challenges of managing anticoagulation in such scenarios. The patient's presentation with capsular warning syndrome further complicates the clinical picture. This case underscores the need for a multidisciplinary approach and the development of tailored treatment strategies for patients with multiple comorbidities (Strahnen et al.).

In "*Middle meningeal artery embolization for chronic subdural hematoma: a systematic review*," by Omura and Ishiguro conducted a systematic review of middle meningeal artery embolization (MMAE) for CSDH. Their analysis suggests that MMAE alone is as effective as evacuation surgery in reducing hematoma, although the effect is not immediate. Additionally, they found that combining MMAE with evacuation surgery results in lower recurrence rates compared to evacuation surgery alone. Given the safety profile of MMAE, the authors recommend considering this procedure for patients with CSDH, particularly those at high risk of recurrence (Omura and Ishiguro).

The study titled "*Effect of decreased platelets on postoperative recurrence of chronic subdural hematoma*" by Yagi et al. investigates the role of thrombocytopenia in the recurrence of CSDH post-surgery. This research highlights a crucial aspect of patient care, underscoring the need for meticulous perioperative management of platelet levels to minimize the risk of recurrence. The findings suggest that lower platelet counts may be a significant risk factor, prompting the need for targeted therapeutic strategies to mitigate this risk (Yagi et al.).

In "*Nontraumatic subdural hematoma in patients on hemodialysis with end-stage kidney disease: a systematic review and pooled analysis*," by Yang L. et al. the authors examine the incidence and outcomes of non-traumatic subdural hematomas in a particularly vulnerable patient population. Patients with end-stage kidney disease (ESKD) on hemodialysis are at increased risk due to anticoagulation and uremic platelet dysfunction. This comprehensive review and pooled analysis provide critical insights into the management of these patients, emphasizing the importance of tailored therapeutic approaches to improve outcomes (Yang L. et al.).

The "*Success of conservative therapy for chronic subdural hematoma patients: a systematic review*" by Foppen et al. explores the viability of non-surgical management of CSDH. This systematic review synthesizes data from multiple studies to evaluate the effectiveness of conservative treatments such as corticosteroids and mannitol. The findings support conservative therapy as a feasible option for certain patient cohorts, particularly those with mild symptoms or significant surgical risk, potentially reducing the need for invasive procedures (Foppen et al.).

Finally, the population-based study "*Incidence, therapy, and outcome in the management of chronic subdural hematoma in Switzerland: a population-based multi-center cohort study*" by El Rahal et al. provides a comprehensive overview of the epidemiology and management practices of CSDH across multiple centers in Switzerland. This cohort study offers valuable epidemiological data and compares the outcomes of various therapeutic interventions,

thereby contributing to the optimization of treatment protocols and healthcare policies (El Rahal et al.).

Collectively, these studies advance our understanding of CSDH by identifying key risk factors, evaluating diverse patient populations, and comparing therapeutic approaches. They underscore the importance of individualized patient care and the need for continued research to refine management strategies. The exact etiology and pathophysiology of CSDH remain controversial, and treatment options, including surgical evacuation, are still debatable. Despite being one of the oldest and simplest neurosurgical procedures, establishing clear recommendations or guidelines on CSDH management may remain a challenging task for the time being.

We hope this Research Topic inspires further research and discussion within the neurology and neurosurgery communities, ultimately leading to enhanced care for CSDH patients.

Author contributions

ML: Writing – original draft, Writing – review & editing. HS: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The authors acknowledge support of the Medical Faculty of the Military Medical Academy, University of Defense in Belgrade project MFVMA/01/24-26.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Uno M. Chronic subdural hematoma-evolution of etiology and surgical treatment. *Neurol Med Chir*. (2023) 63:1–8. doi: 10.2176/jns-nmc.2022-0207

2. Feghali J, Yang W, Huang J. Updates in chronic subdural hematoma: epidemiology, etiology, pathogenesis, treatment, and outcome. *World Neurosurg*. (2020) 141:339–45. doi: 10.1016/j.wneu.2020.06.140

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 06 July 2023
DOI 10.3389/fneur.2023.1218334

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Adam James Wells,
University of Adelaide, Australia
Taichi Ishiguro,
Tokyo Women's Medical University Yachiyo Medical Center, Japan

*CORRESPONDENCE
Zong-Ping Li
✉ jing_zp@sina.com
Xiao-Shuang Yin
✉ 17003405@qq.com

RECEIVED 07 May 2023
ACCEPTED 16 June 2023
PUBLISHED 06 July 2023

CITATION
Huang Y-W, Li Z-P and Yin X-S (2023) Intraoperative irrigation of artificial cerebrospinal fluid and temperature of irrigation fluid for chronic subdural hematoma: a systematic review and meta-analysis. *Front. Neurol.* 14:1218334. doi: 10.3389/fneur.2023.1218334

Intraoperative irrigation of artificial cerebrospinal fluid and temperature of irrigation fluid for chronic subdural hematoma: a systematic review and meta-analysis

Yong-Wei Huang[1], Zong-Ping Li[1]* and Xiao-Shuang Yin[2]*

[1]Department of Neurosurgery, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, Sichuan, China, [2]Department of Immunology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, Sichuan, China

Purpose: To systematically review the different types of irrigation fluid and the different temperatures of irrigation fluid on postoperative recurrence rates in the evacuation of chronic subdural hematoma (CSDH).

Methods: We conducted a comprehensive search of electronic databases, including PubMed, Embase, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), WanFang, the Chinese VIP Information (VIP), and China Biology Medicine (CBM), and reference lists of relevant studies to identify all eligible studies. Two reviewers independently screened the titles and abstracts for inclusion, and the full-text articles were assessed for eligibility based on predetermined inclusion and exclusion criteria. Data were extracted using a standardized form, and the quality of the studies was assessed using a risk of bias tool. Meta-analyses were performed using a fixed-or random-effects model, and heterogeneity was assessed using the I2 statistic. The primary endpoint was the postoperative recurrence rate.

Results: After stringent screening, a total of 11 studies were identified, including six English publications, four Chinese publications, and one Japanese publication, involving a population of 29,846 patients. Our meta-analysis provides evidence that artificial cerebrospinal fluid (ACF) could decrease the post-operative recurrence rate by 47% after the evacuation of CSDH when compared to normal saline (NS) [(odds ratio) OR 0.53, 95% confidence intervals (CI): 0.31–0.90, $p=0.02$, $I^2=67\%$]. Besides, the irrigation fluid at body temperature could decrease the postoperative recurrence rate of CSDH by 64% when compared to room temperature (OR=0.36, 95% CI=0.22–0.59, $p<0.0001$, $I^2=0\%$).

Conclusion: Our analysis revealed significant difference in the choice of irrigation fluid for CSDH surgery. Notably, we found that irrigation with fluid at body temperature demonstrated superiority over irrigation with fluid at room temperature, resulting in fewer instances of recurrence. This straightforward technique is both safe and widely available, providing an opportunity to optimize outcomes for patients with CSDH. Our findings suggest that the use of body-temperature NS or ACF of room temperature during operation should be considered a standard of procedure in CSDH surgery. Nevertheless, whether

the different temperature of ACF could be considered a standard of procedure in CSDH surgery still need high-quality RCTs to further identify.

Systematic review registration: https://www.crd.york.ac.uk/prospero/; Identifier CRD42023424344.

KEYWORDS

chronic subdural hematoma, irrigation fluid, temperature, recurrence, meta-analysis

Introduction

Chronic subdural hematoma (CSDH) is a condition characterized by the accumulation of aged and degraded blood products within the subdural space of the brain. This process is driven by inflammatory and angiogenetic factors, which can lead to a significant increase in volume and subsequent compression of brain tissue, resulting in a range of symptoms (1). Common symptoms of CSDH include focal neurological deficits, altered mental states, and signs of increased intracranial pressure such as headaches, decreased consciousness, and, in severe cases, death. Older adults, particularly those aged over 65 years, are at heightened risk of developing CSDH due to factors such as brain atrophy, increased frequency of anticoagulant therapy, and a higher incidence of head trauma caused by falls (2). The growing incidence of CSDH is largely attributed to an aging population (3), reaching 58 patients per 100,000 people in those aged 65 years old or more (4). Data from the Nordic countries indicate that the incidence of CSDH has almost tripled over the past 20–30 years, with a corresponding doubling of surgical procedures (5, 6). As one of the most populous countries in the world, China has many elderly people. Therefore, the prevention and treatment of CSDH are particularly important.

The most frequent surgical approach for CSDH is evacuation through one or two burr holes, followed by the insertion of a postoperative drain (7). During surgery, subdural space irrigation is commonly performed (4, 8). However, despite these measures, recurrence rates of CSDH requiring reoperation remain at approximately 10 to 20% (9). Such recurrences are associated with a substantial increase in morbidity and mortality (10, 11). Therefore, reducing recurrence rates is of great importance, not only to improve outcomes for individual patients but also to optimize healthcare resource utilization.

Artificial cerebrospinal fluid (ACF) is an irrigating solution that mimics the composition of human cerebrospinal fluid (CSF). Its efficacy has been demonstrated by over 1,000 medical facilities in Japan where ACF has been commercially available (12). ACF has been shown to possess hemostatic properties and to reduce cerebrovascular permeability, making it a promising irrigation solution for patients with CSDH undergoing burr-hole surgery (13, 14). The use of ACF during surgery may lead to improved outcomes for these patients. Comparative studies have been conducted in recent years to investigate the efficacy of normal saline (NS) and ACF as irrigation solutions in CSDH burr hole surgery (12, 15–17). These retrospective single-center studies have suggested that irrigation with ACF may reduce the recurrence rate of CSDH. However, there is a dearth of multi-center, prospective, randomized controlled trials in this field. Moreover, there has been limited research on the impact of irrigation solutions on postoperative complications in patients undergoing CSDH surgery. Future research should aim to address these gaps in knowledge.

The temperature of the irrigation fluid used during surgery for CSDH may impact recurrence rates, as higher solubility with body temperature fluid may aid in CSDH clearance and lower the risk of coagulation issues (18). Despite these potential benefits, it remains common practice to use irrigation fluid at room temperature (19). A poll conducted in 2017 among 620 neurosurgeons found that 57% used body temperature irrigation, 40% used room temperature, and 3% did not use irrigation at all (20). In order to examine the influence of irrigation fluid temperature on the rates of recurrence in CSDH patients, Bartley et al. (21) conducted a preliminary investigation. Their findings revealed that adjusting the irrigation fluid temperature to match the body temperature resulted in a reduction of recurrences requiring reoperation from 13.4 to 4.5%. To date, the results of investigating the impact of the irrigation fluid temperature and different irrigation fluids on recurrence rates are limited. And the findings are controversial. Hence, we conducted a systematic review and meta-analysis to assess the efficacy of different irrigation fluids and irrigation fluid temperatures in influencing the postoperative recurrence rate.

Methods

Search strategy

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22) and was prospectively registered with PROSPERO[1] under the identifier CRD42023424344 (23). The PRISMA checklist can be found in Supplementary Table S1. Our comprehensive search encompassed multiple databases including PubMed, Embase, the Cochrane Library, Scopus, and the Web of Science, employing the following search terms: ("chronic subdural hematoma" or "CSDH") AND ("irrigation" or "fluids" or "artificial cerebrospinal fluid" or "ACF" or "normal saline" or "NS" or "temperature"). Additionally, Chinese databases such as the China National Knowledge Infrastructure (CNKI), WanFang, Chinese VIP Information (VIP), and China Biology Medicine (CBM) were searched using the terms: ("慢性硬膜下血肿" AND "冲洗"). To ensure inclusiveness, we also searched ClinicalTrials.gov and WHO-ICTRP. The search was conducted on May 2, 2023.

1 https://www.crd.york.ac.uk/PROSPERO/

Language restrictions were not applied, and all relevant articles were considered for inclusion. The detailed search strategy is outlined in Supplementary Table S2.

Study selections

We included studies that met the following PICO (Population, Intervention, Comparisons, and Outcomes) criteria: (1) Population: CSDH patients, including unilateral or bilateral; (2) Intervention: burr-hole irrigation, burr-hole drainage, or YL-1 type hard-channel drilling drainage; (3) Comparisons: ACF vs. normal saline (NS), and body temperature vs. room temperature; (4) Outcomes: post-operative recurrence rate. We excluded systematic reviews and meta-analyses, case reports, reviews, commentaries, and conference abstracts.

Two reviewers (Y-WH and X-SY) independently screened the titles and abstracts of all retrieved records. The same two reviewers separately reviewed the relevant studies in full text and either included or excluded articles based on the eligibility criteria. In cases of discordance, the corresponding authors (Z-PL) made the final decision.

Data extraction

Two reviewers (Y-WH and X-SY) independently extracted data into separate Excel spreadsheets. The spreadsheets were then cross-checked against each other and the source material to ensure accuracy. We collected the following data: first author name, publication year, country, study design, sample size, age, sex, type of CSDH, type of surgery, primary outcomes, and follow-up duration. If we found any discrepancies, we resolved them by consulting the corresponding authors (Z-PL).

Study outcomes

The primary outcome of this study was post-operative recurrence, defined as reoperation of the same side within 6 months after the first surgery.

Bias assessment

Two independent reviewers (Y-WH and X-SY) evaluated the risk of bias in the included studies using the Newcastle-Ottawa Scale (NOS) tool (24) for non-randomized controlled trials (RCTs) and the Cochrane Collaboration's tool (25) for RCTs in a blinded manner. To ensure accuracy, the risk of bias summaries were cross-checked, and any unresolved discrepancies were resolved by the corresponding authors (Z-PL).

Statistical analysis

For binary outcomes, we calculated odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Mean and standard deviation (SD) were estimated using sample size, median, and interquartile range, employing optional estimating methods from McGrath et al. (26), which can be accessed at https://smcgrath.shinyapps.io/estmeansd/. To address clinical heterogeneity, we conducted meta-analyses and subgroup analyses using either random-effects or fixed-effects models (27). Heterogeneity was assessed using the Cochrane Q test, considering $p < 0.1$ or $I^2 > 50\%$ as indicators of significant heterogeneity (28). Statistical significance was defined as $p < 0.05$. Funnel plots were utilized to assess publication bias. All statistical analyses were performed using Review Manager software (version 5.3.3; https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman).

Results

Study selection

On May 2, 2023, a total of 1,537 publications were identified through the search strategy in English databases. After removing 594 duplicates, we screened the remaining 943 publications based on article type, title, and abstracts and excluded 936 unrelated publications, leaving seven studies. We meticulously evaluated the seven publications for potential eligibility (12, 15, 16, 21, 29–31), and all met inclusion criteria. Subsequently, we manually searched the Chinese database for relevant studies and found four additional studies (32–35) that met our inclusion criteria. In summary, we included a total of 11 studies (12, 15, 16, 21, 29–35) in our systematic review and meta-analysis (Figure 1).

Characteristics of the included studies

The 11 studies included in this systematic review and meta-analysis were published between 2012 and 2023. Among them, four articles were RCT (30, 31, 33, 34), and the remaining seven articles (12, 15, 16, 21, 29, 32, 35) were non-RCTs. The studies were conducted in China ($n = 4$), Sweden ($n = 2$), and Japan ($n = 5$), with a total of 29,846 patients included. One study (29) utilized a 1:1 propensity score matching (PSM) method to balance the influence of potential confounding factors, resulting in the inclusion of 27,788 patients in the analysis. 10 studies (12, 15, 16, 21, 29–34) underwent burr-hole surgery with drainage or irrigation. One study (35) underwent YL-1-type hard-channel drilling drainage. The follow-up period ranged from 3 months to 1-year after discharge. The results of the included studies are summarized in Table 1.

Effect of ACF on recurrence

Seven studies (12, 15, 16, 29, 31, 33, 34) looked at the effect of different irrigation fluids on postoperative recurrence, including 28,963 patients. Among them, 14,470 cases were in the ACF group with 916 patients of recurrence and 14,493 cases in the NS group with 1,060 patients of recurrence. Meta-analysis showed some heterogeneity with $I^2 = 67\%$, so a random-effects model was used for the analysis, which showed that the CSDH recurrence rate was lower in the ACF group than in the NS group (OR = 0.53, 95% CI = 0.31–0.90, $p = 0.02$) (Figure 2). In other words, the CSDH recurrence rate in the ACF group was decreased by 47% than that in the NS group.

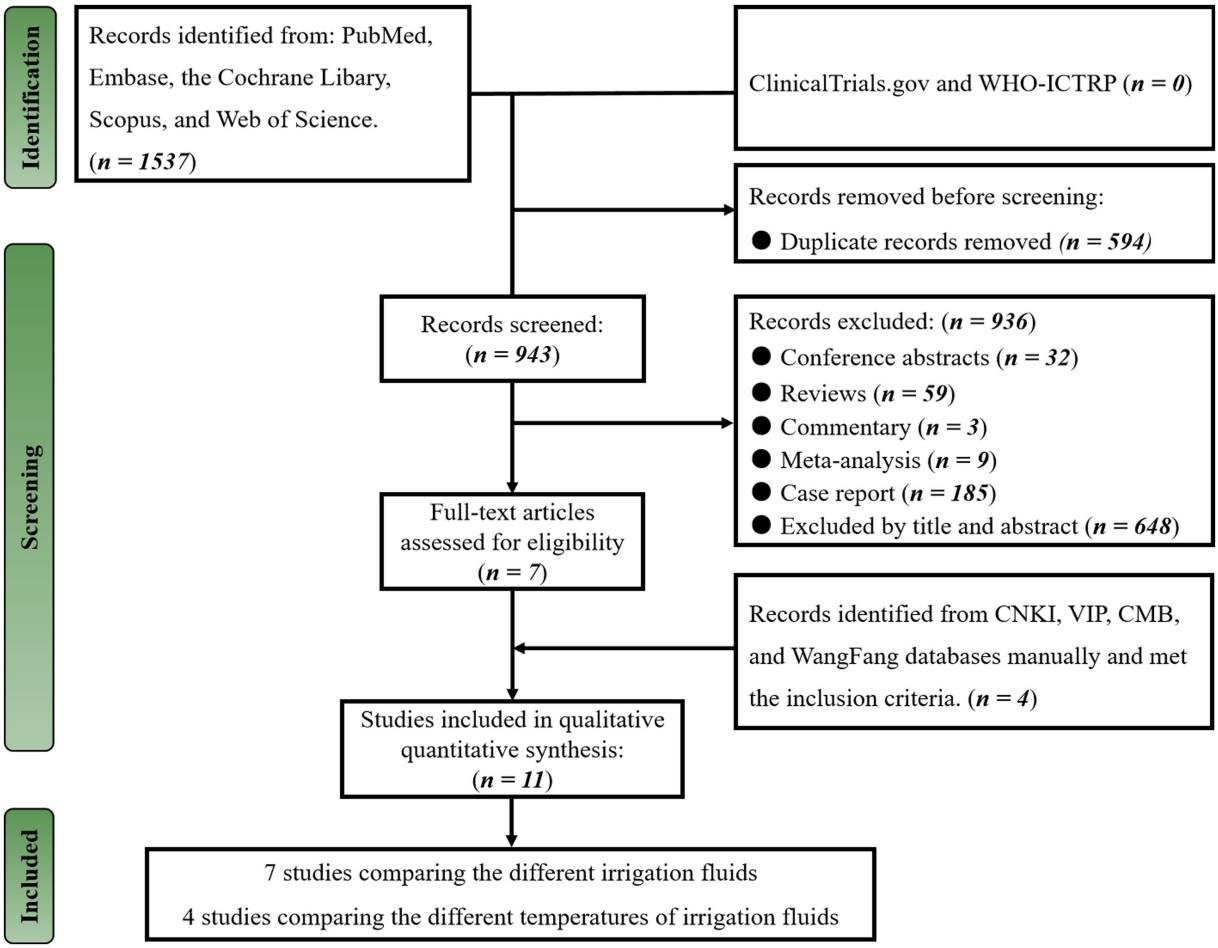


FIGURE 1
PRISMA flowchart of included studies.

Effect of the temperature of irrigation fluid on recurrence

Four studies (21, 30, 32, 35) focused on the different temperatures of irrigation fluids in influencing postoperative recurrence, including 883 patients. Among them, 436 cases were in the body temperature group with 24 patients of recurrence and 447 cases in the room temperature group with 62 patients of recurrence. Meta-analysis showed no heterogeneity with $I^2 = 0\%$, so a fixed-effects model was used for the analysis, which showed that the CSDH recurrence rate was lower in the body temperature group than in the room temperature group (OR = 0.36, 95% CI = 0.22–0.59, $p < 0.0001$; Figure 3). In other words, the CSDH recurrence rate in the body temperature group was decreased by 64% than that in the room temperature group.

Risk of bias assessment and publication bias assessment

The NOS has assessed and awarded a median of seven stars to seven studies, with an range of 6 to 8 stars. Cochrane Collaboration's tool was used to assess RCTs. The methodological quality of the studies included can be found in Supplementary Table S3 and Supplementary Figure S1. Additionally, the probability of publication bias was evaluated through funnel plot results, which are displayed in Supplementary Figure S2.

Discussion

Chronic subdural hematoma (CSDH) can cause various neurological deficits and is an important risk factor affecting the quality of life of the elderly. Burr hole drainage is a common treatment for CSDH and is considered the preferred method due to its simplicity, short surgery time, minimal trauma, and high safety for first-time CSDH cases. However, due to various factors such as advanced age, brain atrophy, use of anticoagulants, liver and kidney dysfunction, and the formation of intrahematomal septa, postoperative hematoma recurrence is common in CSDH patients. Therefore, adequate intraoperative irrigation and postoperative drainage are crucial. Some studies demonstrated that irrigation with ACF could decrease the rate of CSDH recurrence (12, 15, 16, 29). Nevertheless, some other studies showed that no differences in recurrence rate were seen between

TABLE 1 The baseline characteristics of included studies.

Author	Year	Nation	Study design	Participants (*n*)	Male (%)	Age (*y*)	Research topic	Type of CSDH	Type of surgery	Primary outcomes	Follow-up	NOS
Adachi et al. (12)	2014	Japan	non-RCT	120	63.3	76.75 ± 11.43	ACF vs. NS	Unilateral	prefrontal burr-hole and overnight drainage	Recurrence	6 months	7
Kuwabara et al. (15)	2017	Japan	non-RCT	234	67.1	64.07 ± 14.26	ACF vs. NS	Unilateral or bilateral	Burr-hole irrigation	Recurrence	3 months	6
Shibahashi et al.(29)	2023	Japan	non-RCT	27,788 in PSM	68.9	40–90	ACF vs. NS	Unilateral or bilateral or not specified	Burr-hole	Recurrence	1 year	8
Wang et al.(33)	2014	China	RCT	160	54.4	36–79	ACF vs. NS	Unilateral	Burr-hole	Recurrence	6 months	※
Wang et al.(34)	2012	China	RCT	80	58.8	36–79	ACF vs. NS	Unilateral	Burr-hole	Recurrence	6 months	※
Takayama et al. (16)	2012	Japan	non-RCT	239	66.5	16–94	ACF vs. NS	Unilateral or bilateral	Burr-hole	Recurrence	3 months	6
Toi et al.(31)	2019	Japan	RCT	342	72.5	75.41 ± 2.84	ACF vs. NS	Unilateral or bilateral	Burr hole drainage	Recurrence	3 months	※
Bartley et al. (21)	2020	Sweden	non-RCT	172	43.8	74.79 ± 12.47	NS (BT) vs. NS (RT)	Unilateral or bilateral	Burr hole	Recurrence	6 months	7
Bartley et al. (30)	2022	Sweden	RCT	541	73.0	75.80 ± 9.80	NS (BT) vs. NS (RT)	Unilateral or bilateral	Burr hole	Recurrence	6 months	※
Huang et al. (32)	2021	China	non-RCT	84	38.6	68.25 ± 8.27	NS (BT) vs. NS (RT)	Unilateral	Burr hole	Recurrence	6 months	7
Zhang et al. (35)	2021	China	non-RCT	86	74.4	66.53 ± 7.12	NS (BT) vs. NS (RT)	Unilateral or bilateral	YL-1-type hard-channel drilling drainage	Recurrence	6 months	6

※ The Cochrane collaboration's tool was used for RCTs.

CSDH, chronic subdural hematoma; PSM, propensity score matching; ACF, artificial cerebrospinal fluid; NS: normal saline; BT: body temperature; RT, room temperature; NOS, Newcastle-Ottawa Scale; RCT, randomized controlled trials.

10.3389/fneur.2023.1218334

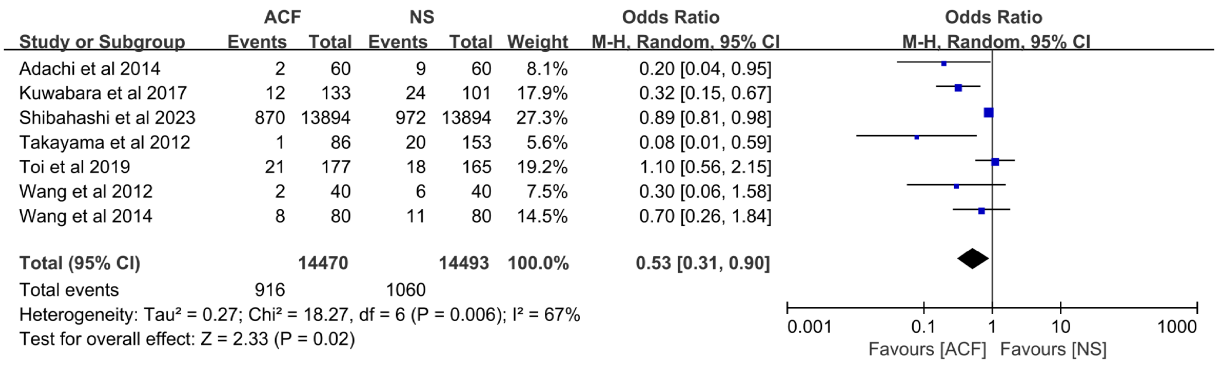


FIGURE 2
Meta-analysis of postoperative recurrence rates between the ACF group and the NS group.

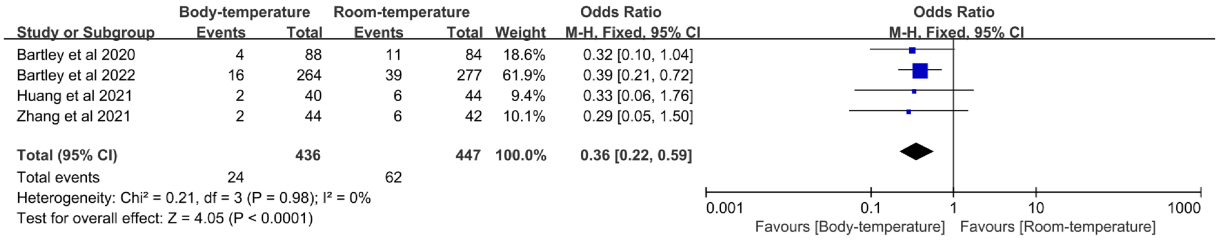


FIGURE 3
Meta-analysis of postoperative recurrence rates between the body-temperature group and the room-temperature group.

ACF and NS (31, 33, 34), and ACF offers sufficient safety as an irrigation fluid for CSDH (31). Wang et al. (33) think that adequate intraoperative irrigation and adequate postoperative drainage are essential to reduce postoperative recurrence rates, and irrigation fluid is not a decisive factor.

In recent years, with the popularity of neuroendoscopic surgery, ACF has been increasingly used in the treatment of neurosurgical diseases. In intracranial aneurysm clipping, ACF is used for intracerebral pool flushing to prevent postoperative vasospasm; lateral ventricular puncture followed by ACF replacement with lumbar pool drainage for severe infections such as meningitis; and ACF replacement for hypertensive ventricular hemorrhage, all of which have achieved better efficacy compared with traditional therapies. ACF is formulated with reference to the concentration of the main biochemical substances in normal CSF, and its crystal concentration, osmotic pressure, and pH value are close to those of CSF, which is basically consistent with the physiological state of CSF circulation and can stabilize the internal environment of brain tissues. It has been shown to be more effective than saline in the treatment of various neurosurgical diseases and is safe and reliable. In a study utilizing a mouse model, it was observed that the choice of irrigation solution employed during neurosurgical procedures could significantly impact the extent of bleeding at the injury site. The study revealed that ACF irrigation was more effective in reducing bleeding as compared to NS (13). Calcium is a crucial component necessary for blood coagulation and vascular smooth muscle contraction, both of which play crucial roles in hemostasis. The prior investigation hypothesized that the presence of Ca^{2+} in ACF could have contributed to the observed reduction in bleeding. In another study, it was reported that ACF irrigation during burr-hole surgery resulted in less damage to CSDH membranes than NS irrigation, leading the authors to speculate that ACF could minimize irritation and promote post-surgical healing (12). These findings suggest that ACF could facilitate hemostasis of the outer hematoma membrane. Moreover, ACF irrigation could help prevent recurrence by washing out inflammatory mediators from the subdural compartment. Excessive inflammation is a primary cause of CSDH, and the overproduction of inflammatory mediators has been linked to hematoma expansion (36). Nevertheless, there are some negative aspects of using ACF, particularly relating to the cost and/or availability of this irrigation fluid worldwide. ACF is not readily available in many neurosurgical centers, but NS most definitely is, as are fluid warmers in most operating suites, and heating NS to body temperature may have a much higher worldwide impact on managing this condition than exploring artificial CSF, particularly in developing countries.

Irrigation at body temperature may be more effective in decreasing postoperative recurrence rates than irrigation at room temperature, partly due to its superior ability to rinse the subdural space of factors that promote hematoma progression. Organic materials' aqueous solubility doubles with every 20°C increase in temperature, making irrigation fluid at room temperature less effective (18). Moreover, irrigation fluid at room temperature may

negatively impact coagulation compared to the fluid at body temperature. Irrigation at body temperature represents a refinement of current surgical practices, easily implemented without any patient-related contraindications or increased risk. Alternatively, irrigation fluid at body temperature may increase hematoma solubility, facilitating evacuation (19).

To our best of knowledge, this is the first meta-analysis investigated the effect of ACF and NS as irrigation fluids, as well as the effect of different irrigation fluid temperatures, on postoperative recurrence rates. The results showed that the ACF group had a lower postoperative recurrence rate than the NS group, possibly due to ACF's protective effect on cerebral vascular permeability. During surgery, the dura mater may be damaged, and the irrigation fluid may come into contact with the surface of the brain. The severe swelling around the incision after surgery can be alleviated by using ACF, which is similar in composition to CSF and can better maintain the stability of vascular endothelial cells. This can minimize cerebral vascular permeability and cell damage and promote faster hemostasis without interrupting normal coagulation, effectively reducing the recurrence of CSDH. The results also showed that the temperature of the irrigation fluid significantly affected the recurrence rate of CSDH, with the use of body temperature being more effective in reducing postoperative hematoma recurrence than using room temperature. Under room-temperature conditions, the irrigation fluid inhibits the clotting process, leading to non-healing and the recurrence of the hematoma. In contrast, under body temperature conditions, the irrigation fluid increases the solubility of the hematoma, thereby promoting its excretion and absorption. Therefore, it can effectively suppress hematoma formation. In summary, ACF irrigation has a good hemostatic effect and high safety. It is superior to NS in CSDH surgical treatment. Additionally, to minimize the stimulating effect of irrigation fluid temperature on brain tissue, it is recommended to heat the irrigation fluid to body temperature during surgery.

However, this study has some limitations. First, there are few comparative studies on the effects of ACF and NS on CSDH and only four studies on the effect of irrigation fluid temperature on CSDH treatment. Second, there is a lack of research on the effect of ACF temperature on the prevention of CSDH recurrence. Third, the number of included studies in this paper is small, with large differences in quality scores among them. There are also significant differences in ethnicity, time period, and country of origin, with only four RCT studies and seven retrospective case–control studies. Therefore, large-sample, multicenter, well-designed RCTs are still needed to supplement and verify the results of this study. Lastly, the study by Shinbashi et al. (29) was a cohort study using the Japanese patient database from 2010 to 2019. Maybe there is data duplication with other original studies from Japan about different irrigation fluids. But we cannot further identify this possibility. Hence, this is a limitation that cannot be solved.

Conclusion

Our analysis revealed a significant difference in the choice of irrigation fluid for CSDH surgery. Notably, we found that irrigation with fluid at body temperature demonstrated superiority over irrigation with fluid at room temperature, resulting in fewer instances of recurrence. This straightforward technique is both safe and widely available, providing an opportunity to optimize outcomes for patients with CSDH. Our findings suggest that the use of body-temperature NS or ACF of room temperature during operation should be considered a standard of procedure in CSDH surgery. Nevertheless, whether the different temperature of ACF could be considered a standard of procedure in CSDH surgery still need high-quality RCTs to further identify.

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 authors.

Author contributions

The present study was conceived through the joint efforts of Y-WH, Z-PL and X-SY. Y-WH developed the initial idea. Z-PL and X-SY subsequently devised and refined the search strategy, while Y-WH and X-SY formulated the study design. Y-WH and X-SY contributed to the original draft, and Z-PL was responsible for revising the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Project of Mianyang Central Hospital (2021YJ006).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1218334/full#supplementary-material

References

1. 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

2. Uno M, Toi H, Hirai S. Chronic subdural hematoma in elderly patients: is this disease benign? *Neurol Med Chir (Tokyo)*. (2017) 57:402–9. doi: 10.2176/nmc.ra.2016-0337

3. Gaist D, García Rodríguez LA, Hellfritzsch M, Poulsen FR, Halle B, Hallas J, et al. Association of antithrombotic drug use with subdural hematoma risk. *JAMA*. (2017) 317:836–46. doi: 10.1001/jama.2017.0639

4. Liu W, Bakker NA, Groen RJ. Chronic subdural hematoma: a systematic review and meta-analysis of surgical procedures. *J Neurosurg*. (2014) 121:665–73. doi: 10.3171/2014.5.JNS132715

5. The Swedish National Board of Health. Online database of statistics. Accessed April 18, 2021. Available at: https://sdb.socialstyrelsen.se/if_ope/val.aspx

6. 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) 132:1147–57. doi: 10.3171/2018.12.JNS183035

7. Ivamoto HS, Lemos HP, 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

8. 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

9. 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 34829 patients. *Ann Surg*. (2014) 259:449–57. doi: 10.1097/SLA.0000000000000255

10. 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

11. Guilfoyle MR, Hutchinson PJ, 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

12. Adachi A, Higuchi Y, Fujikawa A, Machida T, Sueyoshi S, Harigaya K, et al. Risk factors in chronic subdural hematoma: comparison of irrigation with artifcial cerebrospinal fuid and normal saline in a cohort analysis. *PLoS One*. (2014) 9:e103703. doi: 10.1371/journal.pone.0103703

13. Fujita Y, Doi K, Harada D, Kamikawa S. Modulation of physiological hemostasis by irrigation solution: comparison of various irrigation solutions using a mouse brain surface bleeding model. *J Neurosurg*. (2010) 112:824-828. doi: 10.3171/2009.7.JNS09561

14. Koizumi S, Hayasaka T, Goto-Inoue N, Doi K, Setou M, Namba H. Imaging mass spectrometry evaluation of the efects of various irrigation fuids in a rat model of postoperative cerebral edema. *World Neurosurg*. (2012) 77:153–9. doi: 10.1016/j.wneu.2011.03.039

15. Kuwabara M, Sadatomo T, Yuki K, Migita K, Imada Y, Shimizu K, et al. The effect of irrigation solutions on recurrence of chronic subdural hematoma: a consecutive cohort study of 234 patients. *Neurol Med Chir (Tokyo)*. (2017) 57:210–6. doi: 10.2176/nmc.oa.2016-0228

16. Takayama M, Terui K, Oiwa Y. Retrospective statistical analysis of clinical factors of recurrence in chronic subdural hematoma: correlation between univariate and multivariate analysis. *No Shinkei geka Neuro Surg*. (2012) 40:871–6. doi: 10.11477/mf.1436101834

17. Tatsuya N, Tomo O, Takehiro T, Horoshi O, Tamotsu M. Benefts of Artcereb® on the irrigation of chronic subdural hematoma. *Traumatology*. (2011) 34:167–71.

18. Black S, Muller F. On the effect of temperature on aqueous solubility of organic solids. *Org Process Res Dev*. (2010) 14:661–5. doi: 10.1021/op100006y

19. Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma*. (1998) 44:846–54. doi: 10.1097/00005373-199805000-00017

20. Bartley A, Jakola AS, Bartek J Jr, Sundblom J, Förander P, Marklund N, et al. The Swedish study of irrigation-fluid temperature in the evacuation of chronic subdural hematoma (SIC!): study protocol for a multicenter randomized controlled trial. *Trials*. (2017) 18:471. doi: 10.1186/s13063-017-2194-y

21. Bartley A, Jakola AS, Tisell M. The influence of irrigation fluid temperature on recurrence in the evacuation of chronic subdural hematoma. *Acta Neurochir*. (2020) 162:485–8. doi: 10.1007/s00701-019-04150-6

22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol*. (2021) 134:178–89. doi: 10.1016/j.jclinepi.2021.03.001

23. Huang YW, Li ZP, Yin XS. *Intraoperative irrigation of artificial cerebrospinal fluid and temperature of irrigation fluid for chronic subdural hematoma: A systematic review and meta-analysis*. PROSPERO. (2023); CRD42023424344. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID$=$CRD42023424344 (accessed May 6, 2023)

24. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in Meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed February 27, 2020).

25. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0. The Cochrane Collaboration. (2011); Available at: www.handbook.cochrane.org (accessed: August 10, 2021).

26. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti Athe DEPRESsion Screening Data (DEPRESSD) Collaboration. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res*. (2020) 29:2520–37. doi: 10.1177/0962280219889080

27. Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. (1986) 7:177–88. doi: 10.1016/0197-2456(86)90046-2

28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. (2002) 21:1539–58. doi: 10.1002/sim.1186

29. Shibahashi K, Ohbe H, Yasunaga H. Artificial cerebrospinal fluid use during burr-hole surgery and reoperation rate in patients with chronic subdural hematoma: an analysis using a nationwide inpatient database. *Acta Neurochir*. (2023) 165:1289–96. doi: 10.1007/s00701-023-05570-1

30. Bartley A, Bartek J Jr, Jakola AS, Sundblom J, Fält M, Förander P, et al. Effect of irrigation fluid temperature on recurrence in the evacuation of chronic subdural hematoma: a randomized clinical trial. *JAMA Neurol*. (2023) 80:58–63. doi: 10.1001/jamaneurol.2022.4133

31. Toi H, Fujii Y, Iwama T, Kinouchi H, Nakase H, Nozaki K, et al. Determining if cerebrospinal fluid prevents recurrence of chronic subdural hematoma: a multi-center prospective randomized clinical trial. *J Neurotrauma*. (2019) 36:559–64. doi: 10.1089/neu.2018.5821

32. Huang QH, Deng X, Huang PZ, Zhao W, Geng JG, Song YF, et al. Effect of intraoperative body temperature irrigation solution on the surgical outcome of chronic subdural hematoma. *Med J Chin PAP*. (2021) 32:437–8. doi: 10.14010/j.cnki.wjyx.2021.05.018

33. Wang QH, Wang R. Effect of different intraoperative flushing solutions and different flushing volumes on chronic subdural hematoma prognosis of drilled drainage. *Shanxi Med J*. (2014) 43:1407–9. doi: 10.3969/j.issn.0253-9926-0.2014.12.032

34. Wang Y, Qiu B, Du J, Wang YJ. Comparison of two kinds of intropeative irrigation solutions in therapy of chronic subdural hematoma. *Shanxi Med J*. (2012) 41:6–7. doi: 10.3969/j.issn.0253-9926-B.2012.01.002

35. Zhang GQ. Comparison of the effects of body temperature and room temperature irrigation solution on recurrence after chronic subdural hematoma evacuation. *Shanxi Med J*. (2021) 50:1734–5. doi: 10.3969/j.issn.0253-9926.2021.10.058

36. Bounajem MT, Campbell RA, Denorme F, Grandhi R. Paradigms in chronic subdural hematoma pathophysiology: current treatments and new directions. *J Trauma Acute Care Surg*. (2021) 91:e134–41. doi: 10.1097/TA.0000000000003404

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 14 September 2023
DOI 10.3389/fneur.2023.1206996

OPEN ACCESS

EDITED BY
Milan Lepić,
Military Medical Academy, Serbia

REVIEWED BY
Marvin Darkwah Oppong,
Essen University Hospital, Germany
Jagos Golubovic,
Clinical Center of Vojvodina, Serbia

*CORRESPONDENCE
Amir El Rahal
amir.elrahal@uniklinik-freiburg.de

RECEIVED 16 April 2023
ACCEPTED 19 June 2023
PUBLISHED 14 September 2023

CITATION
El Rahal A, Beck J, Ahlborn P, Bernasconi C, Marbacher S, Wanderer S, Burkhardt J-K, Daniel RT, Ferrari A, Hausmann O, Kamenova M, Kothbauer K, Lutz K, Mariani L, Alfieri A, Schöni D, Schucht P, Raabe A, Regli L, Kuhlen D, Seule M, Soleman J, Starnoni D, Zaldivar J, Zweifel C, Schaller K and Fung C (2023) Incidence, therapy, and outcome in the management of chronic subdural hematoma in Switzerland: a population-based multicenter cohort study. *Front. Neurol.* 14:1206996. doi: 10.3389/fneur.2023.1206996

Incidence, therapy, and outcome in the management of chronic subdural hematoma in Switzerland: a population-based multicenter cohort study

Amir El Rahal [1,2]*, Jürgen Beck[2], Peter Ahlborn[3], Corrado Bernasconi[4], Serge Marbacher[5], Stefan Wanderer[5], Jan-Karl Burkhardt[6], Roy Thomas Daniel[7], Andrea Ferrari[3], Oliver Hausmann[8], Maria Kamenova[9], Karl Kothbauer[10], Katharina Lutz[5], Luigi Mariani[9], Alex Alfieri[11], Daniel Schöni[11], Philippe Schucht[4], Andreas Raabe[4], Luca Regli[6], Dominique Kuhlen[12], Martin Seule[2], Jehuda Soleman[9], Daniele Starnoni[7], Julien Zaldivar[7], Christian Zweifel[13], Karl Schaller[1] and Christian Fung[2]

[1]Department of Neurosurgery, University Hospital of Geneva, Faculty of Medicine, Geneva, Switzerland, [2]Department of Neurosurgery, Medical Center, University of Freiburg, Freiburg, Germany, [3]Department of Neurosurgery, Kantonsspital St. Gallen, St. Gallen, Switzerland, [4]Department of Neurosurgery, Bern University Hospital and University of Bern, Bern, Switzerland, [5]Department of Neurosurgery, Cantonal Hospital Aarau, Aarau, Switzerland, [6]Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland, [7]Department of Neurosurgery, University Hospital Center of Lausanne, Lausanne, Switzerland, [8]Department of Neurosurgery, Hirslanden Klinik St. Anna, Luzern, Switzerland, [9]Department of Neurosurgery, University Hospital Basel, Faculty of Medicine, Basel, Switzerland, [10]Department of Neurosurgery, Cantonal Hospital of Lucerne, Lucerne, Switzerland, [11]Department of Neurosurgery, Kantonsspital Winterthur, Winterthur, Switzerland, [12]Department of Neurosurgery, Regional Hospital Lugano (EOC), Lugano, Switzerland, [13]Department of Neurosurgery, Cantonal Hospital Graubünden, Chur, Switzerland

Background: Chronic subdural hematoma (cSDH) is a disease affecting mainly elderly individuals. The reported incidence ranges from 2.0/100,000 to 58 per 100,000 person-years when only considering patients who are over 70 years old, with an overall incidence of 8.2–14.0 per 100,000 persons. Due to an estimated doubling of the population above 65 years old between 2000 and 2030, cSDH will become an even more significant concern. To gain an overview of cSDH hospital admission rates, treatment, and outcome, we performed this multicenter national cohort study of patients requiring surgical treatment of cSDH.

Methods: A multicenter cohort study included patients treated in 2013 in a Swiss center accredited for residency. Demographics, medical history, symptoms, and medication were recorded. Imaging at admission was evaluated, and therapy was divided into burr hole craniostomy (BHC), twist drill craniostomy (TDC), and craniotomy. Patients' outcomes were dichotomized into good (mRS, 0–3) and poor (mRS, 4–6) outcomes. A two-sided *t*-test for unpaired variables was performed, while a chi-square test was performed for categorical variables, and a p-value of <0.05 was considered to be statistically significant.

Results: A total of 663 patients were included. The median age was 76 years, and the overall incidence rate was 8.2/100,000. With age, the incidence rate increased to 64.2/100,000 in patients aged 80–89 years. The most prevalent symptoms were gait disturbance in 362 (58.6%) of patients, headache in 286 (46.4%), and focal

neurological deficits in 252 (40.7%). CSDH distribution was unilateral in 478 (72.1%) patients, while 185 presented a bilateral hematoma with no difference in the outcome. BHC was the most performed procedure for 758 (97.3%) evacuations. CSDH recurrence was noted in 104 patients (20.1%). A good outcome was seen in almost 81% of patients. Factors associated with poor outcomes were age, GCS and mRS on admission, and the occurrence of multiple deficits present at the diagnosis of the cSDH.

Conclusion: As the first multicenter national cohort-based study analyzing the disease burden of cSDH, our study reveals that the hospital admission rate of cSDH was 8.2/100,000, while with age, it rose to 64.2/100,000. A good outcome was seen in 81% of patients, who maintained the same quality of life as before the surgery. However, the mortality rate was 4%.

KEYWORDS

neurosurgery, cSDH, chronic subdural hematoma, incidence, therapy, outcome, multicentric study, management

Introduction

Chronic subdural hematoma (cSDH) is a disease affecting mainly elderly individuals. The reported incidence is highly variable depending on the population and the period being studied. It ranges from 2.0/100,000 person-years in the Swedish population in 1996 to 58 per 100,000 persons-year when considering only patients who are >70 years old, with an overall incidence of 8.2–14.0 per 100,000 persons-year (1–3). Due to an estimated doubling of the population above 65 years between 2000 and 2030, cSDH will become an even more significant concern (3–5). In addition, the increasing use of oral anticoagulation has raised the incidence of cSDH (6). The growing number of patients being affected significantly impinges healthcare costs of cSDH, with current costs of ∼US$ 10,000 per treatment (7, 8). Despite these facts, no evidence-based treatment strategy for cSDH has been established (9). To gain an overview of cSDH hospital admission rates, treatment, and outcome in Switzerland and to characterize the Swiss patient collective for future studies, we performed this retrospective multicenter national cohort study of patients requiring surgical treatment of cSDH.

Materials and methods

We performed a multicenter retrospective cohort study, including patients undergoing surgical drainage of cSDH between 1 January 2013 and 31 December 2013. The neurosurgical centers included in this analysis were Swiss centers accredited for a residency program of at least 1 year of training. Almost all patients with cSDH are referred to one of those centers due to the availability of emergency services. Demographic parameters (sex and age), past medical history, presenting symptoms, and the use of anticoagulant and antiplatelet medication were recorded. Imaging at admission was evaluated according to the localization of the cSDH, and the midline shift in mm on the level of the foramen of Monro was graded according to Nakaguchi et al. into homogeneous, laminar, separated, or trabecular appearance of the cSDH (10). The therapy was divided into single- or two-burr hole craniostomy (BHC), twist drill craniostomy (TDC), and craniotomy. The outcome was assessed using the modified Rankin scale (mRS) during the outpatient clinical visit, close to 6 months after the treatment of cSDH. We defined recurrence rate as the need for reoperation and assessed the timing of recurrence in weeks after primary surgery and complications. We also evaluated clinical parameters that might contribute to poor outcomes and recurrence. Data were entered into a REDCap (2015, Vanderbilt University) database. Regional ethics committees of all the centers approved the study. Informed consent for the scientific exploration of clinical and biological data was consistent with the local ethical standards, and the Declaration of Helsinki was available to all patients. The Swiss Ethics Committees approved the study on research involving humans under the protocol "Swissethics Ec-No: 15-163."

Statistical analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 25). Incidence rates are presented directly standardized using a weighted average of the stratum-specific rates. The weights were obtained using Swiss Population Distribution (Swiss age standardization). Patients' outcomes were dichotomized into good (mRS 0–3) and poor (mRS 4–6) outcomes. A two-sided *t*-test for unpaired variables was performed, while a chi-square test was performed for categorical variables. A p-value of <0.05 was considered to be statistically significant.

Results

A total of 15 neurosurgical centers are accredited for neurosurgical residency programs in Switzerland, of which one

Abbreviations: CSDH, chronic subdural hematoma; GSC, Glasgow Coma Scale; mRS, modified Rankin scale; BHC, burr hole craniostomy; TDC, twist drill craniostomy; IQR, interquartile range.

10.3389/fneur.2023.1206996

was excluded because of its pure spine surgical focus. Therefore, we included patients that had been admitted to the neurosurgical department of the following 14 centers: Cantonal Hospital Aarau, University Hospital of Basel, University Hospital of Bern, University Hospital of Geneva, Cantonal Hospital Graubünden, University Hospital of Lausanne, Cantonal Hospital Lucerne, Hospital St. Anna Lucerne, Cantonal Hospital Lugano, Cantonal Hospital Sion, Cantonal Hospital St. Gallen, Cantonal Hospital Winterthur, University Hospital of Zürich, and Hirslanden clinic, Zürich.

Patient demographics

We included 663 patients in the study with a median age of 76 years (IQR 67–83 years). Of these, 228 (34.4%) were female patients with a median age of 77 years (IQR 69–83 years), and 435 (65.6%) were male patients with a median age of 75 years (IQR 67–83 years). The female-to-male ratio was 1:1.9.

Admission parameters and past medical history

The parameters of clinical presentation and past medical history are displayed in Table 1. Gait disturbance was the most common clinical presentation in 362 (58.6%) patients, followed by headache in 286 (46.4%) patients, focal neurological deficits in 252 (40.7%) patients, and cognitive deterioration in 246 (39.8%) patients. Multiple symptoms at presentations were seen in 505 (81.6%) patients, while 103 (16.6%) patients had one symptom, and 11 (1.8%) were asymptomatic. The median number of symptoms per patient was three (IQR 2–4). Overall median admission GCS was 15 (IQR 14–15). On admission, the median GSC of patients with unilateral or bilateral cSDH showed no significant difference (15, IQR 14–15). The distribution of anticoagulant and antiplatelet medication use is shown in Table 1. Vitamin-K antagonists were the most often used anticoagulants, prescribed in 135 (21.8%) patients. New oral anticoagulants were prescribed in nine (1.5%) patients. Aspirin was used in 169 (27.3%) patients and clopidogrel in 26 (4.2%) patients regularly before admission. Concerning past medical history, the most frequent medical condition was arterial hypertension in 367 (59.3%) patients, followed by cardiac arrhythmias in 160 (25.8%), and ischemic heart disease in 148 (23.9%) patients, respectively.

TABLE 1 Admission parameters and past medical history.

	N (out of)	%
Clinical presentation		
Gait disturbance/fall	362 (618)	58.6
Headache	286 (616)	46.4
Focal neurological deficit	252 (619)	40.7
Cognitive deterioration	246 (618)	39.8
Non-specific deterioration	170 (617)	27.6
Speech disturbance	155 (619)	25.0
Acute confusion	115 (618)	18.6
Drowsiness/coma	109 (618)	17.6
Vomiting/nausea	60 (618)	9.7
Seizure	44 (617)	7.1
Incontinence	30 (615)	4.9
Past medical history		
Hypertension	367 (619)	59.3
Arrhythmia	160 (619)	25.8
Ischemic heart disease	148 (619)	23.9
Diabetes mellitus	96 (619)	15.5
Renal insufficiency	78 (619)	12.6
Dementia	78 (619)	12.6
Cerebrovascular accident	75 (619)	12.1
DVT/PE	54 (619)	8.7
COPD	29 (619)	4.7
Hepatic insufficiency	22 (619)	3.6
Medication		
Aspirin	169 (618)	27.3
Clopidogrel	26 (618)	4.2
Vitramin-K antagonist	135 (619)	21.8
New OAK	9 (618)	1.5

Gait disturbance is the most prevalent symptom, and hypertension is the most common comorbidity. Anticoagulation and antiplatelet drugs were administered, respectively, by 31.5 and 22.3% of the patients.
COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism.

Radiological characteristics

In total, 478 (72.1%) patients presented with a unilateral cSDH, of which 243 (50.1%) affected the left side and 235 (49.2%) the right side, whereas in 185 patients, a bilateral hematoma was present. A median midline shift of unilateral cSDH was 7.0 mm (IQR 4–11 mm), compared to 3 mm (IQR 0–5 to 6 mm) of bilateral cSDH ($p < 0.001$). The hematoma was homogeneous in 308 patients (59.8%), laminar in 75 patients (14.6%), separated in 132 patients (25.6%), and trabecular in 171 (33.2%) cases.

Incidence of cSDH

The overall incidence rate was 8.2/100,000 persons, 10.8 for men and 5.5 for women. Absolute numbers and incidences of cSDH per age group and sex are displayed in Table 2 and Figure 1. The highest absolute number of cSDH in men occurred in the age group of 70–79 years, whereas in women, it was in the age group of 80–89 years. The incidence of cSDH rose steadily to 131.5/100,000 in men who were 90 years or older. In women, the highest incidence rate was in the age group of 80–89 years. Overall, the highest incidence rate was 64.2/100,000 persons in patients 80–89 years old.

TABLE 2 Absolute numbers of cSDH per age group and sex.

	Absolute numbers			Incidences		
Age group	Male	Female	Total	Male	Female	Total
0–9	0	0	0	0	0	0
10–19	1	1	2	0.2	0.2	0.2
20–29	0	2	2	0	0.4	0.2
30–39	3	2	5	0.5	0.4	0.4
40–49	7	8	15	1.1	1.3	1.2
50–59	42	13	55	7.2	2.3	4.8
60–69	84	33	117	19.4	7.3	13.2
70–79	141	78	219	51.1	23.6	36.1
80–89	133	80	213	106.4	38.7	64.2
≥90	24	11	35	131.5	22.6	52.4
Total	435	228	663	10.8	5.5	8.2

The overall incidence rate is 8.2/100,000 people in Switzerland. However, in men, the incidence of cSDH rises steadily to 131.5/100,000 in men who are 90 years or older.

Treatments

The most often used surgical technique as primary treatment for cSDH was BHC. BHC was performed for 758 (97.3%) cSDH cases, of which 166 (21.9%) were 1-BHC, and 592 (87.1%) were 2-BHC. There were 20 patients (2.6%) who were treated by craniotomy, and one was treated using TDC. Additionally, data on drains was available for 600 patients, and 756 patients were operated for cSDH. Subdural drains were inserted during 261 (33.2%) evacuations, and subgaleal drains were inserted during 452 (57.2%) evacuations. In 43 evacuations, no drains were inserted postoperatively. Data for recurrent hematoma was available for 518 (78.1%) patients, of which 104 patients (20.1%) experienced a recurrence after a median of 2 weeks (IQR 1–4 weeks). There were 17 patients (2.6%) who experienced a second recurrence after a median of 3 weeks (IQR 1–10) after surgical drainage of the first recurrence.

Outcome

Before the onset of symptoms related to the cSDH, approximately half of the patients presented with an mRS of 0 (n = 339, 55.1%). In total, 119 patients had an mRS of 1 (19.3%), 70 patients had an mRS of 2 (11.4%), 64 patients had an mRS of 3 (10.4%), 22 patients had an mRS of 4 (3.6%), and one patient had an mRS of 5 (0.2%). After treatment of cSDH, 247 patients presented with an mRS of 0 (42.6%), 151 patients had an mRS of 1 (26%), 70 patients had an mRS of 2 (12.1%), 54 patients had an mRS of 3 (9.3%), 26 patients had an mRS of 4 (4.5%), five patients had an mRS of 5 (0.9%), and 27 patients (4.7%) presented an mRS of 6 ($p < 0.001$) (Figure 2). Median time of outcome assessment was 2 months (IQR 1–6 months) postoperatively. Factors associated with poor outcomes were age, GCS on admission, mRS on admission, and the occurrence of multiple deficits present at the diagnosis of the cSDH. Factors not showing significant association with poor outcome were midline shift, neither in uni- nor in bilateral cSDH, sex, the use of antiplatelet medication or oral anticoagulation, uni- or bilateral cSDH, or the side of cSDH.

Discussion

To the best of our knowledge, this is the first study to evaluate hospital admission rates of cSDH based on a multicenter national cohort including all age groups and all reference treating hospitals. We have shown that the treatment of patients with chronic subdural hematoma in Switzerland was relatively uniform, with a high rate of burr hole evacuation and a high rate of postoperative drainage placement.

Incidence

Our study yielded a hospital admission rate of cSDH of 8.2/100,000 person-years. This aligns with previous studies reporting an incidence of 8.2–14 per 10,000 person-years (1–3, 11). Previous studies have assessed the incidence in confined areas or defined patient collectives (1, 2, 12, 13). The definition of the incidence of cSDH is challenging since many more patients probably present a mild course with spontaneous resolution without presentation to medical care (12). Others might present subdural hygroma with or without transformation into a classical cSDH or are hospitalized without surgical care. Reports about the rate of spontaneous resolution or conservatively treated cSDH are scarce primarily since clinically silent cSDH is not in the physician's attention and symptomatic cSDH is generally treated surgically (14–17). Medically treated patients are limited to small case series. In a recent study by Baiser et al., only 29% of newly diagnosed cSDH required surgical drainage (17–20). Transferred to our results, this would mean a 3-fold increase in the incidence of cSDH in Switzerland. Nevertheless, in the recent trial of dexamethasone for chronic subdural hematoma in symptomatic patients, 94% underwent surgery to evacuate their hematomas (21). This illustrates the difficulties in assessing the incidence of cSDH. A new finding of this study is the reported peak incidence of 131.5 per 100,000 person-years in men ≥ 90 years. Our study shows a steady incidence increase with increasing age up to 89 years. Higher incidences with increasing age have been reported earlier, without reaching an incidence rate of >130/100,000 person-years.

Treatment

The preferred primary treatment of choice was BHC ($n = 758$). Only a minority of patients were treated by craniotomy ($n = 20$) or TDC ($n = 1$). The type of surgical treatment was at the discretion of the treating surgeon. The amount of performed BHC aligns with the results of a previous systematic review by Weigel et al., which states that BHC has a comparable low morbidity rate as TDC but a much lower recurrence rate (22). BHC is also the most common form of treatment in other countries. In 2009, Santarius et al. concluded that the drain's subdural insertion reduces the

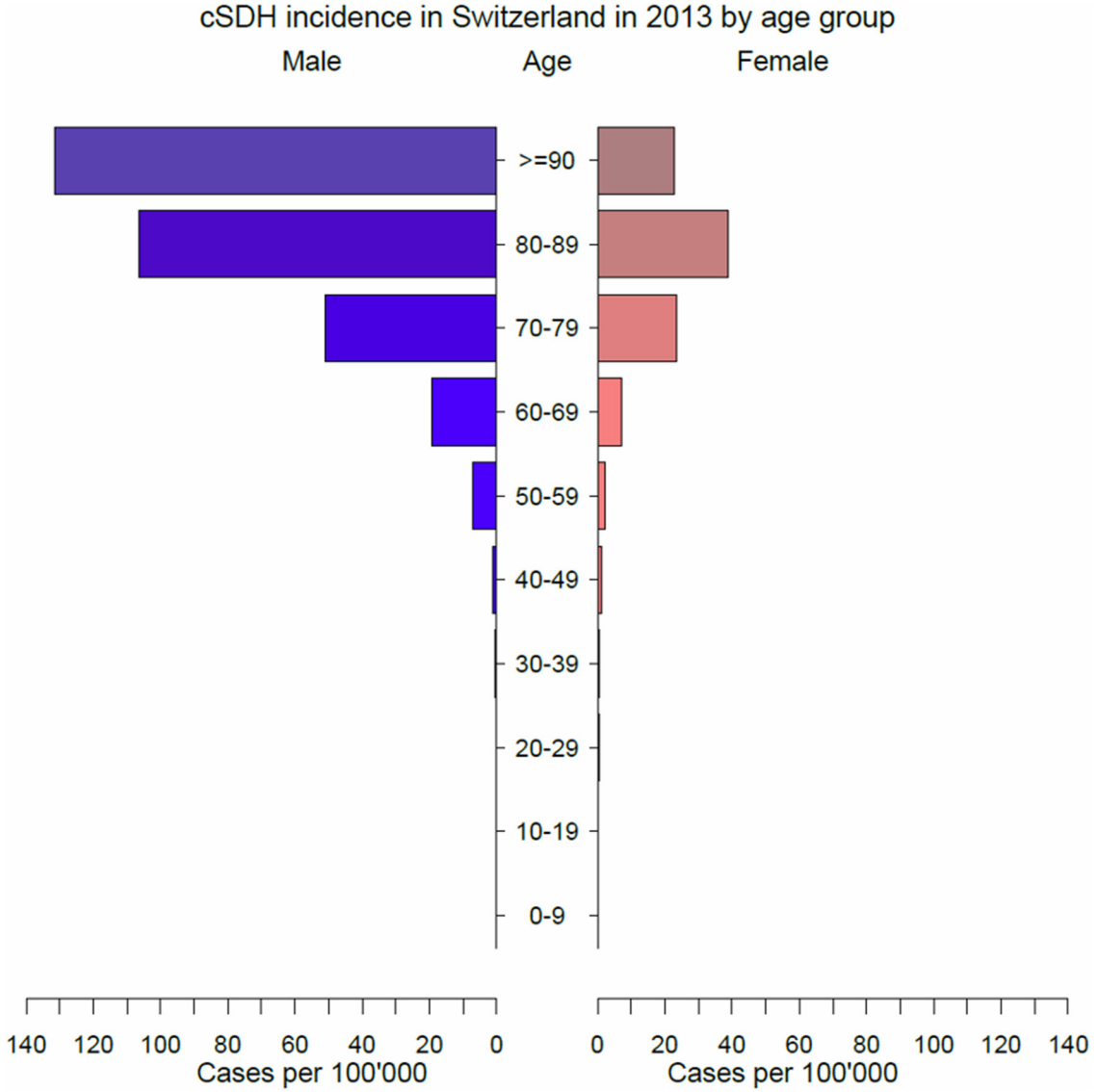


FIGURE 1
Incidence rate of cSDH per age group and sex. The highest incidence rate for women is in the age group 80–89 years, while for men, it is in the 70–79 years age group.

recurrences rate from 24 to 9.3% and the mortality from 18.1 to 8.6% (23). In our series, we inserted a total of 713 drains (261 subdural and 452 subgaleal). The rate of drain placement in Switzerland (>90%), either subdural or subgaleal, is interestingly high compared to the 80% rate found in the international survey by Soleman et al., and this might be attributable to the randomized controlled trial done by Santarius et al. in 2009, which showed a significant benefit in reducing recurrence rates following the use of drains after a burr hole evacuation of cSDH (23). Moreover, Soleman et al. (24) concluded in a recent RCT that subperiosteal drain insertion led to lower recurrence rates, fewer surgical infections, and lower drain misplacement rates compared to subdural drains (25). Häni et al. concluded in a prospective trial that the placement of subgaleal drains rather than subdural drains did not increase the risk of cSDH recurrence. The outcome was also assessed and comparable in both groups (26).

Outcome

We dichotomized the outcome of our patients into favorable outcomes, with an mRS of 0–3, and poor outcomes, with an mRS of 4–6. Higher age, lower GCS and higher mRS on admission, and occurrence of multiple deficits were associated with poor outcomes (Figure 3). This confirms the data observed by Santarius et al. in 2009, where mRS on admission and neurological deficits were strong predictors of a bad outcome. GCS on admission indirectly reflects the patient's neurological status, confirming the significance of these factors and may favor an early surgery before the appearance of neurological deterioration.

No difference was found between the side of the hematomas (right/left) and the outcome of patients, with 31 patients having a bad outcome with left-sided hematomas and 37 with right-sided hematomas. No difference was found between subdural

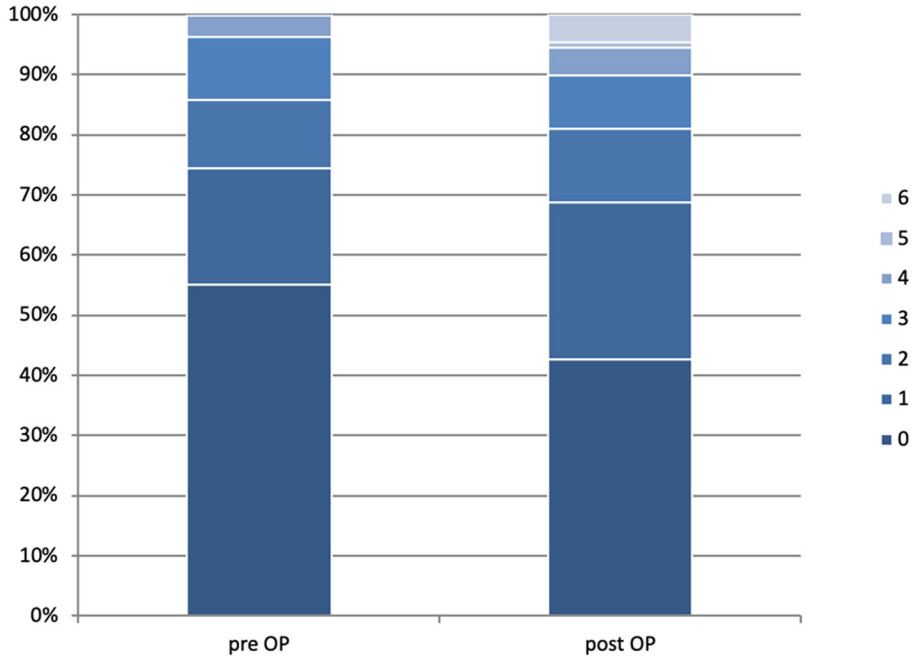


FIGURE 2
Clinical status of patients according to the modified Rankin scale before **(left)** and after **(right)** surgical treatment of their chronic subdural hematoma. The bars represent all assessed patients at respective time points and are set to 100%. We evaluated 615 patients, and 580 were pre-operatively available for the postoperative follow-up assessment. The median time of follow-up assessment was 2 months.

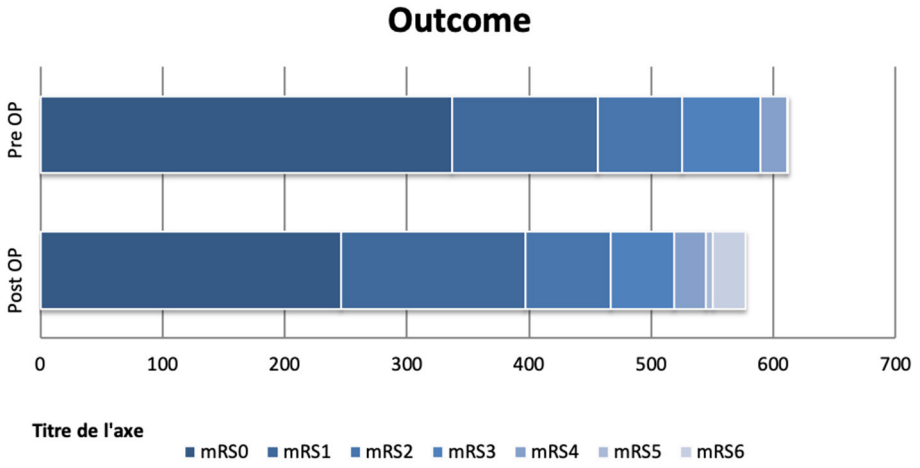


FIGURE 3
Clinical status of patients according to the modified Rankin scale in absolute numbers. The top row represents 615 preoperative assessed patients, and the bottom row 580. Good outcomes (mRS < 3) are seen in almost 81% of patients treated surgically. The outcome was influenced by age, GSC on admission, mRS on admission, and occurrence of multiple neurological deficits at the sickness onset.

vs. subgaleal drains. Santarius et al. conducted their randomized controlled study based on the insertion of subdural drains with the conclusion of a lower recurrence rate. Zhang et al. showed no difference between subdural and subgaleal drains in a retrospective study of 570 patients, which was confirmed by the recent Swiss study conducted by Häni et al. (26, 27). In our cohort, 104 patients (20.1%) experienced a recurrence after a median of 2 weeks (IQR 1–4 weeks) and 17 patients (2.6%) experienced a second recurrence after a median of 3 weeks (IQR 1–10) after surgical drainage of the first recurrence. The usefulness of routine follow-up CT to predict symptomatic recurrence is also questionable and has been recently studied. Schucht et al. showed no benefit for routine follow-up CT after surgery for cSDH, and repeated surgery was fewer in the clinically followed patients (28).

Modern treatment strategies have recently been explored to manage chronic subdural hematoma (CSDH), including middle meningeal artery (MMA) embolization (29, 30). MMA embolization has shown promising results as an option for recurrent or refractory CSDH (31). Link et al. showed in 2018 that MMA embolization may reduce the recurrence rate and the need

for repeated surgeries (32). More extensive research is needed to validate these findings and assess the long-term outcomes.

An additional facet of CSDH management has involved the application of corticosteroids, notably dexamethasone (20). Conclusions drawn from systematic reviews suggest that glucocorticoids may be safe and effective in diminishing the chances of recurrence when used supplementary to surgical intervention. Furthermore, they could serve as independent treatment options to avoid the need for surgical procedures (33–35). Nonetheless, the findings from a randomized, multicenter, placebo-controlled study, which sought to evaluate the impact of dexamethasone on patients suffering from symptomatic chronic subdural hematoma, painted a different picture. The results demonstrated that dexamethasone led to fewer positive outcomes and a higher frequency of undesirable events than placebo at the 6-month mark. As a result, this treatment has since been curtailed in routine medical practice weighing the potential benefits against the risks (21).

This new insight into the effectiveness of dexamethasone underscores the importance of continuous research to evaluate and refine our treatment strategies for cSDH.

Mortality

In our study, the mortality rate at 15 weeks was 4%, equating to 27 patients. The rate was lower than the rate reported by Lukasiewicz et al. in 2016, on 759 patients, which was 17% at 30 days, but consistent with the 4% mortality rate found by Almenawer et al. in a systematic review and meta-analysis of 34,829 patients in 2014 (11). Compared to the recent randomized controlled studies performed in the UK, our cohort's mortality rate was lower. The reported rate by Santarius et al. in 2009 was 8.6% in the drainage group and 18.1% in the non-drainage group, and in the recent study performed by Hutchinson et al., the mortality rate reported was 8.8% in the dexamethasone group and 5% in the placebo group at 6 months. Schucht et al. reported a mortality rate of 5.4% of patients in a recent randomized control trial (28). Lukasiewicz et al. considered only the patients treated by craniotomy and probably included acute subdural hematomas explaining the high mortality (36). In our study, the preferred primary treatment was BHC ($n = 758$). Only a minority of patients were treated by craniotomy ($n = 20$).

Limitations of the study

Our study is limited by the retrospective design. Conservatively treated patients were omitted, and only some might have been treated in private hospitals, minimally impacting our data. Moreover, the study was conducted in a high-income country, which is a factor to consider.

Conclusion

As the first multicenter national cohort-based study analyzing the disease burden of cSDH, our study reveals that the hospital admission rate of cSDH was 8.2/100,000. It increased with age up to 64.2/100,000 persons in patients aged 80–89 years. The mortality rate was 4%, which is lower than the literature reports. Good outcome was seen in almost 81% of the patients but was negatively influenced by higher age, lower GCS on admission, higher mRS on admission, and occurrence of multiple neurological deficits present at the diagnosis of the cSDH.

Data availability statement

The datasets generated and analyzed during this study are not publicly available since their content may compromise the privacy of the research participants. Datasets are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Swissethics (Ec-No: 15-163). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CF, AE, AR, and KS: study design. AE, PA, SM, SW, J-KB, AF, OH, MK, KL, DSc, MS, JS, DSt, JZ, CZ, and CF: data acquisition. AR, LM, LR, KS, DK, and RD: infrastructure. CB, AE, and CF: data analysis. AE and CF along with contributions from all authors: manuscript writing. All authors contributed to manuscript corrections. All authors contributed to the article and approved the submitted version.

Funding

AE received a Scholarship from the Nuovo-Soldati foundation.

In memoriam

Prof. Karl Kothbauer, who contributed to the realization of the manuscript as the past Clinical Director of the Cantonal Hospital of Lucern.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher,

the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly - A North Wales experience. *J R Soc Med.* (2002) 95. doi: 10.1258/jrsm.95.6.290

2. Hiroshi K, Keiichi K, Ichirou I, Hideki S, Norihiko T. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. *Neurol Med Chir.* (1992) 32. doi: 10.2176/nmc.32.207

3. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: Modern management and emerging therapies. *Nat Rev Neurol.* (2014) 10. doi: 10.1038/nrneurol.2014.163

4. Ducruet AF, Grobelny BT, Zacharia BE, Hickman ZL, DeRosa PL, Anderson K, Sussman E, Carpenter A, Connolly ES. The surgical management of chronic subdural hematoma. *Neurosurg Rev.* (2012) 35. doi: 10.1007/s10143-011-0349-y

5. Kevin K, Victoria AV. *Aging World: 2001. International Population Reports. Govt Reports Announcements & Index (GRA&I), Issue 07, 2002* (2001).

6. Cartmill M, Dolan G, Byrne JL, Byrne PO. Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. *Br J Neurosurg.* (2000) 14. doi: 10.1080/02688690050175265

7. Frontera JA, De Los Reyes K, Gordon E, Gowda A, Grilo C, Egorova N, Patel A, Bederson JB. Trend in outcome and financial impact of subdural hemorrhage. *Neurocrit Care.* (2011) 14. doi: 10.1007/s12028-010-9418-2

8. Regan JM, Worley E, Shelburne C, Pullarkat R, Watson JC. Burr hole washout versus craniotomy for chronic subdural hematoma: patient outcome and cost analysis. *PLoS ONE.* (2015) 10:e0115085. doi: 10.1371/journal.pone.0115085

9. Chari A, Hocking KC, Broughton E, Turner C, Santarius T, Hutchinson PJ, Kolias AG. Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on reported outcomes. *J Neurotrauma.* (2016) 33. doi: 10.1089/neu.2015.3983

10. Nakaguchi H, Tanishima T, Yoshimasu N. Factors in the natural history of chronic subdural hematomas that influence their postoperative recurrence. *J Neurosurg.* (2001) 95. doi: 10.3171/jns.2001.95.2.0256

11. 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 34829 patients. *Ann Surg.* (2014) 259. doi: 10.1097/SLA.0000000000000255

12. Baiser 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. doi: 10.3171/2014.9.JNS141550

13. Mellergård P, Wisten O. Operations and re-operations for chronic subdural haematomas during a 25-year period in a well defined population. *Acta Neurochir.* (1996) 138. doi: 10.1007/BF01411476

14. Naganuma H, Fukamachi A, Kawakami M, Misumi S, Nakajima H, Wakao T. Spontaneous resolution of chronic subdural hematomas. *Neurosurgery.* (1986) 19. doi: 10.1097/00006123-198611000-00013

15. Parlato C, Guarracino A, Moraci A. Spontaneous resolution of chronic subdural hematoma. *Surg Neurol.* (2000) 53. doi: 10.1016/S0090-3019(00)00200-7

16. Voelker JL. Nonoperative treatment of chronic subdural hematoma. *Neurosurg Clin N Am.* (2000) 11. doi: 10.1016/S1042-3680(18)30115-3

17. Soleman J, Nocera F, Mariani L. The conservative and pharmacological management of chronic subdural haematoma. *Swiss Med Wkly.* (2017) 147. doi: 10.57187/smw.2017.14398

18. Suzuki J, Takaku A. Nonsurgical treatment of chronic subdural hematoma. *J Neurosurg.* (1970) 33. doi: 10.3171/jns.1970.33.5.0548

19. Kageyama H, Toyooka T, Tsuzuki N, Oka K. Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. *J Neurosurg.* (2013) 119. doi: 10.3171/2013.3.JNS122162

20. Bender MB, Christoff N. Nonsurgical Treatment of Subdural Hematomas. *Arch Neurol.* (1974) 31:73–9. doi: 10.1001/archneur.1974.00490380021001

21. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, et al. Trial of dexamethasone for chronic subdural hematoma. *New Engl J Med.* (2020) 383:2616–27. doi: 10.1056/NEJMoa2020473

22. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: Evidence based review. *J Neurol Neurosurg Psychiatry.* (2003) 74. doi: 10.1136/jnnp.74.7.937

23. 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. doi: 10.1016/S0140-6736(09)61115-6

24. 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. doi: 10.1016/j.wneu.2017.04.134

25. 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). *Clin Neurosurg.* (2019) 85. doi: 10.1093/neuros/nyz095

26. Häni L, Vulcu S, Branca M, Fung C, Z'Graggen WJ, Murek M, et al. Subdural versus subgaleal drainage for chronic subdural hematomas: a *post hoc* analysis of the TOSCAN trial. *J Neurosurg.* (2020) 133. doi: 10.3171/2019.5.JNS19858

27. 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. doi: 10.1016/j.wneu.2019.07.168

28. Schucht P, Fischer U, Fung C, Bernasconi C, Fichtner J, Vulcu S, et al. Follow-up computed tomography after evacuation of chronic subdural hematoma. *New Engl J Med.* (2019) 380. doi: 10.1056/NEJMc1812507

29. 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

30. 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

31. Sattari SA, Yang W, Shahbandi A, Feghali J, Lee RP, Xu R, et al. Middle meningeal artery embolization versus conventional management for patients with chronic subdural hematoma: a systematic review and meta-analysis. *Neurosurgery.* (2023) 92:1142–54. doi: 10.1227/neu.0000000000002365

32. 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

33. 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

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. Yao Z, Hu X, Ma L, You C. Dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis. *Acta Neurochir.* (2017) 159:2037–44. doi: 10.1007/s00701-017-3309-7

36. Lukasiewicz AM, Grant RA, Basques BA, Webb ML, Samuel AM, Grauer JN. Patient factors associated with 30-day morbidity, mortality, and length of stay after surgery for subdural hematoma: a study of the American College of Surgeons National Surgical Quality Improvement Program. *J Neurosurg.* (2016) 124. doi: 10.3171/2015.2.JNS142721

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 15 September 2023
DOI 10.3389/fneur.2023.1251652

OPEN ACCESS

EDITED BY
Milan Lepić,
Military Medical Academy, Serbia

REVIEWED BY
Rana Moshref,
King Faisal Specialist Hospital and Research Centre, Saudi Arabia
Tibor Fulop,
Medical University of South Carolina, United States

*CORRESPONDENCE
Hongyuan Liu
ujoy100@tom.com

†These authors have contributed equally to this work

RECEIVED 02 July 2023
ACCEPTED 05 September 2023
PUBLISHED 15 September 2023

CITATION
Yang L, Li Z, Dai X, Wang L, Wang X and Liu H (2023) Nontraumatic subdural hematoma in patients on hemodialysis with end-stage kidney disease: a systematic review and pooled analysis.
Front. Neurol. 14:1251652.
doi: 10.3389/fneur.2023.1251652

Nontraumatic subdural hematoma in patients on hemodialysis with end-stage kidney disease: a systematic review and pooled analysis

Liling Yang[1†], Zongping Li[2†], Xiaoyu Dai[1], Lijun Wang[1], Xiaoyi Wang[2] and Hongyuan Liu[2*]

[1]Department of Nephrology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, Sichuan, China, [2]Department of Neurosurgery, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China

Background: The original treatment may aggravate when hemodialysis (HD) patients have nontraumatic subdural hematoma (NSDH). End-stage kidney disease patients are at increased risk for NSDH, but its risk factors and outcomes are not sufficiently explored at present.

Methods: Electronic databases, including PubMed, EMBASE, and Web of Science were searched by using various combinations of the keywords "Hemodialysis," "Renal Insufficiency," "Extracorporeal Dialysis," "Subdural Hematoma," "Subdural Hemorrhage," "Subdural Hematomas," and "Subdural Hemorrhages" in accordance with the PRISMA guidelines. Sixteen papers were selected. Relevant patient data were extracted, aggregated, and analyzed.

Results: A total of 74 patients were analyzed, including 37 male, 26 female, and 11 with no gender data, with a mean age of 56 years (range, 16–81 years). There were 43 patients with hypertension, 36 patients with diabetes, 16 patients who used oral anticoagulants before dialysis, and 10 patients with atrial fibrillation. The diagnosis of subdural hematoma (SDH) was made by computed tomography (CT) ($n = 51$), carotid arteriography ($n = 7$), surgical exploration ($n = 3$), and autopsy ($n = 2$). Forty cases underwent surgical treatment, including craniotomy and burr hole (or twist drill) drainage. The 1 year mortality rate of NSDH was 45.9%. The mortality rate after conservative treatment (61.8%) was higher than that after surgical intervention (32.5%). The mortality rate of NSDH in dialysis patients with atrial fibrillation and in those who used oral anticoagulants before hemodialysis (HD) was 90 and 81%, respectively.

Conclusion: NSDH is rare in HD, and mortality is high if NSDH occurs in dialysis patients. Surgical intervention reduces the mortality from NSDH in patients on HD ($p < 0.02$). Patients with atrial fibrillation and those who were taking oral anticoagulants before dialysis have a higher NSDH mortality ($p < 0.01$).

KEYWORDS

end-stage kidney disease, nontraumatic subdural hematoma, hemodialysis, kidney failure, kidney replacement therapy

Introduction

Subdural hematoma (SDH) is a common neurosurgical condition characterized by progressive and recurrent bleeding caused by traumatic tearing of blood vessel(s) (1, 2). Patients with SDH exhibit different clinical symptoms depending on its location in the skull. SDH is classified as acute, subacute, and chronic depending on the time of development. Risk factors for developing SDH include age, head injury, anticoagulant or antiplatelet drug use, low intracranial pressure, and hemodialysis (HD) (3–5).

Chronic kidney disease is a chronic structural or functional abnormality of the kidney with various causes, and is currently a global public health problem. It eventually progresses to end-stage kidney disease (ESKD) (6), which is the final stage of chronic kidney disease and is generally irreversible.

In recent years, the incidence and mortality of ESKD have increased rapidly (7). The primary modality for treating ESKD is kidney replacement therapy (KRT), including HD, peritoneal dialysis (PD), or kidney transplantation. In ESKD patients, the accumulation of toxins leads to various complications.

Patients with ESKD have a 3–10 times higher risk of stroke than the general population (8). Because brain atrophy is common in patients with ESKD, the length of the pontine vein that is prone to tearing increases the incidence of SDH (9). Patients with long-term HD have a 10-fold higher risk of developing SDH than the general population (5, 10). This may be related to HD changes in intracranial pressure, cerebral blood flow, and subdural pressure (11). The occurrence of nontraumatic SDH (NSDH) in ESKD patients undergoing HD has rarely been reported and was mainly presented in the form of case reports or a small case series. To explore the pathophysiology and risk factors for the development of NSDH in HD, we conducted a systematic review and summary analysis of the published literature.

Methods

The analysis and generation of inclusion criteria were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (12).

We searched reports in English up to April 2023 in PubMed, EMBASE, and Web of Science, using Boolean operators "OR" and "AND" in combination OR alone with the following keywords: using various combinations of the keywords "Hemodialysis," "Renal Insufficiency," "Extracorporeal Dialysis," "Subdural Hematoma," "Subdural Hemorrhage," "Subdural Hematomas," and "Subdural Hemorrhages."

First, relevant studies were screened by title and abstract. Second, the assessment was done after downloading the full text. Prospective studies, retrospective studies, and case reports were included. Traumatic SDH, incomplete data, non-English language reports, PD, duplicate articles, reviews, commentaries, or editorials were excluded. This process was carried out independently by three assessors (LY, ZL, and XD). Any disagreements were settled by consensus. All data were collected by two authors (LW and XW). Given that the majority were retrospective studies and individual patient data were not always available, a formal meta-analysis could not be performed.

Statistical analysis

Statistical analysis was performed using SPSS 24.0. Univariate analysis was performed using Fisher's exact test, and categorical variables were compared using chi-square tests. Differences were considered statistically significant at p values lower than 0.05.

Results

By searching the keywords in the title and abstract, 105 duplicates were removed, and a total of 240 papers were obtained. Forty-one articles were obtained by filtering the titles and abstracts. The full-text versions of the 41 articles were evaluated. After excluding traumatic SDH, incomplete data, duplicate data papers, etc., a total of 16 papers were finally obtained (13–28). The PRISMA flow diagram for the selection is shown in Figure 1.

Patient population

Sixteen papers were analyzed, with sample sizes ranging from 1 to 41 patients (Table 1). The 16 papers included 13 case reports or mini case papers (up to four patients), one article mentioning NSDH in an HD patient, and two retrospective case series (11–41 patients). A total of 74 patients were identified, namely 26 female, 37 male, and 11 with no gender data, with a mean age of 56 years (range, 16–81 years).

Kidney failure and anticoagulants

Except for one case of acute anuretic kidney failure undergoing HD, the remaining 73 patients were on chronic HD with unexplained causes of chronic kidney failure. In 14 articles, heparin anticoagulation was used during HD in 72 cases. For two females in two case reports, the authors did not mention whether heparin anticoagulation was used during HD. A total of 16 patients received oral anticoagulants before HD, while 45 cases were not anticoagulated, and the use of anticoagulants was not described in the remaining patients.

Clinical symptoms and past complications

Two retrospective studies analyzed a total of 3,718 patients with chronic maintenance HD, including 52 patients with NSDH whose clinical symptoms at presentation were not described. The main clinical symptoms of 22 patients in 14 articles were headache ($n = 14$), consciousness disturbance ($n = 5$), hemiparesis ($n = 3$), vomiting ($n = 2$), and nausea ($n = 1$).

Of all 74 patients, 43 cases had hypertension, 36 cases had diabetes mellitus, 14 cases had ischemic heart disease, 10 cases had atrial fibrillation, three cases had chronic-disease anemia, and one case had thrombosis, and in five cases no previous diseases were mentioned.

Auxiliary examinations

Hemoglobin level was reported in 59 patients in eight articles, with a mean of 106.4 g/L. Prothrombin time was reported in 55

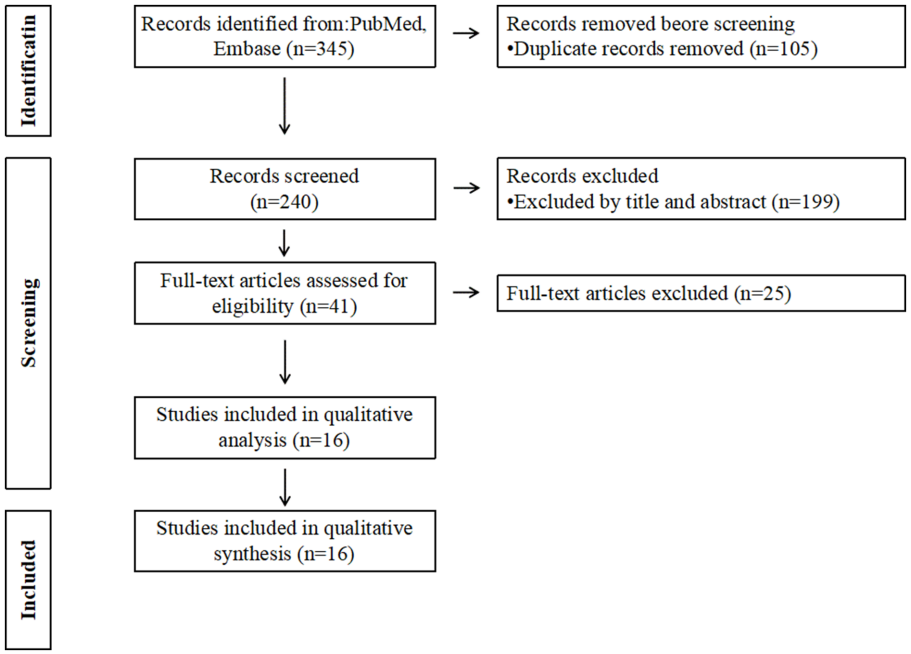


FIGURE 1
PRISMA flow diagram for the selection of literature.

patients in five articles, with an average of 11.74 s. The mean platelet in 55 patients in five articles was 181.27×10^9/L.

The diagnosis of SDH was made by computed tomography (CT) in 51 cases, carotid arteriography in seven cases, surgical exploration in three cases, and autopsy in two cases. Twenty-three cases were acute SDH, 16 cases were chronic SDH, and the nature of SDH was unclear in 35 cases.

Treatment and outcome

Thirty-four cases underwent conservative treatment, such as antihypertensive therapy, anti-epilepsy, and change of anticoagulant for HD, including one case where conservative treatment was followed by burr hole and one case where it was followed by craniotomy. Forty cases underwent surgical treatment, including craniotomy and burr hole (or twist drill) drainage. The 30 days mortality rate of conservative treatment was 61.8%, while the 30 days mortality rate of surgical treatment was 30%. At 1 year, 40 patients survived.

Risk factors for death

Table 2 presents the data on survival and death of the patients with NSDH who underwent HD within 1 year. In the survivor group, 27 (67.5%) of 40 patients underwent surgical intervention, while in the death group, 13 (38.2%) of 34 cases underwent surgical intervention. Aggressive surgical intervention for NSDH on HD was able to reduce the risk of death ($p < 0.02$). Patients with atrial fibrillation or those who were taking oral anticoagulants before HD had increased mortality from SDH ($p < 0.01$). Age, sex, hypertension, diabetes, and type of SDH did not change the outcome of NSDH on HD.

Discussion

Stroke and ESKD are two major risk factors for human health. There is a high risk of stroke in patients with ESKD undergoing dialysis and a high mortality rate in the event of stroke. SDH usually occurs in injured elderly patients, with high morbidity and mortality rate. Fall, age, antiplatelet drugs, and low intracranial pressure are risk factors for the development of SDH (3, 4). Among them, fall and age are common clinical risk factors. In the absence of trauma, SDH is thought to occur spontaneously and may be associated with systemic hypertension, cerebral atrophy, coagulation dysfunction, and use of anticoagulant drugs. Some studies have shown that dialysis modality may affect the incidence of SDH in ESKD (29–32). HD alters hemodynamics, and the use of anticoagulants such as heparin puts HD patients at a higher risk of SDH than PD patients (33). Some studies have shown that HD patients have a higher rate of SDH (5, 10, 34). In two of the studies we collected, 52 out of 3,718 patients developed SDH, with an incidence of 1.4% and an annual incidence of 189 per 100,000/year. By contrast, previous studies have reported an incidence of SDH between 8.2/100,000 and 48/100,000/year (29). The high incidence of NSDH in HD may be related to heparin and other anticoagulants, antiplatelet drugs, atrial fibrillation, and cardiovascular diseases (14). It has also been shown that the increased risk of HD bleeding is due to the uremic state itself and impaired platelet function (14, 33). Although the incidence of NSDH is higher in HD patients, there are few literature reports, and the previous reports were mainly case reports. With insufficient data on the risk

TABLE 1 Summary of the included studies.

Author and Year	No. of Patients	Age/ Average Age (years)	Sex	Study Design	Symptoms	Symptom duration (h)	Type of SDH	Oral Anticoagulants before HD	Anticoagulants for HD	Dose of anticoagulants for HD	SDH-detection method	Treatment modalities
Prasad et al., 2022 (13)	1	27	F	Case Report	Consciousness disturbance	NA	Chronic	NA	NA	NA	CT	Levetiracetam; vitamin K; burr hole
Fayed et al., 2021 (14)	41	56.3	F ($n = 18$), M ($n = 23$)	Retrospective case series	NA	NA	Acute ($n = 15$); Chronic ($n = 7$)	Warfarin ($n = 10$)	Heparin	500 IU at the start of HD; 500 IU every hour	CT	No surgery ($n = 19$); surgery ($n = 22$)
Uchio et al., 2021 (15)	1	81	F	Case Report	Vomiting; nausea	NA	Acute	NA	NA	NA	CT	Fasting and antihypertensives
Power et al., 2010 (16)	11	71.3	NA	Retrospective case series	NA	NA	NA	NA	Heparin	500 IU at the start of HD; 500 IU every hour	NA	No surgery ($n = 8$); surgery ($n = 3$)
Mesquita et al., 2008 (17)	1	65	M	Case Report	Hemiparesis	0.2	Acute	NA	Heparin	NA	CT	Valproic acid; vancomycin; craniotomy
Sengul et al., 2005 (18)	1	26	F	Case Report	Headache; vomiting; hemiparesis	1	Acute	NA	Heparin	NA	CT	Twist drill
Zingale et al., 1999 (19)	1	77	M	Case Report	Consciousness disturbance	NA	Chronic	NA	Heparin	NA	CT	Burr hole
Kopitnik et al., 1989 (20)	1	48	M	Case Report	Consciousness disturbance	NA	Chronic	NA	Heparin	NA	CT	Burr hole
Inzelberg et al., 1989 (21)	1	28	F	Case Report	Hemiparesis	1	Chronic	Warfarin	Heparin	NA	CT	Dexamethasone; antibiotic
Sayre et al., 1987 (22)	1	29	M	Case Report	Consciousness disturbance	NA	NA	NA	Heparin	1,100 IU	CT	Craniotomy
Isiadinso et al., 1976 (23)	4	65	M	Retrospective case series	Headache	NA	Chronic	NA	Heparin	NA	Carotid arteriography	Craniotomy
Bechar et al., 1972 (24)	2	27.5	F, M	Case Report	Headache	NA	Chronic and acute	Sintrom	Heparin	NA	Carotid arteriography	Craniotomy
Talalla et al., 1970 (25)	3	29.3	F ($n = 2$), M	Retrospective case series	Headache	NA	Acute ($n = 1$); Chronic ($n = 2$)	Warfarin ($N = 2$)	Heparin	1,500 IU ($n = 2$)	Surgical exploration ($n = 1$); carotid arteriography ($n = 1$); autopsy ($n = 1$)	Burr hole and craniotomy ($n = 1$); craniotomy ($n = 1$)
Zarowny et al., 1970 (26)	1	46	M	Case Report	Headache	1.5	Acute	Anticoagulant	Heparin	NA	Surgical exploration	Burr hole
Del et al., 1970 (27)	1	28	F	Case Report	Headache	NA	NA	NA	Heparin	45–60 mg	CT	Regional heparinization
Leonard et al., 1969 (28)	3	64.3	M	Retrospective case series	Headache ($n = 2$); consciousness disturbance	NA	Acute ($n = 2$); Chronic ($n = 1$)	NA	Heparin	NA	Autopsy ($n = 1$); surgical exploration ($n = 1$); CT ($n = 1$)	Discontinuation of dialysis ($n = 1$); craniotomy ($n = 2$)

SDH, subdural hematoma; CT, computed tomography; h, hour; NA, not available.

10.3389/fneur.2023.1251652

TABLE 2 Risk factors affecting the survival rate of SDH on HD.

	Survival ($n = 40$)	Death ($n = 34$)	p
Age (years)	52.2 ($n = 35$)	62.4 ($n = 24$)	NS
Male Sex	20/36 (55.6%)	17/27 (62.9%)	NS
Acute subdural hematomas	16/28 (57.1%)	7/14 (50%)	NS
Surgical treatment	27/40 (67.5%)	13/34 (38.2%)	0.02
Diabetes mellitus	19/33 (57.6%)	12/22 (54.5%)	NS
Hypertension	21/34 (64.7%)	15/21 (71.4%)	NS
Atrial fibrillation	1/33 (3%)	9/22 (40.9%)	0.001
Oral anticoagulant medication before HD	3/36 (8.3%)	13/25 (52%)	0.001

SDH, subdural hematoma; HD, hemodialysis.

factors and outcomes, we conducted a systematic review of previous HD patients with NSDH.

The onset of NSDH is relatively insidious, and the common clinical symptoms are headache, consciousness disturbance, and hemiparesis. In our report, the symptoms included headache ($n = 14$), consciousness disturbance ($n = 5$), hemiparesis ($n = 3$), vomiting ($n = 2$), and nausea ($n = 1$). The diagnosis of NSDH was mainly made by imaging, among which 51 cases were found by CT examination and seven cases were found by carotid arteriography. However, before the development and popularization of CT, NSDH was usually detected at autopsy or surgical exploration. In our retrospective analysis, two cases were found by autopsy and three cases by surgical exploration. The treatment of NSDH is similar to that of traumatic SDH. Treatment of SDH usually depends on the patient's symptoms, neurological examination, thickness of blood in the SDH, midline shift, and other factors (35–37). Surgical intervention for SDH is the preferred treatment for patients with symptoms and/or midline displacement >1 cm, or with supratentorial hematoma greater than 30 mL. For subacute or chronic SDH, only external drainage is usually required. However, the burr hole or twist drill should be wide enough to allow continuous free drainage to prevent recurrence of the hematoma. There were no reports of recurrence after burr hole or twist drill in our study. For acute SDH, craniotomy is usually required to determine the site of bleeding. The timing of surgery is critical for acute SDH in patients receiving anticoagulant therapy. Some studies have shown that mortality from early surgery is nearly twice as high as that from late surgery due to coagulopathy and inadequate preparation for surgical intervention (38). In our study, there were 19 cases of acute SDH craniotomy and five cases of death.

In past retrospective studies, it has been reported that the 30 days mortality rate for SDH patients with ESKD requiring dialysis is 19% (34). Two SDH surveys of ESKD patients in Taiwan and the United States have reported mortality rates of 35–39% (5, 39). The 30 days mortality rate for conservative treatment was 61.8%, and the mortality rate for surgical treatment was 30%. The one-year mortality rate was 45.9%. This is broadly consistent with previous reports. We further analyzed the risk factors for death after the development of SDH in HD patients. Surgical intervention, atrial fibrillation, and oral anticoagulants before HD can change the outcome of SDH. Surgical intervention after the occurrence of NSDH in HD can reduce patient mortality ($p < 0.02$). Consistent with other studies (39, 40), we confirmed that atrial fibrillation is associated with an increased risk of death from NSDH in HD ($p < 0.01$). At the same time, our study showed that oral anticoagulants prior to HD increased the risk of death from NSDH ($p < 0.01$). It is possible that the use of oral anticoagulants in the management of atrial fibrillation may exacerbate uremic bleeding (41, 42). However, variables such as age, hypertension, and diabetes do not change the outcome of NSDH occurring in HD.

There are limitations to our study. First, the vast majority of the studies reviewed were retrospective and observational, and such studies are prone to selection and publication bias. Therefore, the strength of our data and the validity of our conclusions are limited. Second, not every data variable could be extracted due to the design of the study and the heterogeneity of the published data. Nevertheless, we were the first to conduct a comprehensive and systematic review of the literature on the occurrence of NSDH in HD patients and to assess the incidence of NSDH in HD and the risk factors for death.

Conclusion

NSDH is rare in HD patients, but has the potential to be a serious complication, with a possible mortality rate of 39–45%. If NSDH occurs on HD, conservative treatment is associated with a twofold increased risk of death compared with surgical intervention. Patients with atrial fibrillation or those who were taking oral anticoagulants before dialysis have a greater risk of death when NSDH occurs during dialysis. Given the significance of our findings, prospective studies may be needed to help accurately determine the incidence, risk factors, and outcomes of this complication to develop effective prevention and treatment strategies for this population.

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.

Author contributions

LY and HL: conceptualization. XW and HL: methodology and supervision. ZL, XD, and LW: data curation. LY and ZL: writing – original draft preparation. HL: writing – review and editing and project administration. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Foundation Program of the Sichuan Provincial Health Commission (no. 21PJ181).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1251652/full#supplementary-material

References

1. Miah IP, Tank Y, Rosendaal FR, Peul WC, Dammers R, Lingsma HF, et al. Radiological prognostic factors of chronic subdural hematoma recurrence: a systematic review and meta-analysis. *Neuroradiology*. (2021) 63:27–40. doi: 10.1007/s00234-020-02558-x

2. Liu HY, Yang LL, Dai XY, Li ZP. Local anesthesia with sedation and general anesthesia for the treatment of chronic subdural hematoma: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. (2022) 26:1625–31. doi: 10.26355/eurrev_202203_28230

3. 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

4. Nordström A, Nordström P. Cognitive performance in late adolescence and the subsequent risk of subdural hematoma: an observational study of a prospective nationwide cohort. *PLoS Med*. (2011) 8:e1001151. doi: 10.1371/journal.pmed.1001151

5. Wang IK, Lin CL, Wu YY, Kuo HL, Lin SY, Chang CT, et al. Subdural hematoma in patients with end-stage renal disease receiving hemodialysis. *Eur J Neurol*. (2014) 21:894–900. doi: 10.1111/ene.12406

6. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One*. (2016) 11:e0158765. doi: 10.1371/journal.pone.0158765

7. Luo D, Zhao W, Lin Z, Wu J, Lin H, Li Y, et al. The effects of hemodialysis and peritoneal dialysis on the gut microbiota of end-stage renal disease patients, and the relationship between gut microbiota and patient prognoses. *Front Cell Infect Microbiol*. (2021) 11:579386. doi: 10.3389/fcimb.2021.579386

8. Masson P, Kotwal S, Kelly PJ, Craig JC, Lindley RI, Gallagher M, et al. Risk factors for stroke in people with end-stage kidney disease: a cohort study. *Cerebrovascular Diseases*. (2016) 42:428–38. doi: 10.1159/000445067

9. Yang AI, Balser DS, Mikheev A, Offen S, Huang JH, Babb J, et al. Cerebral atrophy is associated with development of chronic subdural haematoma. *Brain Inj*. (2012) 26:1731–6. doi: 10.3109/02699052.2012.698364

10. Sozio SM, Armstrong PA, Coresh J, Jaar BG, Fink NE, Plantinga LC, et al. Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. *Am J Kidney Diseases Off J Natl Kidney Found*. (2009) 54:468–77. doi: 10.1053/j.ajkd.2009.01.261

11. Fang D, Chabrier-Rosello JO, BA MM, Fülöp T, Achanti A. Achieving osmotic stability in the context of critical illness and acute kidney injury during continuous renal replacement therapy. *ASAIO J*. (2020) 66:e90. doi: 10.1097/MAT.0000000000001100

12. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), (2020). Flow diagram template. Available at: https://journalsplosorg/plosmedicine/article/figure?id=101371/journalpmed1003583g001

13. Prasad RM, Liu JZ, Garces C, Duwadi A, Choi J, Anwar F, et al. Uncommon cause of internal mammary artery pseudoaneurysm. *Ochsner J*. (2022) 22:244–8. doi: 10.31486/toj.21.0090

14. Fayed A, Tarek A, Refaat MI, Abouzeid S, Salim SA, Zsom L, et al. Retrospective analysis of nontraumatic subdural hematoma incidence and outcomes in Egyptian patients with end-stage renal disease on hemodialysis. *Ren Fail*. (2021) 43:1322–8. doi: 10.1080/0886022X.2021.1979038

15. Uchio N, Miyano R, Matsumoto H. Symmetrical interhemispheric subdural hematoma. *Cureus*. (2021) 13:e13711. doi: 10.7759/cureus.13711

16. Power A, Hamady M, Singh S, Ashby D, Taube D, Duncan N. High but stable incidence of subdural haematoma in haemodialysis – a single-centre study. *Nephrol Dial Transp Off Publ Eur Dial Transp Assoc Eur Renal Assoc*. (2010) 25:2272–5. doi: 10.1093/ndt/gfq013

17. Mesquita M, Damry N, Gazagnes MD. Fatal cerebritis and brain abscesses following a nontraumatic subdural hematoma in a chronic hemodialyzed patient. *Hemodial Int*. (2008) 12:426–30. doi: 10.1111/j.1542-4758.2008.00305.x

18. Sengul G, Tuzun Y, Kadioglu HH, Aydin IH. Acute interhemispheric subdural hematoma due to hemodialysis: case report. *Surg Neurol*. (2005) 64:S113–4. doi: 10.1016/j.surneu.2005.07.050

19. Zingale A, Chibbaro S, Florio A, Distefano G, Porcaro S. Management of chronic subdural hematoma in patients treated with anticoagulation. *J Neurosurg Sci*. (1999) 43:277–84.

20. Kopitnik TA, De Andrade R, Gold MA, Nugent GR. Pressure changes within a chronic subdural hematoma during hemodialysis. *Surg Neurol*. (1989) 32:289–93. doi: 10.1016/0090-3019(89)90232-2

21. 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

22. Sayre MR, Roberge RJ, Evans TC. Nontraumatic subdural hematoma in a patient with osteogenesis imperfecta and renal failure. *Am J Emerg Med*. (1987) 5:298–301. doi: 10.1016/0735-6757(87)90355-X

23. Isiadinso OA. Early diagnosis of subdural hematoma in hemodialysis patients: use of carotid arteriography. *Angiology*. (1976) 27:491–3. doi: 10.1177/000331977602700901

24. Bechar M, Lakke JP, van der Hem GK, Beks JW, Penning L. Subdural hematoma during long-term hemodialysis. *Arch Neurol*. (1972) 26:513–6. doi: 10.1001/archneur.1972.00490120053005

25. Talalla A, Halbrook H, Barbour BH, Kurze T. Subdural hematoma associated with long-term hemodialysis for chronic renal disease. *JAMA*. (1970) 212:1847–9. doi: 10.1001/jama.1970.03170240051007

26. Zarowny DP, Rose I. Acute subdural hematoma during maintenance hemodialysis. *Can Med Assoc J*. (1970) 103:634.

27. Del Greco F, Krumlovsky F. Subdural haematoma in the course of haemodialysis. *Lancet*. (1969) 294:1009–10. doi: 10.1016/S0140-6736(69)90563-7

28. Leonard CD, Weil E, Scribner BH. Subdural haematomas in patients undergoing haemodialysis. *Lancet*. (1969) 294:239–40. doi: 10.1016/S0140-6736(69)90006-3

29. Stubbs DJ, Vivian ME, Davies BM, Ercole A, Burnstein R, Joannides AJ. Incidence of chronic subdural haematoma: a single-centre exploration of the effects of an ageing population with a review of the literature. *Acta Neurochir*. (2021) 163:2629–37. doi: 10.1007/s00701-021-04879-z

30. Alaraj AM, Chamoun RB, Dahdaleh NS, Haddad GF, Comair YG. Spontaneous subdural haematoma in anabolic steroids dependent weight lifters: reports of two cases and review of literature. *Acta Neurochir*. (2005) 147:85–8. doi: 10.1007/s00701-004-0415-0

31. Farhat Neto J, Araujo JL, Ferraz VR, Haddad L, Veiga JC. Chronic subdural hematoma: epidemiological and prognostic analysis of 176 cases. *Revista do Colegio Brasileiro de Cirurgioes*. (2015) 42:283–7. doi: 10.1590/0100-69912015005003

32. Kostić A, Kehayov I, Stojanović N, Nikolov V, Kitov B, Milošević P, et al. Spontaneous chronic subdural hematoma in elderly people - arterial hypertension and other risk factors. *J Chin Med Assoc JCMA*. (2018) 81:781–6. doi: 10.1016/j.jcma.2018.03.010

33. Wang IK, Cheng YK, Lin CL, Peng CL, Chou CY, Chang CT, et al. Comparison of subdural hematoma risk between Hemodialysis and peritoneal dialysis patients with ESRD. *Clin J Am Soc Nephrol*. (2015) 10:994–1001. doi: 10.2215/CJN.08140814

34. Hsieh CY, Lai CC, Lee JS, Tseng CC. Subdural Hemorrhage in patients with end-stage renal disease requiring dialysis: a single-center study. *Acta Neurol Taiwanica*. (2018) 27:9–17.

35. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, et al. Surgical management of acute subdural hematomas. *Neurosurgery*. (2006) 58:S2-16–24. doi: 10.1227/01.NEU.0000210364.29290.C9

36. 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 Off J Neurosurg Soc Austr*. (2018) 50:7–15. doi: 10.1016/j.jocn.2018.01.050

37. Robinson D, Khoury JC, Kleindorfer D. Regional variation in the management of nontraumatic subdural hematomas across the United States. *World Neurosurg*. (2020) 135:e418–23. doi: 10.1016/j.wneu.2019.12.011

38. Lisowska-Myjak B. Uremic toxins and their effects on multiple organ systems. *Nephron Clin Pract*. (2014) 128:303–11. doi: 10.1159/000369817

39. Sood P, Sinson GP, Cohen EP. Subdural hematomas in chronic dialysis patients: significant and increasing. *Clin J Am Soc Nephrol*. (2007) 2:956–9. doi: 10.2215/CJN.03781106

40. 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

41. Andrassy K, Ritz E. Uremia as a cause of bleeding. *Am J Nephrol*. (1985) 5:313–9. doi: 10.1159/000166955

42. Elliott MJ, Zimmerman D, Holden RM. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. *Am J Kidney Diseases Off J Natl Kidney Found*. (2007) 50:433–40. doi: 10.1053/j.ajkd.2007.06.017

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 15 September 2023
DOI 10.3389/fneur.2023.1249332

OPEN ACCESS

EDITED BY
Milan Lepić,
Military Medical Academy, Serbia

REVIEWED BY
Adam James Wells,
University of Adelaide, Australia
Asra Al Fauzi,
Airlangga University, Indonesia

*CORRESPONDENCE
M. Foppen
✉ m.foppen@amsterdamumc.nl

RECEIVED 28 June 2023
ACCEPTED 28 August 2023
PUBLISHED 15 September 2023

CITATION
Foppen M, Bandral HV, Slot K-AM, Vandertop WP and Verbaan D (2023) Success of conservative therapy for chronic subdural hematoma patients: a systematic review. *Front. Neurol.* 14:1249332. doi: 10.3389/fneur.2023.1249332

Success of conservative therapy for chronic subdural hematoma patients: a systematic review

M. Foppen[1,2]*, Harssh Verdan Bandral[1,2], Kari-Anne Mariam Slot[1,2], W. P. Vandertop[1,2] and D. Verbaan[1,2]

[1]Department of Neurosurgery, Amsterdam UMC Location University of Amsterdam, Amsterdam, Netherlands, [2]Amsterdam Neuroscience, Neurovascular Disorders, Amsterdam, Netherlands

Background: Conservative therapy for chronic subdural hematoma (cSDH) is an option for patients who express no, or only mild symptoms, thereby preventing surgery in some. Because it is not clear for whom conservative therapy is successful, we aimed to estimate the success rate of conservative therapy and to identify which factors might influence success.

Methods: We systematically searched MEDLINE and EMBASE databases to identify all available publications reporting outcome of conservative therapy for cSDH patients. Studies containing >10 patients were included. The primary outcome was the success rate of conservative therapy, defined as "no crossover to surgery" during follow-up. In addition, factors possibly associated with success of conservative therapy were explored. Bias assessment was performed with the Newcastle Ottowa Scale and the Cochrane risk-of-bias tool. We calculated pooled incidence and mean estimates, along with their 95% confidence intervals (CIs), using OpenMeta[Analyst] software.

Results: The search yielded 1,570 articles, of which 11 were included in this study, describing 1,019 conservatively treated patients. The pooled success rate of conservative therapy was 66% (95% CI: 50–82%). One study ($n = 98$) reported smaller hematoma volume to be associated with success, whilst another study ($n = 53$) reported low hematoma density and absence of paresis at diagnosis to be associated with success.

Conclusion: Conservative therapy is reported to be successful in the majority of cSDH patients who have either no, or only mild symptoms. Hematoma volume, low hematoma density and absence of paresis could be factors associated with success. However, further research is warranted in order to establish factors consistently associated with a successful conservative therapy.

Other: No funding was acquired for this study. The study was not registered nor was a study protocol prepared.

KEYWORDS

hematoma, subdural, chronic, humans, treatment outcome, incidence, risk factors

Introduction

Chronic subdural hematoma (cSDH) is a frequently occurring disease mainly affecting elderly patients. Risk factors are brain atrophy, anticoagulation or antiplatelet therapy, male gender and (minor) head trauma (1, 2). The incidence of cSDH is projected to triple by 2040, making its occurrence in daily neurological and neurosurgical practice even more common (3, 4).

There is no consensus concerning the optimal treatment strategy. For patients with severe symptoms (e.g., depressed level of consciousness, hemiparesis, Intractable headache), surgical therapy is the mainstay of treatment. The most frequently used surgical modality is burr hole craniostomy with subdural or subgaleal drainage and in a minority of cases (15%), a craniotomy or twist-drill craniostomy is performed (5). Surgical evacuation is not without disadvantages as it exposes these, often elderly and frail, patients to concomitant risk of complications such as post-operative intracranial haemorrhage, pneumocephaly, seizures, delirium and pneumonia (up to 15%) (6–8). Hematoma recurrence is another well-known complication that arises in the weeks following surgery in approximately 13% of patients (9–11).

Patients who experience relatively mild, or no symptoms, or who are unfit for surgery, can be treated conservatively (wait-and-watch) (12). The frequency of non-surgical therapy as primary treatment has been rising over the last 30 years, but despite this rising frequency, studies regarding the efficacy and outcome are limited (13). Therefore, vital elements such as success rate (i.e., the ability to avoid surgery with good clinical outcome) and factors associated with success have not yet been established.

The absence of clarity results in uncertain and unsubstantiated decisions regarding optimal treatment and follow-up strategy, leading to considerable practice variation (14–16). In order to elucidate these gaps, we reviewed the literature. The primary aim of this study is to (1) determine the reported success rate of conservative therapy and (2) identify factors possibly associated with success.

Methods

Search strategy

For this systematic review, we followed the guidelines stated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. We searched MEDLINE and EMBASE databases with the following terms: "chronic subdural hematoma," "chronic subdural hygroma,", "conservative treatment," "non-surgical," and "observative and observational treatment." For the detailed search strategy, see Supplement 1. The search was last executed on May 30th, 2023. No other data filters were applied.

Study selection

Two independent reviewers (MF and HVB) first individually screened the titles and abstracts and subsequently full-text for eligibility. Studies were included if (1) they contained patients diagnosed with a cSDH; (2) age was >18 years old; (3) initial treatment strategy was conservative. Conservative therapy was defined as: "wait-and-scan" or "wait-and-watch." Studies were also included if only a subgroup received conservative therapy and data of this group could be reliably extracted. For example, if a subgroup received placebo or no treatment (in placebo controlled drug studies or observational studies). Studies were excluded if (1) initial treatment consisted of surgery, middle meningeal artery embolization, medication, epidural blood patch or abstinent therapy; (2) studies contained less than 10 patients; (3) no distinct data of the conservative group could be distilled (also if the success percentage of the conservative group could not be determined due to a missing denominator); (4) wrong publication type (letter to editors, editorials or studies with repeated study population); (5) the language was other than English; (6) it was explicitly described that cSDH occurred after decompressive craniotomy or craniectomy; (7) the hematoma was located infratentorial or other than along the convexity (for supratentorial hematomas); (8) the full-text version was not available. A third adjudicator (DV) was consulted in the case of any discrepancies between the two initial reviewers regarding the in-or exclusion of studies.

Outcomes

The primary outcome was success of conservative treatment. Conservative therapy was deemed successful if surgical evacuation for the cSDH was not required during follow-up. Other outcomes included factors associated with success of conservative therapy, mortality, Glasgow Outcome Scale (GOS) score, time until complete hematoma resolution in the success group (confirmed by CT-scan), and time to, and criteria for, crossover to surgery.

Data collection

Two reviewers (MF and HVB) independently collected the variables of interest. Extracted data items included: article information (title, author, year of publication, study design), study in-and exclusion criteria, the total number of patients treated conservatively, criteria for crossover to surgery, clinical characteristics [age, sex, head trauma, use and possible cessation of anticoagulation or antiplatelet therapy, Glasgow Coma Scale (GCS) or Markwalder Grading Scale (MGS)], radiological parameters (hematoma laterality, presence and amount of midline shift, hematoma thickness and volume), GOS, mortality, follow-up time, percentage of successfully treated patients, time from diagnosis of the cSDH to crossover to surgery and time until complete hematoma resolution as confirmed by CT imaging.

Risk of bias assessment

Two authors (HVB and DV) independently assessed the methodological quality of the included articles using the revised Cochrane "Risk of Bias" tool for Randomized Clinical Trials (RoB 2.0) and the Newcastle-Ottawa Scale (NOS) for observational studies (17, 18). Any discrepancies were discussed until consensus was reached. The RoB 2.0 assesses bias based on five domains: (1) Randomization process; (2) Deviation from intended interventions; (3) Missing outcome data; (4) Measurement of the outcome; (5)

Selection of the reported result. Each study is assigned "low concerns of bias" or "some concerns of bias" per domain. The overall bias grade is based on the scores per domain conform RoB 2.0 criteria (19). The NOS can assign up to nine points across three domains for studies with minimum risk of bias. The domains are as follows: (1) Selection of study groups (maximum of four points); (2) Comparability of groups (maximum of two points); (3) Ascertainment of exposure and outcomes (maximum of three points). However, in the case of some studies—particularly those focusing only on chronic subdural hematoma and not on other types of SDH—an unexposed cohort (i.e., a group without the condition) simply could not exist. For these studies, a maximum of three points could be awarded in the first domain, as it was not possible to include a non-exposed cohort. This adjustment resulted in a maximum overall score of eight, rather than nine, for these studies. We converted the NOS ratings to Agency for Healthcare Research and Quality (AHRQ) terms—poor, fair, good—in line with standard conventions. For studies that could obtain nine points "good quality" was awarded if they had three or four points in the first domain, one or two points in the second domain and two or three points in the third domain. For studies that could obtain eight points "good quality" was awarded if they had two or three points in the first domain, one or two points in the second domain and two or three points in the third domain.

Statistical analysis

For continuous variables, means and 95% confidence intervals (CI) were calculated for all patients treated with conservative therapy. For dichotomous outcomes, a pooled estimate with 95% CI was calculated. All statistical analyses were performed using OpenMeta[Analyst] (CEBM, Brown University, 2012) (20).

Results

Search

The initial search yielded 1,570 studies. After removing duplicates and screening the title and abstract 329 full-text articles were assessed for eligibility. Upon reviewing the full-text articles, a total of 11 studies were included (Figure 1) (21).

Study characteristics

Of the 11 included studies, six were retrospective cohort studies, two prospective cohort studies, one a pilot RCT, one a RCT and one a

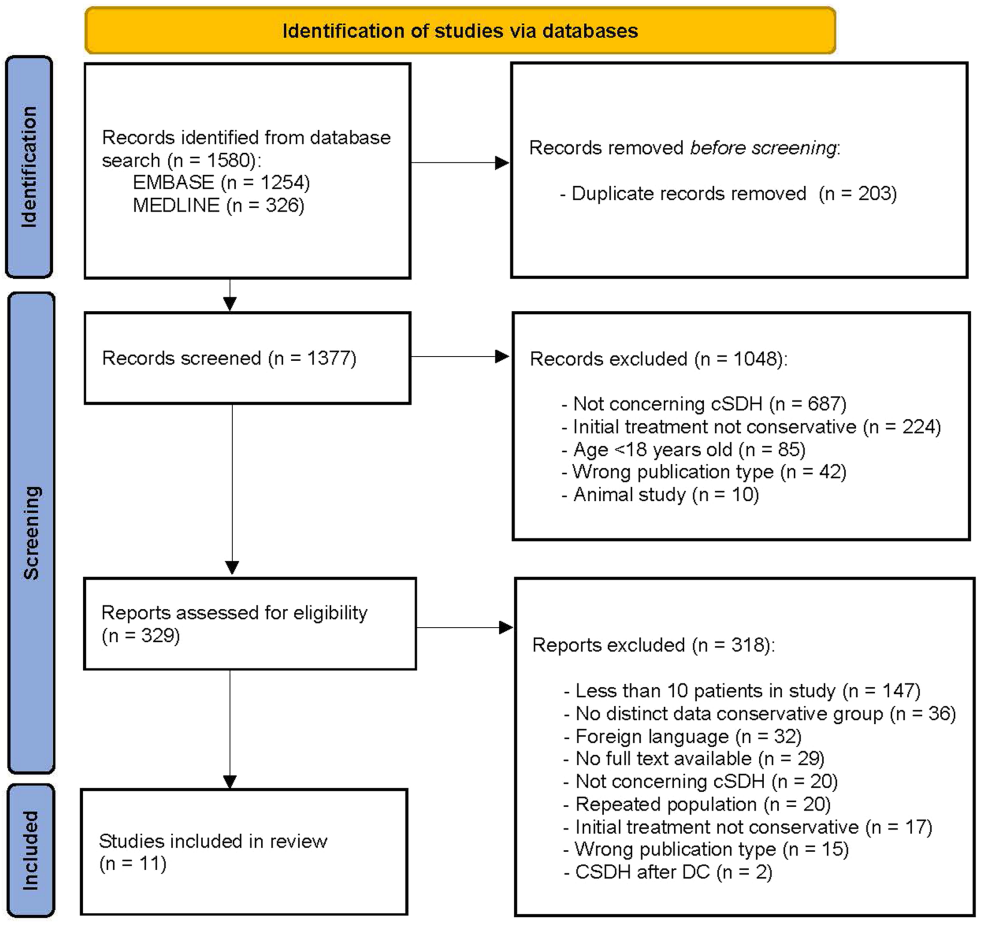


FIGURE 1
PRISMA flow diagram of study selection process (21). DC, decompressive craniectomy.

post-hoc analysis of a previous RCT. The date of publication ranged from 1974 to 2022. Two cohort studies provided a direct comparison between patients treated successfully with conservative therapy and patients for whom conservative therapy had failed (22, 23). In the pilot RCT the effect of dexamethasone was compared to placebo and in the RCT the effect of etizolam was compared to no treatment (24, 25). The study of Wang et al. (22), was a *post-hoc* analysis of an RCT in which the effect of atorvastatin vs. placebo was investigated (22, 26). The mean follow-up duration of all studies was 4.6 months. See Table 1 for study characteristics.

Risk of bias assessment

The AHRQ quality was "poor" in seven of the nine included cohort studies. The quality was "good" in the studies by Hirashima et al. (25) and by Rauhala et al. (13). The risk of bias per domain, as assessed by the NOS, is summarized for each study in Table 2. Among the two randomized studies, one had a low risk of bias, while the other raised some concerns (Figure 2).

Patient characteristics

All studies contained a total of 1,019 patients treated with conservative therapy. The mean age was 66.8 years (95% CI: 64.5–69.2, $n = 71$,) and the population was predominantly male (82%, 95% CI: 70.9–90.6%, $n = 191$) (Table 3). The Glasgow Coma Scale was reported for 369 patients, of which 353 had scores between 14-15 (95.7%) (23, 28, 30, 32). The Markwalder Grading Scale was reported for 196 patients, with 136 scoring between 0 and 2 (69.4%) (22–24, 27, 28). The mean midline shift was 4.6 millimeters (95% CI: 2.0–9.8 millimeters) in 124 patients and the mean hematoma thickness was 15.9 millimeters (95% CI: 13.7–18.0) in 124 patients (22–24). In 114 patients, hematoma volume was reported and had a mean of 55.2 milliliters (95% CI: 38.8–72.4 milliliters) (22, 23).

Outcomes

The success rate of conservative therapy was 66.0% (95% CI: 49.2–82.3%), ranging from 6.9–100% (Table 1). Factors associated with crossover to surgery were evaluated in three studies (Table 4) (22, 23, 25). Larger hematoma volume was a predictor of crossover to surgery in one study (OR 1.019, 95% CI: 1.002–1.037) (22). In another study, hematoma volume was lower in the success group, albeit not significant (43.2 milliliters vs. 62 milliliters, $p = 0.146$) (23). In one study, paresis at diagnosis was associated with crossover to surgery (OR 6.35, 95% CI: 1.04–38.7) and low hematoma density was negatively associated with crossover to surgery (OR: 0.125, 95% CI: 0.01–0.85) (25). Criteria for crossover to surgery were provided in eight studies. The mean period between diagnosis and crossover to

TABLE 1 Included studies, study characteristics and outcomes.

Study	Study type	*N*	Success (%)	Time till crossover	Time till complete resolution on CT	Mortality	Follow-up	Glasgow outcome scale (%)
Bender et al. (27)	R	60	48 (80)	NA	NA	NA	30 months	NA
Hirashima et al. (25)	RCT	29	2 (6.9)	NA	NA	NA	6 months	NA
Prud'homme et al. (24)	Pilot RCT	10	7 (70)	NA	24 weeks	0 (0)	6 months	NA
Kim et al. (23)	R	16	13 (81.3)	39 days	17 weeks (4–96 weeks)	0 (0)	Until nearly complete hematoma resolution	5 (100)
Chan et al. (28)	R	12	5 (41.7)	NA	NA	NA	6 months	5 (17) 4 (83)
Asan et al. (29)	R	163	133 (85.6)	NA	NA	NA	23 days	NA
Hou et al. (30)	P	26	26 (100)	NA	10 weeks	0 (0)	73 days	NA
Ban et al. (31)	P	67	11 (16.4%)	NA	NA	NA	6 months	NA
Rauhala et al. (13)	R	223	170 (76.2)	24 days	NA	NA	Minimally 24 months or until death	NA
Petralia et al. (32)	R	315	293 (93.0)	NA	NA	NA	1 month	NA
Wang et al. (22)	*Post-hoc* RCT analysis	98	75 (76.5)	25 days	NA	0 (0)	6 months	5 (67) 4 (10) 3 (23)[§]
Total *n**		1,019	783/1,019 (76.8%)	25 days ($n = 79$)	14.7 weeks ($n = 49$)	0/150 (0.0%)	4.6 months ($n = 780$)	5 (66) 4 (16) 3 (17)
Pooled estimate (95% CI)			66.0% (49.7–82.3)			0.0 (0.0–2.0)		

R, retrospective cohort study; P, prospective cohort study; RCT, randomized controlled trial; NA, not available; CI, confidence interval. *Averages were calculated were possible. For the outcomes time till crossover, time till complete resolution and follow-up no 95% CI could be calculated since measures of dispersion were not provided. [§]The GOS was determined 8 weeks after diagnosis in 88 patients.

TABLE 2 Risk of bias and quality assessment for observational studies with NOS-scale.

Study	Selection	Comparability	Exposure	Quality
Bender et al. (27)	★		★★	Poor
Hirashima et al. (25)	★★	★★	★★★	Good
Kim et al. (23)	★★		★★	Poor
Chan et al. (28)	★★		★★★	Poor
Asan et al. (29)*	★★★★		★★	Poor
Hou et al. (30)	★		★★	Poor
Ban et al. (31)		★★	★★★	Poor
Rauhala et al. (13)	★★★	★	★★★	Good
Petralia et al. (32)	★		★★	Poor

The last column indicates AHRQ quality standards. *Was only study that could be assigned nine stars due to its methodology.

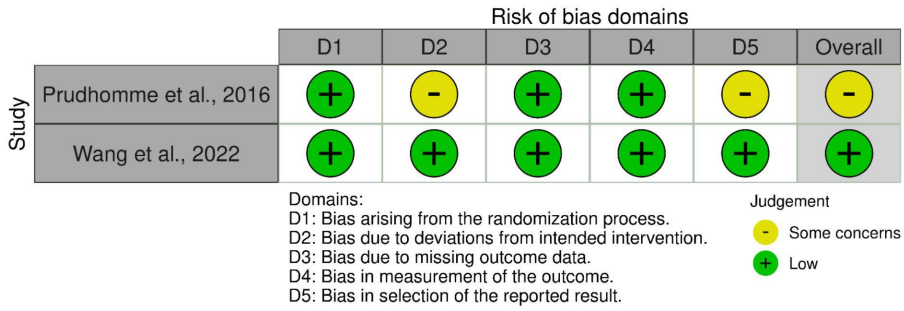


FIGURE 2
Risk of bias and quality assessment of randomized studies with the Risk of Bias 2.0.

surgery was 25 days ($n = 79$) (13, 22, 23). Time until complete resolution of the cSDH was reported in three studies and with a mean of 14.7 weeks ($n = 46$) (23, 24, 30). Mortality was (95% CI: 0.0–2.0%) in 150 cases (22–24, 30). The GOS was reported for 116 patients, of whom 77 had a good recovery (66.4%, GOS 5), 19 had a moderate disability (16.4%, GOS 4) and 20 patients had a severe disability (17.2%, GOS 3) at the end of follow-up (22, 23, 28).

Discussion

This systematic literature review shows that the mean success rate of conservative treatment for cSDH patients with no, or only mild symptoms is reported to be 66%. Hematoma volume, low hematoma density and absence of paresis at diagnosis could be factors associated with success of conservative therapy.

This study demonstrates that the success rate of a wait-and-scan, or a wait-and-watch, strategy can be quite high in a selected group of patients with cSDH. Although success is primarily defined as "no need for surgery," true success should of course be defined as good clinical outcome. However, specific and reliable data are usually lacking. Nevertheless, the range of successful conservative strategy varied greatly in all studies. This could largely be attributed to study heterogeneity regarding indication for conservative therapy and applied in-and exclusion criteria. Studies including patients with larger hematomas reported a higher crossover rate, whereas studies with smaller hematomas tended to report a lower crossover rate (31, 32).

Interestingly, conservative therapy can also be successful in patients with noteworthy clinical expression of their cSDH (e.g., patients with a Markwalder score of 1 or 2). This raises the question of whether it would be justified, and potentially beneficial, to postpone and withhold surgery in more patients than currently is being practiced in standard care. If so, an unnecessary number of patients could well be exposed to anesthetic and surgical risks by not considering conservative therapy more often. Vice versa, evaluating the success rate of conservative therapy in asymptomatic patients (e.g., patients with a Markwalder score of 0) would also be interesting as the success rate is potentially higher for these patients than found in this study. In a recent study by Parry et al. (33) the crossover to surgery rate was determined in a highly pre-selected asymptomatic cohort of 106 cSDH patients (all Markwalder score 0) receiving conservative therapy. Only one patient (0.9%) required neurosurgical intervention within three months after diagnosis. In our study we could not determine success rate stratified per Markwalder scale, as it was not reported in such detail. More prospective research is required to provide insight into this matter.

In our study we also assessed potential factors associated with success of conservative therapy. Yet, there was a lack of consistency, as none of the described factors were associated with success across multiple studies. In fact, hematoma volume was associated with success in the study by Wang et al. (22), but not in the study of Kim et al. (23). Hence, factors associated with success have to be investigated more thoroughly before they can aid clinical decision making in the future. Nowadays, physicians are still unable to identify which hematomas will resolve spontaneously and which

TABLE 3 Demographical, clinical and radiological characteristics of patients per study.

Study	Age	Male (%)	Head trauma (%)	AC/AP use (%)	GCS	MGS	Unilateral (%)	Midline shift (%)	Midline shift (mm)	Hematoma thickness (mm)	Hematoma volume (ml)
Bender et al. (27)	NA	NA	NA	NA	NA	0–3	NA	NA	NA	NA	NA
Hirashima et al. (25)	68.1 (8.6)	22 (75.9)	25 (100)	NA	NA	NA	15 (51.7)	NA	NA	NA	NA
Prud'homme et al. (24)	69.4 (8.8)	10 (100)	7 (70)	8 (80)	NA	0–2	NA	NA	8.0 (3.4)	20.4 (6.1)	NA
Kim et al. (23)	64.7 (16.9)	11 (68.8)	13 (81.2)	3 (18.8)	>8	0–2	13 (81.2)	12 (75)	7.3 (4.6)	14.2 (3.0)	46.2 (17.4)
Chan et al. (28)	79.5 (58–95)	7 (58.3)	NA	6 (50)	14	0–2	12 (100)	NA	2 (1–4)	13 (7.8–21)	41.4 (25–65)
Asan et al. (29)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hou et al. (30)	64.4 (9.6)	19 (73.1)	26 (100)	0 (0)	15	NA	17 (65.4)	NA	<5 mm	NA	NA
Ban et al. (31)	NA	NA	NA	NA	NA	NA	NA	67 (100)	>10 mm	NA	NA
Rauhala et al. (13)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Petralia et al. (32)	NA	NA	NA	NA	14–15	NA	NA	NA	<3 mm	NA	NA
Wang et al. (22)	67 (26–89)	88 (89.8)	NA	NA	NA	0–2	61 (62.2)	NA	2.7 (3.5)	15.3 (5.4)	63.8 (33.9)
Total *n* (%)	71	157/191 (78.1)	71/81 (95.5)	17/64 (26.6)			118/181 (65.7)	79/83 (95.2)	124	124	114
Pooled estimate (CI)[¥]	66.8 (64.5–69.2)	82.0 (70.9–90.6)	87.7 (76.6–99.6)	36.1 (1.6–70.7)			71.8 (54.5–89.0)	89.5 (66.2–100)	4.6 (2.0–9.8)	15.9 (13.7–18.0)	55.2 (38.0–72.4)

NA, not available; AC, anticoagulant; AP, antiplatelet; GCS, Glasgow Coma Scale; MGS, Markwalder Grading scale; mm, millimeter; ml, milliliter. [¥]For dichotomous and continuous variables a 95% confidence interval was calculated.

10.3389/fneur.2023.1249332

TABLE 4 Indications for conservative therapy, antithrombotic strategy and indications for crossover to surgery.

Study	Indication conservative therapy		AC/AP strategy	Criteria for crossover	Factors associated with success or crossover
	Inclusion	Exclusion			
Bender et al. (27)	NA	NA	NA	NA	NA
Harishima et al. (25)	If patient could walk and eat without help	Massive hematoma, impeding sign of brain herniation, severe headache, vomiting, paresis or complications (cardiopulmonary, hepato-renal or metabolic)	NA	Increase in hematoma size and aggravation of symptoms	Low density hematoma*, paresis at diagnosis**
Prud'homme et al. (24)	MGS 0-2	Cranial surgery in last year, if AC therapy could not be stopped for 6 months	NA	Sudden increase in hematoma volume, midline shift >10 mm, deterioration of level of consciousness	NA
Kim et al. (23)	Hematoma that exerts mass effect, mild symptoms	GCS < 8	NA	Newly or progressive neurological deficits	No significant factors found
Chan et al. (28)	MGS 0-2, GCS 14-15	No immediate surgery indication, cSDH secondary to underlying hematological disorder or malignancy	Stopped during period of conservative therapy	Any worsening of symptoms, GCS decrease, new focal neurological deficits or radiological hematoma progression	NA
Asan et al. (29)	NA	NA	NA	NA	NA
Hou et al. (30)	Head trauma in 3 months prior to cSDH, midline shift >10 mm, GCS 15, no evidence of intracranial hypertension	Coagulopathy or AC/AP use, predisposing diseases to cSDH	Patients with AP/AC use excluded from study	Enlargement of cSDH, progressive aggravation of the neurologic deficit and signs of intracranial hypertension	NA
Ban et al. (31)	>20 years old, asymptomatic	CSDH due to underlying condition, shift <10 mm or no mass effect	NA	Occurrence of symptoms and/or increase in hematoma thickness	NA
Rauhala et al. (13)	No significant neurological symptoms	NA	Discontinued at diagnosis	Increase in cSDH size	NA
Petralia et al. (32)	GCS 14-15, shift <3 mm	No other intracranial bleeds (<20cm^3)	NA	NA	NA
Wang et al. (22)	No risk of cerebral herniation, MGS/GCS < 3	Antiplatelet medication	Excluded patients with AP, no comment on patients with AC	Neurologic function deterioration, radiological hematoma progression or > 1 cm shift	Hematoma volume*

The most notable in-and exclusion criteria per study are provided. *Associated with crossover to surgery;**Negatively associated with crossover to surgery. AC, anticoagulant therapy; AP, antiplatelet therapy.

10.3389/fneur.2023.1249332

will progress to become symptomatic. This implies that every patient is to be followed with similar caution since it is not possible to distinguish potential surgical candidates from patients who are not.

An important limitation of this review is the risk of selection bias in the included studies. Most studies were retrospective and all included patients were presented to a neurological or neurosurgical department. Thus, some asymptomatic patients (those not seeking medical attention) are missed. This arguably resulted in an underestimation of the true success rate. Also, the indication for crossover to surgery differed between most studies and was rather subjective and inevitable since specific criteria for crossover are not available. This certainly influenced the primary outcome of this study. Although to what extent this resulted in over-or underestimation of the crossover rate is not clear, since preference of the attending physicians regarding treatment strategy was not objectified. Finally, the lack of data for other aspects of conservative therapy, especially data concerning clinical outcome, precluded assessing the overall effect of conservative therapy. Therefore, no definite conclusions about clinical outcome or indication of conservative therapy can be drawn.

In order to provide more high-quality evidence regarding the effect of conservative therapy for cSDH patients additional research is required. Ideally, such future studies are prospective and multicenter, and a joint venture of neurological and neurosurgical departments due to the nature of this disease and its treatment paradigm. Furthermore, rigorous data regarding clinical outcome are to be incorporated in future studies. With regard to outcomes of conservative therapy of future studies we recommend using the results of the Delphi-survey of the CODE-CSDH project when available (34). This consortium aims to establish core outcomes for cSDH, thereby preventing heterogeneity in this field of research (35).

Conclusion

Success of a wait-and-scan, or a wait-and-watch, strategy is reported to be quite high in the majority of a selected group of patients with cSDH. We could not establish any consistent factors that influence success of conservative therapy. Due to the high risk of selection bias in existing literature, the absence of high-quality methodological studies and the scarcity of available data, further research regarding outcome of conservative therapy is necessary to establish its definite place and value in cSDH treatment.

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.

Author contributions

MF, DV, and WV initiated the study and designed the research plan. MF and HB performed the data selection, data analysis, and drafted the manuscript. DV and HB performed the quality assessment of included studies. K-AMS, DV, and WV critically revised the final manuscript before submission. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to thank A. Malekzadeh (medical librarian) for his help with the online literature search.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1249332/full#supplementary-material

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. Sahyouni R, Goshtasbi K, Mahmoodi A, Tran DK, Chen JW. Chronic subdural hematoma: a historical and clinical perspective. *World Neurosurg*. (2017) 108:948–53. doi: 10.1016/j.wneu.2017.09.064

3. Stubbs DJ, Vivian ME, Davies BM, Ercole A, Burnstein R, Joannides AJ. Incidence of chronic subdural haematoma: a single-Centre exploration of the effects of an ageing population with a review of the literature. *Acta Neurochir*. (2021) 163:2629–37. doi: 10.1007/s00701-021-04879-z

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. Cenic A, Bhandari M, Reddy K. Management of chronic subdural hematoma: a national survey and literature review. *Can J Neurol Sci*. (2005) 32:501–6. doi: 10.1017/S0317167100004510

6. Pang CH, Lee SE, Kim CH, Kim JE, Kang HS, Park CK, 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

7. 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

8. Chen FM, Wang K, Xu KL, Wang L, Zhan TX, Cheng F, et al. Predictors of acute intracranial hemorrhage and recurrence of chronic subdural hematoma following burr hole drainage. *BMC Neurol*. (2020) 20:92. doi: 10.1186/s12883-020-01669-5

9. 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

10. Henry J, Amoo M, Kissner M, Deane T, Zilani G, Crockett MT, et al. Management of Chronic Subdural Hematoma: a systematic review and component network Meta-analysis of 455 studies with 103 645 cases. *Neurosurgery*. (2022) 91:842–55. doi: 10.1227/neu.0000000000002144

11. Lodewijkx R, Foppen M, Slot KM, Vandertop WP, Verbaan D. Recurrent chronic subdural hematoma after burr-hole surgery and postoperative drainage: a systematic review and meta-analysis. *Operative neurosurgery (Hagerstown, Md.)*. (2023). 25, 216–241. doi: 10.1227/ons.0000000000000794

12. Soleman J, Nocera F, Mariani L. The conservative and pharmacological management of chronic subdural haematoma. *Swiss Med Wkly*. (2017) 147:w14398. doi: 10.57187/smw.2017.14398

13. Rauhala M, Helén P, Huhtala H, Heikkilä P, Iverson GL, Niskakangas T, et al. Chronic subdural hematoma-incidence, complications, and financial impact. *Acta Neurochir*. (2020) 162:2033–43. doi: 10.1007/s00701-020-04398-3

14. Berghauser Pont LM, Dippel DW, Verweij BH, Dirven CM, Dammers R. Ambivalence among neurologists and neurosurgeons on the treatment of chronic subdural hematoma: a national survey. *Acta Neurol Belg*. (2013) 113:55–9. doi: 10.1007/s13760-012-0130-1

15. Holl DC, Blaauw J, Ista E, Dirven CMF, Kho KH, Jellema K, et al. National survey on the current practice and attitudes toward the management of chronic subdural hematoma. *Brain Behav*. (2022) 12:e2463. doi: 10.1002/brb3.2463

16. Laldjising ERA, Cornelissen FMG, Gadjradj PS. Practice variation in the conservative and surgical treatment of chronic subdural hematoma. *Clin Neurol Neurosurg*. (2020) 195:105899. doi: 10.1016/j.clineuro.2020.105899

17. BS GA Wells, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. (2021). Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. (2019) 366:l4898. doi: 10.1136/bmj.l4898

19. JPT Higgins, Savović J, Page M.J., Sterne J.A.C. Revised Cochrane risk-of-bias-tool for randomized trials (RoB 2). (2019). Available at: https://guides.library.uq.edu.au/referencing/vancouver/webpages (Accessed 13 June, 2023).

20. 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

21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

22. Wang D, Tian Y, Wei H, Gao C, Fan Y, Yang G, et al. Risk factor analysis of the conservative treatment in chronic subdural hematomas: a substudy of the ATOCH trial. *Adv Ther*. (2022) 39:1630–41. doi: 10.1007/s12325-022-02057-w

23. Kim HC, Ko JH, Yoo DS, Lee SK. Spontaneous resolution of chronic subdural hematoma: close observation as a treatment strategy. *J Korean Neurosurg Soc*. (2016) 59:628–36. doi: 10.3340/jkns.2016.59.6.628

24. 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

25. Hirashima Y, Kurimoto M, Nagai S, Hori E, Origasa H, Endo S. Effect of platelet-activating factor receptor antagonist, etizolam, on resolution of chronic subdural hematoma--a prospective study to investigate use as conservative therapy. *Neurol Med Chir (Tokyo)*. (2005) 45:621–6; discussion 6. doi: 10.2176/nmc.45.621

26. 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

27. Bender MB, Christoff N. Nonsurgical treatment of subdural hematomas. *Arch Neurol*. (1974) 31:73–9. doi: 10.1001/archneur.1974.00490380021001

28. Chan DY, Chan DT, Sun TF, Ng SC, Wong GK, 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

29. Asan Z. Growth potential of subdural hematomas under clinical observation: which subdural hematomas tend to grow and why they do. *World Neurosurg*. (2018) 113:e598–603. doi: 10.1016/j.wneu.2018.02.106

30. Hou K, Zhu X, Zhao J, Zhang Y, Gao X, Jiang K, et al. Efficacy of reinforced restriction of physical activity on chronic subdural hematoma: prospective pilot study. *World Neurosurg*. (2018) 110:e1011–6. doi: 10.1016/j.wneu.2017.11.155

31. 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

32. Petralia CCT, Manivannan S, Shastin D, Sharouf F, Elalfy O, Zaben M. Effect of steroid therapy on risk of subsequent surgery for neurologically stable chronic subdural hemorrhage-retrospective cohort study and literature review. *World Neurosurg*. (2020) 138:e35–41. doi: 10.1016/j.wneu.2020.01.160

33. Parry D, Baskaran R, Lima A, Dagnan R, Jaber H, Manivannan S, et al. Asymptomatic chronic subdural haematoma - does it need neurosurgical intervention? *Br J Neurosurg*. (2023) 1-6:1–6. doi: 10.1080/02688697.2023.2210224

34. Holl DC, Chari A, Iorio-Morin C, Dammers R, van der Gaag NA, Kolias AG, et al. Study protocol on defining Core outcomes and data elements in chronic subdural Haematoma. *Neurosurgery*. (2021) 89:720–5. doi: 10.1093/neuros/nyab268

35. Chari A, Hocking KC, Broughton E, Turner C, Santarius T, Hutchinson PJ, et al. Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on reported outcomes. *J Neurotrauma*. (2016) 33:1212–9. doi: 10.1089/neu.2015.3983

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 10 October 2023
DOI 10.3389/fneur.2023.1259647

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Amir El Rahal,
University of Freiburg Medical Center, Germany
Zefu Li,
Binzhou Medical University Hospital, China

*CORRESPONDENCE
Taichi Ishiguro
✉ ishiguro.taichi@twmu.ac.jp

RECEIVED 16 July 2023
ACCEPTED 25 September 2023
PUBLISHED 10 October 2023

CITATION
Omura Y and Ishiguro T (2023) Middle meningeal artery embolization for chronic subdural hematoma: a systematic review. *Front. Neurol.* 14:1259647. doi: 10.3389/fneur.2023.1259647

Middle meningeal artery embolization for chronic subdural hematoma: a systematic review

Yoshihiro Omura and Taichi Ishiguro*

Department of Neurosurgery, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Chiba, Japan

Background: Chronic subdural hematoma (cSDH) is one of the most common diseases in neurosurgery. Middle meningeal artery embolization (MMAE) is reportedly an option to prevent recurrence or avoid surgery in patients with cSDH. This study was performed to review the evidence on MMAE for cSDH and evaluate its safety, efficacy, indications, and feasibility.

Methods: We systematically reviewed the literature according to the PRISMA guidelines using an electronic database. The search yielded 43 articles involving 2,783 patients who underwent MMAE.

Results: The hematoma resolution, recurrence, and retreatment rates in the MMAE-alone treatment group (n = 815) were 86.7%, 6.3%, and 9.6%, respectively, whereas those in the prophylactic MMAE with combined surgery group (n = 370) were 95.6%, 4.4%, and 3.4%, respectively. The overall MMAE-related complication rate was 2.3%.

Conclusion: This study shows that MMAE alone is, although not immediate, as effective as evacuation surgery alone in reducing hematoma. The study also shows that combined treatment has a lower recurrence rate than evacuation surgery alone. Because MMAE is a safe procedure, it should be considered for patients with cSDH, especially those with a high risk of recurrence.

KEYWORDS

embolization, chronic subdural hematoma, middle meningeal artery, recurrence, endovascular

Introduction

Chronic subdural hematoma (cSDH) is a common disease with an incidence of up to 58.1 per 100,000 person-years in patients aged > 65 years (1). cSDH is commonly treated by surgical evacuation through burr hole(s) to relieve the symptom caused by the mass effect of the hematoma. However, the recurrence rate ranges from 10% to 20% (2, 3). The use of antiplatelet drugs or anticoagulants, multiple recurrences, and advanced age are known risk factors for cSDH recurrence (4, 5).

The pathophysiology of cSDH involves the formation of neomembranes with fragile neovascularization, perfused mainly by distal branches of the middle meningeal artery (MMA) that have formed by inflammatory remodeling of the dura matter (6, 7). Therefore, endovascular MMA embolization (MMAE) has recently emerged as an alternative or adjunct modality to conventional surgical treatment to prevent the recurrence of cSDH.

This study was performed to review all published cases of MMAE for cSDH and assess the safety, efficacy, and indications of the procedure.

Methods

Study design

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8).

Literature search

An electronic literature search of the PubMed database was performed on 28 May 2023 using the following key terms: chronic subdural hematoma, meningeal artery, and embolization. All articles published from January 1976 to May 2023 were identified. Two reviewers (Y.O. and T.I.) independently screened the articles based on their title and abstract. One reviewer (Y.O.) then reviewed the full text of all relevant articles in detail to further assess the eligibility of the studies.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used for the systematic review.

Inclusion criteria

- Original research involving more than five cases of MMAE published in any peer-reviewed journal.
- English language.
- Sufficient post-embolization outcome data (at least one post-MMAE clinical and/or radiological follow-up and reporting of the rescue surgical treatment rate).
- Adult patients (>18 years old) treated for the first time by MMAE for cSDH.

Exclusion criteria

- Review articles, meta-analyses, comments, letters, and editorials.
- cSDH due to a vascular malformation (e.g., dural arteriovenous fistula, arteriovenous malformation) or intracranial tumor, or the presence of intracranial hypotension.
- Studies from the same author with duplicate patients.

Data extraction and analysis

Data extraction was performed by one reviewer (Y.O.) using a predefined data extraction form. The following data were collected and analyzed: study design, sample population and size, patients' baseline characteristics, antithrombotic therapy use, management strategy (including surgical and endovascular treatment), endovascular treatment success, outcome, follow-up duration, complications, cSDH recurrence rate, and the need for subsequent surgery.

Several definitions of resolution after MMAE were used among the studies, including complete resolution, near complete resolution (reduction of ≥90%), suboptimal resolution (reduction of ≥50%), and partial reduction, the latter two of which were ambiguous. Among these definitions, there were further differences in measurement methods, with some researchers using the hematoma volume for measurement and others using the hematoma thickness. In this study, we focused on the necessity of rescue surgery and defined resolution as radiological improvement.

Some reports included in this review defined recurrent cSDH as only symptomatic re-accumulation after surgical intervention, while others defined recurrent cSDH as also asymptomatic re-accumulation after surgical intervention. Both were included in recurrent cSDH in this review.

In MMAE for cSDH treatment, there are differences in the purpose of treatment and the characteristics of patients between MMAE as a sole treatment and MMAE as prophylaxis, in which surgery is performed before and after MMAE. In this study, we compared the data between reports in which all patients were treated with MMAE alone and reports in which all patients were treated with MMAE combined with surgery.

MMAE treatment success was defined as the successful embolization of the target vessel. All patients who failed to achieve embolization, including MMAE abort, were considered treatment failures. Complications of treatment were counted after excluding those considered to be complications related to surgery (evacuation), those with unknown details, and those with an unknown relationship to MMAE.

Results

Study characteristics

Our search strategy yielded 245 articles. Of these, 202 articles were excluded based on the exclusion criteria of the present review. A flow diagram of this study shown in Figure 1.

Forty-three articles were included in the final analysis, including 2 prospective uncontrolled studies, 1 prospective randomized study, and 40 retrospective studies involving 7 to 530 patients per series.

Patient demographics and clinical and radiographic characteristics

A total of 2,783 patients underwent MMAE in the selected studies (Table 1). Their mean age was 71.2 years, and 71.1% were male. The available data showed that 90.6% of patients had symptomatic cSDH and that 19.9% had bilateral cSDH. Concurrent antiplatelet or anticoagulant use at the time of cSDH treatment was reported in 50.3% of patients.

Characteristics and outcomes of MMAE for cSDH

In total, 3,027 MMAE procedures were performed on 2,783 patients. The MMAE treatment success rate was 98.8%. In principle,

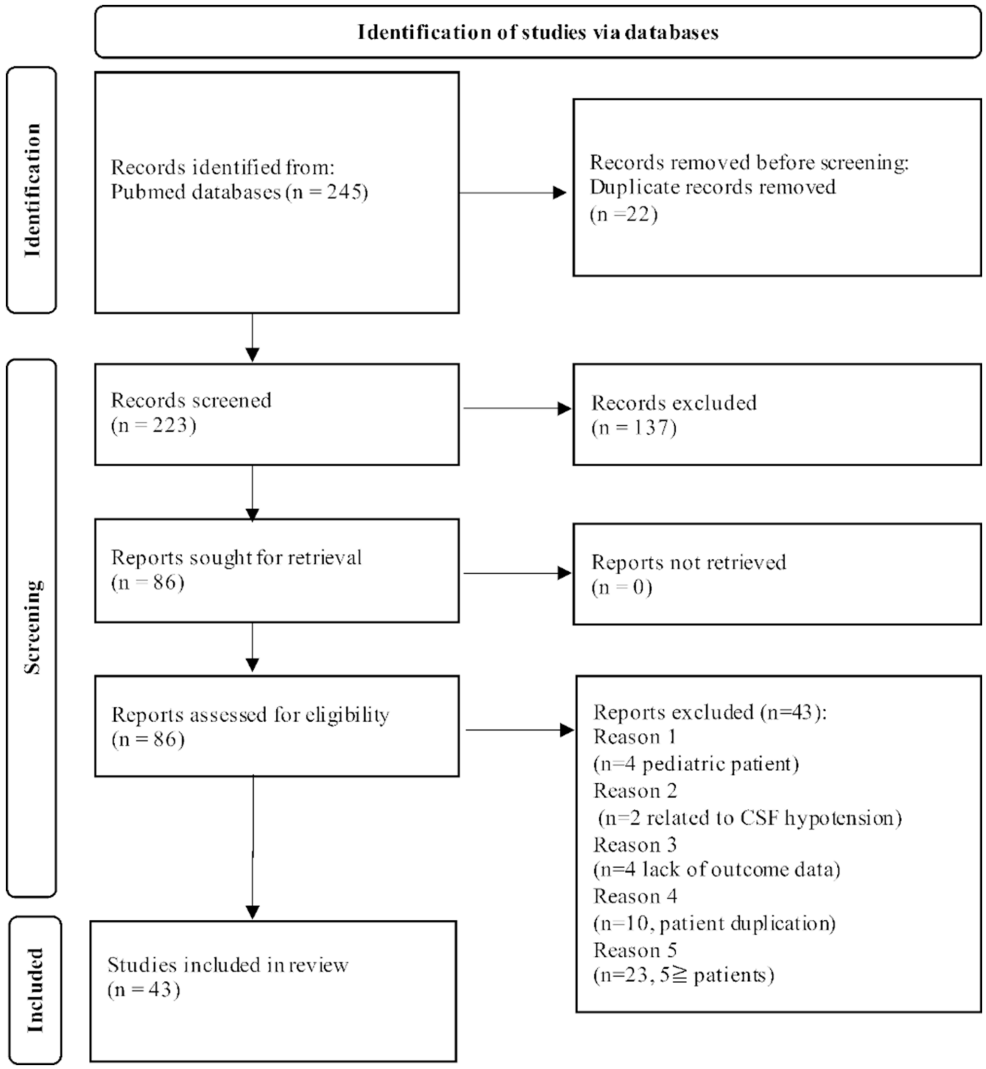


FIGURE 1
PRISMA flow chart of our systematic review. CSF, cerebrospinal fluid.

treatment for bilateral cSDH was considered two embolization procedures, but some studies counted it as one treatment. This is clearly indicated in Table 2.

MMAE was performed as the sole treatment in 69.1% of patients and prophylactically after or before surgical evacuation in 30.7%. The details in six (0.2%) patients were not reported.

Among all cases, 23.7% were recurrent cSDH after previous surgical evacuation, and 52.7% were treated as upfront MMAE.

The embolic agents included particles, liquid agents, and coils and were used alone or in combination. Details are shown in Table 1. The mean follow-up duration ranged from 20 days to 5 years.

Following MMAE, the rates of cSDH resolution, recurrence, and surgical rescue at the last follow-up were 83.8%, 6.2%, and 6.4%, respectively.

In most studies, no serious complications occurred after MMAE. The rate of severe complications associated with MMAE was 1.0% (28 of 2,783 patients), including 10 cases of cerebral infarction, 5 cases of visual loss, 4 cases of facial palsy, 2 cases of cerebral hemorrhage, 3 cases of MMA arteriovenous fistula, 1 case of MMA rupture, 1 case of aortic dissection, 1 case of femoral artery occlusion, and 1 case of catheter entrapment. The rate of overall complications associated with MMAE was 2.3% (58 of 2,783 patients), including seizures, headache, renal dysfunction, transient neurological symptoms (diplopia and aphasia), and puncture site hematoma. Two overall treatment-related mortalities due to cerebral hemorrhage and femoral artery occlusion were observed.

Rescue surgery rate in MMAE-alone treatment group and prophylactic MMAE group

The hematoma resolution, recurrence, and retreatment rates in the MMAE-alone treatment group ($n = 815$) were 86.7%, 6.3%, and 9.6%, respectively, whereas those in the prophylactic MMAE with combined surgery group ($n = 370$) were 95.6%, 4.4%, and 3.4%, respectively. The percentage of symptomatic patients in the

TABLE 1 Studies and patient characteristics in this review.

Study	Year	Study design	No of patients	No of embolizations	Age (mean)	Male (%)	Unilateral/ Bilateral	Symptomatic cSDH (%)	Antithrombotic therapy (%)
Kim et al. (5)	2017	Retrospective	20	20*	73.7	14 (70.0)	14/6	20 (100)	9 (45.0)
Ban et al. (9)	2018	Retrospective	72	72*	69.5	48 (66.7)	53/19	45 (62.5)	29 (40.3)
Waqas et al. (10)	2019	Retrospective	8	8	63.6	5 (62.5)	7/1	8 (100)	8 (100)
Saitoh et al. (11)	2019	Retrospective	8	8*	79	8 (100)	6/2	NR	2 (25.0)
Okuma et al. (4)	2019	Retrospective	17	17*	76.4	12 (70.6)	13/4	17 (100)	11 (64.7)
Nakagawa et al. (12)	2019	Retrospective	20	20*	78.3	14 (70)	12/8	20 (100)	4 (20.0)
Link et al. (13)	2019	Retrospective	49	60	69	32 (65.3)	38/11	NR	39 (77.5)
Yajima et al. (14)	2020	Retrospective	18	18*	78.5	16 (88.9)	15/3	NR	3 (16.7)
Shotar et al. (15)	2020	Retrospective	89	89*	74	68 (76.4)	74/15	89 (100)	71 (79.7)
Rajah et al. (16)	2020	Prospective	46	46*	71.7	31 (67.3)	40/6	44 (100)	14 (31.8)
Ng et al. (17)	2020	Prospective randomized	19	22	77.4	10 (52.9)	16/3	19 (100)	7 (31.8)
Mureb et al. (18)	2020	Retrospective	8	8	75.4	7 (87.5)	8/0	NR	NR
Joyce et al. (19)	2020	Retrospective	121	151	77.5	99 (81.8)	91/30	NR	66 (54.3)
Fan et al. (20)	2020	Retrospective	7	7	NR	NR	7/0	7 (100)	NR
Wei et al. (21)	2021	Retrospective	10	20	63.3	10 (100)	0/10	10 (100)	NR
Tiwari et al. (22)	2021	Retrospective	10	13	71.4	NR	7/3	10 (100)	6 (60.0)
Tanoue et al. (23)	2021	Retrospective	15	15	78	10 (66.7)	15/0	15 (100)	1 (6.6)
Schwarz et al. (24)	2021	Retrospective	41	44	73.3	33 (75.0)	38/3	44 (100)	19 (43.1)
Petrov et al. (25)	2021	Retrospective	10	15	66	7 (70.0)	5/5	10 (100)	0 (0)
Lee et al. (26)	2021	Retrospective	22	31	63.9	16 (72.7)	13/9	31 (100)	4 (18.2)
Kan et al. (27)	2021	Prospective	138	138*	69.8	98 (71.0)	122/16	NR	72 (52.2)
Gomez-Paz et al. (28)	2021	Retrospective	23	27	74	10 (43.5)	19/4	20 (87.0)	13 (56.5)
scovile et al. (29)	2022	Retrospective	208	208	NR	115 (55.3)	NR	NR	106 (52.0)
Saway et al. (30)	2022	Retrospective	100	100*	73	68 (68.0)	64/32	97 (97)	66 (66.0)
Samarage et al. (31)	2022	retrospective	37	37*	76.9	25 (67.6)	23/15	26 (70)	17 (45.9)
Salie et al. (32)	2022	Retrospective	52	52	74.2	38 (73.1)	52/0	47 (90.4)	37 (71.2)
Onyinzo et al. (33)	2022	Retrospective	50	50	79.6	42 (84.0)	50/0	NR	35 (70.0)
Mir et al. (34)	2022	Retrospective	56	56*	73	43 (76.8)	51/5	NR	23 (41.1)
Magidi et al. (35)	2022	Retrospective	61	61*	62.5	48 (78.7)	39/22	NR	34 (55.8)

(Continued)

10.3389/fneur.2023.1259647

TABLE 1 (Continued)

Study	Year	Study design	No of patients	No of embolizations	Age (mean)	Male (%)	Unilateral/ Bilateral	Symptomatic cSDH (%)	Antithrombotic therapy (%)
Khorasanizadeh et al. (36)	2022	Retrospective	78	94	72	50 (64.1)	62/32	65 (83.3)	52 (66,7)
Housley et al. (37)	2022	Retrospective	44	48	73.3	25 (56.8)	40/4	NR	21 (47.7)
Fuentes et al. (38)	2022	Retrospective	322	322	NR	228 (70.8)	NR	NR	58 (18.0)
Enriquiz-Marulanda et al. (39)	2022	Retrospective	36	45	76	28 (62.2)	27/9	43 (95.6)	34 (75.5)
Dofuku et al. (40)	2022	Retrospective	9	9	85	6 (66.7)	9/0	9 (100)	5 (55.5)
Catapano et al. (41)	2022	Retrospective	66	84	70	51 (77.3)	48/18	50 (75.8)	32 (48.5)
Carpenter et al. (42)	2022	Retrospective	23	23*	80	15 (65.2)	13/10	NR	20 (87.0)
Wali et al. (43)	2023	Retrospective	8	8	80.5	6 (75.0)	3/5	NR	NR
Shehabeidin et al. (44)	2023	Retrospective	97	97	78	71 (73.2)	NR	NR	50 (51.5)
Seok et al. (45)	2023	Retrospective	9	13	77.3	8 (88.8)	13/0	13 (100)	7 (77.7)
Salem et al. (46)	2023	Retrospective	530	636	71.9	38 6(72.8)	424/106	NR	281 (53.0)
Martinez-Gutierrez et al. (47)	2023	Retrospective	57	66	66	45 (78.9)	48/9	NR	28 (49.5)
Liu et al. (48)	2023	Retrospective	53	53	68.1	42 (79.2)	53/0	NR	20 (38.7)
Krothapalli et al. (49)	2023	Retrospective	116	116	NR	80 (68.9)	116/0	NR	80 (69.0)
			2,783	3,027	71.2	1,968 (71.1)	1,748/435	759 (90.6)	1,384 (50.3)

cSDH, chronic subdural hematoma; NR, not reported. *Treatment of bilateral cSDH counted as one treatment.

10.3389/fneur.2023.1259647

TABLE 2 Details and outcomes of MMAE.

Study	No of patients	No of embolizations	Mean follow-up	Embolization material (*n*)	MMAE alone (%)	Prophylactic MMAE (%)	Upfront-MMAE (%)	Recurrent cSDH (%)	Complications (%)	Resolution (%)	Recurrence (%)	Rescue surgery (%)
Kim et al. (5)	20	20*	3 months†	PVA (20)	20 (100)	0 (0)	0 (0)	20 (100)	0 (0)‡	19 (95.0)	1 (5.0)	0 (0)
Ban et al. (9)	72	72*	6 months†	PVA (72)	27 (37.5)	45 (62.5)	27 (37.5)	0 (0)	0 (0)	NR	1 (1.4)	1 (1.4)
Waqas et al. (10)	8	8	3.3 months	Onyx (8)	8 (100)	0 (0)	6 (75)	2 (25.0)	0 (0)	8 (100)	0 (0)	0 (0)
Saitoh et al. (11)	8	8*	28.9 months	NBCA (7) NBCA+PVA (1)	1 (12.5)	7 (87.5)	0 (0)	8 (100)	0 (0)	NR	1 (12.5)	1 (12.5)
Okuma et al. (4)	17	17*	26.3 months	NBCA (11) Embosphere (3) both (3) coil (1)	2 (11.8)	15 (88.2)	2 (11.8)	11 (64.7)	0 (0)	NR	0 (0)	0 (0)
Nakagawa et al. (12)	20	20*	24 weeks†	NBCA (20)	0 (0)	20 (100)	0 (0)	20 (100)	0 (0)	NR	0 (0)	0 (0)
Link et al. (13)	49	60	>6 weeks	PVA (49)	50 (83.3)	10 (16.7)	42 (70.0)	8 (13.3)	0 (0)	41 (91.1)	4 (8.9)	4 (8.9)
Yajima et al. (14)	18	18*	18.1 months	NBCA (18)	2 (11.1)	16 (88.9)	2 (11.1)	15 (83.3)	0 (0)	NR	0 (0)	0 (0)
Shotar et al. (15)	89	89*	3 months†	Microspheres with or without coil (81) coil (5) NBCA (5)	0 (0)	89 (100)	0 (0)	22 (21.2)	6 (6.6)	NR	7 (7.7)	4 (2.2)
Rajah et al. (16)	46	46*	8 weeks	Onyx (43) NBCA (1)	42 (91.3)	4 (8.7)	37 (80.4)	5 (10.9)	0 (0)	38 (86.5)	5 (11.4)	5 (11.4)
Ng et al. (17)	19	22	3 months	PVA and/or coil (21)	0 (0)	22 (100)	0 (0)	0 (0)	0 (0)	NR	1 (4.5)	1 (4.5)
Mureb et al. (18)	8	8	89 days	PVA (8)	8 (100)	0 (0)	8 (100)	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)
Joyce et al. (19)	121	151	90 days†	Coil (6) liquid (30) particles (38) liquid + coil (2) particles + coil (72) particles + liquid (1)	134 (88.7)	17 (11.3)	79 (52.3)	55 (36.4)	3 (2.0)	130 (94.2)	9 (7.4)	9 (7.4)
Fan et al. (20)	7	7	4–6 months	Absolute alcohol (7)	0 (0)	7 (100)	0 (0)	NR	0 (0)	7 (100)	0 (0)	0 (0)
Wei et al. (21)	10	20	112 days	Coil (10)	0 (0)	20 (100)	0 (0)	0 (0)	0 (0)	NR	0 (0)	0 (0)

(Continued)

10.3389/fneur.2023.1259647

TABLE 2 (Continued)

Study	No of patients	No of embolizations	Mean follow-up	Embolization material (*n*)	MMAE alone (%)	Prophylactic MMAE (%)	Upfront-MMAE (%)	Recurrent cSDH (%)	Complications (%)	Resolution (%)	Recurrence (%)	Rescue surgery (%)
Tiwari et al. (22)	10	13	160 days	Embospheres and/or coil/gel-form (8)	13 (100)	0 (0)	7 (53.8)	6 (46.2)	0 (0)	12 (92.3)	0 (0)	0 (0)
Tanoue et al. (23)	15	15	28 days†	NBCA (13) Embosphere (2)	15 (100)	0 (0)	15 (100)	NR	0 (0)	NR	3 (20.0)	3 (20.0)
Schwarz et al. (24)	41	44	321 days	PVA (44)	0 (0)	44 (100)	0 (0)	NR	0 (0)	40 (90.9)	2 (4.5)	2 (4.5)
Petrov et al. (25)	10	15	111 days	Squid (15)	15 (100)	0 (0)	9(60)	6 (40.0)	0 (0)	10 (100)	0 (0)	0 (0)
Lee et al. (26)	22	31	>2 weeks	Liquid (11) PVA (9) PVA and coil (11)	31 (100)	0 (0)	28 (90.3)	3 (13.6)	1 (3.2)	15 (48.4)	2 (6.5)	2 (6.5)
Kan et al. (27)	138	138*	94.9 days	PVA + coil (70) PVA (38) liquid (37) coil (5) liquid + coil (2)	138 (100)	0 (0)	92 (66.7)	42 (33.3)	3 (2.2)	134 (87.0)	10 (7.2)	9 (6.5)
Gomez-Paz et al. (28)	23	27	3 months	PVA + coil (27)	27 (100)	0 (0)	27 (100)	0 (0)	0 (0)	27 (100)	1 (3.7)	3 (11.1)
Scovile et al. (29)	208	208	6 months†	Particles; PVA, Embosphere (154) liquid; NBCA, Onyx (54)	192 (92.1)	16 (7.9)	133 (63.9)	59 (28.3)	11 (5.3)‡	126 (60.6)	NR	10 (4.8)
Saway et al. (30)	100	100*	1.9 months	Onyx (29) Particles (58) particle and coil (13)	0 (0)	100 (100)	0 (0)	10 (10.0)	1 (1.0)	100 (100)	2 (2.0)	2 (2.0)
Samarage et al. (31)	37	37*	NR	NBCA (38) PVA (9) Onyx (3) combination (17)*	19 (51.4)	18 (49)	19 (51.4)	NR	3 (8.1)	18 (48.6)	5 (13.5)	5 (13.5)
Salie et al. (32)	52	52	100 days	Particle coil Liquid combination (NR)	0 (0)	52 (100)	0 (0)	NR	NR	47 (90.4)	3 (5.8)	2 (3.8)
Onyinzo et al. (33)	50	50	3.4 months	PVA and/or coil (50)	19 (38.0)	31 (62.0)	19 (38.0)	NR	0 (0)	13 (59.0)	1 (4.5)	1 (4.5)

(Continued)

10.3389/fneur.2023.1259647

TABLE 2 (Continued)

Study	No of patients	No of embolizations	Mean follow-up	Embolization material (*n*)	MMAE alone (%)	Prophylactic MMAE (%)	Upfront-MMAE (%)	Recurrent cSDH (%)	Complications (%)	Resolution (%)	Recurrence (%)	Rescue surgery (%)
Mir et al. (34)	56	56*	90 days	PVA and/or coil (NA) Onyx (NA) NBCA (NR)	56 (100)	0 (0)	35 (62.5)	21 (37.5)	2 (3.6)	35 (62.5)	1 (1.8)	1 (1.8)
Magidi et al. (35)	61	61*	3 months†	NBCA (61)	61 (100)	0 (0)	31 (50.8)	30 (49.2)	2 (3.3)	59 (96.7)	3 (4.9)	2 (3.3)
Khorasanizadeh et al. (36)	78	94	114 days	PVA and coil (82) coil (12)	80 (85.1)	14 (14.9)	72 (76.6)	8 (8.5)	2 (2.1)	67 (78.8)	8 (8.5)	8 (8.5)
Housley et al. (37)	44	48	12–60 weeks	Onyx (48)	48 (100)	0 (0)	48 (100)	0 (0)	NR	38 (79.2)	2 (4.2)	2 (4.2)
Fuentes et al. (38)	322	322	5 years	NR	322 (100)	0 (0)	286 (88.8)	36 (11.2)	NR	NR	NR	55 (17.1)
Enriquiz-Marulanda et al. (39)	36	45	72 days	PVA + coil (43) coil (2)	35 (77.7)	10 (22.2)	35 (77.7)	NR	1 (2.2)	28 (71.8)	1 (2.6)	5 (11.1)
Dofuku et al. (40)	9	9	103 days	NBCA (9)	0 (0)	9(100)	0 (0)	9 (100)	0 (0)	NR	0 (0)	0 (0)
Catapano et al. (41)	66	84	180 days†	Onyx (66) PVA or coil or both (13) NBCA (5)	53 (63.1)	31 (36.9)	53 (63.1)	NR	1 (1.2)	67 (91.8)	3 (3.6)	3 (3.6)
Carpenter et al. (42)	23	23*	4.1 months	PVA (23)	0 (0)	23 (100)	0 (0)	NR	6 (26.0)	NR	2 (9.1)	2 (9.1)
Wali et al. (43)	8	8	>3 months	PVA and helical coil (8)	7 (87.5)	1 (12.5)	7 (87.5)	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)
Shehabeidin et al. (44)	97	97	4.2 months (Onyx) 3.0 months (PVA)	Onyx (49) PVA (48)	48 (53.3)	NR	48 (53.3)	NR	0 (0)	NR	18 (18.6)	13 (13.4)
Seok et al. (45)	9	13	4.7 months	PVA and Gelform (8)	8 (61.5)	5 (38.5)	8 (61.5)	4 (30.8)	0 (0)	12 (92.3)	1 (7.7)	1 (7.7)
Salem et al. (46)	530	636	121 days	coil and particles (248) liquid (228)	468 (74.3)	162 (25.8)	318 (50.4)	150 (23.9)	16 (3.0) ‡	490 (87.5)	36 (6.8)	36 (6.8)

(Continued)

10.3389/fneur.2023.1259647

TABLE 2 (Continued)

Study	No of patients	No of embolizations	Mean follow-up	Embolization material (*n*)	MMAE alone (%)	Prophylactic MMAE (%)	Upfront-MMAE (%)	Recurrent cSDH (%)	Complications (%)	Resolution (%)	Recurrence (%)	Rescue surgery (%)
Martinez-Gutierrez et al. (47)	57	66	20 days	Particles (NR) coil (NR) Onyx (NR)	66 (100)	0 (0)	25 (37.9)	41 (62.1)	NR	NR	11 (16.7)	4 (6.1)
Liu et al. (48)	53	53	6 months†	PVA and NBCA (53)	31 (58.5)	22 (41.5)	31 (58.5)	NR	NR	48 (90.6)	1 (2.4)	0 (0)
Krothapalli et al. (49)	116	116	29 days (liquid) 35 days (particles)	NBCA (48) PVA (68)	68 (58.6)	48 (41.4)	68 (58.6)	NR	1 (0.9)	NR	6 (5.2)	2 (1.7)
	2,783	3,027			2,114 (69.8)	907 (31.0)	1,617 (53.4)	591 (24.6)	58 (2.4)	1,645 (83.8)	155 (6.2)	197 (6.4)

NR, not reported; MMAE, middle meningeal artery embolization; cSDH, chronic subdural hematoma; PVA, polyvinyl alcohol; NBCA, N-butyl cyanoacrylate. *Treatment of bilateral cSDH counted as one treatment. †Follow-up period was set as the evaluation period in the study. ‡Complications with unknown details or unknown association with MMAE were not counted.

MMAE-alone group and prophylactic MMAE group was 94.0% and 97.7%, respectively. These results are shown in Table 3.

Discussion

The standard treatment for cSDH is still surgical treatment, however cSDH has a high recurrence rate (10%–20%) after a single surgical evacuation (2, 3).

The medical treatment options for cSDH have been extensively investigated, these studies had no remarkable effectiveness in preventing recurrence of cSDH (2, 3, 50–52) and an optimal treatment strategy for preventing cSDH recurrence has not yet been established.

The pathophysiology of cSDH involves formation of inflammatory membranes and self-sustaining neoangiogenesis and fibrinolysis, leading to a high prevalence of rebleeding from fragile capillaries (6, 7). These vessels are derived from the dura matter and perfused mainly by the distal branches of the MMA; therefore, MMAE could be an interesting paradigm for the treatment of cSDH.

During the past few years, the number of reports on the efficacy of MMAE has rapidly increased. In the present systematic review, the cSDH resolution, recurrence, and rescue surgical treatment rates at the last follow-up after MMAE in all patients were 83.8%, 6.2%, and 6.4%, respectively.

MMAE can be divided into two main categories according to the purpose of treatment: curative MMAE with the expectation of hematoma reduction to avoid surgical intervention (or in place of surgical hematoma removal) and prophylactic MMAE as a preventive treatment for recurrence in combination with hematoma evacuation.

MMAE as a sole treatment for cSDH

The three initially reported indications for MMAE alone were failure of conservative treatment or asymptomatic or mildly symptomatic patients (to avoid surgery), advanced age and use of antiplatelet or anticoagulant drugs (as an alternative treatment considering the invasiveness of surgery), and prevention of recurrence in patients with recurrent disease after surgical treatment (53).

In an evaluation of the efficacy of MMAE alone, Housley et al. (37) compared the outcomes of 48 propensity-matched patients with cSDH who underwent either surgery alone or MMAE alone as initial treatment. There was a significant hematoma reduction in the surgery group immediately after surgery; after 12 weeks of treatment, however, there was no significant difference in hematoma reduction between the two groups. Furthermore, the recurrence rate was significantly lower in the MMAE group (22.9% vs. 4.2%) (37). Kim (5) compared the outcomes of 23 patients who received conventional treatment and 20 patients who received MMAE among 43 patients who developed recurrent cSDH after surgical treatment. The MMAE group showed better prevention of recurrence and earlier brain re-expansion despite the fact that patients of advanced age were significantly more likely to use antithrombotic drugs in the MMAE group (5). These studies show that the effect of MMAE alone for reducing a hematoma is equivalent to evacuation surgery alone in long-term follow-up, and the effect of preventing recurrence may surpass the effect of evacuation surgery alone.

Some studies showed a good hematoma reduction effect of MMAE alone, even for massive cSDH. Gomez-Paz et al. (28) reported

TABLE 3 Comparison between reports of MMAE-alone treatment and reports of prophylactic MMAE treatment.

	MMAE alone	Prophylactic MMAE
Total no of patients	797	370
Total no of embolization	815	386
Age (mean)	68.8	74.6
Antithrombotic therapy (%)	271(34.3)	229 (64.9)
Symptomatic cSDH (%)	109 (94.0)	256 (97.7)
Recurrent cSDH (%)	205 (25.9)	61 (35.9)
Resolution (%)	353 (86.7)	194 (95.6)
Recurrence (%)	31 (6.3)	17 (4.4)
Rescue surgery (%)	78 (9.6)	13 (3.4)

MMAE, middle meningeal artery embolization; cSDH, chronic subdural hematoma.

that patients with massive cSDH with a midline shift of ≥5 mm were treated with upfront MMAE and showed good improvement in symptoms and imaging findings under careful follow-up.

In the present review, surgical evacuation was needed in 9.6% of patients in the MMAE-alone group, suggesting that some patients developed hematoma enlargement or neurological deterioration even after MMAE. Therefore, careful follow-up is important, especially in the early postoperative period after patients undergo MMAE alone.

Some reports also suggested that MMAE alone is superior to surgery alone in terms of cost-effectiveness because of the reduced need for additional therapeutic intervention in the treatment of cSDH (54, 55).

MMAE combined with evacuation for cSDH

In this study, prophylactic MMAE showed a favorable hematoma reduction rate, recurrence rate, and reoperation rate. The major advantage of MMAE is its effect in preventing recurrence. In this review, the reoperation rate was 1.4% to 4.9% in the MMAE with surgical treatment group and 11.6% to 18.8% in the conventional surgical treatment group (9, 15, 32, 33).

Okuma et al. (4) reported the following predictive factors for refractory cSDH after burr-hole surgery: use of antiplatelet drugs or anticoagulants, blood coagulation disorder, hepatic dysfunction, hemodialysis, terminal malignancy, advanced age (>80 years), cerebral atrophy, large preoperative hematoma volume (>150 mL), niveau formation, post cerebrospinal fluid shunt placement, no placement of a drain during surgery, postoperative residual air (>20%), and multiple recurrences. The authors also stated that such predictive factors have the potential to be good indications for prophylactic MMAE.

The selection of appropriate cases with respect to the indication for prophylactic MMAE is important from the standpoint of medical economics. Further investigation of the indications for prophylactic MMAE is warranted.

Complications of MMAE

The rate of MMAE-related complications in this review was 2.3%. Although serious complications such as cerebral infarction, visual loss, and facial palsy rarely occurred, their development suggests the possibility of stray embolic material entering high-risk anastomosis sites. Because of the potential for anastomosis in MMAs that involve the retinal artery and vasa nervorum of the facial nerve, embolization can lead to serious and permanent complications such as blindness and facial nerve palsy (29). During the embolization procedure, the microcatheter should be positioned distal to the branch, and attention should be paid to the findings of reflux during embolic agent injection (44). In addition, in patients with a high risk of migration of embolic material to a compromised anastomosis, it is important to perform a provocation test using lidocaine and abort the embolization based on the result of this test, if necessary (16). Although MMAE is a safe and easy procedure, close attention is needed when working with high-risk anastomoses to prevent complications during MMAE.

Factors that predict a good outcome after MMAE

With the increase in reports of MMAE for treatment of cSDH, there has also been an increase in reports regarding factors that affect the efficacy of MMAE. Salem et al. (46) evaluated various factors in 530 patients treated with MMAE; they found that an MMA main trunk diameter of <1.5 mm and anticoagulant medication use were factors associated with higher retreatment rates and that the use of liquid embolic material was a factor associated with lower retreatment rates. Some reports have suggested that the use of liquid embolic material is as effective and safe as the use of particles (29, 44, 49).

In addition, distal (midline) penetration of the embolizing material has been cited as a factor that shortens the time to hematoma clearance (31, 41). Among all anticoagulants, only factor Xa inhibitors were reported to be associated with retreatment (38).

Limitations

This review had three main limitations. First, most of the reports were retrospective, and they contained various indications for MMAE and definitions of resolution. Thus, the statistical examination was limited, leaving potential for important selection bias. Second, the content of the articles was mixed, with some studies limited to MMAE (whether upfront MMAE, prophylactic MMAE, or MMAE for recurrence after surgery), others comparing MMAE with surgery, and still others focusing on the clinical course or radiographic findings. Third, some studies lacked information on the timing of MMAE and surgical treatment and did not clearly indicate whether complications in cases of combined surgery and MMAE were caused by surgery or MMAE. These factors made statistical evaluation difficult in this review. Further prospective randomized trials are required to establish the clear indications for MMAE as an initial treatment or combined treatment with evacuation surgeries.

Conclusion

This study shows that MMAE alone is, although not immediate, as effective as evacuation surgery alone in reducing hematoma. The study also shows that combined treatment has a lower recurrence rate than evacuation surgery alone. Because MMAE is a safe procedure, it

should be considered for patients with cSDH, especially those with a high risk of recurrence.

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.

Author contributions

YO: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. TI: Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors gratefully acknowledge the work of past and present members of the Department of Neurosurgery of Tokyo Women's Medical University Yachiyo Medical Center.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Link TW, Schwarz JT, Paine SM, Kamel H, Knopman J. Middle meningeal artery embolization for recurrent chronic subdural hematoma: a case series. *World Neurosurg*. (2018) 118:e570–4. doi: 10.1016/j.wneu.2018.06.241

2. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, et al. Trial of dexamethasone for chronic subdural hematoma. *N Engl J Med*. (2020) 383:2616–27. doi: 10.1056/NEJMoa2020473

3. Miah IP, Holl DC, Blaauw J, Lingsma HF, den Hertog HM, Jacobs B, et al. Dexamethasone versus surgery for chronic subdural hematoma. *N Engl J Med*. (2023) 388:2230–40. doi: 10.1056/NEJMoa2216767

4. 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

5. 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

6. Gandhoke GS, Kaif M, Choi L, Williamson RW, Nakaji P. Histopathological features of the outer membrane of chronic subdural hematoma and correlation with clinical and radiological features. *J Clin Neurosci*. (2013) 20:1398–401. doi: 10.1016/j.jocn.2013.01.010

7. 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

8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

9. 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

10. 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

11. 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

12. Nakagawa I, Park HS, Kotsugi M, Wada T, Takeshima Y, Matsuda R, et al. Enhanced hematoma membrane on DynaCT images during middle meningeal artery embolization for persistently recurrent chronic subdural hematoma. *World Neurosurg*. (2019) 126:e473–9. doi: 10.1016/j.wneu.2019.02.074

13. 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

14. Yajima H, Kanaya H, Ogino M, Ueki K, Kim P. Middle meningeal artery embolization for chronic subdural hematoma with high risk of recurrence: a single institution experience. *Clin Neurol Neurosurg*. (2020) 197:106097. doi: 10.1016/j.clineuro.2020.106097

15. Shotar E, Meyblum L, Premat K, Lenck S, Degos V, Grand T, et al. Middle meningeal artery embolization reduces the post-operative recurrence rate of at-risk chronic subdural hematoma. *J Neurointerv Surg*. (2020) 12:1209–13. doi: 10.1136/neurintsurg-2020-016048

16. Rajah GB, Waqas M, Dossani RH, Vakharia K, Gong AD, Rho K, et al. Transradial middle meningeal artery embolization for chronic subdural hematoma using Onyx: case series. *J Neurointerv Surg*. (2020) 12:1214–8. doi: 10.1136/neurintsurg-2020-016185

17. 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

18. Mureb MC, Kondziolka D, Shapiro M, Raz E, Nossek E, Haynes J, et al. DynaCT enhancement of subdural membranes after middle meningeal artery embolization: insights into pathophysiology. *World Neurosurg*. (2020) 139:e265–70. doi: 10.1016/j.wneu.2020.03.188

19. Joyce E, Bounajem MT, Scoville J, Thomas AJ, Ogilvy CS, Riina HA, et al. Middle meningeal artery embolization treatment of nonacute subdural hematomas in the elderly: a multiinstitutional experience of 151 cases. *Neurosurg Focus*. (2020) 49:E5. doi: 10.3171/2020.7.FOCUS20518

20. Fan G, Wang H, Ding J, Xu C, Liu Y, Wang C, et al. Application of absolute alcohol in the treatment of traumatic intracranial hemorrhage via interventional embolization of middle meningeal artery. *Front Neurol*. (2020) 11:824. doi: 10.3389/fneur.2020.00824

21. Wei Q, Fan G, Li Z, Wang Q, Li K, Wang C, et al. Middle meningeal artery embolization for the treatment of bilateral chronic subdural hematoma. *Front Neurol*. (2021) 12:651362. doi: 10.3389/fneur.2021.651362

22. Tiwari A, Dmytriw AA, Bo R, Farkas N, Ye P, Gordon DS, et al. Recurrence and Coniglobus volumetric resolution of subacute and chronic subdural hematoma post-middle meningeal artery embolization. *Diagnostics*. (2021) 11:257. doi: 10.3390/diagnostics11020257

23. Tanoue S, Ono K, Toyooka T, Okawa H, Wada K, Shirotani T. The short-term outcome of middle meningeal artery embolization for chronic subdural hematoma with mild symptom: case series. *World Neurosurg*. (2023) 171:e120–5. doi: 10.1016/j.wneu.2022.11.090

24. Schwarz J, Carnevale JA, Goldberg JL, Ramos AD, Link TW, Knopman J. Perioperative prophylactic middle meningeal artery embolization for chronic subdural hematoma: a series of 44 cases. *J Neurosurg*. (2021) 67:1627–35. doi: 10.1093/neuros/nyaa447_318

25. Petrov A, Ivanov A, Rozhchenko L, Petrova A, Bhogal P, Cimpoca A, et al. Endovascular treatment of chronic subdural hematomas through embolization: a pilot

study with a non-adhesive liquid embolic agent of minimal viscosity (squid). *J Clin Med*. (2021) 10:4436. doi: 10.3390/jcm10194436

26. Lee S, Srivatsan A, Srinivasan VM, Chen SR, Burkhardt JK, Johnson JN, et al. Middle meningeal artery embolization for chronic subdural hematoma in cancer patients with refractory thrombocytopenia. *J Neurosurg*. (2021) 136:1273–7. doi: 10.3171/2021.5.JNS21109

27. Kan P, Maragkos GA, Srivatsan A, Srinivasan V, Johnson J, Burkhardt JK, et al. Middle meningeal artery embolization for chronic subdural hematoma: a multi-center experience of 154 consecutive Embolizations. *Neurosurgery*. (2021) 88:268–77. doi: 10.1093/neuros/nyaa379

28. Gomez-Paz S, Akamatsu Y, Salem MM, Enriquez-Marulanda A, Robinson TM, Ogilvy CS, et al. Upfront middle meningeal artery embolization for treatment of chronic subdural hematomas in patients with or without midline shift. *Interv Neuroradiol*. (2021) 27:571–6. doi: 10.1177/1591019920982816

29. Scoville JP, Joyce E, D AT, Bounajem MT, Thomas A, Ogilvy CS, et al. Radiographic and clinical outcomes with particle or liquid embolic agents for middle meningeal artery embolization of nonacute subdural hematomas. *Interv Neuroradiol*. (2022):159101992211046. doi: 10.1177/15910199221104631

30. Saway BF, Roth W, Salvador CD, Essibayi MA, Porto GBF, Dowlati E, et al. Subdural evacuation port system and middle meningeal artery embolization for chronic subdural hematoma: a multicenter experience. *J Neurosurg*. (2022) 1-8:1–8. doi: 10.3171/2022.10.JNS221476

31. Samarage HM, Kim WJ, Zarrin D, Goel K, Chin-Hsiu Wang A, Johnson J, et al. The "bright Falx" sign-midline embolic penetration is associated with faster resolution of chronic subdural hematoma after middle meningeal artery embolization: a case series. *Neurosurgery*. (2022) 91:389–98. doi: 10.1227/neu.0000000000002038

32. Salih M, Shutran M, Young M, Vega RA, Stippler M, Papavassiliou E, et al. Reduced recurrence of chronic subdural hematomas treated with open surgery followed by middle meningeal artery embolization compared to open surgery alone: a propensity score-matched analysis. *J Neurosurg*. (2022) 1-7:1–7. doi: 10.3171/2022.11.JNS222024

33. Onyinzo C, Berlis A, Abel M, Kudernatsch M, Maurer CJ. Efficacy and mid-term outcome of middle meningeal artery embolization with or without burr hole evacuation for chronic subdural hematoma compared with burr hole evacuation alone. *J Neurointerv Surg*. (2022) 14:297–300. doi: 10.1136/neurintsurg-2021-017450

34. Mir O, Yaghi S, Pujara D, Burkhardt JK, Kan P, Shapiro M, et al. Safety of antithrombotic resumption in chronic subdural hematoma patients with middle meningeal artery embolization: a case control study. *J Stroke Cerebrovasc Dis*. (2022) 31:106318. doi: 10.1016/j.jstrokecerebrovasdis.2022.106318

35. Majidi S, Matsoukas S, De Leacy RA, Morgenstern PF, Soni R, Shoirah H, et al. Middle meningeal artery embolization for chronic subdural hematoma using N-butyl cyanoacrylate with D5W push technique. *Neurosurgery*. (2022) 90:533–7. doi: 10.1227/neu.0000000000001882

36. Khorasanizadeh M, Shutran M, Garcia A, Enriquez-Marulanda A, Moore JM, Ogilvy CS, et al. Middle meningeal artery embolization with isolated use of coils for treatment of chronic subdural hematomas: a case series. *World Neurosurg*. (2022) 165:e581–7. doi: 10.1016/j.wneu.2022.06.099

37. Housley SB, Monteiro A, Khawar WI, Donnelly BM, Lian MX, Fritz AG, et al. Volumetric resolution of chronic subdural hematomas treated with surgical evacuation versus middle meningeal artery embolization during immediate, early, and late follow up: propensity-score matched cohorts. *J Neurointerv Surg*. (2022) 15:943–7. doi: 10.1136/jnis-2022-019427

38. Fuentes AM, Khalid SI, Mehta AI. Predictors of subsequent intervention after middle meningeal artery embolization for treatment of subdural hematoma: a Nationwide analysis. *Neurosurgery*. (2023) 92:144–9. doi: 10.1227/neu.0000000000002151

39. Enriquez-Marulanda A, Gomez-Paz S, Salem MM, Mallick A, Motiei-Langroudi R, Arle JE, et al. Middle meningeal artery embolization versus conventional treatment of chronic subdural hematomas. *Neurosurgery*. (2021) 89:486–95. doi: 10.1093/neuros/nyab192

40. Dofuku S, Sato D, Nakamura R, Ogawa S, Torazawa S, Sato M, et al. Sequential middle meningeal artery embolization after Burr hole surgery for recurrent chronic subdural hematoma. *Neurol Med Chir*. (2023) 63:17–22. doi: 10.2176/jns-nmc.2022-0164

41. Catapano JS, Ducruet AF, Srinivasan VM, Rumalla K, Nguyen CL, Rutledge C, et al. Radiographic clearance of chronic subdural hematomas after middle meningeal artery embolization. *J Neurointerv Surg*. (2022) 14:1279–83. doi: 10.1136/neurintsurg-2021-018073

42. Carpenter A, Rock M, Dowlati E, Miller C, Mai JC, Liu AH, et al. Middle meningeal artery embolization with subdural evacuating port system for primary management of chronic subdural hematomas. *Neurosurg Rev*. (2022) 45:439–49. doi: 10.1007/s10143-021-01553-x

43. Wali AR, Himstead A, Bravo J, Brandel MG, Hirshman BR, Pannell JS, et al. Helical coils augment embolization of the middle meningeal artery for treatment of chronic subdural hematoma: a technical note. *J Cerebrovasc Endovasc Neurosurg*. (2023) 25:214–23. doi: 10.7461/jcen.2023.E2022.08.001

44. Shehabeldin M, Amllay A, Jabre R, Chen CJ, Schunemann V, Herial NA, et al. Onyx versus particles for middle meningeal artery embolization in chronic subdural hematoma. *Neurosurgery*. (2023) 92:979–85. doi: 10.1227/neu.0000000000002307

45. Seok JH, Kim JH, Kwon TH, Byun J, Yoon WK. Middle meningeal artery embolization for chronic subdural hematoma in elderly patients at high risk of surgical treatment. *J Cerebrovasc Endovasc Neurosurg*. (2023) 25:28–35. doi: 10.7461/jcen.2022.E2022.08.003

46. Salem MM, Kuybu O, Nguyen Hoang A, Baig AA, Khorasanizadeh M, Baker C, et al. Middle meningeal artery embolization for chronic subdural hematoma: predictors of clinical and radiographic failure from 636 Embolizations. *Radiology*. (2023) 307:e222045. doi: 10.1148/radiol.222045

47. Martinez-Gutierrez JC, Zeineddine HA, Nahhas MI, Kole MJ, Kim Y, Kim HW, et al. Middle meningeal artery embolization for chronic subdural hematomas with concurrent Antithrombotics. *Neurosurgery*. (2023) 92:258–62. doi: 10.1227/neu.0000000000002222

48. Liu Z, Wang Y, Tang T, Zhang Y, Sun Y, Kuang X, et al. Time and influencing factors to chronic subdural hematoma resolution following middle meningeal artery embolization. *World Neurosurg*. (2023) 23:370–4. doi: 10.1016/j.wneu.2023.03.050

49. Krothapalli N, Patel S, Fayad M, Elmashad A, Killory B, Bruno C, et al. Outcomes of particle versus liquid embolic materials used in middle meningeal artery embolization for the treatment of chronic subdural hematoma. *World Neurosurg*. (2023) 173:e27–36. doi: 10.1016/j.wneu.2023.01.077

50. Yamada T, Natori Y. Prospective study on the efficacy of orally administered tranexamic acid and Goreisan for the prevention of recurrence after chronic subdural hematoma Burr hole surgery. *World Neurosurg*. (2020) 134:e549–53. doi: 10.1016/j.wneu.2019.10.134

51. Qiu S, Zhuo W, Sun C, Su Z, Yan A, Shen L. Effects of atorvastatin on chronic subdural hematoma: a systematic review. *Medicine*. (2017) 96:e7290. doi: 10.1097/MD.0000000000007290

52. Poulsen FR, Munthe S, Søe M, Halle B. Perindopril and residual chronic subdural hematoma volumes six weeks after burr hole surgery: a randomized trial. *Clin Neurol Neurosurg*. (2014) 123:4–8. doi: 10.1016/j.clineuro.2014.05.003

53. Di Cristofori A, Remida P, Patassini M, Piergallini L, Buonanno R, Bruno R, et al. Middle meningeal artery embolization for chronic subdural hematomas. A systematic review of the literature focused on indications, technical aspects, and future possible perspectives. *Surg Neurol Int*. (2022) 13:94. doi: 10.25259/SNI_911_2021

54. Salih M, Khorasanizadeh M, McMillan N, Gomez-Paz S, Thomas AJ, Ogilvy CS, et al. Cost comparison for open surgery versus middle meningeal artery embolization in patients with chronic subdural hematomas: a propensity score-matched analysis. *World Neurosurg*. (2023) 172:e94–9. doi: 10.1016/j.wneu.2022.12.042

55. Catapano JS, Koester SW, Srinivasan VM, Rumalla K, Baranoski JF, Rutledge C, et al. Total 1-year hospital cost of middle meningeal artery embolization compared to surgery for chronic subdural hematomas: a propensity-adjusted analysis. *J Neurointerv Surg*. (2022) 14:804–6. doi: 10.1136/neurintsurg-2021-018327

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 11 October 2023
DOI 10.3389/fneur.2023.1244006

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Hiroaki Matsumoto,
Yoshida Hospital, Japan
Rakesh Mishra,
Banaras Hindu University, India

*CORRESPONDENCE
Christian Iorio-Morin
christian.iorio-morin@usherbrooke.ca

RECEIVED 21 June 2023
ACCEPTED 28 September 2023
PUBLISHED 11 October 2023

CITATION
Langlois A-M, Touchette CJ, Mathieu D and Iorio-Morin C (2023) Classification of subdural hematomas: proposal for a new system improving the ICD Coding Tools.
Front. Neurol. 14:1244006.
doi: 10.3389/fneur.2023.1244006

Classification of subdural hematomas: proposal for a new system improving the ICD Coding Tools

Anne-Marie Langlois, Charles J. Touchette, David Mathieu and Christian Iorio-Morin*

Division of Neurosurgery, Department of Surgery, Université de Sherbrooke, Sherbrooke, QC, Canada

Background: The International Statistical Classification of Diseases (ICD) classifies subdural hematoma (SDH) as traumatic or non-traumatic. In clinical settings, however, SDH is typically described as either acute or chronic.

Objective: The goal of this study was to assess how the ICD Coding Tools captures the clinical terminology and propose an improved classification that would increase the system's usefulness in administrative, statistical and research applications.

Methods: We performed a retrospective analysis of patients who presented to our center with an ICD diagnostic code for either traumatic or non-traumatic SDH. A qualitative analysis of patients' charts was performed to identify elements relevant to management and prognosis, following which a meeting between expert investigators was held to elaborate a new classification of SDH. Imaging from all patients was then reviewed and cases were reclassified according to our proposed system.

Results: A total of 277 SDH cases were included. Themes documented in the charts included chronicity, etiology, side, and symptoms. We created a new classification which distinguishes acute SDH (aSDH) from membrane-associated SDH (mSDH). aSDH were further divided into traumatic aSDH (taSDH) and non-traumatic aSDH (ntaSDH), while mSDH were divided into acute on chronic (a/cSDH), subacute (sSDH) and chronic (cSDH) categories.

Conclusion: The ICD coding system correctly identifies taSDH and ntaSDH. However, it remains non-specific for mSDH. We propose this new SDH classification system to better capture chronicity and etiology – factors felt to impact management and prognosis.

KEYWORDS

subdural hematoma, trauma, intracranial hemorrhage, ICD, chronic subdural hematoma

Introduction

Subdural hematoma (SDH) is among the most frequent reasons for neurosurgical consult (1, 2). Acute SDH (aSDH) typically results from the traumatic laceration of a bridging vein, leading to a subdural accumulation of blood (3). Large aSDH are a neurosurgical emergency and require prompt evacuation through a craniotomy (4, 5), with or without bone flap

removal (6). Small, asymptomatic aSDH, on the other hand, are usually observed. While most will resolve spontaneously, a proportion of aSDH may progress into chronic SDH (cSDH) (3, 7). cSDH have a completely different pathophysiology and prognosis. They usually result from repeated bleeding from the SDH outer membrane, which results from an inflammatory reaction to the initial aSDH. Anticoagulant and fibrinolytic factors within the hematoma promote these recurrent bleeds, preventing membrane thrombosis and driving cSDH growth. Acute rebleeding within the cSDH can occur spontaneously and patients usually present with non-specific symptoms of imbalance, headaches, confusion with or without focal neurologic deficits. Surgical evacuation is the mainstay of treatment of cSDH, and typically consists of burr-hole evacuation (3).

The International Statistical Classification of Diseases and Related Health Problems is a diagnostic tool that allows for the standardized reporting and classification of all diseases. As a WHO-sponsored effort, it is the most widely used framework for reporting medical diagnoses for administrative, financial, statistical, and research purposes. In its latest revision (ICD-11), SDH is classified as either *traumatic* (code NA07.6) or *nontraumatic* (code 8B02). The origin and rationale for this mechanistic distinction is unclear (2, 3, 8).

When designing the Tranexamic Acid in Chronic Subdural hematomas (TRACS) study (9), we queried our hospital database for cSDH incidence and were unable to reliably distinguish aSDH from cSDH using the ICD diagnostic codes, which were in their 10th version at the time yet remained identical to the current ICD-11 categories. This same challenge was reported in 2016 by a group from Denmark (8). Among the 936 cases of SDH they reviewed, cSDH represented 57% of overall cases, of which 56% had been recorded under code S06.5 and 54% under code I62.0 using the previous ICD-10 diagnostic codes. They concluded that the ICD classification did not allow for proper distinction between cSDH and aSDH, as cSDH were practically equally classified under both *traumatic* and *nontraumatic* codifications (8). In January 2022, the 11th version of the ICD Coding Tools, the ICD-11, was adopted, however the classification of SDH remains unchanged apart from its attributed diagnostic codes, i.e., *traumatic* (code NA07.6, previously S06.5) or *nontraumatic* (code 8B02, previously I62.0) SDH.

Because the pathophysiology, management and prognosis of SDH depend not on the mechanism of the injury as much as on the existence of a chronic outer membrane, we propose a new classification of SDH that would better capture this element, with the goal of improving the classification's usefulness in administrative, statistical and research applications.

Methods

We reviewed all cases of SDH seen at our center between 2016 and 2017, at which time the ICD-10 codes were in use. Patients were included in the study if they had been assigned the ICD-10 diagnostic codes for either *traumatic* (S06.5) or *nontraumatic* SDH (I62.0) upon admission or throughout their hospital stay. The list of all patients included was then crossed with the TRACS screening log to validate that no cases were missed by the medical archivists. A qualitative analysis of the diagnoses written on the consult was performed to identify elements deemed relevant to management and prognosis by the treating physicians. After the cases were reviewed, a meeting was held between the investigators to elaborate a classification that would capture the diagnoses used in the patient charts. Then, imaging from all patients was reviewed and cases were reclassified according to our proposed system.

This study was approved by our Research Ethics Board (*Comité d'éthique de le recherche du CIUSSS de l'Estrie-CHUS*, FWA 00005894 and IRB00003849) under the protocol 14-213. Because of the retrospective and administrative nature of the study, consent from patients was not required.

Results

Elements relevant to SDH management

A total of 285 patients were screened and 277 met the inclusion criteria for analysis (Figure 1). Upon chart review, themes most commonly documented in the diagnostic summary of the initial consultation were:

- Acute vs. subacute vs. chronic vs. acute on chronic vs. subacute on chronic vs. hygroma.
- Right-sided vs. left-sided vs. bilateral.
- Symptomatic vs. asymptomatic.
- Primary vs. recurrent vs. secondary (ex: in the setting of TBI, aneurysmal SAH or ICH).

Typical diagnoses included "right aSDH secondary to severe TBI," "right, asymptomatic cSDH," "symptomatic recurrence of left cSDH" or "bilateral, symptomatic, acute on chronic SDH." The concept of traumatic vs. non-traumatic was not specified in the final diagnosis in most cases, even though a trauma might have been described in the history of present illness. Trauma was mostly documented in cases of aSDH.

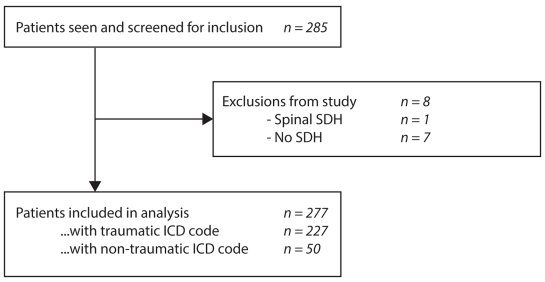


FIGURE 1
Flow diagram of patient selection.

Abbreviations: SDH, subdural hematoma; cSDH, chronic subdural hematoma; aSDH, acute subdural hematoma; mSDH, membrane-associated subdural hematoma; taSDH, traumatic acute subdural hematoma; ntaSDH, non-traumatic acute subdural hematoma; a/cSDH, acute on chronic subdural hematoma; sSDH, subacute subdural hematoma.

Proposed classification

In light of the elements identified above, we propose a new classification detailed in Table 1. The system starts by assessing the chronicity of the lesion, which appeared as the most important factor in determining management. New, acute lesions are classified as aSDH whereas we suggest the name *membrane-associated SDH* (mSDH) to refer to SDH resulting from the bleeding of a membrane (the entity considered as the classical chronic SDH). Etiology is then described for aSDH, while imaging aspect is used to further detail mSDH. The presence of symptoms and the side of the lesion were not felt to add much to the system and were thus not used in the classification.

The *aSDH* entity is defined as a hyperdense subdural collection that is assumed to be new (6). We divided this entity with the *traumatic* (taSDH) and *non-traumatic* (ntaSDH) subcategories since we believe the mechanism of injury between those two categories is very different and might have prognostic implication within the aSDH category (6, 10). *Traumatic aSDH* therefore encompasses all aSDH resulting from an immediate trauma and this code can be viewed as a form of SDH-complicated TBI. *Non-traumatic aSDH* captures cases secondary to processes other than TBI, such as spontaneous ICH or aneurysmal SAH contaminating the subdural space. The radiological evolution of the aSDH (resolution versus conversion to mSDH) is expected to be similar with both *traumatic* and *non-traumatic* aSDH, while the patient's prognosis in these cases will likely depend on the mechanism (i.e., severe TBI versus ICH versus SAH).

On the other hand, *mSDH* refers to a known or assumed *aSDH* that, instead of resolving, went on to develop an organized outer membrane which is now the main driver of the pathology (3). The prognosis of *mSDH* is probably independent of the initial aSDH and rather depends on the vascularity of the membrane, the occurrence of rebleeding and patient factors such as age (1–3, 11, 12), comorbidities (7, 11, 12), and the need for antithrombotic and anticoagulant medications (3, 13, 14). As will be discussed below, a traumatic incident can sometimes be identified, although many patients might have suffered only a minor fall or hit that was never documented. In our opinion, further classifying mSDH into traumatic or non-traumatic subcategories would be unreliable and irrelevant as it would not inform management or prognosis. In our qualitative chart review, mSDH were usually further described as *acute on chronic* (a/cSDH), *subacute* (sSDH), or *purely chronic* (cSDH). SDH were classified as *acute on chronic* if there were hyperdense components within the hypodense subdural collection; as *subacute* if the collection was isodense in relation to the brain parenchyma; and finally as *purely chronic* when the collection was homogeneously hypodense in relation to the brain parenchyma. While we have no evidence that this subclassification has any prognostic implication, it could relate to the mode of presentation and is typically documented in CT scan reports. As such, we decided to include these categories in our proposed classification as it allows the continuing use of current clinical terminology. Figure 2 presents representative examples of lesions from each category.

Finally, some chronic subdural collections identified in the charts were proven to be hygromas. Hygroma is defined as a subdural collection of CSF (3, 15, 16). Hygroma does not exist in the current ICD classification, yet is a well described entity with a completely benign course and usually no need for surgical intervention (3). Because it is part of the differential diagnosis of mSDH, we believe it would be relevant to add it to a future ICD classification as a separate entity, although it is not formally part of our proposed classification.

TABLE 1 Proposed classification for SDH.

I. Acute Subdural Hematoma (aSDH)
i. Traumatic (taSDH)
ii. Non-traumatic (ntaSDH)
II. Membrane-associated subdural hematoma (mSDH)
i. Acute on chronic (a/cSDH)
ii. Subacute (sSDH)
iii. Purely chronic (cSDH)

Comparison between ICD-10 and our proposed classification

Among the 285 patients in our cohort, 229 (80%) were initially classified as *traumatic SDH* (code S06.5) and 56 (20%) as *non-traumatic SDH* (code I62.0) as per the ICD-10 classification. In Table 2, we present a cross comparison of the ICD classification and our proposed system.

Among the SDH initially classified as *traumatic* ($n = 229$) according to ICD-10 codes, 57.6% were reclassified as *taSDH*, 2% as *ntaSDH*, and 37.6% as *mSDH*. In contrast, patients admitted under the *non-traumatic SDH* code ($n = 56$) were reclassified as *taSDH* in 5.4% of cases, as *ntaSDH* in 17.9% of cases and as *mSDH* in 64.2% of cases. Upon patient chart and imaging review of all SDH recorded under either *traumatic* or *non-traumatic* codes, 6 were reclassified as *hygromas*, 1 as a *spinal* SDH and 7 as *no* SDH. It is interesting to note that the case of spinal SDH resulted from a spinal dural fistula, which developed in the context of a traumatic spinal subarachnoid hemorrhage. While the pathogenesis of spinal SDH is unknown, it is indeed proposed that it can often result from a spinal SAH caused by trauma or any increase in intra-abdominal or intra-thoracic pressure such as was the case here (17). However, considering it remains a rare entity which does not enter the differential diagnosis of *mSDH*, we opted to simply exclude this entity from our classification.

When starting from our proposed classification and analyzing the official admission code, 97.8% of all *taSDH* ($n = 135$) had accordingly been recorded under *traumatic* upon admission, while 71.4% of *ntaSDH* ($n = 14$) were coded under *non-traumatic* ICD codes. Regarding the 122 cases of *mSDH* identified upon review ($n = 122$), 70.5% had been initially classified as *traumatic* and 29.5% as *non-traumatic*. Interestingly, among these cases of *mSDH*, 44.3% were subclassified as a/cSDH, 33.6% as sSDH and 22.1% as cSDH. Table 3 presents the sensitivity, specificity, positive predictive value and negative predictive value of the *traumatic* ICD code to detect *taSDH* and the *non-traumatic* ICD code to detect mSDH.

Discussion

Membrane-associated subdural hematoma remains a common disease which typically occurs in older patients often resulting from less severe injury than acute subdural hematoma. Both entities vary greatly in their clinical presentation, preferred management approach and overall prognosis. In this study, we showed that chronicity, lesion side, presence of symptoms and etiology are the most reliably documented factors in the charts of SDH patients. We postulated that

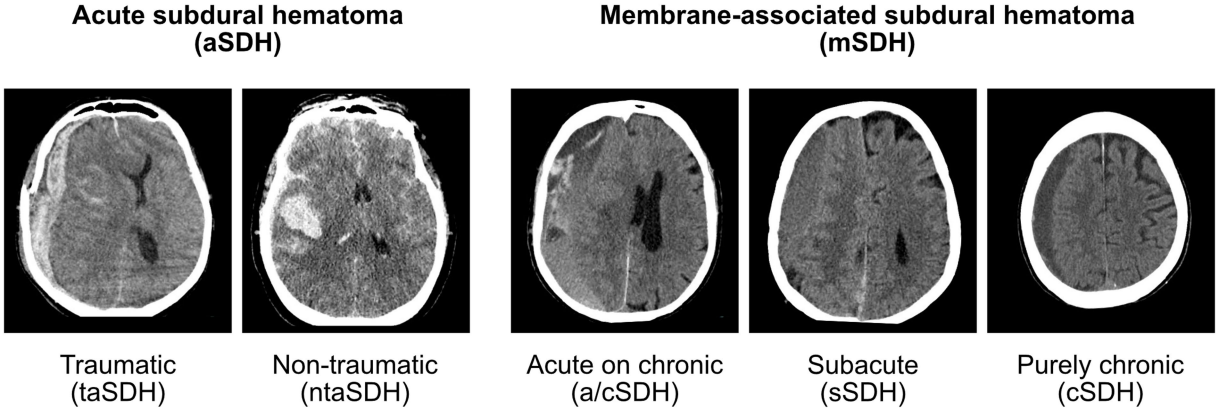


FIGURE 2
Representative cases for each diagnosis within our new classification.

TABLE 2 Distribution of SDH cases under ICD-10 and our proposed classification.

ICD-10	Acute SDH		Membrane-associated SDH				Hygromas	TOTAL
	Traumatic	Non-traumatic	Total	Acute on chronic	Sub-acute	Purely chronic		
Traumatic	132 (97.8%)	4 (28.6%)	86 (70.5%)	39 (72.2%)	33 (80.5%)	14 (51.9%)	5 (83.3%)	227 (82%)
Non-traumatic	3 (2.2%)	10 (71.4%)	36 (29.5%)	15 (27.8%)	8 (19.5%)	13 (48.1%)	1 (16.7%)	50 (18%)
TOTAL	135 (100%)	14 (100%)	122 (100%)	54 (100%)	41 (100%)	27 (100%)	6 (100%)	277 (100%)

*Note that the 1 case of spinal SDH and the 7 cases of no SDH were not included in the table above.

these data inform management more than the concept of trauma and designed a classification that would capture this information.

When comparing our patients' diagnosis between our classification and the previous ICD-10 diagnostic codes, it is notable that the ICD coding remained adequate for classifying *taSDH* (97.8% sensitivity) and to a certain extent *ntaSDH* (71.4% sensitivity). Nonetheless, it remains inaccurate in classifying *mSDH* (29.5% sensitivity) and its subcategories, *acute on chronic*, *subacute* and *purely chronic*. In fact, all patients initially coded as *traumatic* by the ICD codes were later almost equally reclassified as either *taSDH* and *mSDH* according to our classification. These findings suggest that ICD is unable to adequately differentiate acute from membrane-associated SDH – a conclusion also reached by the Danish team in 2016 (8). And while the ICD Coding Tool appears sensitive to identify *taSDH* and *ntaSDH*, the categories are contaminated by *mSDH*, which are distributed between the *traumatic* and *non-traumatic* categories, making this classification non-specific (Table 3). This remains true for the newer ICD-11 Coding Tools, which encompasses an identical classification of SDH with simply updated diagnostic codes.

Between 2013 and 2017, an annual average of 138 publications using the term *chronic subdural hematoma* were indexed in PubMed (18), making this a widely accepted and described entity. The inability of the ICD classification to capture mSDH within the larger and heterogeneous SDH spectrum is a significant problem. From an administrative standpoint, it can lead to inaccuracy in hospital patient record and identification of disease burden in a given population. From a research standpoint, it hinders retrospective identification of *mSDH*, forcing researchers to manually review each case of SDH to confirm chronicity. This adds complexity, time and cost to retrospective projects and renders power calculations for prospective studies such as TRACS (9) either extremely fastidious, or unreliable.

TABLE 3 Performance of ICD-10 codes to detect taSDH and mSDH.

	Using ICD-10 *traumatic* code to detect *taSDH*	Using ICD-10 *traumatic* code to detect *mSDH*	Using ICD-10 *non-traumatic* to detect *mSDH*
Sensitivity	98%	70%	30%
Specificity	30%	2%	79%
Positive predictive value	61%	39%	92%
Negative predictive value	92%	8%	61%

Conclusion

We propose this new SDH classification system to better capture chronicity and etiology – factors felt to impact management and prognosis. Depending on its acceptance and validation by the scientific community, this system could be submitted as an update to the future ICD classification and solve the currents issues we highlighted with ICD-10 as well as the newer ICD-11.

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 humans were approved by Comité d'éthique de le recherche du CIUSSS de l'Estrie-CHUS, FWA00005894 and IRB00003849. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a retrospective study of radiological data.

Author contributions

A-ML and CT were responsible for the data collection and data analysis. A-ML wrote the first draft of the manuscript. DM and CI-M were involved in the project conception, critical review, and manuscript revision and finalization. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Cousseau DH, Echevarría Martín G, Gaspari M, Gonorazky SE. Chronic and subacute subdural haematoma. An epidemiological study in a captive population. *Rev Neurol.* (2001) 32:821–4. doi: 10.33588/rn.3209.2000458

2. 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

3. 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

4. Karibe H, Hayashi T, Hirano T, Kameyama M, Nakagawa A, Tominaga T. Surgical management of traumatic acute subdural hematoma in adults: a review. *Neurol Med Chir.* (2014) 54:887–94. doi: 10.2176/nmc.cr.2014-0204

5. Phan K, Moore JM, Griessenauer C, Dmytriw AA, Scherman DB, Sheik-Ali S, et al. Craniotomy versus decompressive craniectomy for acute subdural hematoma: systematic review and meta-analysis. *World Neurosurg.* (2017) 101:677–685.e2. doi: 10.1016/j.wneu.2017.03.024

6. Lavrador JP, Teixeira JC, Oliveira E, Simão D, Santos MM, Simas N. Acute subdural hematoma evacuation: predictive factors of outcome. *Asian J Neurosurg.* (2018) 13:565–71. doi: 10.4103/ajns.AJNS_51_16

7. Drapkin AJ. Chronic subdural hematoma: pathophysiological basis for treatment. *Br J Neurosurg.* (1991) 5:467–73. doi: 10.3109/02688699108998475

8. Poulsen FR, Halle B, Pottegård A, García Rodríguez LA, Hallas J, Gaist D. Subdural hematoma cases identified through a Danish patient register: diagnosis validity, clinical characteristics, and preadmission antithrombotic drug use. *Pharmacoepidemiol Drug Saf.* (2016) 25:1253–62. doi: 10.1002/pds.4058

9. Iorio-Morin C, Blanchard J, Richer M, Mathieu D. Tranexamic acid in chronic subdural hematomas (TRACS): study protocol for a randomized controlled trial. *Trials.* (2016) 17:235. doi: 10.1186/s13063-016-1358-5

10. Woertgen C, Rothoerl RD, Schebesch KM, Albert R. Comparison of craniotomy and craniectomy in patients with acute subdural haematoma. *J Clin Neurosci.* (2006) 13:718–21. doi: 10.1016/j.jocn.2005.08.019

11. Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly – a North Wales experience. *J R Soc Med.* (2002) 95:290–2. doi: 10.1258/jrsm.95.6.290

12. Borger V, Vatter H, Oszvald Á, Marquardt G, Seifert V, Güresir E. Chronic subdural haematoma in elderly patients: a retrospective analysis of 322 patients between the ages of 65–94 years. *Acta Neurochir.* (2012) 154:1549–54. doi: 10.1007/s00701-012-1434-x

13. Gaist D, García Rodríguez LA, Hellfritzsch M, Poulsen FR, Halle B, Hallas J, et al. Association of antithrombotic drug use with subdural hematoma risk. *JAMA.* (2017) 317:836–46. doi: 10.1001/jama.2017.0639

14. Guha D, Coyne S, Macdonald RL. Timing of the resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study. *J Neurosurg.* (2016) 124:750–9. doi: 10.3171/2015.2.JNS141889

15. Nakaguchi H, Tanishima T, Yoshimasu N. 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

16. Vega RA, Valadka AB. Natural history of acute subdural hematoma. *Neurosurg Clin N Am.* (2017) 28:247–55. doi: 10.1016/j.nec.2016.11.007

17. Wang Y, Zheng H, Ji Y, Lu Q, Li X, Jiang X. Idiopathic spinal subdural hematoma: case report and review of the literature. *World Neurosurg.* (2018) 116:378–82. doi: 10.1016/j.wneu.2018.05.155

18. Iorio-Morin C, Touchette C, Lévesque M, Effendi K, Fortin D, Mathieu D. Chronic subdural hematoma: toward a new management paradigm for an increasingly complex population. *J Neurotrauma.* (2018) 35:1882–5. doi: 10.1089/neu.2018.5872

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 20 October 2023
DOI 10.3389/fneur.2023.1279292

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Rick Gill,
Loyola University Chicago, United States
Brandon Peter Lucke-Wold,
University of Florida, United States

*CORRESPONDENCE
Jin Hu
✉ hujin@fudan.edu.cn
Gang Wu
✉ woogangng@sina.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 18 August 2023
ACCEPTED 09 October 2023
PUBLISHED 20 October 2023

CITATION
Yang W, Chen Q, Yao H, Zhang J, Zhang Q, Fang J, Wu G and Hu J (2023) Predicting the progression of chronic subdural hematoma based on skull density.
Front. Neurol. 14:1279292.
doi: 10.3389/fneur.2023.1279292

Predicting the progression of chronic subdural hematoma based on skull density

Weijian Yang[1,2,3,4,5†], Qifang Chen[1,2,3,4,6†], Haijun Yao[1,2,3,4,7†], Jun Zhang[1,2,3,4,5], Quan Zhang[1,2,3,4,5], Jiang Fang[1,2,3,4,5], Gang Wu[1,2,3,4,5*] and Jin Hu[1,2,3,4,5*]

[1]Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China, [2]National Center for Neurological Disorders, Shanghai, China, [3]Shanghai Key Laboratory of Brain Function Restoration and Neural Regeneration, Shanghai, China, [4]Neurosurgical Institute of Fudan University, Shanghai, China, [5]Shanghai Clinical Medical Center of Neurosurgery, Shanghai, China, [6]Department of Nursing, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China, [7]Department of Neurosurgery and Neurocritical Care, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

Objective: The objective of this study was to investigate potential correlations between skull density and the progression of chronic subdural hematoma (CSDH).

Methods: Patients with unilateral CSDH were retrospectively enrolled between January 2018 and December 2022. Demographic and clinical characteristics, as well as hematoma and skull density (Hounsfield unit, Hu), were collected and analyzed.

Results: The study enrolled 830 patients with unilateral CSDH until the resolution of the CDSH or progressed with surgical treatment. Of the total, 488 patients (58.80%) necessitated surgical treatment. The study identified a significant correlation between the progression of CSDH and three variables: minimum skull density (MiSD), maximum skull density (MaSD), and skull density difference (SDD) ($p < 0.001$). Additionally, in the multivariable regression analysis, MiSD, MaSD, and SDD were independent predictors of CSDH progression. The MiSD + SDD model exhibited an accuracy of 0.88, as determined by the area under the receiver operating characteristic curve, with a sensitivity of 0.77 and specificity of 0.88. The model's accuracy was validated through additional analysis.

Conclusion: The findings suggest a significant correlation between skull density and the CSDH progression.

KEYWORDS

chronic subdural hematoma, skull density, midline shift, surgery, progression

1. Introduction

Chronic subdural hematoma (CSDH), characterized by a collection of blood products in the subdural space, is likely to become the most common neurosurgical disease in adults by the year 2030 (1). The annual incidence of CSDH is approximately 13.3 per 100,000 patients in the general population, with significantly greater rates occurring in older adults at up to 58 per 100,000 (2). Surgical evacuation of the subdural hematoma is the main treatment modality for symptomatic patients (3). Research has indicated that the implementation of middle meningeal artery (MMA) embolization has yielded favorable outcomes in select individuals (4).

Anatomical considerations support the pathogenesis of CSDH and rationale for MMA embolization, as the blood supply to CSDH originates from MMA, which traverses the dura mater to establish connections with delicate vessels within the outer membrane of the hematoma (5). Recent research has revealed the existence of significant anastomosis among CSDH, dura, and skull (6). This suggests that there is a substantial interconnection between the blood supply of the skull and the dura mater, which may have a crucial role in the development of CSDH.

A significant correlation between the Hounsfield unit (Hu) values of the skull and bone mineral density has been previously established (7). Furthermore, it was reported that patients exhibiting lower bone mineral density are at a heightened risk of experiencing recurrent CSDH (8). As a result, we have formulated the hypothesis that skull density is correlated with the progression of CSDH.

2. Materials and methods

2.1. Participants and study settings

The studies involving humans were approved by the Ethics Committee of the Evaluation of Biomedical Research Projects of Huashan Hospital. The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. The study evaluated all inpatient and outpatient individuals diagnosed with CSDH at Huashan Hospital, a university teaching hospital affiliated to Fudan University, from January 2018 to December 2022. The recruiting criteria were as follows: (1) patients presenting primary unilateral CSDH as diagnosed by computed tomography (CT) and (2) age $\geq$ 18 years. The exclusion criteria were as follows: (1) Patients with a history of tumor, intracerebral arteriovenous malformation, arachnoid cyst, ventriculoperitoneal shunts, immunodeficiency or thrombocytopenia, (2) Patients on immunosuppressants at admission, (3) Patients with bilateral or middle meningeal artery embolization, (4) Patients who were lost to follow-up. The patients were classified into two groups: recovery and progression. Recovery was defined as the resolution of CDSH on CT without surgical intervention. Hematoma progression was characterized by a significant decline in neurological function (such as worsening headache, progressive limb paralysis, or altered levels of consciousness) or by the observation of hematoma enlargement and/or midline shift (>1 cm) on follow-up CT scans (9). The patients were followed for a period of six months.

2.2. Data collection

The study collected demographic information, clinical characteristics, hematoma density, and skull density of enrolled patients. The collected data encompassed gender, age, etiology, clinical symptoms, medical history, therapeutic records, and CT data. The following CT data were acquired from the initial diagnosis: initial midline shift (IMS) and initial hematoma thickness (IHT). The following CT data were acquired at the time of peak midline shift (MS) and/or maximal hematoma thickness (HT). The CT data comprised MS, HT in the axial plane, minimum hematoma density (MiHD), maximal hematoma density (MaHD), minimum skull density (MiSD), and maximal skull density (MaSD). The present study employed millimeters (mm) as the unit of measurement for both MS and HT. Hu was utilized to determine the density value for CT data. The MS was operationally defined as the line extending from the septum pellucidum, perpendicular to the midline, between the most anterior and posterior parts of the falx cerebri (10). HT was measured from the brain surface, perpendicular to the tangent line of inner compact bone. Hematoma density difference (HDD) was computed as the difference between the MaHD and the MiHD. Skull density was measured at the level of maximum hematoma thickness. Skull density difference (SDD) was calculated as the difference between MaSD and the MiSD. The data measurement method on CT is depicted in Figure 1. To ensure accuracy, three neurosurgeons from the university faculty confirmed all radiologic findings. The clinical data was blinded using the picture archiving and communication system (PACS).

2.3. Statistical analysis

Continuous data with a normal distribution were expressed as mean $\pm$ standard deviation ($\bar{X} \pm SD$). The student's unpaired t-test or Chi-square test was used to compare variables between the groups. Enumeration data were described in frequency or percentage. Univariable and multivariable logistic regression models were employed to assess the patient parameters. Receiver operating characteristic (ROC) curve analysis was subsequently adopted to discriminate the capacity of this model. The Youden index was used to identify sensitivity and specificity based on the coordinate points of the highest combination of these two parameters on ROC curve. The model's capacity for discrimination, accuracy in prediction, and clinical utility were evaluated through the utilization of a ROC curve, calibration plot, and decision curve analysis. To mitigate overfit bias, one thousand bootstrap resamples were utilized. SPSS 20.0 software (The IBM SPSS software Company) was used for statistical analysis, and $p < 0.05$ were considered statistically significant. The visualization figures were produced by Darwin[1] (accessed on October 4, 2023) and genescloud[2] (accessed on October 4, 2023), while the pattern diagram was generated by Figdraw[3] (accessed on October 4, 2023).

3. Results

3.1. Demographic and clinical characteristics of patients

For statistical analysis, a cohort of 830 patients diagnosed with unilateral CSDH was included. The mean age of the cohort was 68.53 $\pm$ 12.99 years, with 669 (80.60%) males. The incidence of CSDH was highest among patients aged 61 to 80 years, accounting for 65.18% of cases. The most commonly observed clinical symptom was

1 https://darwin-online.yizhun-ai.com/
2 https://www.genescloud.cn
3 https://www.figdraw.com/static/index.html

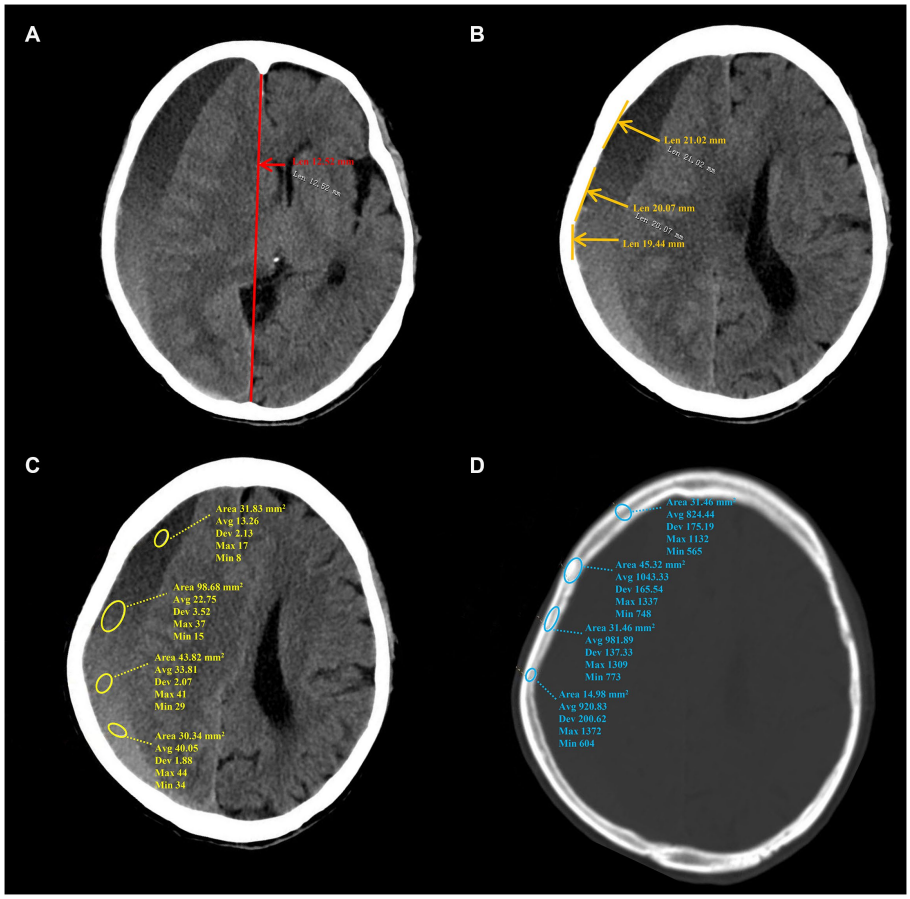


FIGURE 1
The data measurement method on CT. **(A–D)** Show the measurement method of MS, HT, hematoma density and skull density, separately. MS, midline shift; HT, maximal hematoma thickness.

headache (45.33%), followed by dyskinesia (37.63%) and impaired awareness (5.71%). The relevant data is presented in Table 1.

Among the cohort of 830 patients, a majority of 514 individuals (61.93%) reported experiencing head trauma within the preceding three months, while 316 (38.07%) did not report any such incidents. Of the total, 89 patients (10.72%) were undergoing long-term antithrombotic treatment at the time of CSDH confirmation through neuroimaging, while the remaining 741 (89.28%) were not receiving such therapy. The patients were subsequently categorized into two groups based on their recovery status, with 342 (41.20%) individuals classified as belonging to the recovery group and 488 (58.80%) to the progression group. The relevant data is presented in Table 1.

3.2. Varied characteristics of recovery and progression patients

The analysis revealed no statistically significant differences in sex, anticoagulation therapy and antiplatelet therapy between the two groups, with p values of 0.09, 0.98 and 0.50, respectively. However, age, history of head trauma, and all CT characteristics exhibited significant differences between the recovery and progression patients, with a p value of less than 0.001. The detailed data can be found in Table 2.

The present study conducted a further analysis of the relationship between skull density parameters (MiSD, MaSD, SDD) and CT data of hematoma (MS, HT, MiHD, MaHD, HDD). The results indicated a positive correlation between SDD and CT data of hematoma (MS, HT, MiHD, MaHD, HDD), albeit with a small correlation coefficient. Specifically, the correlation coefficient between SDD and MS was found to be the highest (0.63). In contrast, MiSD displayed a strong inverse correlation with CT data of hematoma (MS, HT, MiHD, MaHD, HDD), exhibiting correlation coefficients of −0.89, −0.97 and −0.98, respectively. The elliptical shape appears more elongated (approaching a straight line), suggesting a linear relationship. The results suggest a linear correlation between MiSD and hematoma CT data. These findings are presented in Figure 2.

3.3. Skull density related to CSDH progression

Following the univariable and Correlation analyses, a multivariable logistic regression analysis was conducted to examine the variables that displayed statistical significance. The results indicated that MiSD, MaSD, and SDD were significant independent predictors of CSDH progression in the multivariable model ($p < 0.001$), as presented in Table 3.

TABLE 1 Demographic and clinical characteristics of patients.

Variable	*N* = 830
Sex (male)	669 (80.60%)
Age (years, mean ± SD)	68.53 ± 12.99
<60	166 (20.00%)
61 ≤ Age < 80	541 (65.18%)
≥81	123 (14.82%)
Neurological deficits	
Headache	524 (45.33%)
Dyskinesia	435 (37.63%)
Impaired awareness	66 (5.71%)
Aphasia	61 (5.28%)
Amnesia	51 (4.41%)
Seizure	19 (1.64%)
History of head trauma	
Yes	514 (61.93%)
No	316 (38.07%)
Antithrombotic drug	
Yes	89 (10.72%)
No	741 (89.28%)
Group	
Recovery group	342 (41.20%)
Progression group	488 (58.80%)

The independent predictors derived from the multivariate logistic regression model were utilized in constructing the ROC model. While the multivariate analysis did not demonstrate a significant enhancement in efficacy, it did exhibit a potential for improving sensitivity as illustrated in Figure 3A and Table 4. The variables' cut-off, sensitivity, specificity, Youden index, and AUC values are presented in Table 4.

3.4. Internal validation, calibration, and decision curve analysis

The accuracy of the MiSD+SDD model was confirmed through a bootstrap method involving 1,000 resamples, resulting in an AUC of 0.87 (Figure 3B). Furthermore, the predicted probabilities generated by the MiSD+SDD model exhibited a strong correlation with the clinical outcomes (Figure 3C), and the decision curve analysis demonstrated the potential clinical utility of the model (Figure 3D).

4. Discussion

This is the first study to investigate the association between skull density and CSDH progression. Our findings indicate that MiSD, MaSD, and SDD are all independent risk factors for the progression of CSDH. Furthermore, MiSD and SDD were utilized to construct a model for the assessment and validation of CSDH progression, which is a crucial step in identifying this condition.

TABLE 2 Varied characteristics of patients in recovery and progression group.

Variables	Recovery group *N* = 342 (41.20%)	Progression group *N* = 488 (58.80%)	*P*
Sex (male)			0.09
Female	76 (22.22%)	85 (17.42%)	
Male	266 (77.78%)	403 (82.58%)	
Age (years, mean ± SD)	66.86 ± 14.35	69.70 ± 11.83	0.002
<60	87 (25.44%)	79 (16.19%)	
61 ≤ Age < 80	205 (59.94%)	336 (68.85%)	
≥81	50 (14.62%)	73 (14.96%)	
History of head trauma			
Yes	240 (70.18%)	274 (56.15%)	< 0.001
No	102 (29.82%)	214 (43.85%)	
Anticoagulation therapy			0.98
Yes	9 (2.63%)	13 (2.66%)	
No	333 (97.37%)	475 (97.34%)	
Antiplatelet therapy			0.50
Yes	25 (7.31%)	42 (8.61%)	
No	317 (92.69%)	446 (91.39%)	
CT characteristics			
IMS (mm, mean ± SD)	3.74 ± 2.16	3.98 ± 2.86	0.17
IHT (mm, mean ± SD)	9.45 ± 5.42	9.57 ± 4.91	0.74
MS (mm, mean ± SD)	5.70 ± 2.20	12.63 ± 2.94	< 0.001
HT (mm, mean ± SD)	18.89 ± 6.34	26.28 ± 5.40	< 0.001
MiHD (Hu, mean ± SD)	22.43 ± 8.88	25.24 ± 10.43	< 0.001
MaHD (Hu, mean ± SD)	40.04 ± 10.29	52.77 ± 9.28	< 0.001
HDD (Hu, mean ± SD)	17.61 ± 8.98	27.53 ± 10.21	< 0.001
MiSD (Hu, mean ± SD)	701.70 ± 118.17	565.09 ± 151.37	< 0.001
MaSD (Hu, mean ± SD)	1378.63 ± 157.68	1500.60 ± 193.99	< 0.001
SDD (Hu, mean ± SD)	676.93 ± 126.66	935.51 ± 204.10	< 0.001

IMS, Initial Midline shift; IHT, Initial Hematoma thickness; MS, Midline shift; HT, Hematoma thickness; MiHD, Min Hematoma density; MaHD, Max Hematoma density; HDD, Hematoma density difference; MiSD, Min skull density; MaSD, Max skull density; SDD, Skull density difference.

With the development of population aging, the prevalence of CSDH is expected to escalate annually, ultimately emerging as a prominent disease posing a significant threat to the elderly population (11). The preferred method of treatment for CSDH is surgical evacuation of the hematoma via Burr-hole with drainage (12). Despite the widespread acceptance of the aforementioned surgical approach, several alternative options including bedside twist drill craniotomy with placement of a subdural drain or subdural evacuation port system, endoscope-assisted evacuation and MMA embolization have been increasingly implemented. Bedside subdural evacuation port system placement has gained popularity due to its ability to eliminate the requirement for general anesthesia and the need for availability of an operating room. Consequently, patients with multiple comorbidities are more inclined to undergo this procedure (13). The utilization of

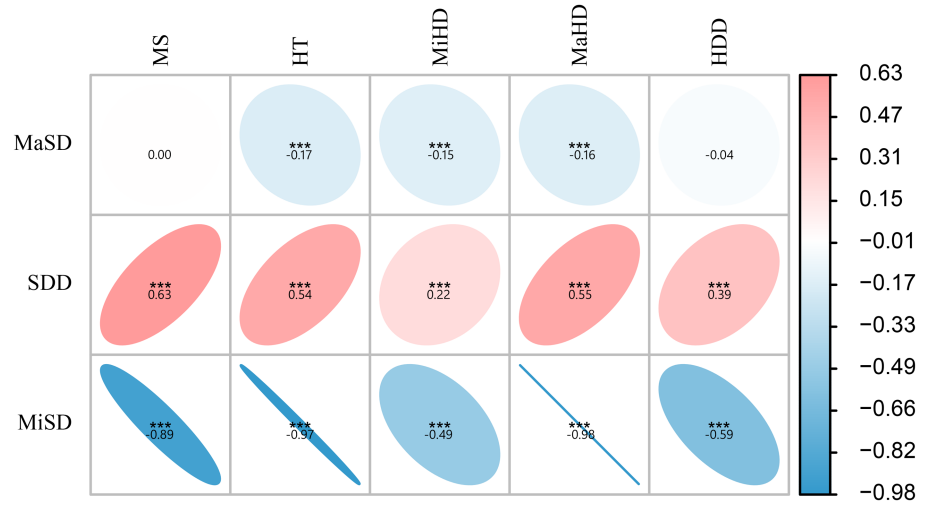


FIGURE 2
Correlation analysis between skull density and hematoma density. ***$p < 0.001$, otherwise $p > 0.05$. The data in the figure represent the correlation coefficients. The elliptical shape appears more elongated (approaching a straight line), suggesting a linear relationship.

TABLE 3 Multivariable logistic regression analysis of predictors of CSDH progression.

Factor	*B*	SE	Wald	df	Sig.	Exp (B) (95% CI)
MiSD	−0.0039	0.0007	30.8587	1	< 0.001	0.996 (0.995–0.997)
MaSD	0.0080	0.001	142.7102	1	< 0.001	1.008 (1.007–1.009)
SDD	0.0091	0.001	190.6521	1	< 0.001	1.009 (1.008–1.010)

B, regression coefficient; SE, standard error; Wald, Wald score; df, degrees of freedom; Sig., level of significance; MiHD, Min Hematoma density; MiSD, Min skull density; MaSD, Max skull density; SDD, Skull density difference.

endoscope-assisted evacuation in conjunction with MMA embolization has the potential to effectively reduce the recurrence of CSDH by improving hematoma evacuation, removing membranes, coagulating at-risk blood vessels, strategically placing surgical drains, assessing embolization efficacy, coagulating fragile membranes, and eliminating acute clot (14). The formation of subdural hematoma involves the MMA and its branches, and MMA embolization has been found to have a therapeutic effect (15). Despite surgery being the primary treatment for CSDH, the recurrence rate post-surgery varies significantly, and drug therapy is also a viable treatment option for CSDH (16). Nonetheless, the absence of concrete evidence-based guidelines for surgical indications (17), coupled with divergent reports that suggest a case-by-case approach to surgery (18, 19).

Underscores the need to determine the CSDH progression, as this will significantly influence the available treatment options. Our study showed that antithrombotic therapy is not associated with CSDH volume progression, which is consistent with the results of others (20). Although there were statistically significant differences in age and of trauma between the two groups, we focused on the correlation between skull density and the progression of hematoma. It was found that the vessels of the dura exhibited significant anastomoses with the vessels of the skull (6). Furthermore, postoperative recurrence was found to be associated with skull density (8). Empirical evidence has demonstrated that patients with MMA embolization display extensive anastomosis among subdural hematoma, dura, and skull, as depicted in Figures 4A,B. The pattern diagram in Figure 4C provides a detailed illustration of the anastomosis among hematoma, dura, and skull. Consequently, it is hypothesized that skull density is linked to the progression of CSDH.

Various radiological measures, including the midline shift, brain atrophy, hematoma density, and maximum width of the hematoma, are utilized to assess the extent and space-occupying effect of different intracranial masses (10, 11). Previous studies have shown a significant correlation between Hu values and bone mineral density (21). Furthermore, it was reported that patients with lower bone mineral density were at a higher risk of CSDH recurrence (8). The present study reveals that patients with CSDH progression exhibit lower MiSD, higher MaSD and SDD. The findings indicate a negative correlation between MiSD and hematoma progression. Furthermore, in the multi-variable regression analysis, MiSD, MaSD, and SDD emerged as significant independent predictors of CSDH progression. The accuracy of the MiSD+SDD model, as estimated by the area under the ROC, was 0.88 (with a sensitivity of 0.77 and specificity of 0.88). The validation analysis confirmed the high accuracy of the model.

The treatment options for CSDH display variations in terms of indication, timing, and type of surgical intervention, duration of drainage, concomitant membranectomy, and the necessity of MMA embolization (22). We found that patients with CSDH progression exhibit lower MiSD (Cut-off 634 Hu), higher MaSD (Cut-off 1,597 Hu) and SDD (Cut-off 830 Hu). The findings of this study may have significant implications for the early assessment of CSDH progression and the determination of the necessity for surgical intervention. The use of MMA embolization shows promise in preventing re-bleeding and recurrence (23). The meningeal branch of the MMA is highly

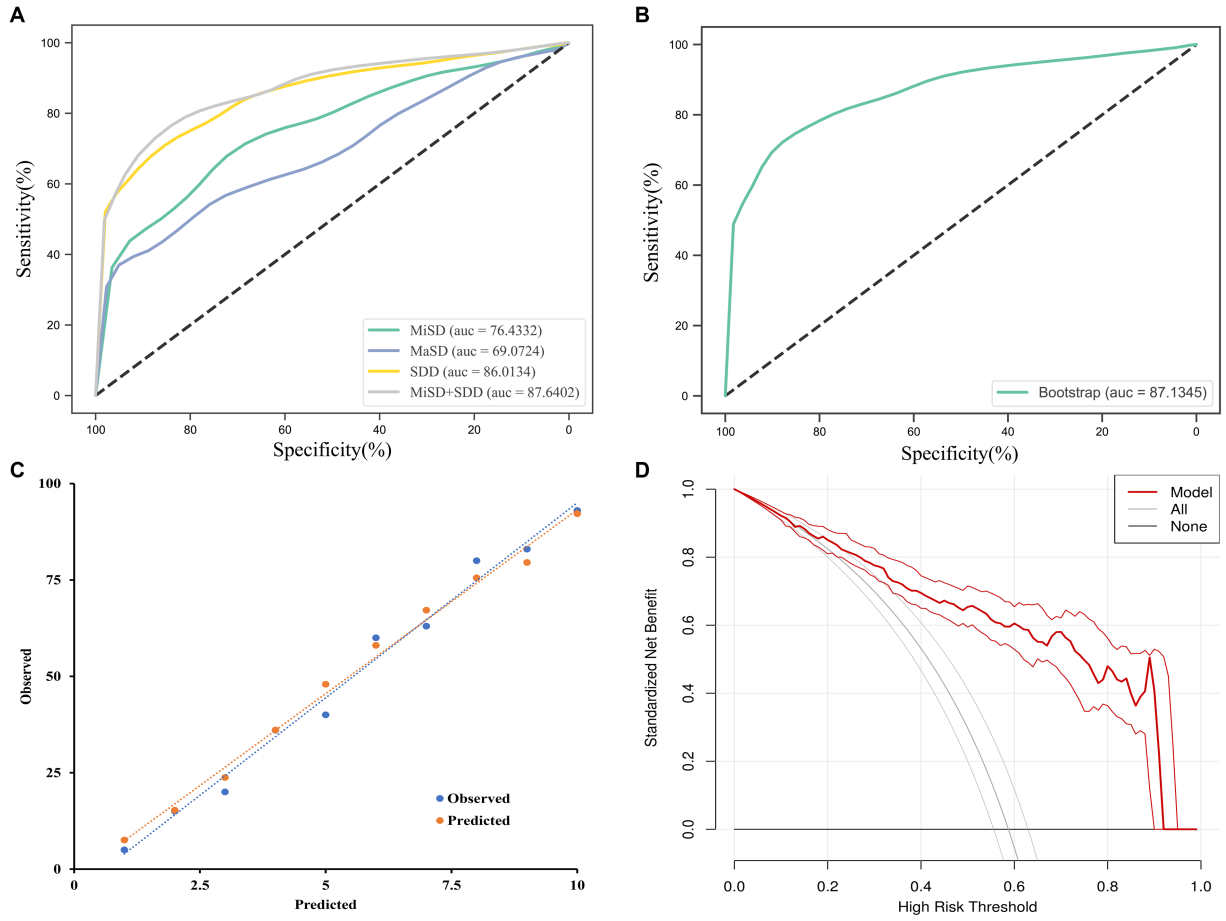


FIGURE 3
ROC curves analysis and evaluation of the model. **(A)** The ROC curves for the MiSD, MaSD, SDD and MiSD+SDD. **(B)** The ROC curve for the MiSD+SDD model generated using bootstrap resampling (1,000 times). **(C)** Calibration plot. The closer the blue calibration curve and the red standard curve are, the better the calibration ability of the model is suggested. **(D)** Decision curve analysis for the MiSD+SDD model. The red line is from the MiSD+SDD model, the gray line indicates progression, and the horizontal line indicates recovery. The graph depicts the expected standardized net benefit per patient relative to the prediction of progression. The standardized net benefit increases as the model curve is extended. MiHD, Min Hematoma density; MiSD, Min skull density; MaSD, Max skull density; SDD, Skull density difference.

TABLE 4 **Prognostic accuracy of CSDH progression.**

Variables	Cut-off	Sensitivity	Specificity	Youden index	AUC
MiSD (Hu)	634	0.73	0.71	0.44	0.76
MaSD (Hu)	1,597	0.39	0.96	0.35	0.69
SDD (Hu)	830	0.69	0.89	0.58	0.86
MiSD + SDD	-	0.77	0.88	0.65	0.88

AUC, area under the curve; GCS, Glasgow Coma Scale; MiHD, Min Hematoma density; MiSD, Min skull density; MaSD, Max skull density; SDD, Skull density difference.

extensive, encompassing various regions such as the orbital, frontal, top, occipital, posterior fossa, and base of the middle cranial fossa, depending on the blood supply location (24). The literature states that the meningeal arteries provide blood supply to both the skull and dura mater (25). A study has indicated that the distal penetration of the liquid embolic agent may be linked to a faster clearance of hematoma (26). The findings imply that the branch of the MMA supplying the skull was subjected to embolization. Our investigation revealed a correlation between skull density and the progression of CSDH. This finding holds significant value in terms of facilitating the early detection of hematoma progression and the timely implementation of MMA embolization as a treatment approach. However, additional research is required to ascertain the potential correlation between skull density and the effectiveness of MMA embolization in mitigating the recurrence of CSDH.

Nonetheless, it is crucial to note that the interpretation of these findings is subject to three significant caveats. Firstly, as with prior retrospective case–control studies, the ability to establish causal inference is constrained. Secondly, despite the confirmation of all radiologic findings by three faculty neurosurgeons who were blinded to the clinical data using PACS, the measurement may have been influenced by individualistic differences, leading to potential selection

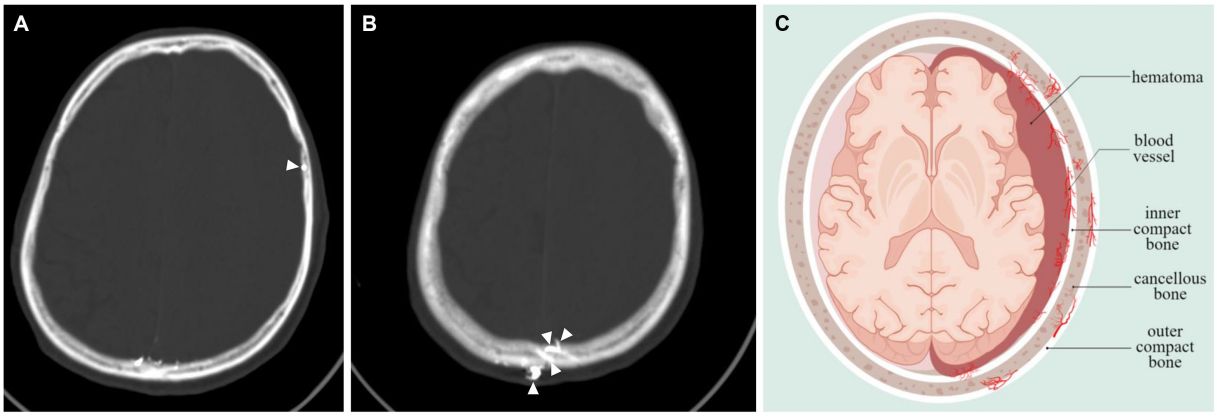


FIGURE 4
Vascular anastomosis of hematoma, dura and skull. **(A,B)** Middle meningeal artery embolization revealed extensive anastomoses vessels between dura and skull (indicated by arrows). **(C)** Hematoma-dura-skull relationships, emphasizing the "vascular anastomosis" principle.

bias. Lastly, while our model was validated using bootstraps with 1,000 resamples, further prospective multicenter studies are necessary to externally validate our results.

5. Conclusion

The findings of the study indicate that lower MiSD, higher MaSD and higher SDD are significantly correlated with CSDH progression. To enhance the predictive accuracy of CSDH progression and facilitate treatment decision-making, we constructed a MiSD+SDD model and validated it through 1,000 bootstrap resamples. This model holds promise for clinical application.

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 authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Evaluation of Biomedical Research Projects of Huashan Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

WY: Data curation, Funding acquisition, Writing – original draft. QC: Data curation, Writing – review & editing. HY: Data curation, Writing – review & editing. JZ: Formal analysis, Writing – review & editing. QZ: Formal analysis, Writing – review & editing. JF: Formal analysis, Writing – review & editing. GW: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. JH: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by Research foundation of Huashan Hospital affiliated to Fudan University (2021QD026), Shanghai Shenkang Hospital Development Center promoted and optimized management of diagnosis and treatment technology in municipal hospitals (SHDC22022210 and SHDC22022210) and Hainan Academician Innovation Platform Fund (YSPTZX202033).

Acknowledgments

We thank all the staffs in the Department of Radiology, Neurosurgery and Medical Record for their kind help.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Laeke T, Kalleklev L, Tirsit A, Moen BE, Lund-Johansen M, Sundstrom T. Surgical treatment and outcome of chronic subdural hematoma: a comparative study between Ethiopia and Norway. *Acta Neurochir*. (2023) 165:49–59. doi: 10.1007/s00701-022-05435-z

2. Bounajem MT, Campbell RA, Denorme F, Grandhi R. Paradigms in chronic subdural hematoma pathophysiology: current treatments and new directions. *J Trauma Acute Care Surg*. (2021) 91:e134–41. doi: 10.1097/TA.0000000000003404

3. Mainka N, Borger V, Hadjiathanasiou A, Hamed M, Potthoff A, Vatter H, et al. Dehydration status at admission predicts recurrence in patients with traumatic chronic subdural hematoma. *J Clin Med*. (2022) 11:1178. doi: 10.3390/jcm11051178

4. Desir LL, Narayan V, Ellis J, Gordon D, Langer D, Ortiz R, et al. Middle meningeal artery embolization in the Management of Chronic Subdural Hematoma: a comprehensive review of current literature. *Curr Neurol Neurosci Rep*. (2023) 23:109–19. doi: 10.1007/s11910-023-01262-6

5. Catapano JS, Nguyen CL, Wakim AA, Albuquerque FC, Ducruet AF. Middle meningeal artery embolization for chronic subdural hematoma. *Front Neurol*. (2020) 11:557233. doi: 10.3389/fneur.2020.557233

6. Shapiro M, Walker M, Carroll KT, Levitt MR, Raz E, Nossek E, et al. Neuroanatomy of cranial dural vessels: implications for subdural hematoma embolization. *J NeuroInterventional Surg*. (2021) 13:471–7. doi: 10.1136/neurintsurg-2020-016798

7. Han M, 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. Ha BJ, Bae I, Kim JM, Cheong JH, Ryu JI, Han M. Effects of possible osteoporotic conditions on the recurrence of chronic subdural hematoma. *Front Neurol*. (2020) 11:538257. doi: 10.3389/fneur.2020.538257

9. Wang D, Gao C, Xu X, Chen T, Tian Y, Wei H, et al. Treatment of chronic subdural hematoma with atorvastatin combined with low-dose dexamethasone: phase II randomized proof-of-concept clinical trial. *J Neurosurg*. (2020) 134:235–43. doi: 10.3171/2019.11.JNS192020

10. Bechstein M, Mcdonough R, Fiehler J, Zanolini U, Rai H, Siddiqui A, et al. Radiological evaluation criteria for chronic subdural hematomas. *Clin Neuroradiol*. (2022) 32:923–9. doi: 10.1007/s00062-022-01138-1

11. Shen J, Yuan L, Ge R, Wang Q, Zhou W, Jiang XC, et al. Clinical and radiological factors predicting recurrence of chronic subdural hematoma: a retrospective cohort study. *Int J Care Inj*. (2019) 50:1634–40. doi: 10.1016/j.injury.2019.08.019

12. Greuter L, Lutz K, Fandino J, Mariani L, Guzman R, Soleman J. Drain type after burr-hole drainage of chronic subdural hematoma in geriatric patients: a subanalysis of the cSDH-drain randomized controlled trial. *Neurosurg Focus*. (2020) 49:E6. doi: 10.3171/2020.7.FOCUS20489

13. Mohan A, Malnik S, Grady C, Lucke-Wold B, Kubilis P, Hoh BL. Inversed probability case-control analysis of operative burr hole evacuation versus subdural evacuating port system for chronic subdural hematomas: clinical and economic outcomes. *Clin Neurol Neurosurg*. (2022) 220:107356. doi: 10.1016/j.clineuro.2022.107356

14. Cutler C, Azab M, Lucke-Wold B, Grandhi R, Karsy M. Endoscope-assisted evacuation of nonacute subdural hematoma: a technical case series and systematic review. *World Neurosurg*. (2022) 168:e636–44. doi: 10.1016/j.wneu.2022.10.037

15. Fiorella D, Arthur AS. Middle meningeal artery embolization for the management of chronic subdural hematoma. *J NeuroInterventional Surg*. (2019) 11:912–5. doi: 10.1136/neurintsurg-2019-014730

16. Feghali J, Yang W, Huang J. Updates in chronic subdural hematoma: epidemiology, Etiology, pathogenesis, treatment, and outcome. *World Neurosurg*. (2020) 141:339–45. doi: 10.1016/j.wneu.2020.06.140

17. Jensen TSR, Haldrup M, Hjortdal Grønhøj M, Miscov R, Larsen CC, Debrabant B, et al. National randomized clinical trial on subdural drainage time after chronic subdural hematoma evacuation. *J Neurosurg*. (2021):1–8. doi: 10.3171/2021.10.JNS211608

18. Christopher E, Poon MTC, Glancz LJ, Hutchinson PJ, Kolias AG, Brennan PM. Outcomes following surgery in subgroups of comatose and very elderly patients with chronic subdural hematoma. *Neurosurg Rev*. (2019) 42:427–31. Online ahead of print. doi: 10.1007/s10143-018-0979-4

19. Lee L, Ker J, Ng HY, Munusamy T, King NKK, Kumar D, et al. Outcomes of chronic subdural hematoma drainage in nonagenarians and centenarians: a multicenter study. *J Neurosurg*. (2016) 124:546–51. doi: 10.3171/2014.12.JNS142053

20. Lucke-Wold BP, Turner RC, Josiah D, Knotts C, Bhatia S. Do age and anticoagulants affect the natural history of acute subdural hematomas? *Arch Emerg Med Crit Care*. (2016) 1:1010.

21. Hendrickson NR, Pickhardt PJ, Del RA, Rosas HG, Anderson PA. Bone mineral density T-scores derived from CT attenuation numbers (Hounsfield units): clinical utility and correlation with dual-energy X-ray absorptiometry. *Iowa Orthop J*. (2018) 38:25–31.

22. Solou M, Ydreos I, Gavra M, Papadopoulos EK, Banos S, Boviatsis EJ, et al. Controversies in the surgical treatment of chronic subdural hematoma: a systematic scoping review. *Diagnostics*. (2022) 12:2060. doi: 10.3390/diagnostics12092060

23. Onyinzo C, Berlis A, Abel M, Kudernatsch M, Maurer CJ. Efficacy and mid-term outcome of middle meningeal artery embolization with or without burr hole evacuation for chronic subdural hematoma compared with burr hole evacuation alone. *J NeuroIntervent Surg*. (2022) 14:297–300. doi: 10.1136/neurintsurg-2021-017450

24. Bonasia S, Smajda S, Ciccio G, Robert T. Middle meningeal artery: anatomy and variations. *Am J Neuroradiol*. (2020) 41:1777–85. doi: 10.3174/ajnr.A6739

25. Shapiro M, Raz E, Nossek E, Srivatanakul K, Walker M, Mir O, et al. Dural venous system: angiographic technique and correlation with *ex vivo* investigations. *J NeuroIntervent Surg*. (2022) 14:196–201. doi: 10.1136/neurintsurg-2020-017237

26. Catapano JS, Ducruet AF, Srinivasan VM, Rumalla K, Nguyen CL, Rutledge C, et al. Radiographic clearance of chronic subdural hematomas after middle meningeal artery embolization. *J NeuroIntervent Surg*. (2022) 14:1279–83. doi: 10.1136/neurintsurg-2021-018073

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 20 December 2023
DOI 10.3389/fneur.2023.1308991

OPEN ACCESS

EDITED BY
Milan Lepić,
Military Medical Academy, Serbia

REVIEWED BY
Hiroshi Yatsushige,
National Hospital Organization Disaster Medical Center, Japan
Zhouping Tang,
Huazhong University of Science and Technology, China

*CORRESPONDENCE
Kenji Yagi
✉ kenji-yagi@mail.goo.ne.jp

RECEIVED 07 October 2023
ACCEPTED 05 December 2023
PUBLISHED 20 December 2023

CITATION
Yagi K, Matsubara M, Kanda E, Minami Y and Hishikawa T (2023) Effect of decreased platelets on postoperative recurrence of chronic subdural hematoma.
Front. Neurol. 14:1308991.
doi: 10.3389/fneur.2023.1308991

Effect of decreased platelets on postoperative recurrence of chronic subdural hematoma

Kenji Yagi[1]*, Maoki Matsubara[1], Eiichiro Kanda[2], Yukari Minami[1] and Tomohito Hishikawa[1]

[1]Department of Neurosurgery, Kawasaki Medical School, Kurashiki, Okayama, Japan, [2]Department of Medical Science, Kawasaki Medical School, Kurashiki, Okayama, Japan

Introduction: Chronic subdural hematoma (CSDH) is commonly treated using simple burr hole surgery. However, postoperative recurrence occurs at a relatively high rate of 10–20%. A decrease in platelet count (PC) may be associated with recurrence via a hemostasis disorder; however, this association has not been well-studied. Therefore, this study aimed to investigate the association between PC and postoperative CSDH recurrence.

Methods: We retrospectively reviewed the data for CSDHs in 488 cerebral hemispheres of 431 patients who underwent burr hole surgery at our institution between January 2013 and December 2022. The association between preoperative PC and postoperative CSDH recurrence was investigated. We used the first quartile of PC, PC < $170 \times 10^3/\mu L$ to define a threshold for decreased PC.

Results: In total, 459 cerebral hemispheres with CSDHs in 405 patients were followed up postoperatively for at least 3 months or until CSDH disappeared. CSDH recurred in 39 (8.5%) cerebral hemispheres. The recurrence rate was gradually increased in parallel with a decreasing PC. Among 109 CSDHs with a decreased PC (<$170 \times 10^3/\mu L$), 15 (13.8%) recurred, whereas only 24 (6.9%) of 350 CSDHs without a decreased PC recurred ($p = 0.03$). In univariable logistic analysis, eosinophil-rich blood (≥100/μL eosinophils in peripheral blood) and a decreased PC were significant risk factors. Multivariable analysis showed that eosinophil-rich blood (adjusted odds ratio, 2.51; 95% confidence interval, 1.26–4.99; $p = 0.009$) and a decreased PC (adjusted odds ratio, 2.15; 95% confidence interval, 1.07–4.35; $p = 0.03$) were independent risk factors for recurrence.

Conclusion: Our study showed that a decrease in PC was associated with postoperative CSDH recurrence. Patients with CSDH and a decreased PC require careful postoperative follow-up.

KEYWORDS

chronic subdural hematoma, postoperative recurrence, eosinophil, platelet, burr hole surgery

1 Introduction

Chronic subdural hematoma (CSDH) is a common disease that is being treated surgically more frequently worldwide (1). For symptomatic CSDH, a simple surgery such as burr hole irrigation or drainage of CSDH is widely performed as a standard treatment. However, postoperative recurrence occurs at a relatively high rate of 10–20%; subsequently, these patients require additional surgery (2).

The progression and recurrence of CSDH have recently been considered to be associated with recurrent hemorrhage, fibrinolysis, inflammation, and angiogenesis (3, 4), Various risk factors have been reported, which include old age, male sex, diabetes mellitus, anticoagulant therapy, eosinophil-rich blood, and blood type A (5–7). However, the risk factors for postoperative recurrence of CSDH have not been fully established.

Platelets play a pivotal role in hemostasis, and a decrease in platelet count (PC) leads to a bleeding tendency (8). The hemostasis disorder may facilitate the progression and recurrence of CSDH via recurrent hemorrhage. However, the effect of PCs on postoperative CSDH recurrence has not been well-studied and remains unclear. Moreover, the number of platelets required to suppress postoperative recurrence is unknown.

This retrospective, exploratory study investigated the association between a decreased PC and postoperative CSDH recurrence.

2 Materials and methods

2.1 Study design

This study aimed to evaluate the effect of a decreased PC on postoperative recurrence of traumatic or spontaneous CSDH after the first burr hole surgery. Thus, we reviewed 488 cerebral hemispheres with CSDHs in 431 patients who were treated with burr hole surgery at our institution between January 2013 and December 2022. CSDH was diagnosed using computed tomography or magnetic resonance imaging. Four CSDHs in four patients who underwent middle meningeal artery embolization in combination with burr hole surgery were excluded. Peripheral blood was obtained at admission for examination, including preoperative platelet and eosinophil counts {median [interquartile range (IQR)], 0 day (0–1 day)}. The distribution of PCs is shown in Figure 1. Its median [IQR] was 208 [172–250] (10^3/μL) and the mean ± standard deviation was $214 \pm 70 \times 10^3$/μL. However, these preoperative blood examinations were not performed in the seven CSDH surgeries in six patients; thus, they were excluded from the study. The remaining 477 CSDHs in 421 patients were included in the study (Supplementary Figure S1).

2.2 Definition of clinical characteristics

Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or the current use of antihypertensive drugs. Diabetes mellitus was defined as a glycosylated hemoglobin A1C level of >6.5% or treatment with hypoglycemic medications. The use of antiplatelet or anticoagulant drugs was recorded. An activated partial thromboplastin time of ≥40 s or a prothrombin time with an international normalized ratio of >1.4 was defined as coagulopathy. An eosinophil count of ≥100/μL in the peripheral blood was defined as "eosinophil-rich" (7). A PC of $<100 \times 10^3$/μL was defined as thrombocytopenia, whereas PC of $<170 \times 10^3$/μL was defined as a "decreased PC," based on the first quartile value of PCs. The preoperative CSDH volume was calculated according to the XYZ/2 method (7, 9). When the CSDHs on both sides were operated on simultaneously or the CSDH in one hemisphere was operated on within 7 days before or after surgery on the other side, the CSDH in each hemisphere was recorded as having contralateral surgery. The baseline and clinical characteristics of patients are presented in Table 1.

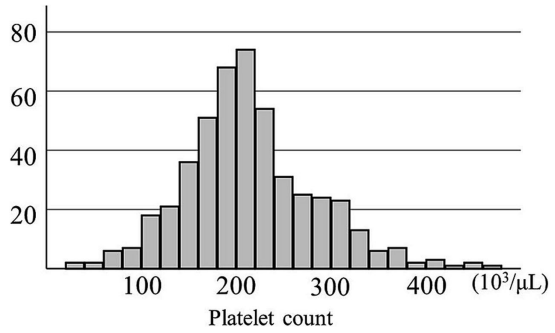


FIGURE 1
Distribution of preoperative platelet counts in 477 chronic subdural hematomas.

TABLE 1 Baseline and radiographical characteristics of 477 chronic subdural hematomas in 421 patients.

	Total (*n* = 477)
Mean age, years	78.8 ± 9.3
Male sex	327 (68.6%)
Hypertension	201 (42.1%)
Diabetes mellitus	112 (23.5%)
Use of antiplatelet drugs	67 (14.0%)
Use of anticoagulant drugs	65 (13.6%)
Coagulopathy	43 (9.0%)
Eosinophil-rich	197 (41.3%)
Platelet transfusion	5 (1.0%)
Hematoma volume (mL)	124.2 ± 42.4
Contralateral surgery	86 (18.0%)

Data are presented as the mean ± standard deviation or number (%).

2.3 Surgical procedure and perioperative management

Surgery with burr hole irrigation was performed under local anesthesia. CSDH was evacuated and the hematoma cavity irrigated with normal saline or artificial cerebrospinal fluid (Artcereb irrigation and perfusion solution for cerebrospinal surgery, Otsuka Pharmaceutical Factory Inc.) (10). A drainage tube was typically placed in the hematoma cavity and removed within 2 days after surgery. However, in three CSDH cases (0.6%), a drainage tube could not be placed because of the narrowing of the hematoma cavity after the evacuation of the CSDH. Because of the severely decreased PC, platelet transfusion was performed before four surgeries for five CSDHs, according to the decision of the attending physicians. To avoid postoperative thromboembolic complications (11, 12), antithrombotic therapy at presentation was continued or discontinued for only few days postoperatively (it was reinitiated soon after confirming no postoperative acute bleeding).

2.4 Postoperative CSDH recurrence and acute bleeding

Postoperative recurrence of CSDH was defined as symptomatic (causing severe headache, dementia, impaired consciousness, or neurological deficits such as gait disturbance or weakness in the extremities) ipsilateral enlargement of the CSDH, indicating the need for repeated surgery between 7 days and 3 months postoperatively. Postoperative early subdural hemorrhage before postoperative day 6 was considered a surgical complication but not a recurrence. On one hemisphere with CSDH, an acute subdural hematoma was found the day after the burr hole surgery; it was completely evacuated and removed via the same burr hole. Because the hematoma was not associated with a bleeding tendency, such as thrombocytopenia in PC, use of antithrombotic drugs, or coagulopathy, this acute hemorrhage was not considered as a postoperative CSDH recurrence. Patients with no recurrence were followed up postoperatively for at least 3 months or until resolution, as indicated by the disappearance of CSDH on computed tomography. Postoperative recurrence within 3 months was recorded in each hemisphere with CSDH.

2.5 Statistical analyses

Statistical analyses were conducted using SPSS version 28 (IBM Corp., Tokyo, Japan). Categorical variables are expressed as numbers (percentages) and numerical data as mean ± standard deviation or median (IQR). Fisher's exact test and Student's *t*-test were performed for intergroup comparisons. A receiver operating characteristic (ROC) curve was created from the PC for postoperative CSDH recurrence, and area under the curve and 95% confidence interval (CI) were analyzed. Logistic regression analysis was performed to investigate the risk factors for CSDH recurrence. Odds ratios (OR) were calculated using univariable and multivariable models. Variables with a p value of <0.10 in univariable analyses were applied for multivariable analysis. A decrease in PC was assessed as a continuous variable and categorical variable in models 1 and 2, respectively. Statistical significance was set at a p value of <0.05.

3 Results

3.1 Postoperative recurrence

In total, 459 cerebral hemispheres with CSDHs in 405 patients were followed up. CSDHs recurred in 39 (8.5%) cerebral hemispheres; 18 CSDHs in 16 patients were not followed up after surgery and were not included in the following analyses (Supplementary Figure S1).

3.2 Association of PCs and postoperative recurrence

Platelet count was significantly lower in 39 CSDHs with recurrence than in 420 CDSHs without recurrence ($189 \pm 69 \times 10^3/\mu L$ vs. $216 \pm 69 \times 10^3/\mu L$, $p = 0.02$). The recurrence rate was gradually increased in parallel with a decrease in the PC (Figure 2).

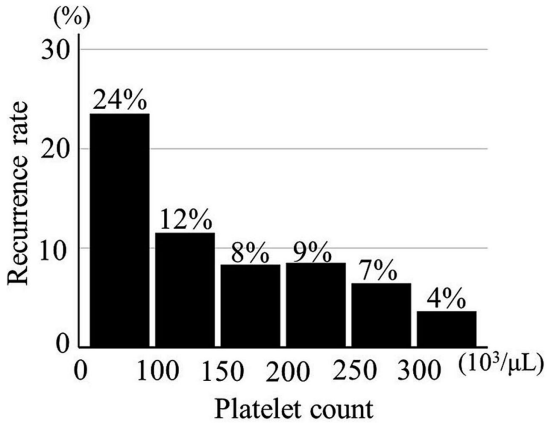


FIGURE 2
Relationship between recurrence of chronic subdural hematoma and platelet count ($n = 459$).

An ROC curve of PCs for the CSDH recurrence was created as shown in Supplementary Figure S2. According to the distribution of PC, its first quartile was $170 \times 10^3/\mu L$, based on which the threshold for the decreased PC ($<170 \times 10^3/\mu L$) was defined. Thereafter, the value of decreased PC was confirmed to predict the CSDH recurrence well by ROC analysis. Of 109 CSDHs with a decreased PC, 15 (13.8%) recurred; only 24 (6.9%) of 350 CSDHs without a decreased PC recurred ($p = 0.03$). The sensitivity and specificity were 38.5 and 77.6%.

3.3 Logistic analyses for the CSDH recurrence

Logistic analyses of postoperative recurrence were performed in 459 cerebral hemispheres with CSDHs (Table 2). In the univariable model, a decrease in the PC significantly increased the risk of recurrence; a decreased PC ($<170 \times 10^3/\mu L$) was a significant risk factor. In addition, eosinophil-rich blood was associated with the CSDH recurrence. Next, multivariable analysis was performed with the variables with a value of $p < 0.10$ in the univariable analysis. When PC was assessed as a continuous variable in model 1, a decrease in PC was associated with CSDH recurrence in model 1 (per $5 \times 10^3/\mu L$ decrease: OR, 1.36; 95% CI, 1.05–1.76; $p = 0.02$) When PC was assessed as a categorical variable in model 2, decreased PC was an independent risk factor for the recurrence (adjusted OR, 2.15; 95% CI, 1.07–4.35; $p = 0.03$). In addition, eosinophil-rich blood was an independent risk factor in both model 1 (adjusted OR, 2.63; 95% CI, 1.31–5.27, $p = 0.007$) and model 2 (adjusted OR, 2.51; 95% CI, 1.26–4.99, $p = 0.009$).

3.4 Relationship between PC and eosinophil-rich blood

The PCs in the groups with (197 CSDHs) and without eosinophil-rich blood (280 CSDHs) were compared to evaluate the relationship between PCs and eosinophil-rich blood. No significant difference was observed between the groups (non-eosinophil-rich vs. eosinophil-rich: $211 \pm 76 \times 10^3/\mu L$ vs. $217 \pm 60 \times 10^3/\mu L$; $p = 0.38$).

TABLE 2 Univariable and multivariable logistic regression analyses for the chronic subdural hematoma recurrence in 459 cerebral hemispheres with CSDHs.

Factor	Univariable			Multivariable model 1			Multivariable model 2		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (per 10-year increase)	0.85	0.61–1.19	0.36						
Male sex	2.21	0.95–5.14	0.07	1.64	0.68–3.94	0.27	1.69	0.70–4.04	0.24
Hypertension	0.66	0.33–1.32	0.24						
Diabetes mellitus	1.50	0.73–3.07	0.27						
Antiplatelet drugs	1.52	0.64–3.61	0.35						
Anticoagulant drugs	1.91	0.83–4.39	0.13						
Coagulopathy	1.66	0.60–4.55	0.33						
Eosinophil-rich	2.40	1.22–4.71	0.01*	2.63	1.31–5.27	0.007*	2.51	1.26–4.99	0.009*
Platelet count (per 5×10^3/μL decrease)	1.36	1.05–1.76	0.02*	1.39	1.06–1.84	0.02*	–	–	–
Decreased platelet (<170×10^3/μL)	2.17	1.09–4.30	0.03*	–	–	–	2.15	1.07–4.35	0.03*
Platelet transfusion	2.74	0.30–25.11	0.38						
Hematoma vol (10 mL per increase)	1.07	1.00–1.16	0.06	1.06	0.98–1.15	0.15	1.06	0.98–1.15	0.16
Contralateral surgery	0.82	0.33–2.03	0.67						

OR, Odds ratio; CI, Confidence interval. *Indicates statistically significant ($p<0.05$). Decreases in the PC are assessed as continuous and categorical variables in model-1 and -2, respectively.

3.5 Thrombocytopenia and platelet transfusion

Regarding 16 surgery for 17 CSDHs with coexisting thrombocytopenia, platelet transfusions were performed before four surgeries for five CSDHs to suppress perioperative acute bleedings. In contrast, platelet transfusion was not administered for the remaining 12 surgeries for 12 CSDHs. PCs were significantly lower in the surgery with platelet transfusion than in that without transfusion ($42\pm18\times10^3$/μL vs. $79\pm13\times10^3$/μL; $p=0.001$).

In three of the four surgeries with platelet transfusion, PC did not increase over 100×10^3/μL after platelet transfusion. In only one CSDH, PC increased over 100×10^3/μL after the platelet transfusion. The effect of platelet transfusion was not sustained for a long time; on 5 or 6 days after surgery, the PC was not significantly different from those before the platelet transfusion ($52\pm22\times10^3$/μL vs. $42\pm18\times10^3$/μL; $p=0.52$).

One (20%) of the five CSDHs with platelet transfusion and 4 (33.3%) of the 12 CSDHs without platelet transfusion recurred, respectively. No significant differences were found between them ($p>0.99$).

4 Discussion

Our study focused on the effect of PC values on postoperative recurrence of CSDH after burr hole surgery. Decrease in PC was shown to affect the postoperative recurrence of CSDH, and that risk was gradually increased in parallel with decrease in the PC. CSDH with preoperatively decreased PC (<170×10^3/μL) recurred with double the frequency of those without a deceased PC (13.8 vs. 6.9%).

Continuous bleeding and exudation play pivotal roles in CSDH formation and progression. Ito et al. (11) reported a new hemorrhage accounting for 6.7% (range, 0.2–28.6%) of the hematoma content in 6–24 h. Bleeding is considered to be mediated by inflammation, angiogenesis, and fibrinolysis (5, 7, 12, 13). Numerous newly formed capillary vessels in the outer membrane of the CSDH tear easily and are permeable under focal inflammation, which can result in re-bleeding and exudation. Hemostatic disorders may facilitate CSDH progression and recurrence.

Platelets play a pivotal role in hemostasis; poor PC results in a bleeding tendency, and thrombocytopenia is associated with a high risk of intracranial hemorrhage (14). Therefore, a sufficient PC may be needed to prevent recurrence. In contrast, platelets have the potential to facilitate inflammation and may drive the regrowth of CSDH (13, 15). In patients with cancer, platelet transfusion was reported to increase perihematomal edema after intracerebral hemorrhage (15). Although platelets may have a two-sided effect on the postoperative recurrence of CSDH, the hemostatic effect of platelets may be more closely associated with the recurrence of CSDH, according to our findings. In the present study, antithrombotic therapy was not associated with the CSDH recurrence. Hemostatic disorder by decrease in PC may influence the CSDH stronger than inhibited hemostasis by antithrombotic agent. However, it may be attributed to mechanisms other than hemostatic disorder; in addition, deceased PC may reflect an unidentified factor. Further study is needed to elucidate the mechanisms.

A PC of $150–450\times10^3$/μL is considered normal in adults (16). It can be affected by various conditions, including infection, cancer, leukemia, myelosuppression, liver cirrhosis, and malignancy (14–16). A PC > 100×10^3/μL is believed to be needed for safe cranial surgery; even in emergency surgeries, a PC should be >80×10^3/μL (8, 17). In the recurrence of CSDH, the effect of a decreased PC has not been well investigated and remains controversial (7, 18–21). The present study focused on PCs and CSDH recurrence and showed that CSDH recurrence was increased with a decrease in the PC. Moreover, even if a PC was within the normal range, CSDH with a greater PC recurred less frequently than CSDH with a lower PC. To facilitate the use of PCs in clinical settings, a PC value <170×10^3/μL was defined as a "decreased PC" that might effectively predict recurrence. Threshold for decreased PC might be higher considering normal PC value ($150–450\times10^3$/μL) and other clinical conditions: in patients with cancer PC <60×10^3/μL is associated with bleeding; in those with

aplastic anemia, spontaneous fecal blood loss could occur at PC $<10\times10^3/\mu L$ and remarkably increased at PC $<5\times10^3/\mu L$ (22). However, bleeding risks because of a decrease in PC depend on the underlying disease. In anemic women with term singleton pregnancies, increased postpartum hemorrhage at PC $<150\times10^3/\mu L$ was reported, where the threshold of PC was close to the one defined in the present study (23). During CSDH progression, continuous bleeding and exudation occur, which might be different from acute bleedings, resulting in higher threshold for decreased PC.

In an aging society, the use of antithrombotic agents increases (24). In addition to hemostasis disorder caused by a decreased PC, antithrombotic agents inhibit hemostasis and may theoretically be a risk factor for CSDH recurrence. In meta-analyses by Wang et al. and Poon et al., the use of antiplatelet and anticoagulant drugs increased the risk of recurrence (25, 26). In a meta-analysis review of randomized trials, Bakheet et al. (27) showed that the incidence of subdural hematoma was greater in patients using dual antiplatelet drugs than in those using aspirin alone. In contrast, in a retrospective study with a large sample size, Yu et al. (28) reported that antiplatelet therapy did not affect the recurrence rate of CSDH. In a systematic review by Nathan et al. (6), the use of anticoagulant medication was concluded to be associated with an increased re-bleeding risk with CSDH, but antiplatelet medication was not. In a multicenter, prospective cohort study with a large sample size, Poon et al. showed that neither antiplatelet nor anticoagulant drug use was associated with CSDH recurrence. In the present study, neither antiplatelet nor anticoagulant drug use was associated with CSDH recurrence. The effect of these drugs on CSDH recurrence remains controversial; it may be smaller than that of a decreased PC based on our findings. Further studies are needed to elucidate this issue.

The present study showed that eosinophil-rich blood was another independent risk factor for postoperative CSDH recurrence, as we have previously reported (7). In contrast, PCs were not associated with eosinophil-rich blood. A decreased PC and increased eosinophil count may relate to different mechanisms of CSDH recurrence, including hemostasis disorders and inflammation. We suggest that preoperative examination of platelet and eosinophil counts is important for predicting postoperative recurrence by assessing both hemostasis disorders and inflammation.

This study had some limitations. First, this study was retrospectively conducted at a single institution. Second, not all patients were included or evaluated. However, most patients were included in the analysis, and the selection bias might be small. Third, PCs were assessed at admission; however, changes were not evaluated during the postoperative course. However, the PC at admission might be affected by a patient's general and homeostatic condition and effectively predict CSDH recurrence. Fourth, the effect of platelet transfusion on recurrence was not evaluated because of the small number of patients. However, the effect of platelet transfusion on the CSDH is considered limited because the increase in the PC from platelet transfusion is minimal and not sustained for a long period.

5 Conclusion

Our study showed that a decrease in the PC affected the postoperative recurrence of CSDH, and the risk was gradually increased in parallel with a decrease in the PC. CSDH with a preoperatively decreased PC ($<170\times10^3/\mu L$) recurred with double the frequency of those without a decreased PC. Therefore, CSDH patients with decreased PCs might require careful follow-up.

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 humans were approved by Institutional review board of Kawasaki Medical School. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin.

Author contributions

KY: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. MM: Data curation, Writing – review & editing. EK: Conceptualization, Writing – original draft. YM: Data curation, Writing – review & editing. TH: Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was partly supported by a research grant from Kawasaki Medical School.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1308991/full#supplementary-material

References

1. Uno M. Chronic subdural hematoma-evolution of etiology and surgical treatment. *Neurol Med Chir (Tokyo)*. (2023) 63:1–8. doi: 10.2176/jns-nmc.2022-0207

2. 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

3. Holl DC, Fakhry R, Dirven CMF, Te Braake FAL, Begashaw OK, Moudrous W, et al. Surgery after primary dexamethasone treatment for patients with chronic subdural hematoma—a retrospective study. *World Neurosurg*. (2022) 162:e358–68. doi: 10.1016/j.wneu.2022.03.014

4. Idowu OE, Oyeleke SO, Vitowanu JM. Impact of inflammatory cell ratio, biomarkers, activated partial thromboplastin time and prothrombin time on chronic subdural haematoma severity and outcome. *Eur J Trauma Emerg Surg*. (2022) 48:1085–92. doi: 10.1007/s00068-021-01665-5

5. Hirai S, Yagi K, Hara K, Kanda E, Matsubara S, Uno M. Postoperative recurrence of chronic subdural hematoma is more frequent in patients with blood type a. *J Neurosurg*. (2021) 135:1203–7. doi: 10.3171/2020.7.JNS202330

6. Nathan S, Goodarzi Z, Jette N, Gallagher C, Holroyd-Leduc J. Anticoagulant and antiplatelet use in seniors with chronic subdural hematoma: systematic review. *Neurology*. (2017) 88:1889–93. doi: 10.1212/WNL.0000000000003918

7. Matsubara M, Yagi K, Minami Y, Kanda E, Sunada Y, Tao Y, et al. Preoperative elevated eosinophils in peripheral blood for prediction of postoperative recurrence of chronic subdural hematoma. *J Neurosurg*. (2023) 12:1–6. doi: 10.3171/2022.12.JNS222432

8. Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Italian Society of Transfusion Medicine and Immunohaematology Working Party. Recommendations for the transfusion of plasma and platelets. *Blood Transfus*. (2009) 7:132–50. doi: 10.2450/2009.0005-09

9. Sucu HK, Gokmen M, Gelal F. The value of XYZ/2 technique compared with computer-assisted volumetric analysis to estimate the volume of chronic subdural hematoma. *Stroke*. (2005) 36:998–1000. doi: 10.1161/01.STR.0000162714.46038.0f

10. Toi H, Fujii Y, Iwama T, Kinouchi H, Nakase H, Nozaki K, et al. Determining if cerebrospinal fluid prevents recurrence of chronic subdural hematoma: a multi-center prospective randomized clinical trial. *J Neurotrauma*. (2019) 36:559–64. doi: 10.1089/neu.2018.5821

11. Ito H, Yamamoto S, Saito K, Ikeda K, Hisada K. Quantitative estimation of hemorrhage in chronic subdural hematoma using the 51Cr erythrocyte labeling method. *J Neurosurg*. (1987) 66:862–4. doi: 10.3171/jns.1987.66.6.0862

12. Fan Y, Wu D, Zhang X, Jiang W, Nie M, Liu X, et al. The inflammatory cellular feature in the peripheral blood of chronic subdural hematoma patients. *J Clin Lab Anal*. (2022) 36:e24706. doi: 10.1002/jcla.24706

13. Guresir A, Coch C, Heine A, Mass E, Lampmann T, Vatter H, et al. Red blood cell distribution width to platelet count ratio facilitates preoperative prediction of recurrence in surgically treated chronic subdural hematoma. *Front Neurol*. (2022) 13:884231. doi: 10.3389/fneur.2022.884231

14. Cornelissen LL, Kreuger AL, Caram-Deelder C, Middelburg RA, JLH K, Von Dem Borne PA, et al. Thrombocytopenia and the effect of platelet transfusions on the occurrence of intracranial hemorrhage in patients with acute leukemia—a nested case-control study. *Ann Hematol*. (2021) 100:261–71. doi: 10.1007/s00277-020-04298-7

15. Gusdon AM, Nyquist PA, Torres-Lopez VM, Leasure AC, Falcone GJ, Sheth KN, et al. Perihematomal edema after intracerebral hemorrhage in patients with active malignancy. *Stroke*. (2020) 51:129–36. doi: 10.1161/STROKEAHA.119.027085

16. Giles C. The platelet count and mean platelet volume. *Br J Haematol*. (1981) 48:31–7. doi: 10.1111/j.1365-2141.1981.00031.x

17. Abdelfatah M. Management of chronic subdural hematoma in patients with intractable thrombocytopenia. *Turk Neurosurg*. (2018) 28:400–4. doi: 10.5137/1019-5149.JTN.18825-16.1

18. Chen S, Shao L, Ma L. Peripheral blood eosinophil and classification of residual hematoma help predict the recurrence of chronic subdural hematoma after initial surgery. *Front Surg*. (2022) 9:970468. doi: 10.3389/fsurg.2022.970468

19. Tahsim-Oglou Y, Beseoglu K, Hanggi D, Stummer W, Steiger HJ. Factors predicting recurrence of chronic subdural haematoma: the influence of intraoperative irrigation and low-molecular-weight heparin thromboprophylaxis. *Acta Neurochir*. (2012) 154:1063–8. doi: 10.1007/s00701-012-1334-0

20. Maher Hulou M, McLouth CJ, Hayden CS, Sheldrake AK, Parekh M, Dillen WL, et al. Predictors of re-operation in the setting of non-acute subdural hematomas: a 12-year single center retrospective study. *J Clin Neurosci*. (2020) 81:334–9. doi: 10.1016/j.jocn.2020.09.052

21. 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*. (2019) 10:1401. doi: 10.3389/fneur.2019.01401

22. Vinholt PJ. The role of platelets in bleeding in patients with thrombocytopenia and hematological disease. *Clin Chem Lab Med*. (2019) 57:1808–17. doi: 10.1515/cclm-2019-0380

23. Kazma J, Ebner M, Whitley J, Ahmadzia HK. Impact of anemia and thrombocytopenia on postpartum hemorrhage risk among women with term singleton pregnancy. *J Thromb Thrombolysis*. (2023) 55:571–5. doi: 10.1007/s11239-022-02756-9

24. Chon KH, Lee JM, Koh EJ, Choi HY. Independent predictors for recurrence of chronic subdural hematoma. *Acta Neurochir*. (2012) 154:1541–8. doi: 10.1007/s00701-012-1399-9

25. 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 (Baltimore)*. (2019) 98:e13972. doi: 10.1097/MD.0000000000013972

26. Poon MTC, Al-Shahi SR. Association between antithrombotic drug use before chronic subdural haematoma and outcome after drainage: a systematic review and meta-analysis. *Neurosurg Rev*. (2018) 41:439–45. doi: 10.1007/s10143-017-0860-x

27. Bakheet MF, Pearce LA, Hart RG. Effect of addition of clopidogrel to aspirin on subdural hematoma: meta-analysis of randomized clinical trials. *Int J Stroke*. (2015) 10:501–5. doi: 10.1111/ijs.12419

28. Yu X, Wu L, Ou Y, Xu L, Guo X, Yang C, et al. Clinical characteristics and outcomes of chronic subdural hematoma in patients with a history of antiplatelet therapy. *Clin Neurol Neurosurg*. (2021) 208:106817. doi: 10.1016/j.clineuro.2021.106817

frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 20 February 2024
DOI 10.3389/fneur.2024.1358237

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Adria Arboix,
Sacred Heart University Hospital, Spain
Matteo Foschi,
Azienda Unità Sanitaria Locale (AUSL) della Romagna, Italy

*CORRESPONDENCE
Daniel Strahnen
✉ daniel.strahnen@uniklinik-freiburg.de

RECEIVED 19 December 2023
ACCEPTED 06 February 2024
PUBLISHED 20 February 2024

CITATION
Strahnen D, Stathi A, Beck J, Roelz R and Vasilikos I (2024) Case report: Concurrent low-volume subdural hematoma and ipsilateral ischemic stroke presenting as capsular warning syndrome: a complex case with anticoagulation dilemma and dual pathology.
Front. Neurol. 15:1358237.
doi: 10.3389/fneur.2024.1358237

Case report: Concurrent low-volume subdural hematoma and ipsilateral ischemic stroke presenting as capsular warning syndrome: a complex case with anticoagulation dilemma and dual pathology

Daniel Strahnen*, Angeliki Stathi, Jürgen Beck, Roland Roelz and Ioannis Vasilikos

Department of Neurosurgery, University Medical Center Freiburg, Freiburg, Germany

Background: The simultaneous emergence of low-volume subdural hematoma and ipsilateral ischemic stroke in an atrial fibrillation patient who is under anticoagulation therapy is a rare and intricate clinical case. This report accentuates the diagnostic and treatment complexities associated with these consecutive neurological conditions.

Case presentation: An 83 years-old male patient initially presented with acute dyspnea, raising the suspicion of pulmonary embolism. After exclusion of pulmonary embolism through CT angiography, the patient experienced a sudden onset of left-sided hemiparesis without prior history of head trauma but with chronic intake of apixaban due to atrial fibrillation. Subsequent cranial CT tomography revealed a small right parietal subdural hematoma. After reversal of the anticoagulation therapy, surgical evacuation of the subdural hematoma was successfully performed. However, in the postoperative period, the patient developed new neurological symptoms that could not be explained by the reduced size of the subdural hematoma on a follow-up CT scan. Cranial MRI revealed the coexistence of acute ischemic stroke in the right corona radiata. The recent surgical procedure precluded guideline-recommended stroke treatment.

Discussion: This case underscores the complexities of diagnosing and treating concomitant small volume subdural hematoma and ischemic stroke, especially if the latter occurs in the corona radiata resulting in fluctuating symptoms known as "capsular warning syndrome." Reversal and secondary discontinuation of anticoagulant therapy for surgical intervention highlight the inherent risk of thrombotic events in anticoagulated patients. The development of tailored treatment strategies requires a multidisciplinary approach, and further research and guidelines are required in similar complex scenarios.

Conclusion: The presence of both a small subdural hematoma and an ipsilateral ischemic stroke presenting as capsular warning syndrome in an anticoagulated patient highlights the intricacy of their care. This case calls for a comprehensive and collaborative strategy to address complicated clinical scenarios.

KEYWORDS

capsular warning syndrome, subdural hematoma (SDH), ischemic stroke, antithrombotic treatment, computer tomography (CT), magnetic resonance imaging (MRI)

Introduction

Subdural hematoma and ischemic stroke are separate neurological emergencies, each with distinct diagnostic criteria and therapeutic considerations. The simultaneous occurrence of both conditions in a single patient, although infrequent, poses a significant clinical complexity. The potential risk for subsequent stroke is introduced as antithrombotic medications are often discontinued when surgical evacuation of the subdural hematoma is indicated.

Subdural hematomas stem from blood accumulation between the dura mater and arachnoid membrane, which vary in acuity from acute to chronic (1). Diagnosis of subdural hematomas relies on comprehensive neurological assessment and neuroimaging studies, including computed tomography (CT) or magnetic resonance imaging (MRI), to determine the size, location, and chronicity (2). Hematoma management is dictated by the characteristics of the hematoma and its clinical presentation. Smaller asymptomatic hematomas may be monitored conservatively, while larger or symptomatic hematomas often require surgical evacuation. Different methods for surgically evacuating subdural hematomas are available; however, there is no conclusive evidence indicating the superiority of a specific approach (3). Unfortunately, surgical intervention frequently mandates the discontinuation of antithrombotic medications, which poses a clinical dilemma and may increase the risk of subsequent thrombotic events (4).

Rapid and accurate diagnosis is imperative for ischemic stroke, which arises from the occlusion of the cerebral arteries. Diagnostic procedures involve clinical assessment and imaging tests like CT or MRI, as well as advanced methods such as CT angiography or magnetic resonance angiography to identify vascular occlusions or stenoses (5). The management of ischemic stroke has significantly progressed with the essential administration of intravenous thrombolysis and endovascular thrombectomy when appropriate. The goal of these interventions is to re-establish blood flow to the affected brain tissue, but they may entail specific risks and require a cautious approach, particularly in patients with prior utilization of antithrombotic medication (6). Capsular warning syndrome (CWS) is a unique entity characterized by recurrent transient ischemic attacks (TIAs) that typically present with motor or sensory symptoms, heralding a significant risk of imminent stroke, often within the initial days following the first TIA episode. Considering the critical nature of CWS, it is essential to underscore the urgency for prompt identification and rapid intervention in cases of recurrent TIAs. Timely antithrombotic treatment plays a pivotal role in clinical practice, given the substantial risk of recurrent stroke in the short term following a TIA episode, as an immediate and robust response was shown to be necessary to prevent the progression to irreversible cerebrovascular events by swift diagnostic and therapeutic measures (7, 8). Despite the urgency associated with CWS, there remains a notable gap in the literature regarding the definitive effectiveness of various treatment strategies, such as single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), intravenous thrombolysis (IVT), and anticoagulants, in preventing progression to irreversible stroke. This uncertainty stems from the fact that current management guidelines are largely based on observational studies rather than randomized controlled trials (RCTs), rendering treatment approaches speculative to a certain extent (7, 8). Therefore, our case report not only contributes to the body of knowledge on the rare co-occurrence of CWS and SDH and its complex clinical management but also serves as a critical reminder of the urgency required in the clinical management of TIAs. By highlighting these aspects, especially considering the need to halt antithrombotic medications during surgical evacuation of the hematoma, we aimed to reinforce the importance of early recognition and intervention in such cases, which could be pivotal in mitigating the risk of adverse outcomes in patients presenting with recurrent TIAs.

This study examines the diagnostic complexity and treatment choices encountered by healthcare providers when handling this distinct clinical situation.

Case description

An 83 years-old male patient with a medical history of atrial fibrillation was undergoing apixaban anticoagulation therapy. The only known preexisting conditions were alcohol abuse and chronic folic acid deficiency. He was admitted to an external hospital for acute dyspnea and was diagnosed with suspected pulmonary embolism. However, computed tomography (CT) angiography of the thorax negated the diagnosis of pulmonary embolism as the cause of the patient's dyspnea. The plasma clotting was normal during the initial assessment.

Further examination was necessary after the patient experienced sudden left-sided hemiparesis that fluctuated in severity following elimination of a pulmonary embolism. There was no sign of a traumatic event at any point during clinical presentation. A non-contrast cranial CT scan was conducted, which indicated a low-volume subdural hematoma localized to the right parietal hemisphere (Figure 1A). Importantly, no evidence of other intracranial pathologies was detected in the initial CT scan. In addition, the patient reported no relevant headaches, nausea, or vomiting.

Owing to the severity of the patient's neurological findings, he was transferred to our tertiary referral hospital for specialized care. A twist-drill craniostomy was performed, and a subdural drain was inserted parietally in the right hemisphere due to the size of the subdural hematoma and its neurological symptoms. In preparation for the surgical procedure, 3,500 international units of prothrombin complex concentrate were administered to safely reverse the effects of anticoagulation therapy.

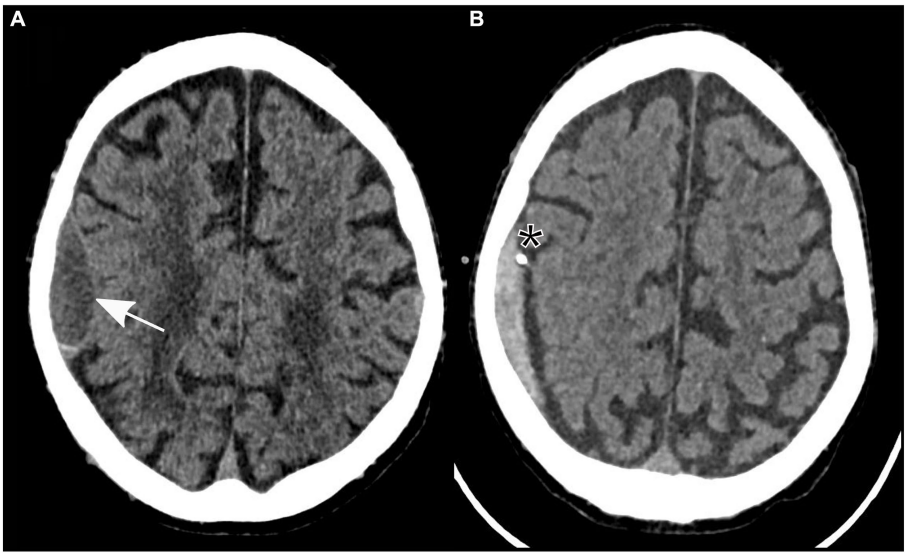


FIGURE 1
Non-contrast axial computed tomography showing a subdural hematoma in the parietal lobe (identified by an arrow) prior to **(A)** and following insertion of a subdural drain (asterisk) through a twist-drill craniostomy **(B)**.

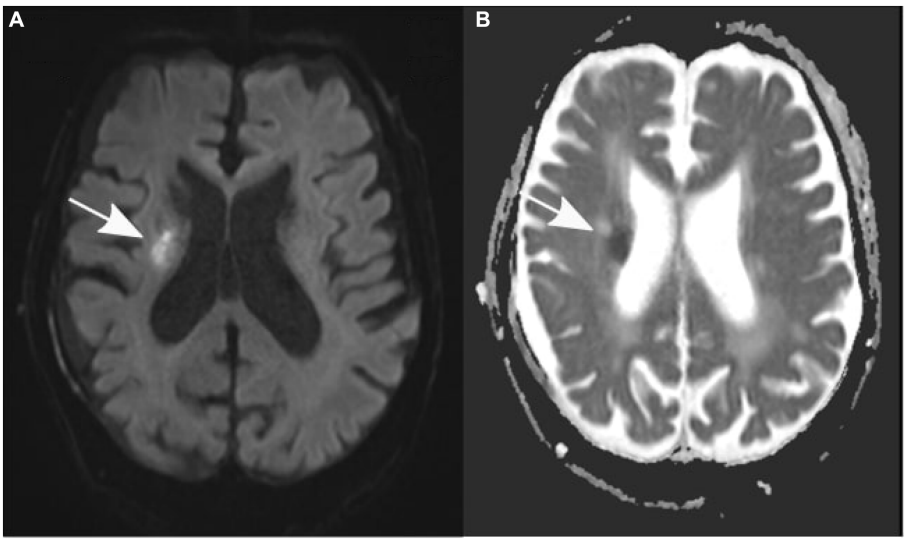


FIGURE 2
Axial diffusion-weighted magnetic resonance images **(A)** show an elevation in signal, while apparent diffusion coefficient values **(B)** are decreased in the right corona radiata (indicated by an arrow).

After the patient underwent successful surgery, he was transferred to the standard ward for postoperative monitoring. Nevertheless, the following morning, the patient displayed new neurological symptoms, such as dysarthria and exacerbated left-sided hemiparesis. A subsequent cranial CT scan verified the correct positioning of the subdural drain and revealed a decrease in the size of the subdural hematoma (Figure 1B). Sudden onset of dysarthria and worsening hemiparesis on the left side during the postoperative phase necessitated further imaging. Follow-up cranial CT revealed a decrease in the size of the subdural hematoma; however, this could not explain the aggravated neurological symptoms. An MRI scan of the brain revealed the coexistence of an ischemic stroke in the hyperacute phase of the right corona radiata in the supply area of the right anterior choroidal artery. It exhibited increased brightness on diffusion-weighted imaging (DWI) and reduced apparent diffusion coefficient (ADC) values (Figure 2). Further neurological assessment revealed moderate stenosis of the left middle cerebral artery in the distal M1 segment. A pivotal clinical challenge that has emerged is the lack of clear guidelines on the timing of antithrombotic restart following the occurrence of SDH. This challenge was further compounded by the high risk of very early stroke

(within 24 h) in our patient, who presented with recurrent TIAs suggestive of CWS. Given this high risk, the immediate initiation of secondary prevention is a critical consideration. However, considering the recent surgery and the absence of large intracranial artery occlusion, no antithrombotic treatment was initiated.

This limitation highlights the challenges posed by the sequential occurrence of these two neurological conditions and their associated therapeutic decisions (see Figure 3).

Discussion

The patient's history of atrial fibrillation and apixaban use was a crucial factor in this case. The reversal of anticoagulation treatment to prepare for subdural hematoma evacuation emphasizes the inherent risk of thrombotic events in these patients. While atrial fibrillation mandates anticoagulation for stroke prevention, such anticoagulation also presents potential obstacles during surgical procedures.

It is important to note that while the patient initially presented with symptoms indicative of lacunar syndrome, specifically pure motor hemiparesis, subsequent investigations revealed that these symptoms were not the result of a lacunar infarct. This distinction is critical, as lacunar syndromes are commonly associated with small deep cerebral infarctions; however, as demonstrated in our case and supported by the existing literature, they do not always signify lacunar infarcts. This phenomenon, where lacunar syndromes are not attributed to lacunar infarcts, has been documented in the medical literature, with studies indicating that such cases account for approximately 16.6% of lacunar syndrome presentations (9). In the context of our case, understanding this distinction is pivotal for guiding our diagnostic and therapeutic approaches. The initial presentation of pure motor hemiparesis could have led to a presumptive diagnosis of a lacunar infarct; however, further investigations pointed towards a different pathology, underscoring the importance of thorough clinical and radiological assessment in cases with such presentations. This case highlights the need for clinicians to be aware of the diversity in the presentation of lacunar syndromes and the potential for non-lacunar pathologies to present with similar symptoms. This reinforces the importance of comprehensive diagnostic processes in stroke-like presentations, particularly in complex cases with coexisting pathologies, as observed in our patient.

Furthermore, the symptoms of our patients were characterized by episodic sudden onset weakness with partial resolution of symptoms in between. His symptoms and signs were becoming persistent despite the addition of surgical evacuation of the subdural hematoma. The history we describe is classical of capsular warning syndrome (CWS). Capsular warning syndrome is a rare clinical syndrome characterized by recurrent and frequent transient episodes of focal neurological deficits with a high risk of infarction (10). The exact physiological mechanism of CWS remains unclear, but it is most commonly believed to be a result of hemodynamic insufficiency in diseased small penetrating vessels (11). As many as 71% of patients with CWS eventually develop permanent infarction, little has been published about its prognosis, management strategies, and treatment outcomes. Studies have shown that the mean duration of recurrent TIA episodes in CWS varies from 6 to 24 min, and the internal capsule remains the most frequently involved location of established infarct on MRI in 50%–70% of cases (12).

In contemplating the intricate interplay between intracranial pressure (ICP) dynamics and stroke aetiology, one intriguing hypothesis arises: could hemodynamic alterations driven by elevated ICP contribute to the occlusion of small penetrating arteries, thereby leading to lacunar stroke? Theoretically, increased ICP may affect cerebral perfusion, particularly in small vessels, which are critically dependent on stable perfusion pressures. Such hemodynamic instability could potentially result in reduced blood flow or even trigger vasoconstriction, potentially predisposing patients to lacunar infarcts. However, it is important to recognize that current scientific literature does not provide substantial direct evidence linking increased ICP specifically to lacunar stroke via these mechanisms. This gap highlights the necessity for more targeted research exploring how fluctuations in ICP might influence the pathophysiology of lacunar stroke. Investigating this relationship could yield pivotal insights into stroke mechanisms, and foster the development of nuanced prevention and treatment strategies. Our case adds to this discussion by presenting a scenario where such hemodynamic considerations might be relevant, underscoring the need for further exploration of this complex and potentially significant aspect of stroke pathophysiology.

Regarding the possible limitations of the present case, as with any case report, the findings presented here are based on the unique clinical presentation and management of a single patient, which may not be broadly applicable to other patients with similar conditions. The rarity and complexity of the patient's presentation, involving simultaneous subdural hematoma and ischemic stroke during anticoagulation therapy, may limit the applicability of our findings to more common clinical scenarios. The diagnostic and treatment approaches employed in this case were constrained by available resources and may not reflect the full spectrum of options available in different clinical settings. For example, it could be argued that the

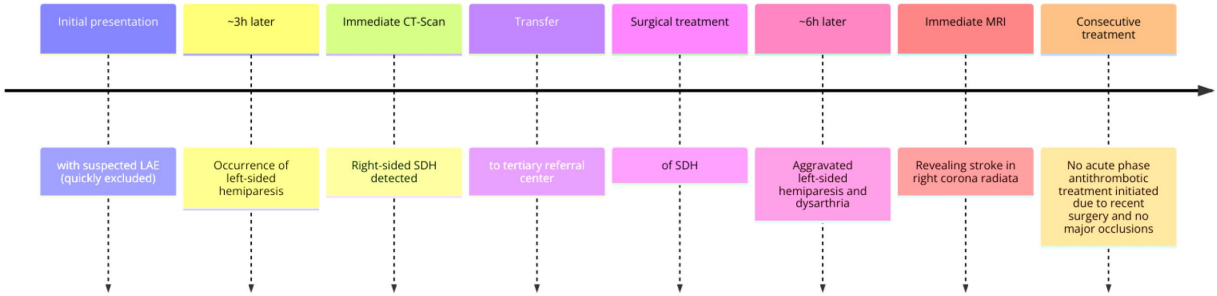


FIGURE 3
Approximate timeline of events. LAE, lung artery emboly; CT, computer tomography; SDH, subdural hematoma; MRI, magnetic resonance imaging.

worsening of hemiparesis was just another fluctuation in the context of CWS; therefore, a FLAIR negative MRI indicating a <4 h stroke might have been convincing evidence for separate events, whereas the CT scan, as in our case, was not sensitive enough in the acute phase in such locations. In addition, the potential influence of unreported or unidentified confounding variables, such as genetic predispositions or other comorbidities, cannot be ruled out in this case.

As this case report sheds light on the complexities involved in managing concurrent low-volume subdural hematoma and ipsilateral ischemic stroke in a patient undergoing anticoagulation therapy, it opens several avenues for future research. First, large-scale studies are needed to better understand the incidence and outcomes of such dual pathologies, which will aid in the development of more refined management protocols. Additionally, the role of anticoagulation in patients with coexisting conditions that warrant and contraindicate its use presents a significant clinical challenge. Research focused on the optimization of anticoagulation strategies in such scenarios is crucial. Furthermore, the potential genetic, physiological, and pharmacological factors that contribute to the development of such concurrent pathologies warrant further investigation. Lastly, long-term follow-up studies are essential to assess the outcomes and quality of life of patients treated for simultaneous occurrence of stroke and subdural hematoma, particularly in the context of anticoagulation therapy. By addressing these research gaps, we hope to enhance clinical decision making and improve patient outcomes in similarly complex cases.

Conclusion

This case report highlights the challenges in managing patients with both low-volume subdural hematoma and ischemic stroke. Additional research and guidelines are necessary to manage such cases. A multidisciplinary approach comprising neurologists, neurosurgeons, and neuroradiologists is essential to customize treatment strategies for each patient's specific needs. Furthermore, it is crucial to carefully consider approaches that address both coagulopathy management and optimal care of acute neurological conditions.

In conclusion, this case highlights the complex clinical challenges of managing a patient on anticoagulation therapy with a small subdural hematoma and ipsilateral ischemic stroke that was not initially visible on a CT scan. These challenges require a comprehensive and collaborative approach that encompasses the diagnostic, therapeutic, and preventive aspects.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should 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 to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the participants' legal guardian/next of kin for publication of this case report and any accompanying details and images.

Author contributions

DS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JB: Writing – original draft, Writing – review & editing. RR: Writing – original draft, Writing – review & editing. IV: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. 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

2. 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

3. Duerinck J, Van Der Veken J, Schuind S, Van Calenbergh F, van Loon J, Du Four S, et al. Randomized trial comparing Burr hole craniostomy, minicraniotomy, and twist drill craniostomy for treatment of chronic subdural hematoma. *Neurosurgery*. (2022) 91:304–11. doi: 10.1227/neu.0000000000001997

4. Nouri A, Gondar R, Schaller K, Meling T. Chronic subdural hematoma (cSDH): a review of the current state of the art. *Brain Spine*. (2021) 1:100300. doi: 10.1016/j.bas.2021.100300

5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211

6. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2015) 46:3020–35. doi: 10.1161/STR.0000000000000074

7. Foschi M, Pavolucci L, Rondelli F, Spinardi L, Favaretto E, Filippini M, et al. Prospective observational cohort study of early recurrent TIA: features, frequency, and outcome. *Neurology*. (2020) 95:e1733–44. doi: 10.1212/WNL.0000000000010317

8. Purroy F, Jiménez Caballero PE, Gorospe A, Torres MJ, Alvarez-Sabin J, Santamarina E, et al. Recurrent transient ischaemic attack and early risk of stroke: data from the PROMAPA study. *J Neurol Neurosurg Psychiatry*. (2013) 84:596–603. doi: 10.1136/jnnp-2012-304005

9. Arboix A, Massons J, García-Eroles L, Targa C, Comes E, Parra O. Clinical predictors of lacunar syndrome not due to lacunar infarction. *BMC Neurol*. (2010) 10:31. doi: 10.1186/1471-2377-10-31

10. Sales C, Calma AD. Stroke warning syndrome. *Clin Neurol Neurosurg*. (2022) 213:107120. doi: 10.1016/j.clineuro.2022.107120

11. Martínez HR, Figueroa-Sanchez JA, Arreola-Aldape CA, Moran Guerrero JA, Trujillo-Bracho AL, Cantú LA. Capsular warning syndrome and its clinical awareness and therapeutic approach: two case reports and a systematic review of the literature. *Front Neurol*. (2023) 14:1177660. doi: 10.3389/fneur.2023.1177660

12. Foschi M, Pavolucci L, Rondelli F, Barone V, Rinaldi R, Spinardi L, et al. Capsular warning syndrome: features, risk profile, and prognosis in a large prospective TIA cohort. *Cerebrovasc Dis*. (2023) 52:218–25. doi: 10.1159/000525954

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 22 April 2024
DOI 10.3389/fneur.2024.1359354

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Anton Fruhs,
Charité University Medicine Berlin, Germany
Daniel Dubinski,
University Hospital Rostock, Germany

*CORRESPONDENCE
Tiantian Liu
✉ 1050759938@qq.com

RECEIVED 09 January 2024
ACCEPTED 13 March 2024
PUBLISHED 22 April 2024

CITATION
Pan W, Hu J, Huang X, Jin E, Yao L, Han J and Liu T (2024) Effectiveness of tranexamic acid on chronic subdural hematoma recurrence: a meta-analysis and systematic review. *Front. Neurol.* 15:1359354. doi: 10.3389/fneur.2024.1359354

Effectiveness of tranexamic acid on chronic subdural hematoma recurrence: a meta-analysis and systematic review

Wani Pan[1], Jinyang Hu[1], Xin Huang[1], Erlang Jin[1], Longfei Yao[1], Jing Han[1] and Tiantian Liu[2]*

[1]Department of Neurosurgery, The First College of Clinical Medical Science, Three Gorges University, Yichang Central People's Hospital, Yichang, China, [2]Department of Oncology, The First College of Clinical Medical Science, China Three Gorges University, Yichang Central People's Hospital, Yichang, China

Objectives: Our objective was to compare the effectiveness of TXA in improving recurrence in patients with chronic subdural hematoma (CSDH).

Methods: Eligible randomized controlled trials (RCTs), prospective trials and retrospective cohort studies were searched in PubMed, Cochrane Library, Embase, and CNKI from database inception to December 2023. After the available studies following inclusion and exclusion criteria were screened, the main outcome measures were strictly extracted. Reman v5.4. was used to assess the overall recurrence rate. A random-effects model was used to assess pooled ORs, with the Mantel–Haenszel estimation method applied. Cochran Q (Chi-square) test and I2 statistics were used to assess inter-study heterogeneity. Funnel plots were used to evaluate publication bias.

Results: From the 141 articles found during initial citation screening, 9 literatures were ultimately included in our study. Our NMA results illustrated that patients with newly diagnosed Chronic subdural hematoma revealed a significantly improved recurrence rate when patients were treated with Tranexamic acid (OR: 0.33; 95% CI 0.26–0.41; $p < 0.00001$) compared with standard neurosurgical treatment. There was no significant difference in the incidence rates of thrombosis (OR: 0.84; 95% CI 0.63–1.12; $p = 0.23$) and mortality (OR: 1.0; 95% CI 0.57–11.76; $p = 0.99$), Occurrence of myocardial infarction was significantly less frequent in TXA users than in nonusers (OR: 0.18; 95% CI 0.04–0.82; $p = 0.03$).

Conclusion: TXA can effectively improve the recurrence rate of CDSH. It provides a high level of evidence-based medicine for clinical treatment. In addition, multicenter randomized controlled trials, with dose adjustments, are still needed to determine whether TXA intervention improves neurological function or prognosis.

KEYWORDS

tranexamic acid, chronic subdural hematoma, recurrence, meta-analysis, systematic review

Introduction

Chronic subdural hematoma (CSDH) is frequently a result of head trauma, particularly among the elderly. Studies report an incidence rate as high as 20.6 per 100,000 individuals annually (1), With the aging global population, a marked increase in CSDH cases is anticipated (2). The enlarged subdural space, a consequence of cerebral atrophy common in the elderly, often coexists with the use of oral anticoagulants in this demographic (3). Head trauma typically leads to the rupture and subsequent bleeding of bridging veins. An initial collection of liquefied hematoma develops in the subdural space, encapsulated by a geomembrane rich in capillaries after about three weeks. This membrane is susceptible to recurrent bleeding, which in turn compresses the brain tissue, manifesting as headache, dizziness, and a range of neurological symptoms (4–6).

Surgical intervention through trepanation significantly mitigates these symptoms; however, CSDH frequently recurrence (33%) and is associated with a grim prognosis (7). The mechanisms underlying reoccurrence remain enigmatic, though prevailing theories implicate inflammation (8, 9), angiogenesis (10, 11), and hyperfibrinolysis (12, 13). Therapeutics developed following these theories, including statins and glucocorticoids, have proven effective at reducing postoperative recurrence by targeting inflammation and angiogenesis (14, 15). Nonetheless, recurrence rates remain disconcertingly high, necessitating the discovery of novel treatment targets.

Hyperfibrinolysis leads to the excessive breakdown and liquefaction of blood clots, impeding their reabsorption (16). Tranexamic acid (TXA), an antifibrinolytic agent, is postulated to inhibit the rapid dissolution of blood clots, thereby potentially preventing the recurrence of chronic subdural hematoma (CSDH) and reducing the need for multiple surgical interventions (17). Currently, the therapeutic efficacy of TXA following CSDH surgery is under investigation by numerous researchers through clinical trials. However, the outcomes are still subject to debate, (18–20), pointing to a pressing requirement for rigorous evidence-based medical research. In this context, our study synthesizes the existing data to assess whether TXA administration effectively curtails the recurrence rates of CSDH in affected patients.

Materials and methods

Systematic review

Systematic reviews are conducted by searching PubMed, Embase, Cochrane libraries, and CNKI providing broad access to literature, regardless of year or language. The Medical Subject Headings (Meshi) and the search terms were combined with Boolean logical operators using "Chronic subdural hematoma," "Tranexamic acid," "Prospective cohort studies," "Randomized controlled trials," "Retrospective cohort studies," and other relevant synonyms.

Selection criteria

All eligible citations were evaluated, and citations that did not meet the inclusion criteria or were repeatedly included were excluded. Read the full text carefully to further evaluate the relevance of the article. In addition, the references in the included articles are evaluated for further exploration of relevant research. All references In Endnote X9 (Research Soft, Philadelphia, United States).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) All enrolled patients were diagnosed with Chronic Subdural Hematoma; (2) Comparative studies include randomized controlled trials or prospective studies; (3) At least 16 patients were included in each trial; (4) report key outcome indicators. The exclusion criteria were as follows: (1) recurrent Chronic Subdural Hematoma (2) age under 18 years. The primary outcome measure was the recurrence rate in patients with Chronic Subdural Hematoma. We considered mortality, thrombosis and myocardial infarction as secondary outcomes. Recurrence was defined as the onset of symptomatic Chronic Subdural Hematoma during the study period, requiring a new intervention (based on radiologically and through clinical assessment).

Data extraction and quality assessment

Two authors (Wani Pan and Jinyang Hu) independently extracted and Summarized data eligible for inclusion and exclusion Standards. Analyze demographic characteristics and data from all included articles. Relevant data such as study name, author, year of publication, country, region, and basic characteristics were extracted as baseline data.

Study quality was assessed using the software Review Manager (Version 5.4), which is a tool for evaluating the risk of bias in the included studies.

Statistical analyses

Revan v5.4. was used to assess the overall recurrence rate. A random-effects model was used to assess pooled ORs, with the Mantel–Haenszel estimation method applied. Cochran Q (Chi-square) test and I^2 statistics were used to assess inter-study heterogeneity. The heterogeneity was considered to be moderate if I^2 values were > 25%. significance was determined using 95% CIs or $p < 0.05$ (22).

Results

Study identification and patient characteristics

After a systematic review of the literature, 141 literatures were initially screened, and after further screening, 9 literatures were finally included. Figure 1 shows the process of document selection. The included studies were published between 2012 and 2023. Table 1 summarizes the main characteristics and pharmacological interventions of the participants in the 9 included trials. Patients in

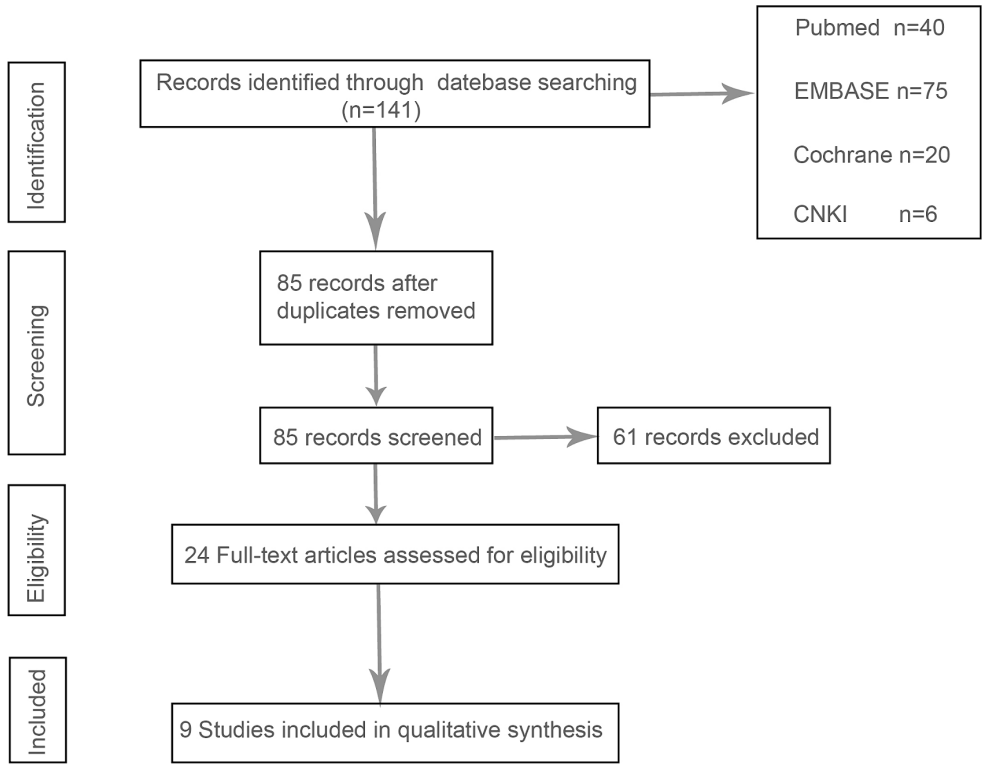


FIGURE 1
PRISMA flow chart.

TABLE 1 Characteristics of included studies.

Publication	Study design	Treatments and sample size	Mean age	Gende (male, %)	Basic treatment	Doses	Treatment duration	Recruiting area
Xie et al. (22)	Prospective	TXA = 25 versus SNT = 25	40–81 (60.4) versus 38–80 (61.6)	13 (26)	Burr hole	1,500 mg once daily	1 weeks	China
Wan et al. (23)	RCT	TXA = 41 versus SNT = 49	72.02 ± 11.79 versus 69.57 ± 13.69	60 (66.7)	Burr hole or craniotomy	500 mg twice daily	3 weeks	Singapore
Yamada and Natori (24)	RCT	TXA =72 versus SNT = 82	78.2 ± 9.2 versus 78.8 ± 10.8	100 (64.9)	Burr hole	750 mg three times per day	12 weeks	Japan
Wakabayashi et al. (25)	RCT	TXA =50 versus SNT = 49	None	None	Burr hole	750 mg per day	4 weeks	Japan
Shibahashi et al. (26)	Prospective	TXA =6,564 versus SNT = 6,564	40–89 (75.6) versus 40–89 (75.5)	9,067 (69.1)	Burr hole	750 mg per day	Started oral TXA within 2 days after surgery	Japan
Miyakoshi et al. (27)	Retrospective	TXA =465 versus SNT = 465	81.3 (7.3) versus 81.1 (6.9)	606 (65.2)	Burr hole	750 mg per day	2 weeks	Japan
de Paula et al. (20)	RCT	TXA =24 versus SNT = 26	75.8 ± 11.8 versus 72.6 ± 11.9	31 (62)	Burr hole	750 mg three times per day	12 weeks	Germany
Yang et al. (28)	Prospective	TXA =41 versus SNT = 114	72 (65–83) versus 71.5 (60–79)	35 (77)	Burr hole	750 mg per day	7 weeks	Korea
Workewych et al. (29)	RCT	TXA =11 versus SNT = 13	70.18 (12.03) versus 70.85 (9.31)	70.9 (46)	Burr hole	500 mg three times per day	8 weeks	Canada

TXA, tranexamic acid, RCT, randomized controlled study, None, not reported. SNT, standard neurosurgical treatment.

each study were patients with CSDH. Five articles were RCTs, and 3 articles were prospective studies,1 article was retrospective. Treatment time varied from 1 to 12 weeks, 7 articles used burr holes,1 article was treated by drilling or craniotomy, and the remaining 1 article was conservative treatment. We summarize the main data from the included trials in Table 2. The results showed that all trials reported recurrence rates, with an overall recurrence rate of approximately 12.3% (5.7–32%) in the intervention group and 6.4% (range 1.4–18%) in the control group.

Risk of bias quality assessment

Of the nine trials included, some trials were described in detail Random sequence generation with a low risk (23–29), Blinding of outcome assessment resulted in an unclear risk in some of the included studies, which may have led to detection bias (22). Some studies were scored high risk or unclear risk because of incomplete outcome data (24, 25). Individual bias and population bias at study level quality were, respectively, summarized in Figures 2, 3.

The details of surgical treatment

Specific surgical protocols were not descripted in the included literature, Here, we describe in detail the procedure for trepanation and drainage of chronic subdural hematoma. First, select the appropriate anesthesia method after the clear indication of surgery. According to the preoperative imaging location, scalp and subcutaneous tissue were cut at the thickest part of the hematoma, the dura was cut after drilling, and the drainage tube was quickly inserted and then fixed by subcutaneous suture. Warm saline repeatedly flushes the hematoma cavity until the outflow liquid is basically clear. Finally, connect the drainage tube with an external drainage bag (30).

Meta-analysis for recurrence rate and secondary outcomes

Meta-analysis of patients with newly diagnosed Chronic subdural hematoma revealed a significantly improved recurrence rate when patients were treated with Tranexamic acid compared with standard

TABLE 2 Recurrence rates included in the study.

Publication	Recurrence rates (%)		OR or HR (95%CI)	*p*-value
	Control	Intervention		
Xie et al. (22)	32	8	Not reported	<0.05
Wan et al. (23)	10.2	4.8	0.51 (0.11–2.47)	0.221
Yamada and Natori (24)	9.8	1.4	Not reported	0.083
Wakabayashi et al. (25)	5.7	10.9	Not reported	<0.05
Shibahashi et al. (26)	6.1	1.9	Not reported	<0.001
Miyakoshi et al. (27)	16.8	6.8	0.38 (0.26–0.56)	<0.05
de Paula et al. (20)	8.3	3.8	Not reported	0.5
Yang et al. (28)	7	2.4	Not reported	<0.05
Workewych et al. (29)	15	18	Not reported	1

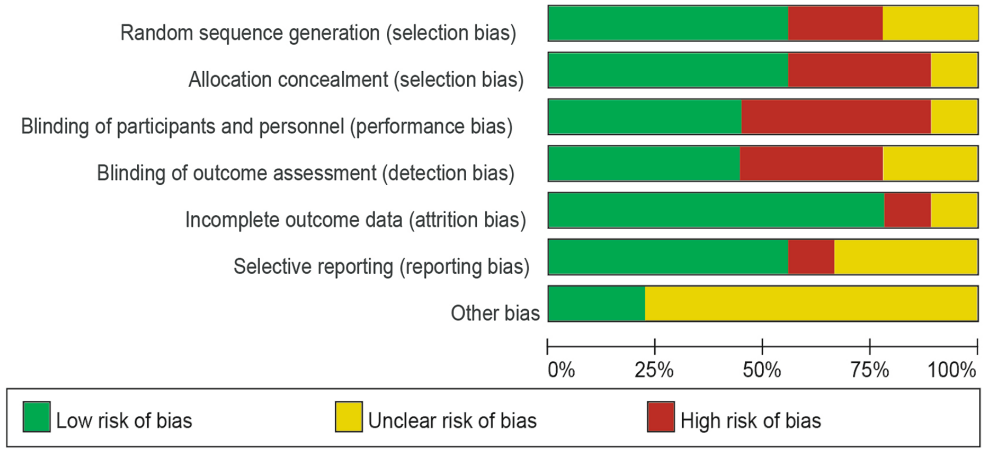


FIGURE 2
Risk of bias graph: the judgments about each risk of bias item are presented as percentages across all included studies.

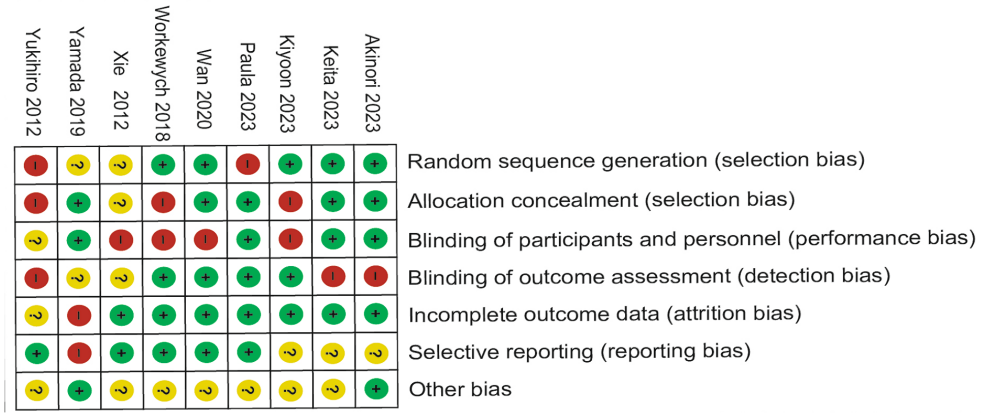


FIGURE 3
Risk of bias summary: the judgments about each risk of bias item for each included study.

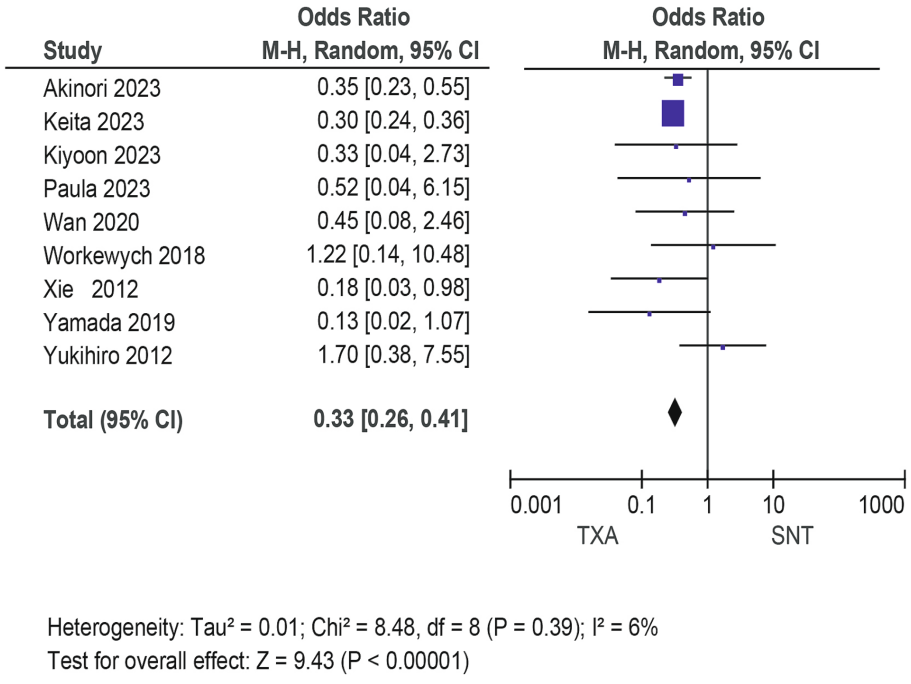


FIGURE 4
The efficacy of the experimental group was compared with that of the control group.

neurosurgical treatment alone (OR: 0.33; 95% CI 0.26–0.41; $p < 0.00001$) Heterogeneity among studies was low ($I^2 = 6\%$, $p = 0.39$; Figure 4). There was no significant difference in the incidence rates of thrombosis (OR: 0.84; 95% CI 0.63–1.12; $p = 0.23$) and mortality (OR: 1.0; 95% CI 0.57–11.76; $p = 0.99$), Occurrence of myocardial infarction was significantly less frequent in TXA users than in nonusers (OR: 0.18; 95% CI 0.04–0.82; $p = 0.03$; Table 3). The funnel plot shows that there are some asymmetrical scattering points in the inverted funnel plot, which indicates that there may be some publication bias (Figure 5).

Discussion

As the global population ages and the use of anticoagulants becomes more prevalent, the incidence and societal impact of CSDH are anticipated to rise, presenting an escalating public health concern (31). The definitive management of chronic subdural hematoma is a topic of ongoing discourse. Surgical intervention remains the sole established treatment option, yet it is associated with substantial recurrence and mortality rates, estimated at 10%, particularly in the elderly and frail demographic (32, 33), The

TABLE 3 Comparison of mortality, thrombosis, and myocardial infarction in the tranexamic acid group vs. the control group.

A						
Publication	Thrombosis				Weight	Risk radio (95%CI)
	TAX		Control			
	Events	Total	Events	Total		
Shibahashi et al. (26)	7	6,564	6	6,564	7.00%	1.17 [0.39, 3.47]
Miyakoshi et al. (27)	63	465	79	465	92.40%	0.80 [0.59, 1.08]
de Paula et al. (20)	1	24	0	26	0.60%	3.24 [0.14, 75.91]
Total	71	7,053	85	7,055	100%	0.84 [0.63, 1.12]
Test for overall effect: $Z = 1.19$ ($p = 0.23$).						

B						
Publication	Mortality				Weight	Risk radio (95%CI)
	TAX		Control			
	Events	Total	Events	Total		
Miyakoshi et al. (27)	24	465	25	465	98.10%	0.96 [0.54, 1.70]
de Paula et al. (20)	1	24	0	26	1.90%	3.38 [0.13, 87.11]
Total	25	489	25	491	100%	1.00 [0.57, 1.76]
Test for overall effect: $Z = 0.01$ ($p = 0.99$).						

C						
Publication	Myocardial infarction				Weight	Risk radio (95%CI)
	TAX		control			
	Events	Total	Events	Total		
Shibahashi et al. (26)	2	6,564	11	6,564	100%	0.18 [0.04, 0.82]
de Paula et al. (20)	0	24	0	26	–	–
Total	2	6,588	11	6,590	100%	0.18 [0.04, 0.82]
Test for overall effect: $Z = 2.22$ ($p = 0.03$).						

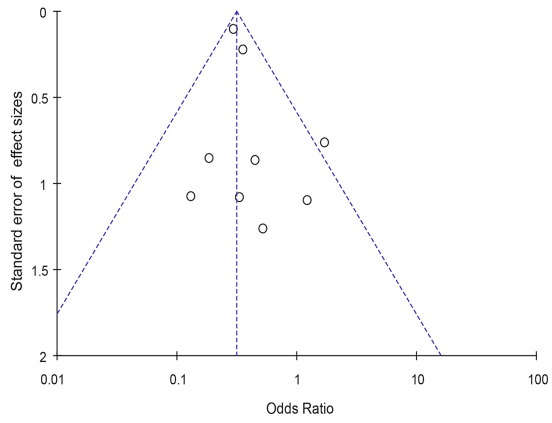


FIGURE 5
Funnel plot for detecting and displaying system heterogeneity.

underlying mechanisms contributing to these postoperative outcomes remain elusive.

Several studies have shown that inflammatory factors and chemokines (IL-6, IL-8, IL-10, MCP1, and TNF-α) are mediators of CSDH development and play a crucial role in hematoma enlargement (34, 35). Additional findings suggest high VEGF levels also increase micro angiogenesis and enhance vascular permeability (10). In addition, in the hematoma of patients with CSDH, the activation of plasmin's leads to a significant increase in thrombosis regulatory protein, and then forms a state of high fibrinolysis, which promotes blood vessel leakage leading to promote CSDH progression (36). Based on the understanding of inflammation, angiogenesis, and hyperfibrinolysis in the development of CSDH, Several related studies have investigated the role of various medical adjuncts, such as atorvastatin (37, 38), dexamethasone (15, 39, 40), TXA (4, 12, 14, 18, 20, 40–43), etc. in reducing their postoperative recurrence rate. However, to date, there is no established best adjuvant treatment.

Currently, low doses of atorvastatin have been used by many neurosurgeons to promote CSDH absorption and improve prognosis and neurological recovery (38). Compared with atorvastatin, dexamethasone can improve recurrence better (14). Some scholars have found that dexamethasone treatment is associated with a lower recurrence rate of CSDH, but no effect of dexamethasone on

improving neurological prognosis and reducing mortality has been observed (43). In addition, dexamethasone increased the risk of all-cause death from CSDH (relative risk = 1.96), and adverse events with dexamethasone are generally severe even when given at megadose (44). Recent studies have shown that TXA is less effective than dexamethasone, but more effective than atorvastatin (14). This offers great potential for TAX to treat CDSH as an adjuvant or combination therapy. Importantly, TXA has favorable security. The most common side effects were mild gastrointestinal symptoms and headache (4), and TXA may promote the formation of thrombosis, then the risk of vascular embolism, however, previous trials have shown that this adverse effect is not clinically significant at doses of 1-2 g, which was higher than the dose regimen used in our trials (45). Besides, drug–drug interactions rarely occur in TXA (42), providing a better potential option for older.

To the authors' knowledge, no conventional meta-analysis has evaluated the efficacy of TXA in reducing CSDH recurrence. This is the first meta-analysis that investigates the role of TXA in reducing the recurrence rate of CSDH. Our results suggest that TXA can significantly reduce the recurrence rate of CDSH (OR: 0.33; 95% CI 0.26–0.41; $p < 0.00001$), and improve the clinical prognosis of patients. However, there are some drawbacks to our study. First, there are not enough randomized controlled trials or prospective studies of TXA interventions, so the evidence based on their efficacy is limited. Second, we did not analyze the side effects of TXA, which could affect clinical treatment strategies. Finally, the low quality of some trials may potentially threaten the validity of our analysis. In the future, multicenter randomized controlled trials are still needed to evaluate TXA as a single or combination intervention to improve neurological function or prognosis.

Conclusion

In summary, our results show that TXA can effectively improve the recurrence rate of CDSH. It provides a high level of evidence-based medicine for clinical treatment. In addition, multicenter randomized controlled trials, with dose adjustments, are still needed to determine whether TXA intervention improves neurological function or prognosis.

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.

Author contributions

WP: Writing – original draft. JyH: Writing – review & editing. XH: Writing – review & editing, Data curation. EJ: Writing – review & editing, Data curation. LY: Writing – review & editing. JgH: Writing – review & editing. TL: Writing – review & editing, Project administration, Formal analysis, Data curation.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the medical health research project of Yichang (A23-1-035).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Yang W, Huang J. Chronic subdural hematoma: epidemiology and natural history. *Neurosurgeon Clin N Am*. (2017) 28:205–10. doi: 10.1016/j.nec.2016.11.002

2. 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 neurosurgeon*. (2015) 123:1209–15. doi: 10.3171/2014.9.JNS141550

3. Fernandes de Oliveira M. Chronic subdural hematomas and pursuit of nonsurgical treatment alternatives. *World neurosurgeons*. (2019) 126:481–3. doi: 10.1016/j.wneu.2019.03.151

4. Takahashi K, Ohbe H, Yasunaga H. Adjuvant oral tranexamic acid and reoperation after burr hole surgery in patients with chronic subdural hematoma: propensity score-matched analysis using a nationwide inpatient database. *J Neurosurg*. (2023) 138:430–6. doi: 10.3171/2022.5.JNS22664

5. Huang YW, Li ZP, Yin XS. Intraoperative irrigation of artificial cerebrospinal fluid and temperature of irrigation fluid for chronic subdural hematoma: a systematic review and meta-analysis. *Front Neurol*. (2023) 14:1218334. doi: 10.3389/fneur.2023.1218334

6. Tonetti DA, Thomas AJ, Bulsara KR. Middle meningeal artery embolization for chronic subdural hematoma: a review. *Operat Neurosurg*. (2023) 24:469–75. doi: 10.1227/ons.0000000000000656

7. Zhang J. Expert consensus on drug treatment of chronic subdural hematoma. *Chin Neurosurg J*. (2021) 7:47. doi: 10.1186/s41016-021-00263-z

8. Hong HJ, Kim YJ, Yi HJ, Ko Y, Oh SJ, Kim JM. Role of angiogenic growth factors and inflammatory cytokine on recurrence of chronic subdural hematoma. *Surg Neurol*. (2009) 71:161-5. doi: 10.1016/j.surneu.2008.01.023

9. 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

10. Hohenstein A, Erber R, Schilling L, Weigel R. Increased mRNA expression of VEGF within the hematoma and imbalance of angiopoietin-1 and -2 mRNA within the neomembranes of chronic subdural hematoma. *J Neurotrauma*. (2005) 22:518–28. doi: 10.1089/neu.2005.22.518

11. Osuka K, Ohmichi Y, Ohmichi M, Honma S, Suzuki C, et al. Angiogenesis in the outer membrane of chronic subdural hematomas through thrombin-cleaved Osteopontin and the integrin α9 and integrin β1 signaling pathways. *Biomedicines*. (2023) 11:1440. doi: 10.3390/biomedicines11051440

12. Tanweer O, Frisoli FA, Bravate C, Harrison G, Pacione D, Kondziolka D, et al. Tranexamic acid for treatment of residual subdural hematoma after bedside twist-Drill evacuation. *World Neurosurg*. (2016) 91:29–33. doi: 10.1016/j.wneu.2016.03.062

13. Yoshikawa K, Fujisawa H, Kajiwara K, Fujii M, Kato S, et al. Cause of hematic cysts of the orbit: increased fibrinolysis and immunohistologic expression of tissue

plasminogen activator. *Ophthalmology*. (2009) 116:130–4. doi: 10.1016/j.ophtha.2008.08.041

14. Yu W, Chen W, Jiang Y, Ma M, Zhang W, Zhang X, et al. Effectiveness comparisons of drug therapy on chronic subdural hematoma recurrence: a Bayesian network Meta-analysis and systematic review. *Front Pharmacol*. (2022) 13:845386. doi: 10.3389/fphar.2022.845386

15. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, et al. Trial of dexamethasone for chronic subdural hematoma. *N Engl J Med*. (2020) 383:2616–27. doi: 10.1056/NEJMoa2020473

16. Holl DC, Volovici V, Dirven CMF, Peul WC, van Kooten F, Jellema K, et al. Pathophysiology and nonsurgical treatment of chronic subdural hematoma: from past to present to future. *World Neurosurg*. (2018) 116:402–411.e2. doi: 10.1016/j.wneu.2018.05.037

17. de Faria JL, da Silva Brito J, Costa ESLT, Kilesse C, de Souza NB, Pereira CU, et al. Tranexamic acid in neurosurgery: a controversy indication-review. *Neurosurg Rev*. (2021) 44:1287–98. doi: 10.1007/s10143-020-01324-0

18. Miyakoshi A, Nakatani E, Kaneda H, Hawke P, Sasaki H, Urano T, et al. Administration of Tranexamic Acid after Burr Hole Craniotomy Reduced Postoperative Recurrence of chronic subdural hematoma in a Japanese regional population. *Neurosurgery*. (2023) 93:1160–7. doi: 10.1227/neu.0000000000002558

19. Wakabayashi Y, Yamashita M, Asano T, Yamada A, Kenai H, Kondoh Y, et al. Effect of Gorei-san with tranexamic acid for preventing recurrence of chronic subdural hematoma. *No shinkei geka Neurological surgery*. (2012) 40:967–71.

20. de Paula M, Ribeiro BDC, Melo MM, de Freitas PVV, Pahl FH, de Oliveira MF, et al. Effect of postoperative tranexamic acid on recurrence rate and complications in chronic subdural hematomas patients: preliminary results of a randomized controlled clinical trial. *Neurosurg Rev*. (2023) 46:90. doi: 10.1007/s10143-023-01991-9

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)*. (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

22. Xie Q, Xiaojun FU, Xinlong XU. Clinical study of tranexamic acid combined and burr hole drainage with irrigation treatments for chronic subdural hematoma. *ZH J J Traumatic*. (2012) 17. doi: 10.3969/j.issn.1009-7147.2012.05.004

23. Wan KR, Qiu L, Saffari SE, Khong WXL, Ong JCL, See AA, et al. An open label randomized trial to assess the efficacy of tranexamic acid in reducing post-operative recurrence of chronic subdural haemorrhage. *J Clin Neurosci Off J Neurosurg Soc Aust*. (2020) 82:147–54. doi: 10.1016/j.jocn.2020.10.053

24. Yamada T, Natori Y. Prospective study on the efficacy of orally administered tranexamic acid and Goreisan for the prevention of recurrence after chronic subdural hematoma Burr hole surgery. *World Neurosurg*. (2020) 134:e549–53. doi: 10.1016/j.wneu.2019.10.134

25. Wakabayashi Y, Yamashita M, Asano T, Yamada A, Kenai H, Kondoh Y, et al. [Effect of Gorei-san with tranexamic acid for preventing recurrence of chronic subdural hematoma]. *No Shinkei Geka*. (2012) 40:967–71.

26. Shibahashi K, Ohbe H, Yasunaga H. Adjuvant oral tranexamic acid and reoperation after burr hole surgery in patients with chronic subdural hematoma: propensity score-matched analysis using a nationwide inpatient database. *J Neurosurg*. (2022) 138:430–436.

27. Miyakoshi A, Nakatani E, Kaneda H, Hawke P, Sasaki H, Urano T, et al. Administration of Tranexamic Acid After Burr Hole Craniotomy Reduced Postoperative Recurrence of Chronic Subdural Hematoma in a Japanese Regional Population. *J Neurosurg*. (2023) 93:1160–1137.

28. Yang K, Kim KH, Lee HJ, Jeong EO, Kwon HJ, Kim SH, et al. Role of Adjunctive Tranexamic Acid in Facilitating Resolution of Chronic Subdural Hematoma after Surgery. *J Korean Neurosurg Soc*. (2023) 66:446–455. doi: 10.3340/jkns.2022.0200

29. Workewych A, Callum J, Saarela O, Montanera W, Cusimano MD. Tranexamic acid in the treatment of residual chronic subdural hematoma: a single-centre, randomized controlled trial (TRACE). *J. Neurotrauma*. (2018) 35:A244–A245. doi: 10.1089/neu.2018.29013

30. Hwang Y, Choi S, Kim YS, Park JS, Choi JH, Jeun SS, et al. Comparative analysis of safety and efficacy in subperiosteal versus subdural drainage after burr-hole trephination for chronic subdural hematoma. *Clin Neurol Neurosurg*. (2022) 212:107068. doi: 10.1016/j.clineuro.2021.107068

31. 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

32. 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) 127:732–739. doi: 10.3171/2016.8.JNS16134.test

33. 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–e834. doi: 10.1093/neuros/nyz095

34. Stanisic M, Aasen AO, Pripp AH, Lindegaard KF, Ramm-Pettersen J, Lyngstadaas SP, et al. Local and systemic pro-inflammatory and anti-inflammatory cytokine patterns in patients with chronic subdural hematoma: a prospective study. *Inflamm Res Off J Euro Histam Res Soc*. (2012) 61:845–52. doi: 10.1007/s00011-012-0476-0

35. Araújo FA, Rocha MA, Mendes JB, Andrade SP. Atorvastatin inhibits inflammatory angiogenesis in mice through down regulation of VEGF, TNF-alpha and TGF-beta1. *Biomed Pharmacother*. (2010) 64:29–34. doi: 10.1016/j.biopha.2009.03.003

36. Katano H, Kamiya K, Mase M, Tanikawa M, Yamada K. Tissue plasminogen activator in chronic subdural hematomas as a predictor of recurrence. *J Neurosurg*. (2006) 104:79–84. doi: 10.3171/jns.2006.104.1.79

37. Tang R, Shi J, Li X, Zou Y, Wang L, Chen Y, et al. Effects of atorvastatin on surgical treatments of chronic subdural hematoma. *World Neurosurg*. (2018) 117:e425–9. doi: 10.1016/j.wneu.2018.06.047

38. 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*. (2021) 44:479–84. doi: 10.1007/s10143-019-01218-w

39. Edlmann E, Thelin EP, Caldwell K, Turner C, Whitfield P, Bulters D, et al. Dex-CSDH randomised, placebo-controlled trial of dexamethasone for chronic subdural haematoma: report of the internal pilot phase. *Sci Rep*. (2019) 9:5885. doi: 10.1038/s41598-019-42087-z

40. Shrestha DB, Budhathoki P, Sedhai YR, Jain S, Karki P, Jha P, et al. Steroid in chronic subdural hematoma: an updated systematic review and Meta-analysis Post DEX-CSDH trial. *World Neurosurg*. (2022) 158:84–99. doi: 10.1016/j.wneu.2021.10.167

41. Yang K, Kim KH, Lee HJ, Jeong EO, Kwon HJ, Kim SH. Role of adjunctive tranexamic acid in facilitating resolution of chronic subdural hematoma after surgery. *J Kor Neurosurg Soc*. (2023) 66:446–55.

42. Lodewijkx R, Immenga S, van den Berg R, Post R, Westerink LG, Nabuurs RJA, et al. Tranexamic acid for chronic subdural hematoma. *Br J Neurosurg*. (2021) 35:564–9. doi: 10.1080/02688697.2021.1918328

43. 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

44. Wang X, Song J, He Q, You C. Pharmacological treatment in the Management of Chronic Subdural Hematoma. *Front Aging Neurosci*. (2021) 13:684501. doi: 10.3389/fnagi.2021.684501

45. Effects of tranexamic acid on death. Disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet (London, England)*. (2019) 394:1713–23. doi: 10.1016/S0140-6736(19)32233-0

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 25 April 2024
DOI 10.3389/fneur.2024.1366238

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Vincent Nguyen,
University of Southern California, United States
Zachary L. Hickman,
Icahn School of Medicine at Mount Sinai, United States
Andrew Steven,
Ochsner Medical Center, United States

*CORRESPONDENCE
Uttam K. Bodanapally
✉ ubodanapally@umm.edu

RECEIVED 05 January 2024
ACCEPTED 14 March 2024
PUBLISHED 25 April 2024

CITATION
Chen H, Colasurdo M, Malhotra A, Gandhi D and Bodanapally UK (2024) Advances in chronic subdural hematoma and membrane imaging.
Front. Neurol. 15:1366238.
doi: 10.3389/fneur.2024.1366238

Advances in chronic subdural hematoma and membrane imaging

Huanwen Chen[1,2], Marco Colasurdo[3], Ajay Malhotra[4], Dheeraj Gandhi[5,6,7] and Uttam K. Bodanapally[5]*

[1]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, United States, [2]Department of Neurology, MedStar Georgetown University Hospital, Washington, DC, United States, [3]Department of Interventional Radiology, Oregon Health & Science University, Portland, OR, United States, [4]Department of Radiology, Yale New Haven Hospital, New Haven, CT, United States, [5]Department of Radiology, University of Maryland Medical Center, Baltimore, MD, United States, [6]Department of Neurology, University of Maryland Medical Center, Baltimore, MD, United States, [7]Department of Neurosurgery, University of Maryland Medical Center, Baltimore, MD, United States

Chronic subdural hematoma (cSDH) is projected to become the most common cranial neurosurgical disease by 2030. Despite medical and surgical management, recurrence rates remain high. Recently, middle meningeal artery embolization (MMAE) has emerged as a promising treatment; however, determinants of disease recurrence are not well understood, and developing novel radiographic biomarkers to assess hematomas and cSDH membranes remains an active area of research. In this narrative review, we summarize the current state-of-the-art for subdural hematoma and membrane imaging and discuss the potential role of MR and dual-energy CT imaging in predicting cSDH recurrence, surgical planning, and selecting patients for embolization treatment.

KEYWORDS

chronic subdural hematoma (cSDH), dual energy (CT), neurosurgery, embolization (therapeutic), neuroimaging (anatomic and functional)

Introduction

Chronic subdural hematoma (cSDH) is a common neurosurgical condition that has been growing in incidence (1, 2), likely due to the aging global population and increased use of antithrombotic medications. By 2030, the incidence of cSDH is expected to surpass that of intracranial tumors to become the most common cranial neurosurgical disease (3). The clinical and radiographic presentation of cSDH is highly heterogeneous, and conventional treatment modalities result in high rates of disease recurrence (4). In recent years, middle meningeal artery embolization (MMAE) has shown promise as a surgical adjunct or standalone treatment to prevent cSDH recurrence (5), and multiple large, randomized trials are currently underway. In this review, we highlight the current landscape of cSDH diagnosis and treatment, with a particular focus on imaging biomarkers that may be valuable in guiding patient selection for cSDH treatments.

Epidemiology

The overall population incidence of cSDH has been reported to be approximately 10 per 100,000 persons in the general population and as high as 100 per 100,000 persons among the elderly population (6). Over time, cSDH incidence has grown, and its incidence is expected to continue increasing over the next two decades (1, 2). With conventional management, cSDH has a high rate of recurrence (4). Overall, patients with cSDH have a lower median survival time compared to non-cSDH patients with comparable health comorbidities (7). Once diagnosed, cSDH is associated with an excess mortality risk for up to 20 years (8). Whether these differences in patient outcomes are due to cSDHs themselves or associated comorbidities that may have facilitated the formation of cSDH (e.g., kidney disease, liver disease, cancer, or anticoagulation use) is unclear, as are details regarding neurological prognosis due to the heterogeneity of presenting symptoms.

On a societal level, cSDH incurs a significant financial burden. In a study of the National Inpatient Sample of hospitalizations in the United States (9), the median cost of hospitalization was $20,341 for non-surgical patients and $35,366 for patients requiring surgery. The total number of hospitalizations for cSDH in the United States is projected to be as many as 60,000 per year by 2030 (3), which could reflect a direct healthcare cost of nearly 2 billion dollars per year.

Pathophysiology and subdural membranes

The pathogenesis of cSDHs, particularly their relationship with head trauma, is not well understood. On the one hand, some cSDH patients start with traumatic acute SDHs that persist and "mature" into a chronic state. On the other hand, a majority of cSDHs arise as a "*de novo*" disease following a minor head injury without a prior acute SDH stage (10). Moreover, many cSDH patients do not have a clear history of trauma. Regardless of the inciting event, it is believed that cSDH formation is initiated by an injury and irritation of the dural border cell layer and is considered to be an angiogenic and chronic inflammatory disease. Minor trauma to the dural border cell layer triggers a variety of reparative, angiogenic, and inflammatory factors similar to wound healing. The resultant granulation tissue organizes into (neo) membranes. The membranes consist of a thick external membrane that fully develops in 1 week and a thin internal membrane that develops in 3 weeks. The external membrane houses leaky, immature capillaries formed by angiogenesis and is considered crucial in the development and growth of cSDH. The immature capillaries are abnormally permeable due to their large gaps and sparse basal membrane. This allows for the continuous exudation of erythrocytes, leukocytes, and plasma into the subdural space, leading to gradual hematoma expansion. The fragile immature capillaries in the external membrane rupture intermittently, resulting in foci of hyperdense blood within cSDH that are seen on CT. Over time, cSDH volume accumulates, and the resulting mass effect can present with neurological symptoms. The external membrane is histologically classified into four types based on the maturity and intensity of the inflammatory reaction (11, 12):

- Type 1: Non-inflammatory. This type of membrane contains immature fibroblasts and collagen fibers, with minimal cell infiltration and neo-capillaries.
- Type 2: Inflammatory. This type of membrane is associated with marked inflammatory cell infiltration and neo-vascularization.
- Type 3: Hemorrhagic-inflammatory. This type of membrane has multiple layers associated with inflammation and many new vessels along the sides of the hematoma cavity, with hemorrhage into the membrane.
- Type 4: Scar-inflammatory. This type features inflammatory cell infiltration, neo-vascularization, and hemorrhage in the outer membrane of cicatricial tissue.

The pathophysiology of cSDHs is depicted pictorially in Figure 1. Further details regarding the pathophysiology of cSDHs are reviewed elsewhere (13, 14).

Conventional treatment modalities

Conventionally, cSDHs are either managed by surgical evacuation (for larger and more severely symptomatic cSDHs) or conservative medical management. While some cSDHs resolve without surgical intervention, many conservatively managed patients will go on to require eventual surgical drainage (15). Surgical procedures are usually required for patients presenting with neurological symptoms. Surgical methods range from burr-holes or twist-drill hole evacuation, with or without adjunct MMAE to craniotomy with membranectomy. Surgical evacuation can rapidly resolve mass effects and alleviate clinical symptoms; however, it carries high recurrence rates of up to 20% (4), suggesting that drainage alone is insufficient in addressing the chronic and recurrent nature of the cSDH disease. Furthermore, attempting an evacuation is bound to fail in hematomas consisting exclusively of solid membranes. Large craniotomies with membranectomy may yield lower rates of recurrence (16) due to the removal of leaky cSDH membranes; however, this major procedure carries substantial morbidity and mortality risk, and may not be appropriate for all cSDH patients, as many of whom are older and have comorbid coagulopathies (17).

Pharmacological treatments for cSDH are currently limited. Dexamethasone, an anti-inflammatory agent, has been extensively explored for cSDH given that aberrant inflammatory responses are thought to underlie cSDH pathophysiology; however, its efficacy data are mixed and overall do not support its routine use (18, 19). Atorvastatin has shown some promise in a phase II clinical trial, where it facilitated hematoma resorption and potentially reduced the need for eventual surgery by 50% among non-surgical cSDH patients (20). Larger trials are needed to further confirm the efficacy of atorvastatin for the treatment of cSDH. Other agents, such as tranexamic acid (pro-coagulant) and bevacizumab (anti-angiogenic agent), are also being investigated (21–23).

Architectural classification and diagnostic criteria on non-contrast CT

Chronic SDHs commonly occur along the cerebral convexities, cranial base, and/or interhemispheric fissure, and their locations vary.

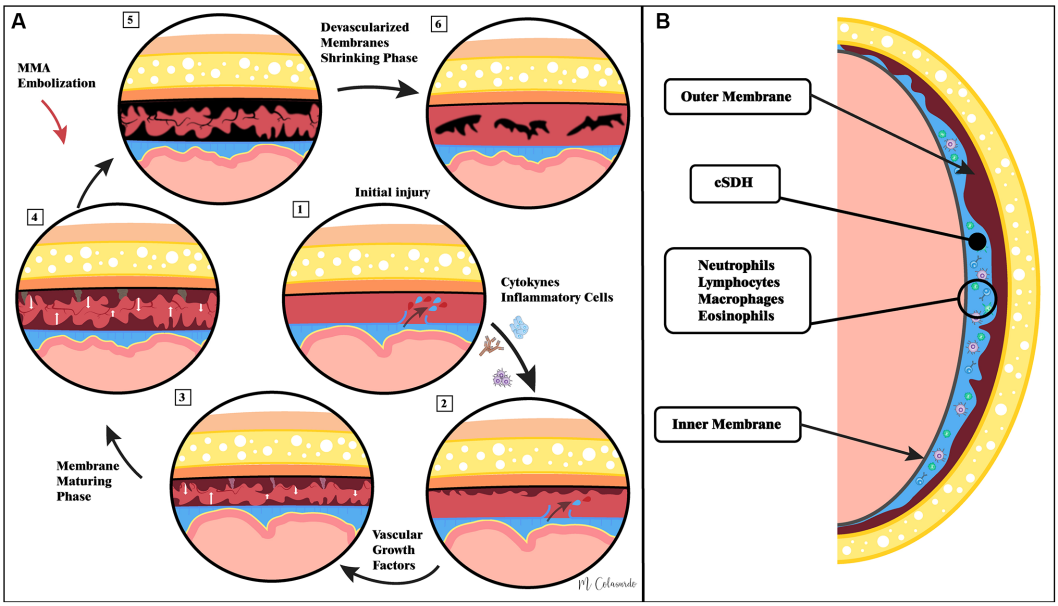


FIGURE 1
Illustrations of the current understanding of cSDH pathophysiology as well as the hypothesized role of middle meningeal artery embolization. Panel **(A)** demonstrates that pathophysiological events in cSDH formation and resolution following middle meningeal artery embolization. Panel **(B)** demonstrates the macro-anatomy of cSDHs.

The radiographic appearances of cSDHs can also be complex, ranging from iso- to hypodense, homogeneous to mixed densities, and single compartment to loculated.

Given their highly variable radiographic appearances, cSDHs do not have standardized diagnostic criteria. One accepted definition is the presence of predominantly iso- or hypodense subdural fluid collections, which is associated with the chronicity of blood products and may distinguish cSDHs from acute traumatic SDHs (18, 19). This definition, however, has limitations, as cSDHs can be difficult to distinguish from subdural hygromas based on radiodensity alone (24). Clinical diagnostic criteria are also challenging to establish, as patients present with a variety of focal neurological symptoms such as weakness, gait instability, and seizures. Given that clinical onset can be insidious, a time criterion for chronicity has limited value in a real-world setting. Surgical exploration can yield insight into the composition of cSDH fluids; however, not all patients will require or are appropriate for surgery. Thus, more sophisticated non-invasive imaging tools are needed to establish more precise criteria for identifying and diagnosing cSDHs.

Measurements of cSDHs are not standardized. Many clinicians and treatment trials use axial cuts on CT to determine maximal cSDH thickness. However, this measurement can be exaggerated due to the curvature of the cranium, especially near the vertex for cSDHs along the cerebral convexities. The mid-line shift is also a commonly used metric; however, it does not provide direct volumetric information regarding cSDHs. Other methods for measurements include subdural width at the center slice, corrected width, and cSDH length. Given the heterogeneity of cSDH morphology, geometry, and location, volumetric analysis likely provides more accurate information regarding cSDH size; however, imaging segmentation of cSDHs can be time- and resource-intensive and is not routinely employed in clinical practice. Artificial intelligence applications are available (25), and they may be employed to allow for rapid quantification of cSDH volumes in clinical use.

The internal architecture of cSDHs can be complex, and multiple classification schemes exist. The most widely cited classification system was published by Nakaguchi et al. (26), and here, cSDHs are categorized into four types—homogenous, laminar, separated, and trabecular. The classification was mostly developed as a radiographic tool to characterize the natural progression of cSDHs and predict cSDH recurrence following treatment using non-contrast CT. Homogenous and laminar subtypes are thought to be "younger," and the separated subtype is thought to be associated with chronicity. The associations of these subtypes with the risk of cSDH recurrence are discussed in a later section.

Imaging of cSDH membranes

Imaging cSDH membranes and analyzing their morphology have always been challenging in clinical practice. Hence, the majority of patients are triaged and treated based on the imaging information and morphology of the hematoma that is obtained on a non-contrast head CT. However, for cSDHs that appear heterogeneous, compartmentalized, or septated, or for those that have recurred after treatment, membrane imaging by contrast MRI or contrast DECT (Figures 2, 3) may yield valuable information to guide treatment and is recommended (27, 28).

Contrast MRI

Contrast-enhanced MRI has long been established as a non-invasive imaging modality for the demonstration of membranes and their morphology (29). Imaging of the membranes not only provides information about the morphology but also the extent of distribution over the cerebral lobes, thus determining the location and extent of craniotomy during surgical treatment (27). Incomplete

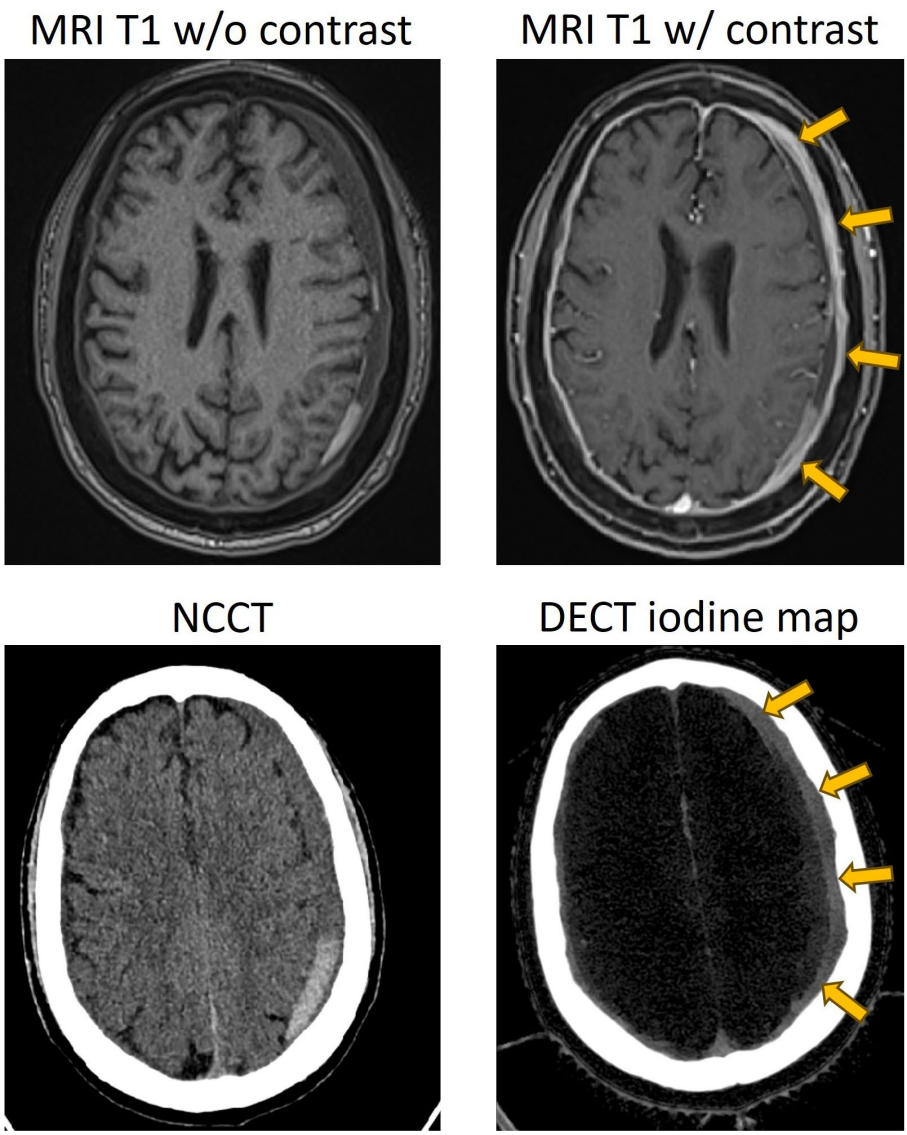


FIGURE 2
Representative case of a separated type of cSDH, with contrasted MR and dual-energy CT showing enhancement of the external membrane of a subdural hematoma (yellow arrows). NCCT, non-contrast CT; DECT, dual-energy CT.

resection of membranes, especially those that are in hard-to-reach sections over the inferior temporal or frontal lobes, is associated with recurrences (26). Hence, localization and assessment of the extent of membrane distribution over the cerebral hemispheres are important before embarking on a craniotomy. Contrast MRI has the additional capability of providing precise information about the liquid and solid components of cSDH, in addition to its ability to better delineate CT-isodense cSDH (30). Spreer et al. (29) observed enhanced external membranes in 16 out of the 17 contrast MRI scans and demonstrated that external membranes can be visualized in an overwhelming majority of patients, independent of the stage of hematoma (Figure 2). Enhancing internal membranes that were demonstrated in 9 out of the 17 scans were all in the late stages of hematoma (Figure 3). Contrast MRI also demonstrates the transition zones between the external and internal membranes that would manifest as triangular spandrel-like thickening (31). The transition zones are found to have abundant newly formed capillaries in histologic studies (32). Hence, meticulous and complete resection of transition zones during membranectomy is essential for reducing recurrences (27). In long-standing hematomas, progressive fibrosis reinforces the external membrane, transforming the hematoma into a completely solid structure (12, 33). Contrast MRI's ability to identify hematomas consisting exclusively of solid membranes can help mitigate unnecessary burr-hole or twist-drill evacuation procedures as these treatments are invariably going to fail (30). Instead, craniotomy with membranectomy should the preferred surgical approach in patients with solid cSDH membranes. Non-contrast CT in such patients with solid membranes tends to demonstrate low-density areas mimicking the liquid component of hematoma (34).

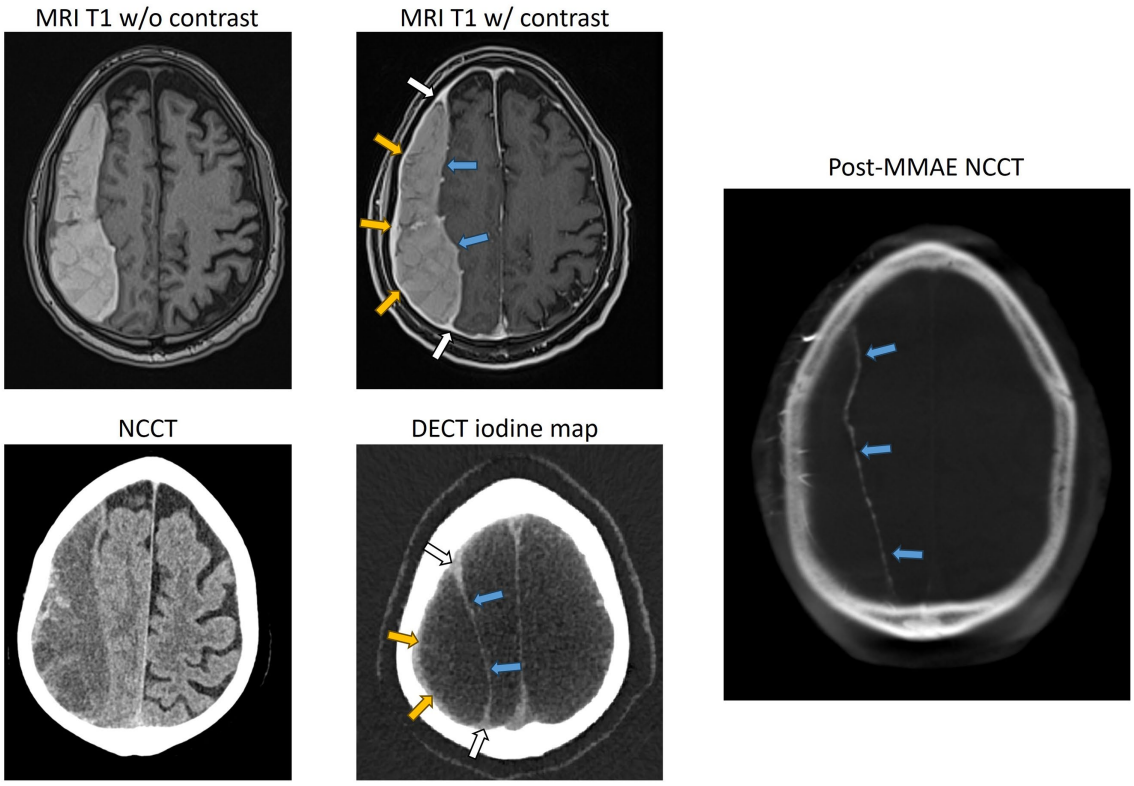


FIGURE 3
Representative case of a trabeculated cSDH, with contrasted MR, dual-energy CT, and DynaCT obtained during endovascular embolization showing the enhancement of the external membrane (yellow arrows), internal membrane (blue arrows), and "spandrel sign" (white arrows). Spandrel sign is defined as triangular thickened granulation tissue that forms the transition zone between the external and internal membranes. NCCT, non-contrast CT; DECT, dual-energy CT.

Dual-energy CT

Similar to contrast MRI, contrast dual-energy CT (DECT) facilitates the visualization and localization of membranes and helps assess the composition of hematomas by providing information about the liquid component of the hematoma. It also provides information about the thickness and complexity of the membranes, helping assess the maturity and grading of the membranes (28). It was demonstrated that iodine maps from 5-min delayed post-contrast DECT facilitate the segregation of membranes (Figures 2, 3). Iodine maps capture iodine and help in demonstrating the tissues that are enhanced with iodinated contrast, utilizing the concept of water-iodine base pairing in basis material decomposition (BMD) (35). Furthermore, the iodine map transforms and references all the remaining tissues that are not enhanced, including the brain parenchyma and hematoma, to water, providing the spectral contrast between the contrast-enhanced membranes and the adjacent tissues (35).

Classification of membranes

Studies using contrast-enhanced MRI and DECT have shown progressive thickening of the external membrane, followed by the development of internal membranes in the late stage. Internal membrane enhancement on MRI and DECT was defined as advanced cSDH with mature membranes (28, 29). Based on the evolution of these changes in the membrane morphology, they are graded on DECT depending on the pattern of membrane enhancement: Grade I-enhanced external membrane, Grade II-early phase of internal membrane formation with "spandrel sign," and Grade III-enhanced external membrane and completely formed internal membrane (28) (Figure 4). The formulated DECT membrane grades on DECT correlated with the degree of hyperdense component in the hematomas (36). Hematoma density has been reported to be associated with cSDH recurrence risk after burr-hole irrigation (37). Nakagawa et al. (38) used a similar grading system based on DynaCT images obtained during middle meningeal embolization. They demonstrated more frequent recurrences in patients with higher membrane grades.

Functional assessment of cSDH membranes

Functional information obtained from the membranes is shown to correlate with recurrences after burr-hole evacuations. An invasive procedure involving the injection of technetium-99 m human serum albumin and measuring the radioactivity level in evacuated hematoma at the burr-hole site has shown that exudation rates from the membranes are an important predictor of hematoma recurrences and are correlated with hematoma size (39). The study showed a higher

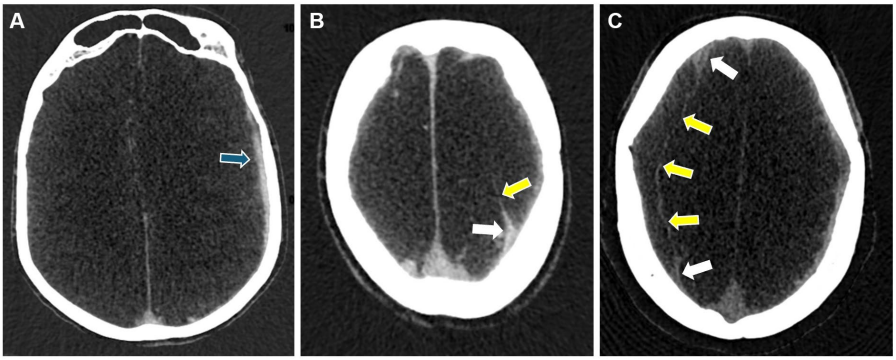


FIGURE 4
Representative images for cSDH membrane subtypes seen on DECT. Panel **(A)** shows a Grade I membrane with an enhanced external membrane (blue arrow). Panel **(B)** shows a Grade II membrane with an additional "spandrel sign" (white arrow) and a partially enhanced internal membrane (yellow arrow). Panel **(C)** shows a Grade III membrane with "spandrel signs" (white arrows) and a completely formed and enhanced internal membrane (yellow arrows).

rate of exudation in hyperdense and mixed-density hematomas than in hypodense and isodense hematomas. Recently, it was shown that DECT after contrast administration has the ability to estimate membrane exudation by using the quantification of iodine leaks through the immature capillaries in the external membrane (36). DECT, by having two attenuation measurements for iodine at two different x-ray spectra, enables the mathematical conversion of attenuation data into estimates of iodine concentration (35). The capacity to quantitatively analyze leaked iodine concentration within the subdural hematoma can be used as a surrogate of membrane exudation and the magnitude of angiogenesis in membranes. The ability to visualize the membranes and measure the iodine concentration on DECT at the same time will help us understand the relation between the morphology and permeability of the membranes, given the dominant role played by the membranes in the origin and sustenance of cSDH. DECT exudation has shown a higher iodine leak in separated-stage hematomas (36). The total iodine leak increased with the chronological stage of the hematomas, reaching its maximum values at the separated stage and then decreasing in the trabecular type of hematoma (36). A high iodine leak in mature membranes supports the findings described by Nakaguchi et al. (26) and histological findings of increasing capillaries and inflammatory cells as the membrane matures to the separated stage. This is followed by a decrease in the trabecular stage, which is considered the resolution stage due to the fibrosis of the membranes. Studies also showed high recurrence rates in separated-type hematomas after burr-hole evacuation (37). Gadolinium contrast leakage can also be seen with contrast MRI; however, its impact on the disease course of cSDH is less clear.

Quantification of membrane exudation, visualization, and grading of the membranes can allow for the examination of longitudinal alterations of the membranes and may provide information about their susceptibility in terms of morphology and permeability changes after different forms of treatments (tranexamic acid, dexamethasone, MMAE, burr-hole washout, etc.). Analysis of these imaging markers and their responses to different treatments can give us a better understanding of the role played by membrane grades and their exudation on the recurrence rates and rate of hematoma volume reduction after specific treatments. Data from such studies should help tailor precision therapies based on imaging findings and provide a framework for better understanding the pathogenesis of CSDH that can later fit into emerging spectral photon-counting molecular CT imaging.

Middle meningeal artery embolization

The middle meningeal artery (MMA) has long been known to provide vascular supply to the dura; thus, it is possible that restricting arterial blood supply by the endovascular embolization of the MMA may lead to the necrosis of subdural membranes and neo-vasculature, which are thought to be responsible for cSDH persistence and recurrence. As such, MMA embolization (MMAE) is hypothesized to be an effective adjunctive treatment to surgical evacuation to reduce the rates of future cSDH recurrence (Figure 1).

MMAE emerged as a promising treatment for cSDHs in 2018 when Ban et al. (5) reported that MMAE resulted in a strikingly low rate of recurrence (1.4%) compared to conventional management (27.5%). Since then, multiple studies have corroborated these findings, with a meta-analysis reporting a recurrence rate of under 5%, followed by MMAE, compared to more than 20% with conventional management (40). In addition to preventing recurrence, MMAE may also be effective in promoting cSDH resorption and resolution without surgical evacuation. In a small, randomized study of 46 patients, Ng et al. showed that adjunctive MMAE in addition to surgical treatment led to a significantly larger cSDH volume resorption at a median of 3 months (41). Catapano et al. also showed that MMAE led to significantly larger decreases in cSDH thicknesses at follow-up compared to conventional management (42). As such, MMAE could also be an effective standalone treatment that can be offered as a non-surgical alternative to patients with smaller hematoma volumes and mild symptoms (43, 44).

In February 2024, preliminary results from the EMBOLISE (45), MAGIC-MT (46), and STEM (47) trials were presented at the International Stroke Conference. All three trials investigated the role of adjunctive MMAE for the treatment of cSDH in addition to standard of care (surgery or observation). All three trials met their primary efficacy endpoints for cSDH recurrence and demonstrated

excellent safety data for MMAE. Given these positive results, it is likely that MMAE will be incorporated into the standard of care for SDHs. The formal conclusion of these landmark trials as well as the final peer-review and publication of the results are now eagerly awaited. Other randomized trials, such as MEMBRANE (NCT04816591) and SWEMMA (NCT05267184), are also underway.

Radiographic predictors for cSDH recurrence

While a substantial portion of cSDH patients experience hematoma recurrence following surgical evacuation, it is important to recognize that most cSDHs resolve after treatment. As such, identifying patients at high risk of surgical recurrence may help providers select patients for treatment modalities targeted at preventing disease recurrence, such as MMAE, regardless of the results of ongoing trials.

The heterogeneity of cSDH's radiographic morphology has been extensively studied as a potential biomarker for disease recurrence. Multiple classification systems exist for characterizing the cSDH internal architecture. The most common scheme is the Nakaguchi classification system (26). In this study, cSDHs are categorized into four types–homogenous, laminar, separated, and trabecular. Homogenous and laminar (the early subtypes) are less likely to recur, while the separated hematoma (the later subtype) is more likely to recur after treatment. Data on outcomes following MMAE stratified by Nakaguchi cSDH subtypes corroborated these results, suggesting that the separate subtype was associated with slower hematoma resorption following MMAE. Trabecular subtypes were thought to be associated with resolving cSDHs with a low risk of recurrence. Representative images of the Nakaguchi classifications are presented in Figure 5. In a separate scheme, Nomura et al. (48) classified cSDHs by pattern of radiodensity (hyperdense, isodense, hypodense, mixed, or layered) and showed that the layered and mixed cSDHs were more likely to recur, while hypodense cSDHs were less likely to recur. Shimizu et al. (49) also demonstrated that gradation density hematomas are at higher risk of recurrence. More recently, Takei et al. (50) proposed modified criteria combining these classification systems into five subtypes—homogenous, gradation, laminar, separated, and trabecular—and showed that this modified system had higher interrater agreement than the Nakaguchi and Nomura classifications and that the gradation subtype was most strongly associated with cSDH recurrence. Research on radiographic predictors of cSDH recurrence remains an active area of investigation.

Given that leaky vessels housed within cSDH membranes are thought to underlie the pathophysiology of cSDH persistence and recurrence, membrane imaging is also of great interest for the prediction of cSDH recurrence. In a study of 40 cSDHs, Tanikawa et al. (51) showed that MR imaging can be used to visualize cSDH membranes and that patients with intrahematoma membranes were significantly more likely to recur following burr-hole drainage compared to craniotomy. On catheter angiogram, highly vascularized cSDH membranes may appear similar to tumor blushes with increased contrast staining during the capillary phase, and this too can be used as a predictor for recurrence risk.

Importantly, early studies showed that a high rate of protein exudation into cSDHs is associated with higher rates of cSDH recurrence (39). In a retrospective study of 27 patients with 29 cSDHs, Mureb showed that MMAE procedures (which involve copious amounts of intra-arterial iodinated contrast administration) led to enhancements of cSDHs and their membranes in all patients (52), suggesting that iodinated contrast enhancement of subdural membranes and leakage into hematomas may be a biomarker for underlying pathophysiology and possibly a predictor of recurrence risk. As previously discussed, DECT also enables the non-invasive and precise quantification of iodine leakage into cSDHs (28). This has been shown to be the highest in separated types of hematomas, which are associated with higher rates of cSDH recurrence after burr-hole evacuation and a slower rate of resolution after sole MMAE (53).

Conclusion

cSDH is a common neurosurgical disease that is expected to rapidly grow in global incidence. Disease recurrence is common despite conventional management. MMAE has emerged as a promising treatment for preventing surgical recurrence, and clinical trials are currently underway. The development of radiographic markers for cSDH recurrence remains an active area of investigation, and DECT techniques are promising for the quantification of iodine

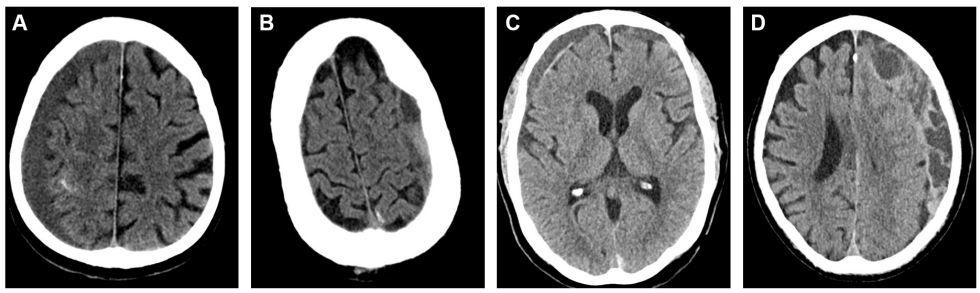


FIGURE 5
Representative images for cSDH subtypes based on the Nakaguchi classification system. Panel **(A)** – homogenous; Panel **(B)** – separated; Panel **(C)** – laminar, Panel **(D)** – trabeculated.

leakage and may be leveraged toward improved patient selection algorithms for cSDH treatment.

Author contributions

HC: Conceptualization, Writing – original draft. MC: Visualization, Writing – original draft. AM: Writing – review & editing. DG: Writing – review & editing. UB: Conceptualization, Project administration, Supervision, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

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*. (2020) 132:1147–57. doi: 10.3171/2018.12.JNS183035

2. Neifert SN, Chaman EK, Hardigan T, Ladner TR, Feng R, Caridi JM, et al. Increases in subdural hematoma with an aging population—the future of American cerebrovascular disease. *World Neurosurg*. (2020) 141:e166–74. doi: 10.1016/j.wneu.2020.05.060

3. 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

4. Ducruet AF, Grobelny BT, Zacharia BE, Hickman ZL, DeRosa PL, Anderson K, et al. The surgical management of chronic subdural hematoma. *Neurosurg Rev*. (2012) 35:155–69. doi: 10.1007/s10143-011-0349-y

5. 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

6. Yang W, Huang J. Chronic subdural hematoma. *Neurosurg Clin N Am*. (2017) 28:205–10. doi: 10.1016/j.nec.2016.11.002

7. 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

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. Dicpinigaitis AJ, Al-Mufti F, Cooper JB, Faraz Kazim S, Couldwell WT, Schmidt MH, et al. Nationwide trends in middle meningeal artery embolization for treatment of chronic subdural hematoma: a population-based analysis of utilization and short-term outcomes. *J Clin Neurosci*. (2021) 94:70–5. doi: 10.1016/j.jocn.2021.10.001

10. Edlmann E, Whitfield PC, Kolias A, Hutchinson PJ. Pathogenesis of chronic subdural hematoma: a cohort evidencing De novo and transformational origins. *J Neurotrauma*. (2021) 38:2580–9. doi: 10.1089/neu.2020.7574

11. 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.

12. Fujioka M, Okuchi K, Miyamoto S, Sakaki T, Tsunoda S, Iwasaki S. Bilateral organized chronic subdural haematomas: high field magnetic resonance images and histological considerations. *Acta Neurochir*. (1994) 131:265–9. doi: 10.1007/BF01808625

13. 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

14. Holl DC, Volovici V, Dirven CMF, Peul WC, van Kooten F, Jellema K, et al. Pathophysiology and nonsurgical treatment of chronic subdural hematoma: from past to present to future. *World Neurosurg*. (2018) 116:402–411.e2. doi: 10.1016/j.wneu.2018.05.037

15. Bender MB, Christoff N. Nonsurgical treatment of subdural hematomas. *Arch Neurol*. (1974) 31:73–9. doi: 10.1001/archneur.1974.00490380021001

16. Sahyouni R, Mahboubi H, Tran P, Roufail JS, Chen JW. Membranectomy in chronic subdural hematoma: Meta-analysis. *World Neurosurg*. (2017) 104:418–29. doi: 10.1016/j.wneu.2017.05.030

17. Licina A, Silvers A, Thien C. Association between frailty and clinical outcomes in patients undergoing craniotomy—systematic review and meta-analysis of observational studies. *Syst Rev*. (2024) 13:73. doi: 10.1186/s13643-024-02479-3

18. Miah IP, Holl DC, Blaauw J, Lingsma HF, den Hertog HM, Jacobs B, et al. Dexamethasone versus surgery for chronic subdural hematoma. *N Engl J Med*. (2023) 388:2230–40. doi: 10.1056/NEJMoa2216767

19. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, et al. Trial of dexamethasone for chronic subdural hematoma. *N Engl J Med*. (2020) 383:2616–27. doi: 10.1056/NEJMoa2020473

20. 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. *JAMA Neurol*. (2018) 75:1338–46. doi: 10.1001/jamaneurol.2018.2030

21. Iorio-Morin C, Blanchard J, Richer M, Mathieu D. Tranexamic acid in chronic subdural hematomas (TRACS): study protocol for a randomized controlled trial. *Trials*. (2016) 17:235. doi: 10.1186/s13063-016-1358-5

22. Khalife J, Tonetti DA, Shaikh H, Jovin T, Patel P, Thomas A. Intraarterial bevacizumab administration through the middle meningeal artery for chronic subdural hematoma. *Stroke*. (2023) 3:3. doi: 10.1161/SVIN.122.000722

23. Suzuki K, Kawataki T, Kanemaru K, Mitsuka K, Ogiwara M, Sato H, et al. A case of complete clearance of chronic subdural hematoma accompanied by recurrent glioblastoma multiforme after administration of bevacizumab. *Neurosurg Rev*. (2016) 39:525–9. doi: 10.1007/s10143-016-0704-0

24. Yu J, Tang J, Chen M, Ren Q, He J, Tang M, et al. Traumatic subdural hygroma and chronic subdural hematoma: a systematic review and meta-analysis. *J Clin Neurosci*. (2023) 107:23–33. doi: 10.1016/j.jocn.2022.11.010

25. Colasurdo M, Leibushor N, Robledo A, Vasandani V, Luna ZA, Rao AS, et al. Automated detection and analysis of subdural hematomas using a machine learning algorithm. *J Neurosurg*. (2022) 1–8:1–8. doi: 10.3171/2022.8.JNS22888

26. Nakaguchi H, Tanishima T, Yoshimasu N. 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

27. Rocchi G, Caroli E, Salvati M, Delfini R. Membranectomy in organized chronic subdural hematomas: indications and technical notes. *Surg Neurol*. (2007) 67:374–80. doi: 10.1016/j.surneu.2006.08.066

28. Bodanapally UK, Fleiter TR, Aarabi B, Malhotra A, Gandhi D. Dual-energy CT imaging of chronic subdural hematoma membranes: technical note. *Eur Radiol*. (2022) 33:797–802. doi: 10.1007/s00330-022-09064-z

29. Spreer J, Ernestus R-I, Lanfermann H, Lackner K. Connective tissue reactions in subdural haematomas: imaging with contrast-enhancement MRI. *Acta Neurochir*. (1997) 139:560–5. doi: 10.1007/BF02751000

30. Hosoda K, Tamaki N, Masumura M, Matsumoto S, Maeda F. Magnetic resonance images of chronic subdural hematomas. *J Neurosurg*. (1987) 67:677–83. doi: 10.3171/jns.1987.67.5.0677

31. Petersen D, Grodd W, Voigt K. Magnetic resonance tomography (1.5 T) of traumatic extracerebral hematomas. *Radiologe*. (1989) 29:416–22.

32. Moon KL, Brant-Zawadzki M, Pitts LH, Mills CM. Nuclear magnetic resonance imaging of CT-isodense subdural hematomas. *AJNR Am J Neuroradiol*. (1984) 5:319–22.

33. Sato S, Suzuki J. Ultrastructural observations of the capsule of chronic subdural hematoma in various clinical stages. *J Neurosurg*. (1975) 43:569–78. doi: 10.3171/jns.1975.43.5.0569

34. Nagasaka M, Omata T, Miyazawa N, Kaneko M, Fukamachi A, Nukui H. Organized chronic subdural hematoma; report of two cases. *No Shinkei Geka*. (1991) 19:861–5.

35. Gaddam DS, Dattwyler M, Fleiter TR, Bodanapally UK. Principles and applications of dual energy computed tomography in neuroradiology. *Semin Ultrasound CT MR*. (2021) 42:418–33. doi: 10.1053/j.sult.2021.07.001

36. Bodanapally UK, Aarabi B, Liang Y, Khalid M, Fleiter TR, Gandhi D. Quantitative DECT of iodine in chronic subdural hematoma as surrogate of membrane exudation: a pilot feasibility study. *J Comput Assist Tomogr*. (2023) 47:951–8. doi: 10.1097/RCT.0000000000001501

37. Miah IP, Tank Y, Rosendaal FR, Peul WC, Dammers R, Lingsma HF, et al. Radiological prognostic factors of chronic subdural hematoma recurrence: a systematic review and meta-analysis. *Neuroradiology*. (2021) 63:27–40. doi: 10.1007/s00234-020-02558-x

38. Nakagawa I, Park HS, Kotsugi M, Wada T, Takeshima Y, Matsuda R, et al. Enhanced hematoma membrane on DynaCT images during middle meningeal artery embolization for persistently recurrent chronic subdural hematoma. *World Neurosurg*. (2019) 126:e473–9. doi: 10.1016/j.wneu.2019.02.074

39. Tokmak M, Iplikcioglu AC, Bek S, Gökduman CA, Erdal M. The role of exudation in chronic subdural hematomas. *J Neurosurg*. (2007) 107:290–5. doi: 10.3171/JNS-07/08/0290

40. Ironside N, Nguyen C, Do Q, Ugiliweneza B, Chen C-J, Sieg EP, et al. Middle meningeal artery embolization for chronic subdural hematoma: a systematic review and meta-analysis. *J Neurointerv Surg*. (2021) 13:951–7. doi: 10.1136/neurintsurg-2021-017352

41. 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

42. Catapano JS, Ducruet AF, Srinivasan VM, Rumalla K, Nguyen CL, Rutledge C, et al. Radiographic clearance of chronic subdural hematomas after middle meningeal artery embolization. *J Neurointerv Surg*. (2022) 14:1279–83. doi: 10.1136/neurintsurg-2021-018073

43. Chen H, Colasurdo M, Kan PT. Middle meningeal artery embolization as standalone treatment versus combined with surgical evacuation for chronic subdural hematomas: systematic review and meta-analysis. *J Neurosurg*. (2023) 1–7:1–7. doi: 10.3171/2023.7.JNS231262

44. Chen H, Salem MM, Colasurdo M, Sioutas GS, Khalife J, Kuybu O, et al. Standalone middle meningeal artery embolization versus middle meningeal artery embolization with concurrent surgical evacuation for chronic subdural hematomas: a multicenter propensity score matched analysis of clinical and radiographic outcomes. *J Neurointerv Surg*. (2023) 6:907. doi: 10.1136/jnis-2023-020907

45. Knopman J, Davies JM, Harbaugh RE, Hassan AE, Khalessi A, Mokin M, et al. *LB28: the EMBOLISE study: embolization of the middle meningeal artery with OnyxTM liquid embolic system in the treatment of subacute and chronic subdural hematoma*. Phoenix, AZ: American Stroke Association (2024).

46. Mao YMAGIC-MT investigators. LB29: the MAGIC-MT trial: managing non-acute subdural hematoma using liquid materials: a Chinese randomized trial of middle meningeal artery treatment. *Trials*. (2023) 24:586. doi: 10.1186/s13063-023-07608-2

47. Arthur A. *LB31: STEM (the squid trial for the embolization of the MMA for the treatment of CSDH)*. Phoenix, AZ: American Heart Association (2024).

48. Nomura S, Kashiwagi S, Fujisawa H, Ito H, Nakamura K. Characterization of local hyperfibrinolysis in chronic subdural hematomas by SDS-PAGE and immunoblot. *J Neurosurg*. (1994) 81:910–3. doi: 10.3171/jns.1994.81.6.0910

49. Shimizu Y, Park C, Tokuda K. Gradation density hematoma is a predictor of chronic subdural hematoma recurrence associated with inflammation of the outer membrane. *Clin Neurol Neurosurg*. (2020) 194:105839. doi: 10.1016/j.clineuro.2020.105839

50. Takei J, Hirotsu T, Hatano K, Ishibashi T, Inomata T, Noda Y, et al. Modified computed tomography classification for chronic subdural hematoma features good interrater agreement: a single-center retrospective cohort study. *World Neurosurg*. (2021) 151:e407–17. doi: 10.1016/j.wneu.2021.04.052

51. Tanikawa M, Mase M, Yamada K, Yamashita N, Matsumoto T, Banno T, et al. Surgical treatment of chronic subdural hematoma based on Intrahematomal membrane structure on MRI. *Acta Neurochir*. (2001) 143:613–9. doi: 10.1007/s007010170067

52. Mureb MC, Kondziolka D, Shapiro M, Raz E, Nossek E, Haynes J, et al. DynaCT enhancement of subdural membranes after middle meningeal artery embolization: insights into pathophysiology. *World Neurosurg*. (2020) 139:e265–70. doi: 10.1016/j.wneu.2020.03.188

53. Uttam BK, Yuanyuan L, Bizhan A, Thorsten FR, Mazhar K, Marco C, et al. Short-term follow-up pilot study of sole middle meningeal artery embolization for chronic subdural hematoma: influence of internal architecture on the radiological outcomes. *Neuroradiology*. (2023) 65:1143–53. doi: 10.1007/s00234-023-03158-1

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 06 May 2024
DOI 10.3389/fneur.2024.1400788

OPEN ACCESS

EDITED BY
Hiroki Sato,
Saitama Medical University International Medical Center, Japan

REVIEWED BY
Daniele Bongetta,
ASST Fatebenefratelli Sacco, Italy
Seokmann Yoon,
Soon Chun Hyang University Cheonan Hospital, Republic of Korea
Raphael Bertani,
University of São Paulo, Brazil
Mustafa Ismail,
University of Baghdad, Iraq

*CORRESPONDENCE
Myungsoo Kim
✉ aldtn85@gmail.com

RECEIVED 14 March 2024
ACCEPTED 25 April 2024
PUBLISHED 06 May 2024

CITATION
Kim M (2024) Preservation of the middle meningeal artery during unruptured aneurysm surgery: an independent risk factor for postoperative chronic subdural hematoma.
Front. Neurol. 15:1400788.
doi: 10.3389/fneur.2024.1400788

Preservation of the middle meningeal artery during unruptured aneurysm surgery: an independent risk factor for postoperative chronic subdural hematoma

Myungsoo Kim*

Department of Neurosurgery, School of Medicine, Kyungpook National University, Daegu, Republic of Korea

Background: Although microsurgical clipping for unruptured aneurysms has become safer and more efficient with modern neurosurgical advances, postoperative chronic subdural hematoma (CSDH) persists as an underrecognized complication. This study investigated the association between preservation of the anterior branch of the middle meningeal artery (MMA) during surgery and CSDH development.

Methods: We retrospectively reviewed 120 patients who underwent clipping for unruptured aneurysms at Kyungpook National University Chilgok Hospital between May 2020 and July 2023. We evaluated the patients on the basis of surgical approach—lateral supraorbital (LSO) or standard pterional craniotomy—and the status of the MMA postoperatively. We employed pre-and post-operative MR angiography to assess MMA preservation and used follow-up computed tomography scans to monitor CSDH development.

Results: Of the 120 patients, 22 (18.3%) developed CSDH. Univariate analysis revealed that male sex, advanced age, and MMA preservation are risk factors for postoperative CSDH. Multivariate analysis supported these findings, indicating a significant association with the development of CSDH. MMA preservation was reported in 65 patients, of whom 60 and 5 underwent LSO and pterional craniotomy, respectively.

Conclusion: Preservation of the anterior branch of the MMA during unruptured aneurysm surgery is a risk factor for postoperative CSDH development. Advanced age and male sex also contribute to the increased risk. These findings highlight the need for further investigation into surgical techniques that could mitigate postoperative CSDH development.

KEYWORDS

chronic subdural hematoma (CSDH), unruptured aneurysm, middle meningeal artery (MMA), microsurgical clipping, pterional approach, lateral supraorbital approach

Introduction

Modern advancements in neurosurgical technology have significantly enhanced the safety and efficacy of microsurgical procedures for unruptured aneurysms. As minimally invasive aneurysm surgery becomes more common, recent data indicate a major surgical morbidity of less than 1% for unruptured aneurysms measuring below 10 mm (1–3). However, postoperative subdural hygromas transitioning to chronic subdural hematomas (CSDH) remain an underestimated complication. A recent study showed that male sex and advanced age are risk factors for CSDH formation following unruptured aneurysm surgery (4, 5).

The middle meningeal artery (MMA), which is commonly cauterized during pterional craniotomy, supplies the outer membrane of CSDH and significantly contributes to the neovascularization of the membrane associated with CSDH (6, 7). Furthermore, previous studies have shown that CSDH mainly occurs in the anterior region and is predominantly supplied by the anterior branch of the MMA, and MMA occlusion during burr hole procedures can reduce the recurrence rates of CSDH (6).

On the basis of these observations, we postulate that MMA preservation during unruptured aneurysm surgery may correlate with CSDH formation. This study aimed to evaluate the risk factors for CSDH in patients undergoing microsurgical clipping for unruptured aneurysms, focusing on the impact of MMA preservation.

Materials and methods

This study was reviewed and approved by the Ethics Committee of Kyungpook National University Chilgok Hospital (IRB No. 2023-10-027).

Patient population

This study enrolled 120 patients who underwent surgical treatment for unruptured aneurysms at Kyungpook National University Chilgok Hospital from May 2020 to July 2023.

The inclusion criteria were as follows: (1) age >18 years; (2) diagnosis of unruptured, nongiant aneurysms arising at the anterior circulation of the circle of Willis, including the supraclinoid internal carotid artery (ICA), anterior cerebral artery (ACA), and middle cerebral artery (MCA); (3) treatment of unruptured aneurysms via lateral supraorbital (LSO) or standard pterional craniotomy; (4) preoperative magnetic resonance angiography (MRA).

The exclusion criteria were (1) diagnosis of ruptured aneurysm with subarachnoid hemorrhage, (2) aneurysm arising at the distal ACA requiring interhemispheric approach, (3) aneurysm arising at the posterior circulation, and (4) no available preoperative MRA data.

Abbreviations: ACA, Anterior cerebral artery; AcoA, Anterior communicating artery; CSDH, Chronic subdural hematoma; CT, Computed tomography; LSO, Lateral supraorbital approach; MRA, Magnetic resonance angiography; MCA, Middle cerebral artery; MMA, Middle meningeal artery; ICA, Internal carotid artery.

Surgical procedure

In this study, either the standard pterional or the LSO approach was employed (3, 8, 9). The pterional approach was performed in a standard manner (Figure 1B), routinely including surgical occlusion of the anterior branch of the MMA during sphenoid ridge bone work. The LSO approach included small craniotomy (diameter of below 4 cm) with MMA preservation, as previously reported by the authors of the present study (Figure 1A) (3, 10). In both surgical techniques, the inner edge of the craniotomy above the orbital rim was refined, and frontal floor protrusions were smoothed for better subfrontal access. After opening the dura, a brain spatula was directed over the base of the frontal lobe to the carotid and optic nerve cisterns. Draining of CSF from these cisterns ensured safe and sufficient frontal lobe retraction.

Data collection

The medical records and radiological findings of the patients were examined to gather pertinent clinical and imaging data. All patients discontinued antiplatelet medication before surgery.

Routine brain computed tomography (CT) scans were performed on the first day postoperatively, upon discharge (between days 5 and 7), and 3 weeks postoperatively. When patients revealed any neurological symptoms or enduring headaches or any intracranial complications, further follow-up CT scans were performed.

A CSDH was defined as a crescent-shaped isodense or slightly hyperdense extra-axial collection in the frontoparietal lesion, which was transformed from the subdural hygroma, with a maximum thickness of >3 mm. The CSDHs were monitored via CT scans every 1–3 months until their resolution (either spontaneously or after surgical treatment).

To confirm surgical occlusion of the anterior branch of the MMA, preoperative and routine postoperative MR angiography was retrospectively analyzed. In CT angiography, if the running of the MMA is confirmed in the axial view, the distinction may be ambiguous due to interference from bone contrast and plates following craniotomy; therefore, additional routine postoperative MR angiography was employed in this study. In the axial view of MR angiography, the anterior branch of the MMA near the sphenoid ridge was identified to confirm the presence of coagulation compared with the preoperative MR angiography. All angiographic images were reviewed by one neurosurgeon (MK).

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, United States). Student's *t*-test or Mann–Whitney *U* test was employed for continuous variables. The chi-squared test and Fisher's exact test were employed for categorical variables, which were expressed as numbers and percentages. Univariate and multivariate analyses were sequentially conducted to analyze the risk factors for CSDH formation.

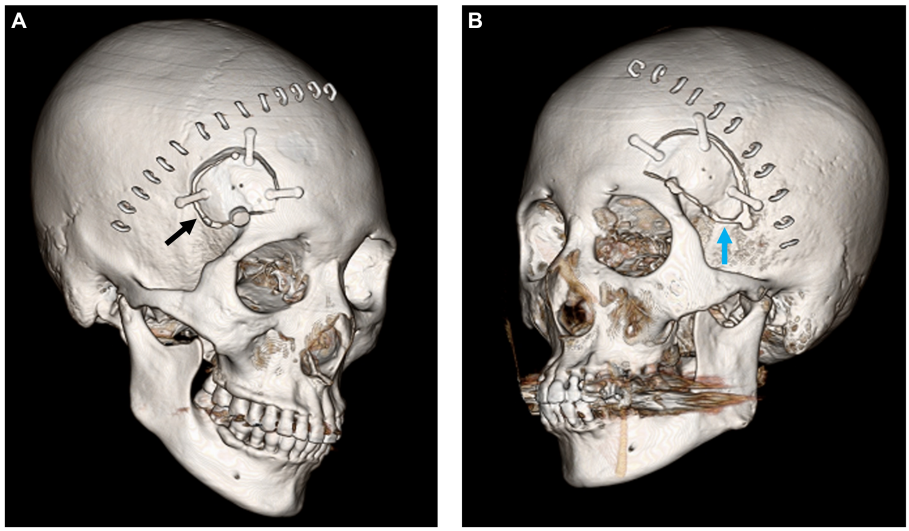


FIGURE 1
(A) Postoperative 3D CT image of lateral supraorbital craniotomy (black arrow). **(B)** Postoperative image of pterional craniotomy with sphenoid bone working (blue arrow).

TABLE 1 **Clinical characteristics of 120 patients who underwent microsurgical clipping for an unruptured intracranial aneurysm.**

Characteristics	Number of patients (%)
Male	37 (30.8)
Mean age, years (SD)	64.6 ± 8.7
Hypertension	69 (57.5)
Diabetes	26 (21.6)
Location of the aneurysm	
Group A	22 (18.3)
ICA aneurysm	21
Proximal A1 aneurysm	1
Group B	25 (20.8)
AcoA aneurysm	23
AcoA and ICA aneurysms	2
Group C	54 (45)
MCA aneurysm	54
Group D	15 (12.5)
AcoA and MCA aneurysms	7
ICA and MCA aneurysms	8
Surgical approach	
Pterional	60 (50)
Lateral supraorbital	60 (50)
Preservation of the anterior branch of MMA	65 (54.1)
Burr hole procedure	3 (2.5)

Results

The clinical characteristics of the 120 patients who underwent craniotomy for an unruptured aneurysm in the anterior circulation are presented in Table 1. Among them, 83 were women and 37 were men, and their mean age was 64.6 ± 8.7 years.

The patients were divided into the following groups based on the extent of arachnoid dissection: Group A, patients with ICA aneurysm ($n = 21$) and proximal A1 aneurysm ($n = 1$); Group B, patients with AcoA aneurysm ($n = 23$) and concomitant aneurysm arising at ICA and AcoA ($n = 2$); Group C, patients with MCA aneurysm ($n = 54$); and Group D, patients with concomitant aneurysm arising at AcoA and MCA ($n = 7$) and concomitant aneurysm arising at ICA and MCA ($n = 8$).

Postoperative CSDH

Of the 120 patients, 22 (18.3%) were diagnosed with CSDH. Of these 22 patients, 19 (%) experienced spontaneous resolution of CSDH, as observed in follow-up CT scans. Due to neurological deterioration, three patients underwent surgical burr hole drainage, all of whom had preserved MMA. One patient experienced CSDH recurrence and subsequently underwent reoperation and transfemoral angiography for MMA embolization (Figure 2A). Superselective angiography of the anterior branch of the MMA showed a diffuse vascular network, consistent with microcapillaries, in the outer membrane of the CSDH (Figure 2B). After MMA embolization and repeated burr hole drainage, the patient recovered without any neurological deficit.

Identification of the middle meningeal artery

This study investigated the preoperative presence of the anterior division of the MMA in all 120 patients in the axial view of MR angiography. The imaging outcomes, showing the pre-and

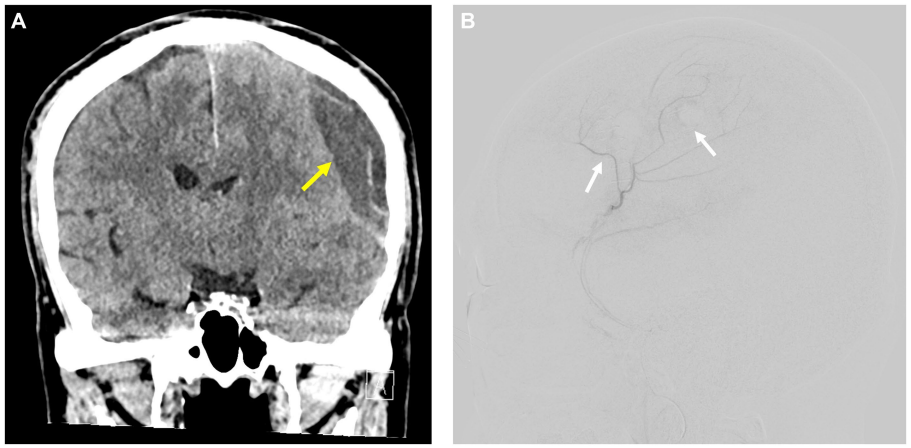


FIGURE 2
(A) Recurrent postoperative CSDH following unruptured aneurysm surgery (yellow arrow). **(B)** Superselective angiography of the anterior branch of the MMA in a patient with recurrent postoperative CSDH showing a widespread capillary network aligned with the microvascular structures found in the external layer of the chronic subdural hematoma (white arrow).

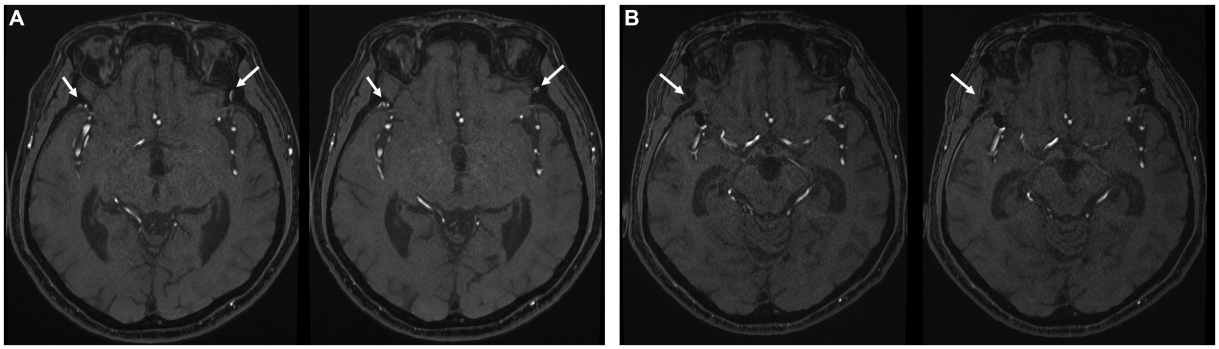


FIGURE 3
(A) Preoperative MR angiography showing the bilateral anterior branch of MMA (white arrow). **(B)** Postoperative MR angiography showing obliteration of the right anterior branch of MMA after pterional craniotomy (white arrow).

postoperative states of the MMA, are presented in Figures 3A,B. Preservation of the anterior branch of the MMA after unruptured aneurysm surgery was confirmed in 65 patients. Specifically, 60 of these patients underwent LSO craniotomy, all of whom demonstrated postoperative MMA preservation. Furthermore, despite the proximity of the sphenoid ridge bone work to the anterior division of the MMA during pterional craniotomy, five patients still exhibited postoperative preservation of the anterior division of the MMA.

Risk factors for chronic subdural hematoma

Univariate analysis revealed that male sex ($p = 0.008$), advanced age ($p < 0.001$), LSO surgical approach ($p = 0.005$), and MMA preservation ($p = 0.004$) were all risk factors for postoperative CSDH. However, aneurysm location according to the extent of arachnoid dissection was not a significant risk factor in this study ($p = 0.329$) (Table 2).

Similarly, multivariate analysis revealed that male sex [odds ratio (OR), 5.535; 95% confidence interval (CI), 1.756–17.451; $p = 0.003$], advanced age (OR, 7.588; 95% CI, 2.262–25.452; $p = 0.001$), and MMA preservation (OR, 4.698; 95% CI, 1.343–16.435; $p = 0.015$) were risk factors for CSDH (Table 3).

Clinical outcomes

Among the 22 patients who developed CSDH, 19 experienced spontaneous resolution without significant neurological deficits and recovered without any neurological impairment. Of them, three required surgical intervention for CSDH and recovered well, although one experienced CSDH recurrence.

Discussion

Postoperative CSDH is an underrecognized complication of unruptured aneurysm clipping surgery. Previous studies have shown

TABLE 2 Risk factors for chronic subdural hematoma following unruptured aneurysm surgery on univariate analysis.

Characteristics	Chronic subdural hematoma	Nonchronic subdural hematoma	*p*-value
Patient	22	98	
Sex			
Male	12	25	0.008
Age >65	17	35	<0.001
Aneurysm location			0.329
Group A	6	16	
Group B	5	20	
Group C	7	51	
Group D	4	11	
Surgical approach			0.005
Pterional	5	55	
Lateral supraorbital	17	43	
MMA preservation	47	18	0.004

TABLE 3 Risk factors for chronic subdural hematoma following unruptured aneurysm surgery on multivariate analysis.

Variable	OR	95% CI	*p*-value
Male	5.535	1.756–17.451	0.003
Age >65	7.588	2.262–25.452	0.001
MMA preservation	4.698	1.343–16.435	0.015

that advanced age, male sex, and extensive arachnoid dissection are risk factors for postoperative CSDH (4, 5, 11–13). Similarly, the present study demonstrated that advanced age and male sex are risk factors for CSDH.

Park et al. (4) reported on the incidence of chronic subdural hematoma (CSDH) and subdural hygroma after unruptured cerebral aneurysm surgeries. However, that analysis was imbalanced due to the predominant use of the supraorbital approach in 79.7% of cases, as opposed to the pterional approach in only 20.3%. In addition, the documentation of middle meningeal artery (MMA) preservation was not methodically executed in that study.

This study is unique in that it investigated the implications of preserving the anterior branch of the MMA during unruptured aneurysm clipping and its association with the incidence of postoperative CSDH.

The underlying mechanisms of CSDH formation remain unclear. However, it seems to stem from the detachment of the border cell layer within the dura, initiating a series of healing processes, such as cell proliferation at the dura border, granulation tissue formation, and macrophage activity (7, 14). This ultimately results in neovascularization of the hematoma membrane.

Previous studies have reported that vessels from the MMA can pass through the dura mater and link with emerging neovessels in the external CSDH membrane. Consequently, MMA appears to have a significant influence on the genesis of CSDH and its recurrence, given the vulnerability of these neovessels (6). There is a growing belief that primary expansion and reoccurrence of CSDH are influenced by blood supply to these membranes. This understanding has prompted the use of endovascular embolization techniques targeting MMA as a promising strategy to mitigate recurrence following hematoma drainage (15, 16).

Pterional craniotomy is a commonly used surgical approach that allows access to the anterior cranial fossa and circle of Willis (8, 9, 17, 18). A crucial phase of this operation is the meticulous drilling of the sphenoid ridge, which expands the surgical field. The MMA enters the middle cranial fossa by passing through the foramen spinosum. After entering the middle cranial fossa, the MMA courses anterosuperiorly over the greater wing of the sphenoid bone. It then divides into two main branches: anterior and posterior. The anterior branch courses over the pterion, running forward and medially on the sphenoid ridge (19, 20). By beveling the prominence of the sphenoid ridge, a surgeon can enhance visibility and access to the skull base. During this step, the anterior branch of the MMA is cauterized.

Haldrup et al. (6) reported that CSDH mainly occurs in the anterior region and is predominantly supplied by the anterior branch of the MMA. They also found that deliberate occlusion of the anterior branch of the MMA during a burr hole procedure can reduce the recurrence rates of CSDH, suggesting that similar MMA coagulation during pterional craniotomy influences the occurrence of postoperative CSDH following unruptured aneurysm surgery (6). This finding indicates the potential impact of anterior MMA management on postoperative outcomes.

The present study demonstrates that preservation of the anterior branch of the MMA during unruptured aneurysm surgery is a risk factor for postoperative CSDH.

According to our data, five patients had preserved the anterior branch of the MMA despite routine sphenoid ridge bone work during pterional craniotomy. Due to the retrospective nature of this study, it is unclear how reliably MMA was coagulated during pterional craniotomy. In these five patients, the pterional approach could have been performed without MMA coagulation or the MMA flow could have been restored despite coagulation.

In previous study, Park et al. (4) identified extensive arachnoid dissection as a contributing factor to CSDH development. Furthermore, Han et al. (5) have associated extensive arachnoid dissection with the occurrence of subdural hygroma and found that the volume of collected subdural fluid is a predictor of CSDH. However, in the present study, we did not find a direct association between the degree of arachnoid dissection and the incidence of CSDH.

Efforts to prevent postoperative CSDH from subdural hygroma have yielded promising outcomes through obstruction of the CSF—subdural space interface. This was achieved by applying fibrin glue to close the arachnoid membrane in the Sylvian fissure during aneurysm surgery (12). Nonetheless, there have been reports of allergic reactions to the fibrin adhesive used in arachnoid plasty, and a comprehensive evaluation of the advantages and potential risks based on extensive case studies is still lacking (21).

This study has several limitations. First, the retrospective nature of the data review from a single institution could introduce selection bias, potentially affecting the generalizability of the results. Second, the relatively small sample size limits the statistical power of our findings and may not sufficiently represent the broader patient population. Finally, variations in surgical technique and individual surgeon experience could have influenced the outcomes, although we attempted to mitigate this by having all surgeries performed by

experienced neurosurgeons. Despite these limitations, our findings might provide valuable insights into the risk factors associated with CSDH after unruptured aneurysm surgery.

Conclusion

Preservation of the anterior branch of the MMA during unruptured aneurysm surgery is a risk factor for postoperative CSDH development. Advanced age and male sex also contribute to increased risk. These findings may provide useful information for predicting postoperative CSDH following unruptured aneurysm surgery. Further studies are warranted to elucidate these findings.

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

The studies involving humans were approved by the Ethics Committee of Kyungpook National University Chilgok Hospital (IRB No. 2023-10-027). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because of the retrospective nature of the study.

Author contributions

MK: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Park J, Woo H, Kang D-H, Sung J-K, Kim Y. Superciliary keyhole approach for small unruptured aneurysms in anterior cerebral circulation. *Neurosurgery*. (2011) 68:300–9. doi: 10.1227/NEU.0b013e3182124810

2. Moroi J, Hadeishi H, Suzuki A, Yasui N. Morbidity and mortality from surgical treatment of unruptured cerebral aneurysms at Research Institute for Brain and Blood Vessels-Akita. *Neurosurgery*. (2005) 56:224–31. doi: 10.1227/01.NEU.0000148897.28828.85

3. Hernesniemi J, Ishii K, Niemelä M, Smrcka M, Kivipelto L, Fujiki M, et al. Lateral supraorbital approach as an alternative to the classical pterional approach. *Acta Neurochir Suppl*. (2005) 94:17–21. doi: 10.1007/3-211-27911-3_4

4. Park J, Cho J-H, Goh D-H, Kang D-H, Shin IH, Hamm I-S. Postoperative subdural hygroma and chronic subdural hematoma after unruptured aneurysm surgery: age, sex, and aneurysm location as independent risk factors. *J Neurosurg*. (2016) 124:310–7. doi: 10.3171/2015.1.JNS14309

5. Han HJ, Kim J-J, Park KY, Park SK, Chung J, Kim YB. Subdural hygroma and hemorrhagic conversion after microsurgical clipping for unruptured intracranial aneurysm. *Acta Neurochir*. (2023) 165:1251–60. doi: 10.1007/s00701-023-05555-0

6. Haldrup M, Munyemana P, Ma'aya A, TSR J, Fugleholm K. Surgical occlusion of middle meningeal artery in treatment of chronic subdural haematoma: anatomical and technical considerations. *Acta Neurochir*. (2021) 163:1075–81. doi: 10.1007/s00701-021-04754-x

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. Vishteh AG, Marciano FF, David CA, Baskin JJ, Spetzler RF. The pterional approach. *Oper Tech Neurosurg*. (1998) 1:39–49. doi: 10.1016/S1092-440X(98)80007-8

9. Yaşargil MG, Reichman MV, Kubik S. Preservation of the frontotemporal branch of the facial nerve using the interfascial temporalis flap for pterional craniotomy: technical article. *J Neurosurg*. (1987) 67:463–6. doi: 10.3171/jns.1987.67.3.0463

10. Esposito G, Dias SF, Burkhardt J-K, Fierstra J, Serra C, Bozinov O, et al. Selection strategy for optimal keyhole approaches for middle cerebral artery aneurysms: lateral supraorbital versus minipterional craniotomy. *World Neurosurg*. (2019) 122:e349–57. doi: 10.1016/j.wneu.2018.09.238

11. Inamasu J, Watabe T, Ganaha T, Yamada Y, Nakae S, Ohmi T, et al. Clinical characteristics and risk factors of chronic subdural haematoma associated with clipping of unruptured cerebral aneurysms. *J Clin Neurosci*. (2013) 20:1095–8. doi: 10.1016/j.jocn.2012.09.024

12. Lee WJ, Jo K-I, Yeon JY, Hong S-C, Kim J-S. Incidence and risk factors of chronic subdural hematoma after surgical clipping for unruptured anterior circulation aneurysms. *J Korean Neurosurg Soc*. (2015) 57:271–5. doi: 10.3340/jkns.2015.57.4.271

13. Mori K, Maeda M. Risk factors for the occurrence of chronic subdural haematomas after neurosurgical procedures. *Acta Neurochir*. (2003) 145:533–40. doi: 10.1007/s00701-003-0026-1

14. 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.

15. Ironside N, Nguyen C, Do Q, Ugiliweneza B, Chen C-J, Sieg EP, et al. Middle meningeal artery embolization for chronic subdural hematoma: a systematic review and meta-analysis. *J NeuroInterv Surg*. (2021) 13:951–7. doi: 10.1136/neurintsurg-2021-017352

16. Catapano JS, Nguyen CL, Wakim AA, Albuquerque FC, Ducruet AF. Middle meningeal artery embolization for chronic subdural hematoma. *Front Neurol*. (2020) 11:557233. doi: 10.3389/fneur.2020.557233

17. Krayenbühl HA, Yaşargil MG, Flamm ES, Tew JM. Microsurgical treatment of intracranial saccular aneurysms. *J Neurosurg*. (1972) 37:678–86. doi: 10.3171/jns.1972.37.6.0678

18. Yasargil MG, Antic J, Laciga R, Jain KK, Hodosh RM, Smith RD. Microsurgical pterional approach to aneurysms of the basilar bifurcation. *Surg Neurol*. (1976) 6:83–91.

19. Al Aiyan A, Balan R. Comprehensive anatomical study of meningeal arteries in dromedaries. *Sci Rep*. (2023) 13:19803. doi: 10.1038/s41598-023-47145-1

20. Tayebi Meybodi A, Mignucci-Jiménez G, Lawton MT, Liu JK, Preul MC, Sun H. Comprehensive microsurgical anatomy of the middle cranial fossa: part II—neurovascular anatomy. *Front Surg*. (2023) 10:1132784. doi: 10.3389/fsurg.2023.1132784

21. Kanazawa R, Sato S, Iwamoto N, Teramoto A. Allergic reaction following arachnoid plasty with a fibrin sealant-case report-: —case report. *Neurol Med Chir*. (2010) 50:608–10. doi: 10.2176/nmc.50.608

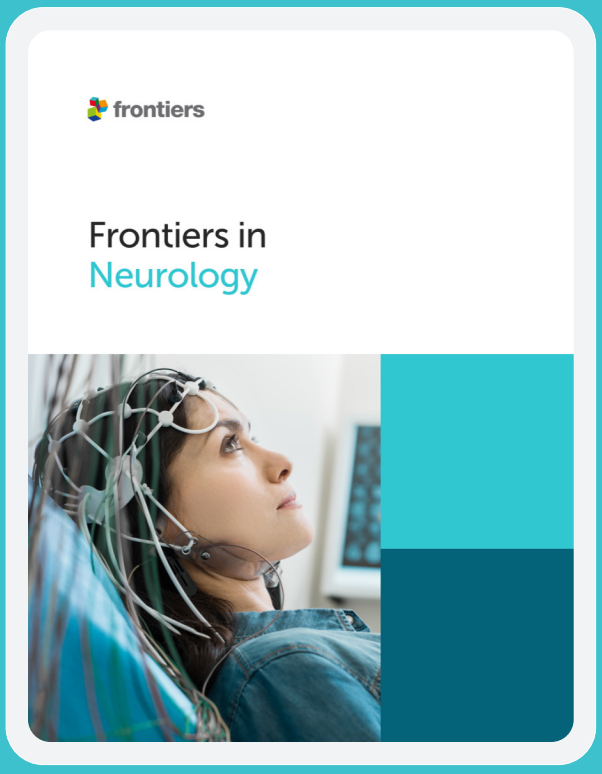
Frontiers in Neurology

Explores neurological illness to improve patient care

The third most-cited clinical neurology journal explores the diagnosis, causes, treatment, and public health aspects of neurological illnesses. Its ultimate aim is to inform improvements in patient care.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact