Tampere University

MINNA RAUHALA

Chronic Subdural Hematoma

Incidence, Outcome and Cost

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ACADEMIC DISSERTATION
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Tampere, August 2020

Minna Rauhala

ABSTRACT

Chronic subdural hematoma (CSDH) represents a common disease in neurosurgical practice, especially among elderly patients. The degeneration of the brains allows the space for CSDH to develop. Other well-known risk factors for CSDH include trauma, alcohol overuse, and antithrombotic therapy.

Surgery is recommended for CSDH patients with neurological symptoms. Burr-hole drainage is the preferred technique. Recurrence is common, ranging from 5% to 30%. The recurrence rate can be decreased with the use of external drains.

Follow-up head computed tomography (CT) scans have been used to assess the possible recurrence of CSDH and the best time to restart antithrombotic therapy, if necessary, or allow the patient to begin exercising or driving again. However, the benefits and costs of routine follow-up head CT scans need to be evaluated. No consensus for how long these patients should continue to be followed exists.

CSDH has long been considered as a benign condition with an excellent outcome. This conclusion arises from the study of selected surgically treated patients. The statistics on the incidence, outcome and cost of all CSDH patients are not so well established. In general, CSDH patients come from an age group with a high baseline mortality. The excess mortality potentially resulting from CSDH needs to be compared to a matched sample from the general population. As the global population of people aged 80 and older is expected to more than triple between 2015 and 2050, CSDH represents an important issue in public health.

This study first aimed to determine the population-based epidemiology of CSDH over a 26-year period from 1990 to 2015 in a defined Finnish population. A large unselected patient cohort (n=1,148) was collected by reviewing consecutive CSDH cases who had lived in the Pirkanmaa region and were treated in the Tampere University Hospital between 1990 and 2015. Also, death certificates for clinically undiagnosed CSDH (n=20) from this period were reviewed.

The second objective was to assess possible long-term excess mortality and the causes of death of patients with CSDH. We compared our CSDH patient cohort to the general population from the same region, matched by sex, age, and calendar time. The causes of death of the CSDH patients were compared to a separate matched reference group.

Thirdly, the study intended to estimate the total direct hospital costs of CSDH treatment from hospital admission until the last neurosurgical follow-up visit in a neurosurgical clinic during a 26-year study period. Related to the costs, we also aimed to evaluate the necessity of a pre-scheduled routine follow-up CT after CSDH.

We concluded that the burden of CSDH has increased markedly in the Pirkanmaa region from 1990 to 2015. The overall incidence of CSDH doubled from 8 to 18/100,000/year. Among adults under 70 years old, the incidence remained quite stable, whereas the incidence nearly tripled among the over 80-year old population, from 47 to 130/100,000/year. The incidence was higher for men than for women after the age of 60 years. The use of antithrombotics has increased (27%-49%), but no change has occurred regarding the ratio between a traumatic (60%) and a spontaneous (40%) CSDH etiology.

Patients with CSDH had long-term excess mortality, which cumulated over time from 9% at one year to 48% at 20 years after CSDH diagnosis. Patient-related characteristics, especially chronic alcohol abuse, anticoagulant medication use, and neurological disability both at admission and at discharge were strongly associated with excess mortality, whereas specific CSDH-related findings were not. A subgroup of patients (n=206) with no comorbidities displayed no excess mortality.

The overall prevalence of dementia in CSDH patients aged 70 years or older was 12%, which is comparable to the prevalence in the population. Even so, dementia represented the most common cause of death among the CSDH patients (21%), but the third most common cause in the reference group (15%, $p<0.001$). As a cause of death, dementia occurred later in CSDH patients than in the reference group. CSDH seemed to increase the risk of dementia.

Despite the increased number of cases, direct hospital costs declined in more recent years. This have occurred in large part due to shortened hospital stays and fewer recurrences of CSDH related to use of subdural drains. The mean cost per patient treated surgically was 4,140 € (min-max=2,170-30,100 €) during the latest study period 2011-2015. The total direct hospital costs averaged 231,000 € per year in 2011-2015, of which 4% (8,300 €) occurred thanks to non-operatively treated patients. Head CT scans accounted for 12% (28,100 €) of the total cost.

Routine four to six weeks' postoperative follow-up head CT scans increased the number of reoperations and thus costs, because asymptomatic patients were operated on due to radiological CSDH recurrence. The majority (92%) of recurrences occurred within 60 days. A two-month follow-up period after CSDH seems sufficient for most, and head CT scan controls are advocated only for symptomatic patients.

In conclusion, the incidence of CSDH has increased markedly among the elderly population. Some excess mortality related to CSDH has occurred, but the comorbidities of CSDH, rather than the disease itself, appear the cause of this excess mortality. Preventive measures that consider prior health conditions as well as fall-related injury risk factors that predispose patients to CSDH should be implemented. Direct hospital costs have not increased in the most recent years, because the mean hospital costs per patient have decreased. The use of follow-up head CT scans for asymptomatic CSDH patients should be minimized.

TIIVISTELMÄ

Krooninen kovakalvonalainen verenpurkauma on tavallinen neurokirurgien hoitama sairaus. Suurin osa potilaista on iäkkäitä. Ikääntymiseen liittyvä aivojen surkastuminen (atrofia) ja kovakalvonalaisen tilan laajentuminen on kroonisen kovakalvonalaisen verenpurkauman tärkein riskitekijä. Muita riskitekijöitä ovat tapaturmat, alkoholin liikakäyttö ja verenhyytymistä estävä (verihiutaleiden estäjät ja antikoagulantit) lääkitys.

Leikkausta suositellaan potilaille, joilla krooninen kovakalvonalainen verenpurkauma aiheuttaa neurologisia oireita, kuten päänsärkyä, puhevaikeutta ja halvausoireita. Tavallisin leikkaustapa on paikallispuudutuksessa tehtävä verenpurkauman tyhjentäminen kalloon tehdyn porareiän (trepanaatio) kautta. Krooninen kovakalvonalainen verenpurkauma uusii 5-30%:lla potilaista. Uusimista vähentää, jos leikkauksen lopuksi jätetään laskuputki eli dreeni.

Seurannassa käytetään pään tietokonetomografia (TT) -kuvausta arvioimaan verenpurkauman uusimista ja sitä, koska on turvallista jatkaa mahdollista verenhyytymistä estävää lääkitystä, kovempaa fyysistä rasitusta tai autolla ajoa. Kontrollikuvauksen hyötyä uusineen verenpurkauman toteamiseksi ei kuitenkaan tiedetä. Yleistä ohjeistusta näiden potilaiden seurantaan ei ole.

Kroonista kovakalvonalaista verenpurkaumaa on pidetty varsin hyvänlaatuisena ja asianmukaisesti hoidettuna hyväennusteisena sairautena. Tämä perustuu kuitenkin leikattujen potilaiden aineistoihin, joista huonokuntoiset on karsittu pois. Potilaat ovat iäkkäitä ja yleisesti ottaen sairastavuus ja kuolleisuus lisääntyvät iän myötä. Mahdollista ylikuolleisuutta ei näin ollen ole mahdollista arvioida ilman ikävakioitua vertailuryhmää. Laajoja väestötason tutkimuksia aiheesta ei ole.

Tässä väitöskirjassa selvitettiin ensin kroonisen kovakalvonalaisen verenpurkauman ilmaantuvuutta ja riskitekijöitä vuosina 1990-2015 Pirkanmaalla. Keräsin takautuvasti kaikki pirkanmaalaiset yli 18-vuotiaat tapaukset (n=1,148) sairaskertomuksista. Lisäksi saman aikajakson kuolintodistuksista löysin 20 tapausta, joilla krooninen kovakalvonalainen verenpurkauma oli jäänyt diagnosoimatta elinaikana.

Toiseksi arvioitiin krooniseen kovakalvonalaiseen verenpurkaumaan liittyvää mahdollista ylikuolleisuutta ja potilaiden kuolemansyitä. Vertasimme potilaita ikä-,

sukupuoli- ja kalenteriaikavakioituun Pirkanmaan väestöön. Potilaiden kuolemansyitä vertasimme erilliseen viiteryhmään.

Kolmanneksi arvioitiin krooniseen kovakalvonalaiseen verenpurkaumaan liittyviä sairaalahoidon kokonaiskustannuksia diagnoosihetkestä viimeiseen kontrollikäyntiin 26 vuoden tutkimusaikana. Kustannuksiin liittyen arvioimme myös pään TT-kontrollikuvauksen aiheellisuutta.

Vuosina 1990-2015 kroonisen kovakalvonalaisen verenpurkauman ilmaantuvuus on kaksinkertaistunut 8 – 18/100,000/vuosi Pirkanmaalla. Alle 70-vuotiailla ilmaantuvuus on pysynyt melko vakaana, mutta yli 80-vuotiailla ilmaantuvuus on melkein kolminkertaistunut 47 – 130/100,000/vuosi. Yli 60-vuotiailla miehillä ilmaantuvuus oli naisia korkeampi. Verenhyytymistä estävien lääkkeiden käyttö lisääntyi 27%:sta 49%:iin, mutta tapaturmaisen (60%) ja ei-tapaturmaisen (40%) verenpurkauman suhde ei muuttunut.

Kroonisen kovakalvonalaisen verenpurkauman sairastaneilla potilailla oli ylikuolleisuutta 9% ensimmäisen vuoden aikana ja 48% 20 vuotta diagnoosista. Potilaaseen liittyvät tekijät, etenkin pitkäaikainen alkoholin väärinkäyttö, antikoagulanttilääkitys ja neurologinen tilanne hoitoon tullessa sekä sen jälkeen, liittyivät ylikuolleisuuteen vahvasti, toisin kuin itse verenpurkaumaan liittyvät löydökset. Potilailla (n=206), joilla ei ollut pitkäaikaissairauksia, ei todettu ylikuolleisuutta.

Dementiaa sairasti 12% yli 70 vuotiaista potilaista, mikä on samaa luokkaa kuin normaaliväestössä. Dementia oli tavallisin kuolemansyy (21%) kroonisen kovakalvonalaisen verenpurkauman sairastaneilla potilailla. Verrokkiryhmällä dementia oli kuitenkin vasta kolmanneksi tavallisin kuolemansyy (15%, $p<0.001$). Kuolemansyynä dementia esiintyi myöhemmin kuin verrokkiväestöllä. Näin ollen, krooninen kovakalvonalainen verenpurkauma voi lisätä dementian riskiä.

Sairaalahoidon kokonaiskustannukset ovat alun kasvun jälkeen vähentyneet viime vuosina lisääntyneestä tapausten lukumäärästä huolimatta. Tämä selittyy lyhentyneillä sairaalahoitojaksoilla ja vähentyneillä uusintaleikkauksilla. Jälkimmäinen liittyy lisääntyneeseen laskuputkien käyttöön. Leikatun potilaan sairaalahoidon kokonaiskustannukset olivat keskimäärin 4,140 € (min-max=2,170-30,100 €) viimeisten vuosien 2011-2015 aikana. Kaikkien pirkanmaalaisten potilaiden vuosikustannukset olivat tällä aikajaksolla 231,000 €. Konservatiivisesti hoidettujen potilaiden osuus kustannuksista oli 4% (8,300 €) ja pään TT-kuvausten osuus 12% (28,100 €).

Rutiininomaiset TT-kontrollikuvaukset lisäsivät uusintaleikkauksia ja kuluja, koska oireettomia potilaita leikattiin kuvauslöydöksen takia. Suurin osa (92%)

verenpurkaumien uusiutumisista ilmaantui 60 vuorokauden kuluessa. Kahden kuukauden seuranta kroonisen kovakalvonalaisen verenpurkauman jälkeen vaikuttaa riittävältä ja TT-kontrollikuvaus lienee aiheellinen ainoastaan oireiden yhteydessä.

Yhteenvetona voidaan todeta, että kroonisen kovakalvonalaisen verenpurkauman ilmaantuvuus on kasvanut merkittävästi iäkkään väestön keskuudessa. Todettu ylikuolleisuus vaikuttaa liittyvän potilaan muihin sairauksiin, ei itse verenpurkaumaan. Näin ollen ylikuolleisuutta voidaan vähentää ennaltaehkäisevillä toimenpiteillä, jotka kohdentuvat pitkäaikaissairauksiin ja kaatumisriskiin. Sairaalakustannukset eivät ole nousseet, koska yksittäisen potilaan hoitokustannukset ovat pienentyneet. Oireettomien potilaiden kuvantamisseurantaan tulisi olla jokin erityisperuste.

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ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ASA	Acetylsalicylic acid
BHC	Burr hole craniostomy
CI	Confidence interval
CSDH	Chronic subdural hematoma
CSF	Cerebrospinal fluid
CT	Computed tomography
DAVF	Dural arteriovenous fistula
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale Extended
GCS	Glasgow Coma Scale
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	Intracerebral hemorrhage
INR	International normalized ratio
IQR	Interquartile range
MLS	Midline shift
MMA	Middle meningeal artery
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk=Risk ratio
SASDH	Subacute subdural hematoma
SD	Standard deviation
SDH	Subdural hematoma
TBI	Traumatic brain injury
TDC	Twist drill craniostomy
TXA	Tranexamic acid
VEGF	Vascular endothelial growth factor

ORIGINAL PUBLICATIONS

This thesis is based on the following three original publications, which are referred to in the text by their Roman numerals I-III. The publications have been reprinted with the kind permission of the copyright holders. Also, some results not included in the publications are presented in the thesis.

I Rauhala M, Luoto TM, Huhtala H, Iverson GL, Niskakangas T, Öhman J, Helén P: The incidence of chronic subdural hematomas from 1990 to 2015 in a defined Finnish population. J Neurosurg. 2019;1-11. doi:10.3171/2018.12.JNS183035

II Rauhala M, Helen P, Seppa K, Huhtala H, Iverson GL, Niskakangas T, Öhman J, Luoto TM: Long-term excess mortality after chronic subdural hematoma. Acta Neurochir (Wien). 2020;162(6):1467-1478. doi:10.1007/s00701-020-04278-w

III Rauhala M, Helén P, Huhtala H, Heikkilä P, Iverson GL, Niskakangas T, Öhman J, Luoto TM. Chronic Subdural Hematoma - Incidence, Complications, and Financial Impact. Acta Neurochir (Wien). 2020;162(9):2033-2043. doi:10.1007/s00701-020-04398-3

1 INTRODUCTION

Chronic subdural hematoma (CSDH) represents a common disease in neurosurgical practice, particularly among elderly patients[4, 16, 28, 196]. The reported annual incidence of CSDH has ranged widely from 1.7 to 20.6 per 100,000 across studies[339]. Although an increase in the number of cases of CSDH has been noted for decades, no large-scale population-based studies have been published[339]. The few studies published to date have examined small patient cohorts[5, 16, 89, 161] and national registries[97, 147]. Moreover, the published epidemiology of CSDH has been predominantly based on surgical series, where the non-operatively treated patients are missing[20, 36, 100, 152, 204, 250, 261]. Furthermore, post-mortem studies examining undiagnosed CSDH cases are lacking. Therefore, true incidence rates are unknown.

The underlying reasons for the greater incidence of CSDH among the elderly are not fully understood. Speculated causes for this phenomenon include brain atrophy[170, 184, 338], high number of falls[98, 239, 289], and broad use of antithrombotic medication[3, 63, 70, 97, 181, 214] within this population. Compared to women, men demonstrate a greater risk for CSDH[339]. The reasons underlying the gender difference are not well studied[44]. Only a few reports have examined gender-related incidences in different age groups[24, 89, 97].

The age-related increase in incidence combined with the growing elderly population[117] poses a major challenge for neurosurgical clinics because a large proportion of these patients are managed operatively[158]. Surgical treatment is recommended in CSDH patients with neurological symptoms, and the preferred surgical technique is burr-hole drainage[200, 285]. Recurrence is common, ranging from approximately 5% to 30%. A reduced recurrence rate is observed with postoperative external subdural drains[185, 230, 325].

Follow-up postoperative head computed tomography (CT) scan can potentially detect recurrent CSDH before clinical deterioration occurs[77]. A concern has been raised, however, that unnecessary revision surgery without symptoms and increased costs may outweigh the benefit of follow-up scanning[229]. The usefulness of follow-up CT to predict symptomatic recurrence is questionable[271]. No guidelines exist on how, or for how long, CSDH patients should be followed.

Generally, CSDH has been considered a relatively benign disease entity. However, almost all the case series published to date come from neurosurgical clinics. These series have tended to include only surgically treated cases, thus excluding conservatively treated patients with multiple comorbidities. Nevertheless, recent years have seen the recognition that CSDH results in worse outcomes than previously assumed[78, 189, 202]. Recent research has speculated that CSDH may represent a sentinel health event, a harbinger of subsequent morbidity and mortality[28, 78, 202]. Age-related brain degeneration with an enlarged potential subdural space is assumed to serve as an important risk factor for CSDH[170, 184, 338]. Conversely, CSDH itself has been associated with a significant increase in the degree of brain atrophy post-CSDH[34].

Reported mortality rates after CSDH vary widely across studies, and a one-year mortality rate of up to 32% has been reported[202]. In general, CSDH patients are from an age group with high baseline expected mortality. Reaching reliable conclusions on whether CSDH is related to excess mortality is not possible without comparing these patients to a matched sample from the general population. No prior studies report long-term mortality in CSDH patients compared to a matched sample from the general population in an unselected, population-based series. Additionally, only two studies have previously reported the causes of death after the diagnosis of CSDH[140, 189].

The global population of people aged 80 and older is expected to more than triple between 2015 and 2050[117]. During this period, the number of 80-89 years old Finns has been estimated to double from 237,939 to 482,554 (Statistics Finland)[218]. Similarly, the number of Finns over 90 years of age will likely almost quadruple from 45,542 to 162,616. Consequently, the healthcare burden from CSDH is growing. Only few studies have described the financial impact of CSDH, one from Switzerland and two from the USA[93, 94, 271].

In this study, we collected and analyzed a large (n=1,148) population-based cohort of patients with CSDH to study the epidemiology, treatment, complications and financial impact of CSDH over a 26-year period from 1990 to 2015 in a defined Finnish population. In addition, we compared the survival of the CSDH patients to the matched general population. Furthermore, we compared the causes of death of the CSDH patients to a separate matched reference group.

2 REVIEW OF THE LITERATURE

2.1 Chronic Subdural Hematoma (CSDH)

2.1.1 History

Trephination, which remains the modern treatment of choice for chronic subdural hematoma (CSDH), has been performed long before CSDH was characterized as a disease entity[171, 324]. It is a surgical procedure, where a hole is drilled, incised or scraped into the skull using simple surgical tools[171]. Trephination is the oldest known surgical procedure and has been practiced since the late Paleolithic era (12 000 BCE) in virtually every part of the world[108]. The overall long-term survival of the trephined in Peru during the Inca period (1400-1500 ACE) has been approximated as high as 83%[165]. The purpose of the ancient trephinations can only be speculated and probably differed with time and cultures[108, 171]. Occasionally, black liquid blood would drain out from the skull accompanied by a rapid recovery of the trephined, which probably encouraged the early surgeons[171, 324].

Johann Wepfer gave the first pathological description of CSDH ('bloody cyst') in 1657[171, 259, 324]. In 1857, Rudolph Virchow described the histology and formation of the membranes and named it 'pachymeningitis hemorrhagica chronica interna'[171, 259, 324]. His theory of inflammation of the dura was widely accepted until Wilfried Trotter proposed a traumatic etiology in 1914 and suggested the name 'chronic subdural hematoma'[310]. Many different theories have arisen since to explain the latent interval between trauma and the onset of symptoms in patients with CSDH[120].

The first description of successful surgical treatment of CSDH was published by James Hill in 1751[120]. In 1925, Tracy Jackson Putnam and Harvey Cushing reviewed 50 patients observing that surgical evacuation of CSDH represented the treatment of choice[246]. They advocated the importance of early diagnosis. However, until the beginning of the twentieth century, the diagnosis of CSDH was clinical. Because CSDH displays no pathognomonic symptoms or signs, the disease was often diagnosed postmortem[246].

Finally, two radiological inventions revolutionized the diagnostics. Walter E. Dandy introduced the 'pneumoencephalography' in 1918[68] and Egas Moniz the 'arterial encephalography' in 1927[186]. Although both imaging techniques visualized indirect signs of intracranial masses, it then became possible to diagnosis and treat CSDH earlier. The direct visualization of the hematoma became possible after the invention of CT scan in the 1970s and magnetic resonance imaging (MRI) in the 1980s[183].

2.1.2 Definition

Chronic subdural hematoma (CSDH) is an encapsulated collection of fluid, blood, and blood degradation products layered between the arachnoid mater and dura mater meninges on the brain's surface (Figure 1)[81, 120].

Subdural hematoma (SDH) is divided into three types: acute (ASDH; within 3 days of trauma), subacute (SASDH; 4-20 days), and chronic (after 20 days)[106, 198]. These types show different clinico-radiological characteristics. However, no definition of CSDH is universally accepted[129]. In particular, the distinction between subacute and chronic SDH is not always obvious, both in relation to time and neuroradiological features. In the 10th revision of the International Classification of Diseases (ICD-10), SDH is only classified as either traumatic or nontraumatic[331].

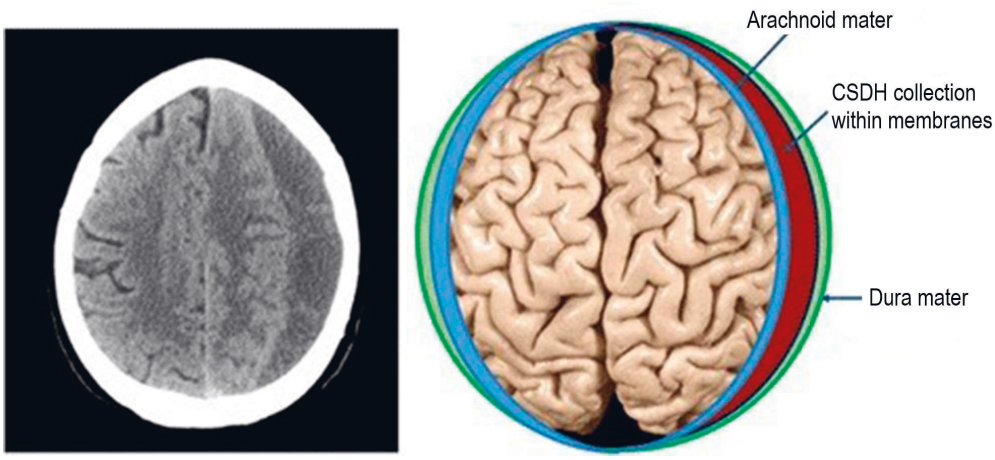


Figure 1. Computed tomography (CT) head scan and schematic representation of a CSDH. Reprinted with Open Access permission from Edlmann et al. 2017. http://creativecommons.org/publicdomain/zero/1.0/

2.1.3 Pathophysiology

CSDH is produced by multiple origins. It can develop spontaneously or modulate from a subdural hygroma or acute subdural hematoma[170]. Following trauma, which is often minor or not even evident, a complex process of inflammation, membrane formation, angiogenesis, and fibrinolysis appears to occur. This eventually leads to the formation of a CSDH that increases in size[81, 120].

The dura is lined with a layer of connective tissue cells, "dural border cells," which is considered as the location of origin of CSDH[112, 128, 173]. Following the pathological cleavage of the dural border cells, two membranes are formed, enclosing a cavity that fills with cerebrospinal fluid (CSF) and blood. The thin internal membrane contiguous to the arachnoid mater is non-functional with respect to CSDH growth[267]. The thick external membrane contains fibroblasts and collagen fibers with an abundance of inflammatory cells such as neutrophils, lymphocytes, macrophages, and eosinophils[91, 131, 143, 291]. Angiogenic stimuli lead to the creation of fragile blood vessels within membrane walls, whilst fibrinolytic processes prevent clot formation, which results in continued hemorrhage[131]. The highly vascular and permeable external membrane serves as the source of inflammatory mediators as well as regular bleedings[81].

The development of CSDH requires sufficient potential subdural space, or else absorption of the subdural fluid exceeds expansion and the subdural fluid will settle[170]. Degeneration of the brain leads to brain atrophy and shrinks the volume of the brain within the cranial vault, thus predisposing the patient to CSDH[170, 338].

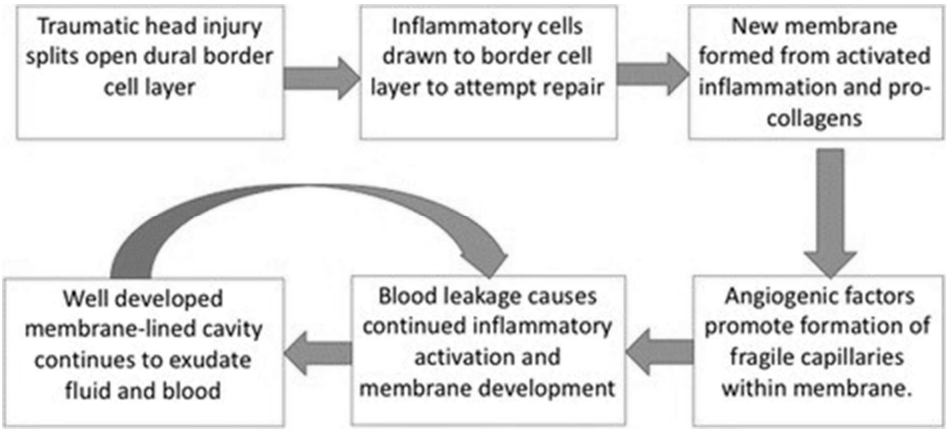


Figure 2. The CSDH cycle. Summary of the pathophysiological processes involved in the formation of a CSDH. Reprinted with Open Access permission from Edlmann et al. 2017. http://creativecommons.org/publicdomain/zero/1.0/

2.1.4 Incidence

A previous study by Fogelholm and Waltimo with 64 Finnish patients (1967-1973) showed that CSDH occurred at a rate of 1.7/100,000 in the general population; the highest incidence was 7.4/100,000 in the age group of 70-79 years[89]. This study also included death certificates, and the authors speculated that one-third of the patients with CSDH will die with an undiagnosed hematoma.

Kudo and colleagues found 66 CSDH patients (1986-1988) on Awaji Island in Japan, reporting an overall incidence of 13.1/100,000/year[161]. They calculated an incidence of 3.4/100,000/year and 58.1/100,000/year in the population under and over 65 years, respectively. In a case series of 40 patients (1996-1999) from North Wales (United Kingdom), Asghar and colleagues estimated an annual CSDH incidence of only 8.2/100,000 among patients over 65 years of age[16]. This incidence in North Wales was updated 15 years later[5]. The authors found that the annual incidence of CSDH in patients over 65 years had increased to 48/100,000[5].

A Japanese registry of 1,445 patients (2005-2007) was evaluated by Karibe and coauthors[147]. They reported an annual CSDH incidence of 20.6/100,000. The incidences in the 70-79 age group and those over 80 years of age were 76.5/100,000/year and 127.1/100,000/year, respectively. A study from the USA by Balser and colleagues (2000-2012) focusing on the veteran population (median age 64 years) observed an overall incidence rate of 79.4/100,000/year for subacute or chronic SDH[24].

In a case-control registry study from Denmark that included 10,010 patients with any SDH during the study period from 2000 to 2015, Gaist and colleagues found that the incidence rate of SDH increased from 10.9 to 19.0/100,000/year[97]. The largest increase in the incidence of SDH occurred among older patients (aged 75-89 years) from 55.1 to 99.7/100,000/year. They estimated that 55% of all the SDH cases were subacute or chronic and that the incidence rates were probably underestimated by 22% due to the registry-based nature of the study[97].

Accordingly, epidemiologic studies have reported a significant increase in the incidence of CSDH in the elderly compared with other age cohorts[339]. However, only a few of these studies were population-based in design (Table 1). The reasons for higher incidence among the elderly include age-related general brain atrophy[184, 338], risk for multiple falls[116, 159, 180], and the frequent use of antithrombotic medication[63, 70, 97, 214]. In addition, improved awareness of CSDH among the medical profession and the wide availability of CT scanners have been proposed as influences on increasing incidence rates[9, 280].

Table 1. Summary of population-based studies on CSDH incidence.

Authors	Country	Time period	n	Incidence (n/100,000)			
				Overall	>65y	70-79y	>80y
Fogelholm & Waltimo 1975[89]	Finland	1967-1973	64	1.7	-	7.4	6.4
Kudo et al. 1992[161]	Japan	1986-1988	66	13.1	58.1	-	-
Asghar et al. 2002[16] *	United Kingdom	1996-1999	40	-	8.2	-	-
Karibe et al. 2011[147] **	Japan	2005-2007	1,445	20.6	-	76.5	127.1
Adhiyaman et al. 2017[5] *	United Kingdom	2014-2015	66	-	48		
Present study***	Finland	1990-2015 1990-1995 2011-2015	1,168 167 354	12.2 8.2 17.6	45.6 28.5 64.3	42.1 32.3 52.1	85.4 46.9 129.5

*Included patients > 65 years old, **Registry study, ***Included patients ≥ 18 years old

2.1.5 Risk Factors

2.1.5.1 Age and Gender

Age-related brain degeneration with an enlarged potential subdural space represents an important risk factor for CSDH[170, 184, 338]. The mean age at presentation of CSDH depends on the study era and population. A registry study from Japan[304] collected all newly diagnosed CSDH patients (n=63,358) during 4/2010-3/2013. Patient age (mean ± SD) was 76 ± 12 years. When patient age was stratified by decade, 4.2% of patients were in their 50s, 15% in their 60s, 33% in their 70s, 37% in their 80s, and 8.5% in their 90s. Women were older than men on average at the time of diagnosis of CSDH[20, 122, 204]. In a Japanese cohort study of patients with CSDH (n=490), the mean age for women was 78 years versus 73 years for men[122].

The existing literature has consistently reported that men dominate cases of CSDH, with an approximate 3:1 ratio of men to women[339]. Potential explanations for this gender difference include the higher risk of head trauma and more frequent chronic alcohol abuse among men[44]. A Danish nationwide register study (1999-2014) reported that anticoagulation usage was more common among men than women[3].

Researchers have also suspected that the vasoprotective effects of estrogen in women may play a role in this difference[261]. A Korean study even speculated that the anatomical difference between genders' cranial size and morphology could represent a predisposing factor[221]. The reasons underlying the gender difference are not well studied[44]. Studies show that male predominance diminishes with age[20, 100, 204, 261, 288].

2.1.5.2 Head Trauma

Head trauma is considered the most important risk factor for CSDH. In most large datasets, 50% to 80% of the patients display a history of trauma[44]. Young patients are more likely to have suffered from more severe trauma, such as traffic accidents, than the elderly[204, 288]. One reason for the greater incidence of CSDH among the elderly may be attributed to a higher number of falls in this population[180].

Finnish follow-up studies have revealed that the incidence of fall-induced brain injury among elderly has increased considerably during the last decades[146, 159, 235]. Older adults (aged ≥ 80 years) may fall more often and more seriously than their predecessors because they live longer and have many chronic disorders and polypharmacy[159]. In elderly, the trauma can also be so minor that it is not remembered[158]. However, in those elderly patients with brain atrophy, even a trivial head trauma may represent sufficient cause for CSDH. Brain atrophy, chronic health conditions, and polypharmacy might contribute to fall-related brain injuries in the elderly [159].

2.1.5.3 Alcohol

One well-known risk factor for CSDH is alcohol overuse, which induces brain atrophy and coagulation dysfunction and increases the risk of head trauma [191]. Reported rates of chronic alcoholism among CSDH patients range from 6 to 35% [280].

2.1.5.4 Coagulopathy and Antithrombotic Medication

Disorders in coagulation have been identified as contributing factors in the pathogenesis of CSDH[44]. Medical conditions leading to a coagulopathic state include renal dialysis, sepsis, and hepatic failure[44]. However, therapeutic anticoagulation

represents the most prevalent cause of coagulopathic states[44]. Patients with CSDH often display comorbidities and the usage of antithrombotics—that is antiplatelet and anticoagulant treatment, is common. In a recent Finnish study by Tommiska et al.[307] (n=97), 65% of CSDH patients were using antithrombotic medication; 34% were using anticoagulants and 35% antiplatelets.

Anticoagulants increase the risk of all intracranial haemorrhages by 7–10 fold, and 30% of haemorrhages occur in the subdural space[115]. Use of warfarin increases the risk of SDH by three-fold relative to antiplatelet therapy[63]. Clopidogrel + acetylsalicylic acid (ASA) has been associated with an increased risk of SDH compared with ASA alone (RR 2.0; 95% CI 1.0-3.8)[22]. The incidence of SDH in the case of ASA therapy has varied from 0.02 per 1000 patient-years for primary prevention trials of middle-aged health professionals to 1-2 per 1000 patient-years for older patients with atrial fibrillation[64]. In a randomized primary prevention trial involving healthy elderly persons (n=19,114)[199], the use of low-dose ASA (100 mg) increased the risk of all subtypes of intracranial bleeding (HR 1.50; 95% CI 1.11-2.02), as well as the risk for subdural or extradural haemorrhage (HR 1.79; 95% CI 1.06-3.02).

Antithrombotic drug use was correlated with a higher risk of SDH, with the risk varying across regimens in a Danish nationwide case-control study[97]. Warfarin was associated with the highest risk of SDH (OR 3.69; 95% CI 3.38-4.03). It was followed by clopidogrel (OR 1.87; 95% CI 1.57-2.24), direct oral anticoagulant (OR 1.73; 95% CI 1.31-2.28), and low-dose ASA (OR 1.24; 95% CI 1.15-1.33) in this order[97]. The highest odds of subdural hematoma were associated with the combined use of warfarin and antiplatelet i.e. warfarin + clopidogrel (OR 7.93; 95% CI 4.49-14.02) and warfarin + ASA (OR 4.00; 95% CI 3.40-4.70)[97].

Studies have shown use of direct oral anticoagulants (DOACs) is associated with a lower risk of intracranial haemorrhage than the use of warfarin[97, 166, 255]. A pooled meta-analysis (2014) of RCTs on the use of dabigatran, rivaroxaban, abixaban and edoxaban demonstrated substantial reduction in intracranial bleeding (RR 0.48; 95% CI 0.39-.059) compared with warfarin[255]. Dabigatran (HR 0.39; 95% CI 0.27-0.56) and rivaroxaban (HR 0.66; 95% CI 0.45-0.98) showed lower intracranial bleeding rates than warfarin in a Danish nationwide cohort study (n=61,678)[166].

The association of antithrombotic medication with CSDH has appeared even stronger in the absence of trauma[17, 70, 280]. Assessing the risk of possible coagulation disorders is important, especially in young CSDH patients (below 65 years), with no history of head trauma, alcohol abuse or anticoagulant therapy[74]. Assessing routine

coagulation parameters pre-operatively and completing screening for unknown coagulation deficits in the follow-up is recommended[74].

2.1.5.5 Intracranial Hypotension

CSDH as a result of intracranial hypotension is a well-known complication after CSF shunting[44, 88, 197, 225]. In a Swedish nationwide registry-based study[99], 10% (152/1457) of patients treated with shunt due to idiopathic normal pressure hydrocephalus developed a CSDH or hygroma (an accumulation of CSF in the subdural space). Male sex, antiplatelet medication, and a lower opening pressure at surgery represented risk factors for CSDH.

Intracranial hypotension can also occur as a result of spontaneous CSF leak, which can cause bilateral subdural hygromas progressing to CSDH[153]. It is clinically important to identify if a spontaneous intracranial hypotension is the cause of CSDH because the treatment strategy differs if this is the case, consisting of epidural blood patch[300]. Also, lumbar puncture in spinal anesthesia have been reported to cause CSDH[12, 201].

2.1.5.6 Arachnoid Cyst

A congenital arachnoid cyst has been established as a statistically significant risk factor for CSDH after a mild head injury in young patients[156]. Sixteen (2.4%) cases of arachnoid cysts among 658 patients with CSDH were analyzed in a retrospective German study[228]. The prevalence of an arachnoid cyst was fivefold among the CSDH patients compared with arachnoid cyst as an incidental finding among 11,487 MRIs[228]. Similarly, a Japanese study found 12 (2.2%) cases of arachnoid cysts among 541 cases of surgically treated CSDH[205]. However, 59% (n=60) of the patients had an arachnoid cyst[225] in a Chinese retrospective analysis of CSDH patients under 40 years of age (n=101) [225]. Still, CSDH is a rare complication in patients with an arachnoid cyst, since they represent common incidental findings in neuroimaging. Arachnoid cysts were identified in 1.4% (n=661) of patients in a retrospective study of a times series of adults (n=48,417) who underwent brain MRI over a 12-year interval[8].

A review by Wu et al. of 182 cases of arachnoid-cyst-associated CSDH found the most common patients were male children, juveniles, and young adults (mean age of 24 years) with recent head trauma or sport-related injuries[332]. Burr hole drainage is

the first-choice surgical procedure in symptomatic cyst-related CSDH patients[332]. Craniotomy and fenestration of the arachnoid cyst membrane is not a requirement in CSDH patients with a pre-existing asymptomatic arachnoid cyst and should be reserved as a secondary procedure[332].

2.1.5.7 Vascular Malformations

A few case reports have demonstrated dural arteriovenous fistula (DAVF) as the cause of bleeding in CSDH[176]. DAVF should be suspected in the case of spontaneous (no evident history of head trauma) CSDH in a relatively young patients lacking coagulopathy or antithrombotic medication.

2.1.6 Clinical Presentation

The typical patient with CSDH has changed considerably in the last decades[129]. Patients are now older[304], they use antithrombotic medication more often[97], and they present with a wider variety of clinical symptoms. Incidental cases of CSDH with no symptoms related to the condition have also been found[129]. Symptom onset and progression can vary from days to weeks[158].

Affected patients can present with a variety of symptoms, such as gait disturbance and recurrent falls, progressive limb weakness, cognitive decline, acute confusion, and headaches[158]. Presentation can mimic stroke or rapidly progressive dementia, thus inspiring the name the "great imitator"[237]. Even reversible parkinsonism has been reported to occur[102]. In a prospective cohort study of 1205 patients from the United Kingdom (UK)[37], patients often presented with multiple symptoms, with the most common including cognitive impairment (58%), hemiparesis (41%), headache (41%), gait disturbance (32%), and dysphasia (14%). Seizure represented the presenting symptom for 4% of patients in the UK study and for 15/244 (6%) of patients with CSDH in a retrospective study from Japan[113].

Symptom distribution of CSDH is related to age[100, 179, 208]. In a Danish retrospective study[26] (n=1,252), adult patients younger than 50 years old (n=52) with CSDH presented more often with signs of increased intracranial pressure—that is headache (87% vs. 38%) and vomiting (25% vs. 5%). On the contrary, patients over 50 years old presented more often with hemispheric symptoms—that is, limb weakness (17% vs. 45%), speech impairment (6% vs. 26%), and gait disturbance or falls (23% vs. 51%).

Severity of the symptoms does not always correlate with hematoma size. To clarify the mechanisms behind severity, a Japanese study group analyzed hematoma thickness, pressure, and tension (n=124)[305]. They revealed that tension was strongly related to hemiparesis. Furthermore, stronger midline shift and greater ratio of midline shift to hematoma thickness were correlated with headache. Even if the volumes and midline shifts generally seem to become larger with a patient's increasing age, the pressures declined in a Norwegian study[296]. In this study, the mean subdural pressure was 15.2 cmH2O (range 0-40), which is within the range of a normal ICP. The mean hematoma volume was 144 ml (range 53-264 ml). Men had significantly larger volumes (mean 158 vs 103 ml) and midline shifts (mean 1.04 vs 0.68 cm) than women.

Most commonly, patients present with a good level of consciousness. In the UK study[37], 81% had a presenting GCS score of 13-15, while only 7% had GCS score of ≤8. However, if left untreated, CSDH may lead to loss of consciousness or even death[336]. Two distinct groups of patients can potentially deteriorate quickly[158]. The first is a group of patients usually younger than 65 years, who present with headaches, but no or minimal neurological deficits. The second is a group of patients with sizeable bilateral collections. Compared with patients with unilateral CSDH, patients with bilateral CSDH present more commonly with symptoms of increased intracranial pressure: headache and nausea or vomiting[123, 311].

To conclude, clinical presentation of CSDH can vary from no symptoms to unconsciousness[336]. Young patients, and patients with bilateral collections are particularly at risk for severe symptom progression and deterioration.

2.1.7 Diagnosis and Imaging

CSDH is suspected based on the patient's history and possible neurological symptoms and/or signs. Head CT is the gold standard in eventually detecting CSDH. On CT, CSDH is seen as a hypodense crescentic collection along the convexity, but may have isodense or hyperdense components[272, 279]. The size and thus the mass effect of CSDH is described as thickness of the hematoma and midline shift (MLS), or as the volume of the hematoma using mathematical formulae, such as the ABC/2 method, or computer-assisted volumetric analysis[42, 190, 295, 330]. In the case of a bilateral CSDH, the mass effect can be significant with no MLS, due to equal but opposing forces on the brain parenchyma, and the ventricles may appear squeezed[200]. Bilateral CSDH comprises 18-30% of all CSDH[123, 124, 204]. MRIs do not

currently play a role in routine clinical practice for patients with CSDH. They are usually performed when other diagnoses were primarily suspected[158].

Many classifications of SDH have been proposed based on clinicopathological characteristics and imaging findings[10, 212, 245, 328, 337]. Nakaguchi *et al.* [210] categorized CSDH into four subtypes (homogeneous, laminar, separated and trabeculated), hypothesizing that these types represented four stages in the natural history of the disease process. They theorized that CSDHs develop initially as the homogeneous type, after which they sometimes progress to the laminar type. A mature CSDH is represented by the separated stage and the hematoma eventually passes through the trabecular stage during absorption. A modified Nakaguchi classification has since been described, with different homogenous subtypes (hypodense, isodense and hyperdense) included (Figure 3)[293].

A variety of subdural pathologies that may mimic hematomas are reported in the literature, including metastasis, lymphoma, sarcoma, and infectious or autoimmune lesions[38]. Identification of atypical history and radiologic features should prompt further diagnostic tests, including an MRI, to elucidate the proper diagnosis.

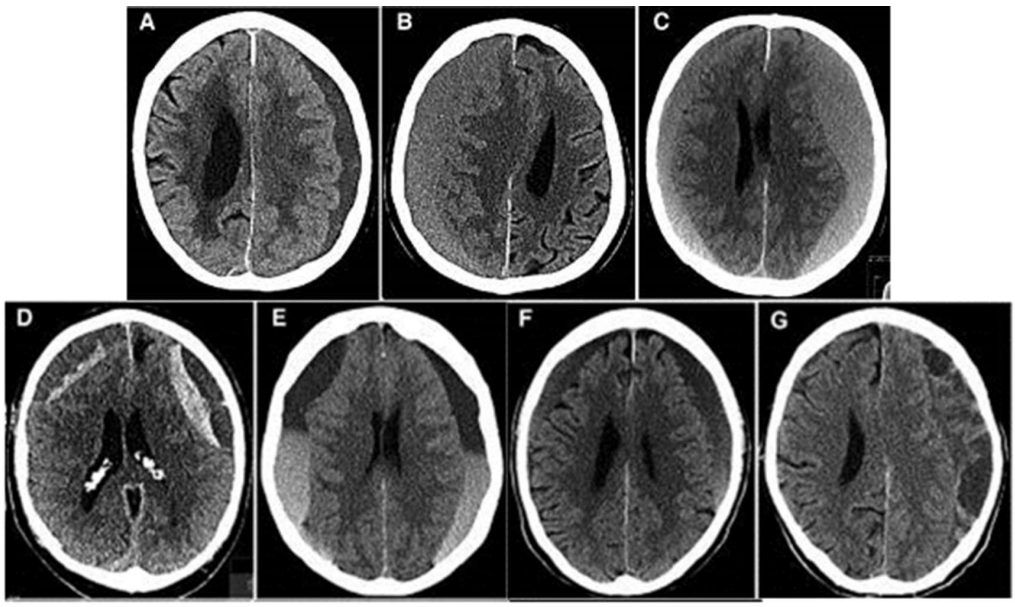


Figure 3. Modified Nakaguchi classification: Examples of CSDH of the (A) hypodense, (B) isodense, (C) hyperdense, (D) laminar, (E) separated, (F) gradation, and (G) trabecular subtypes. Reprinted with Open Access permission from Stanisic and Pripp 2017. http://creativecommons.org/licenses/by-nc-nd/4.0/

2.1.8 Management

The natural history of CSDH remains unclear[287]. The interaction between the premorbid status, the maturation of neomembranes, and the dynamics of absorption and expansion influence the progression or regression of SDH[172] . No clear clinical or radiologic signs indicate whether the CSDH will resolve spontaneously[287]. Symptomatic patients with a confirmed radiological appearance of a hematoma are usually treated surgically, whereas patients with asymptomatic hematomas and small non-space-occupying hematomas can be managed conservatively through careful observation[158].

A patient with CSDH usually slowly develops an intracranial mass lesion. For this reason, urgent interventions are seldom needed[342]. Treatment is individualized, and a one-for-all management strategy is not appropriate[263].

2.1.8.1 Correction of Coagulopathy

Among CSDH patients, pre-existing medical conditions treated with antithrombotic medications are common[97]. Correction of coagulopathy is crucial to amend the conservative treatment or reduce the risks of bleeding during operative intervention and minimize recurrence[158]. The cessation of antithrombotic medication and methods to counteract the effects of these medications when needed are implemented. Discontinuing antithrombotic agents, such as low-dose ASA, in an appropriate period of time (5-7 days pre-operatively) in patients undergoing surgery for CSDH is recommended[158].

However, patients' symptoms often do not allow doctors to wait the recommended amount of time for surgery. In addition, an unnecessary halting of antithrombotic medication increases the patients' risk of complications such as stroke, pulmonary emboli and deep venous thrombosis. Most institutions have local protocols to guide clinicians on the basis of the patient's international normalized ratio (INR), clinical state, and timing of pending surgical intervention.

One Italian study studied the discontinuation of ASA by retrospectively classifying 164 patients into three groups: urgent (surgery at admission), surgery within five days, and surgery five or more days after discontinuation[269]. The data showed no influence of group classification on outcome. Similarly, an analysis of data from an UK-based multicenter, prospective cohort study (n=817, of which 43% were on antithrombotics) did not support delaying surgery in patients on antithrombotic therapy[234]. Patients on an antithrombotic drug pre-operatively

displayed a higher risk of thromboembolic events (3.3% vs 0.9%) with no excess risk of recurrence or worse functional outcome after CSDH drainage. An ongoing Swiss trial aims to discover whether patients taking ASA should discontinue this medication in the peri-operative period or if ASA can be safely continued throughout[55, 145].

2.1.9 Operative Treatment

Surgical treatment of symptomatic CSDH results in the rapid improvement of symptoms[76, 158, 325]. Coupled with relatively low surgical risk, surgical evacuation currently represents the mainstay of management for symptomatic patients[158]. Surgical treatment might generally be indicated in the case of a symptomatic hematoma width more than 10 mm or midline shift over 5 mm[107]. However, although the size of a CSDH may play a role in the decision to operate, absolute size cut-offs should be avoided[76].

Various techniques are suggested for opening the skull to remove CSDH. Three primary surgical techniques are used: i) twist drill craniostomy (TDC) involving small openings (<10 mm) made using a twist drill, ii) burr hole craniostomy (BHC) involving openings of 10–30 mm, and iii) craniotomy involving larger openings (Figure 4)[76, 158, 325]. TDC can be performed bedside and always includes the insertion of an external drain. BHC and craniotomy are performed in the operation theatre with or without a drain insertion.

A meta-analysis (2014) with 34,829 patients showed that bedside TDC was as efficacious as burr holes, whereas craniotomy resulted in a higher morbidity but was a superior treatment for recurrent CSDH[9]. Similarly, no statistically significant differences between the treatment with TDC and BHC were found in the meta-analyses (2016)[132] of the data from four RCTs[104, 111, 209, 282] regarding recurrence rates or outcomes. All three techniques are being directly compared in the Belgian COMPACT study, which has just completed their patient recruitment[52]. A comparison between bedside TDC and BHC performed in an operation theatre is currently being investigated in a multi-center trial in the USA and Canada (DECIDE study)[54].

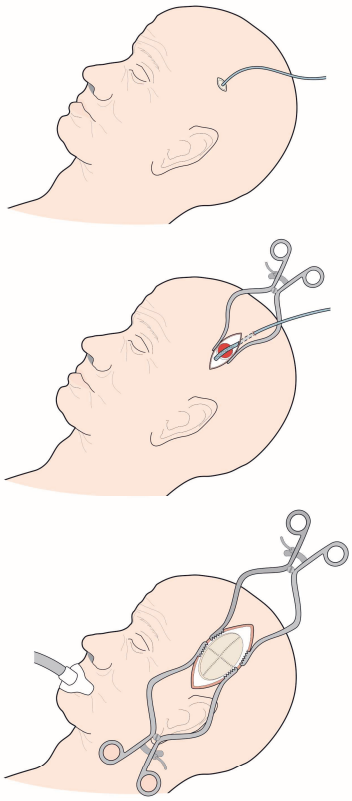


Figure 4. Surgical approaches for CSDH evacuation.

(A) Twist drill craniostomy (TDC) with subdural drain.

(B) Burr hole craniostomy (BHC) with subgaleal drain.

(C) Craniotomy

As TDC can be performed at a patient's bedside, it represents an option for those elderly patients with multiple comorbidities who are poor surgical candidates[76]. Additionally, bedside TDC evacuation is less expensive than a traditional evacuation. The latter is an important aspect, especially in low- and middle-income countries. A modification to the original TDC technique involves the insertion of a hollow screw through a twist-drill hole and a closed drainage system. This technique does not require the insertion of a catheter in the subdural space, thereby minimizing the risks of brain laceration and bleeding from cortical vessels. An analysis of nine retrospective studies (n=796) using this technique suggests similar safety and efficacy profiles to traditional TDC and BHC techniques[43, 83].

Probably the most widely practiced treatment is an evacuation via BHC, which has been shown to be an efficient choice to treat an uncomplicated CSDH[158, 175, 325].

Some neurosurgeons prefer single burr hole craniostomy, whereas others prefer double burr holes[318]. A meta-analysis of 12 studies (3 RCTs) by Wen et al. (2019) demonstrated no significant differences in recurrence, complications, or morbidity between treatment with one or two burr holes[318].

Burr-hole surgery can be done under general or local anesthesia with sedation if necessary[263]. Many neurosurgeons advocate local anesthesia especially on elderly patients, who often have multiple concomitant diseases[101, 236]. Local anesthesia, with or without sedation, has been shown to be a safe and effective technique for burr hole evacuation of CSDH and has been associated with shorter operative time, lesser postoperative complications, and shorter hospital stays than general anesthesia[28, 154, 297]. Two on-going trials are comparing the two, assessing length of stay and functional outcomes, as well as their effects on cognition[47, 61].

The role of intraoperative irrigation for burr-hole evacuation of CSDH is unclear, and contradictory results have been reported. Some studies have reported a significantly lower recurrence rate in CSDH patients undergoing intraoperative irrigation[134, 169], whereas some studies have reported no statistically significant differences in recurrences[111, 127, 130, 298, 320, 341], and some have found even higher recurrence rates in the irrigation subgroups[151, 164]. The Finnish Study of Intraoperative Irrigation Versus Drain Alone After Evacuation of Chronic Subdural Hematoma (FINISH: NCT04203550) has just been initiated[308].

A Swedish study[30] of irrigation fluid temperature demonstrated that intraoperative irrigation fluid at body temperature (37 °C) is associated with lower recurrence rates than irrigation fluid at room temperature (22 °C), with a recurrence rate at 4.5% versus 13%. Body temperature fluid is assumed to have a positive effect on coagulation and solubility of the CSDH, improving evacuation and recurrence rate. To investigate the role of irrigation fluid temperature further, a prospective randomized controlled trial is ongoing[29]. A small Japanese RCT[276] (n=79) concluded that irrigation of the subdural space with thrombin solution in patients with high risk of recurrence might reduce this risk[276].

The insertion of an external drain after evacuation of CSDH decreases the rate of recurrence by up to 50% in most of the reported series[230]. A meta-analysis (2016) of all randomized controlled trials (RCTs) of surgical treatments for CSDH, including a total of 24 RCTs involving 1900 patients, was conducted by Ivamoto et al.[132]. They found eight RCTs with 828 patients that investigated postoperative drainage after burr-hole evacuation and irrigation of the subdural space[6, 84, 135, 167, 262, 281, 312, 316]. Drainage reduced the rate of recurrence (RR 0.48, 95% CI 0.34−0.66) with no other clear benefits or complications. For example, a RCT from the United

Kingdom[262] (n=215) was stopped early due to a significant benefit in reduction of recurrences in the favour for drains (9% vs 24%).

Various types of drains are used, including subdural and subgaleal or subperiosteal with or without suction[336]. The subdural drain catheter tip position does not seem to influence the recurrence rate, although a tendency to favor the frontal position has been reported[103, 211]. Three RCTs[114, 144, 286] as well as three recent meta-analyses[73, 240, 333] have compared burr hole craniostomy of CSDH with subgaleal drainage to subdural drainage. Accordingly, subgaleal drainage may serve as a recommended treatment as it displays a similar or even lower recurrence rate along with a lower incidence of postoperative brain injury than subdural drainage. In a Scandinavian population-based cohort study[283], the authors observed that the use of active subgaleal drainage was associated with reduced CSDH recurrence, arguing that this finding merits further investigation.

The postoperative drainage time in previous studies has lasted approximately 48 hours[262], but no consensus on the recommended drainage time has been reached. A French RCT[126] (n=65) reported that shorter (48 vs 96 hours) drainage duration after TDC was associated with significantly lower rates of general complications with comparable recurrence and improvement rates, even though the mean volume of liquid drained was significantly lower in the first group (120 ml vs 285 ml). A multicenter study performed in the United Kingdom (n=577) observed no apparent advantage to drainage that lasted more than 24 hours[103]. The authors suggested that prompt drain removal may facilitate early mobilization, which could reduce morbidity and improve functional outcomes.

Often, a trainee neurosurgeon performs the operation. A UK study (n=239) did not find any correlation between the seniority of the surgeon and postoperative recurrence of CSDH[232].

Craniotomy and membranectomy is currently considered only under conditions of subdural hematoma re-accumulations, solid hematomas, or instances in which the brain fails to expand and obliterate the subdural space[191, 258, 263]. Neomembranous organization may impede re-expansion of the brain after hematoma evacuation[96, 193], and the technique of opening the internal membrane of the hematoma capsule is theorized to facilitate brain expansion. The lowest recurrence rates were seen in patients who underwent craniotomy and membrane resection as reported in a meta-analysis (2003) by Weigel et al.[325]. However, opening the inner hematoma membrane during the BHC did not provide any benefit in a small (n=52) Austrian RCT, thus leading the investigators to conclude that it might be unnecessary[314].

Other rarely used procedures for refractory CSDH include implantation of a subdural catheter with a reservoir for repeated punctures and aspiration of the hematoma[167, 266], as well as a subduroperitoneal shunt[203, 244, 265]. Endoscopic treatment has also been introduced to evacuate CSDH and release the septa separating the hematoma cavity[33, 317].

2.1.9.1 Postoperative Management

Bed rest following surgical drainage of CSDH has been proposed to facilitate brain expansion and decrease the risk of recurrence[2]. However, this may result in higher risk of postoperative complications, such as pneumonia, thromboembolism, and decubitus ulcers[163, 336]. Placing the patient in an upright position soon after surgical evacuation does not seem to increase the risk of recurrence, according to a meta-analysis (2014) by Almenawer et al.[9]. No adverse effects after postoperative early mobilization have been noted. However, high-quality data is lacking. Comparisons of outcomes between bed rest for 48 hours versus the earliest-possible mobilization represents the subject of study in an ongoing Portuguese RCT[62].

Current practice on the re-initiation of antithrombotic medication after CSDH evacuation varies considerably[213]. Balancing thromboembolic events against the risk of both acute hemorrhage and recurrence presents a challenge in the management of CSDH. The decision when to resume antithrombotics, if at all, postoperatively in CSDH patients remains controversial[90]. In some instances, the indication for antithrombotics is vital, and the risk for rebleeding must be accepted.

Early (vs. late) resumption has been reported to increase the risk of recurrence[214, 233] as well as to protect against it[40, 109]. In selected cases, resuming early (<2 weeks) versus late (>1 month) antithrombotic treatment without additional hemorrhagic complications is feasible, as noted by Phan et al. in a meta-analysis (2018)[231]. The rate of thromboembolism was statistically lower in those who resumed antithrombotics early (2.9% vs 6.8%). An ongoing Swiss RCT aims to discover whether patients taking ASA should have this medication stopped in the peri-operative period or whether it can be safely continued throughout[56].

In the same way, the use of postoperative imaging is not standardized[200]. Some recommend early postoperative head CT, while others only recommend this for symptomatic patients with suspected recurrence[264].

2.1.9.2 Complications

Perioperative complications can be divided into two categories: surgical and nonsurgical[158]. Procedure-specific complications include focal brain injury, postoperative acute subdural or intracranial hemorrhage (ICH), cerebral edema, tension pneumocephalus, seizures, surgical site infection, and subdural empyema. Medical complications include hospital-acquired infections (respiratory and urinary), venous thromboembolism, myocardial infarction, and stroke.

Among CSDH patients treated by BHC, the following complication rates were reported: acute local bleeding (14%), acute remote bleeding (3%), wound infection (6%), subdural empyema (5%), pulmonary embolism (3%), and pneumonia (27%), as reviewed by Lega et al.[175]. Nine percent (0-25%) of BHC cases resulted in complications in the review and meta-analysis by Ducruet et al.[76] (n=2,274). Postoperative acute intracranial bleeding developed in 14, or 4.6%, (11 ASDH and three ICH, with four of these patients dying) of 303 Korean CSDH patients, and hematological disease or a history of prior shunt surgery increased the risk[227].

Acute subdural hematoma may be caused by bleeding from the scalp wound; hence, meticulous hemostasis during surgery is vital[204]. On the contrary, the mechanism of intracerebral hemorrhage is suspected to be immediate hyperemia after rapid decompression of the brain in CSDH surgery[220]. This underlies the importance of carefully managing blood pressure perioperatively.

The incidences of early (within 7 days) and late (within 2 years) seizures were 5.3% and 10%, respectively, in a systematic review (2017) by Won et al.[329]. The risk factors for seizures included alcohol abuse (OR 14.3), change of mental status (OR 7.2), previous stroke (OR 5.3) and hematoma density on the CT (OR 3.8); patients with mixed-density hematomas were more prone to seizures than those with low-isodense hematomas. Due to the controversial findings on prophylactic antiepileptic drugs, no consensus on recommendations for their use in CSDH patients has been reached[31, 223, 257].

Higher age has been associated with increased CSDH-related morbidity[36, 78, 140, 202]. The overall complication rate of cardiac and pulmonal pathologies has been reported to be higher in patients ≥85 years[208]. The morbidity may be lower, if the surgery is performed under local anesthesia instead of general anesthesia[28, 154]. In the elderly population, even trivial complications can result in unfavorable outcomes. Their health providers must make efforts to prevent these complications when possible, and diagnose and treat them efficiently should they occur[158].

2.1.9.3 Recurrence

A systematic review[41] on common data elements in CSDH revealed seven different definitions for the term "recurrence," with the most common definition as "symptomatic and radiological recurrence requiring reoperation." The decision to reoperate is therefore based on the presence of symptoms and imaging signs of cerebral compression. Time-points for recurrence varied a great deal; the most common was three months after the primary operation.

The recurrence rates range from 5% to 30%. Reduced recurrence is observed with external subdural drains as discussed previously[185, 230, 307, 325]. The contemporary consensus is that the reoperation rate is 10–20%[158]. The following factors have been proposed to predict recurrence: brain atrophy[275], multiple comorbidities[195], antithrombotic medication[46, 181, 233, 256], large hematoma size and midline shift both pre- and postoperatively[46, 305], hematoma density on imaging[138, 252, 292, 334], bilateral hematoma[162, 309], intraoperative visualization of poor brain re-expansion and thick membranes[250], and postoperative pneumocephalus[204, 222, 340]. A factor considered pivotal in hematoma recurrence is the failure of the brain to fill the dead space resulting from hematoma evacuation[204].

Recurrence rates increased in the separated subtype (36%) and decreased in the trabecular subtype (0%) than in the homogeneous and laminar subtypes (15% and 19%, respectively), as reported by Nakaguchi et al.[210] . These findings have since been further supported using a modified Nakaguchi classification[46, 252]. However, these results have not led to a stratified approach to the treatment of CSDH in routine clinical practice.

No widely adopted grading system exists yet to predict recurrence. Jack et[133] al presented a three-tier model, selecting age with a cut-off of 80 years, a preoperative volume with a cut-off of 160 ml, and the presence or absence of hematoma septation as components of the grading system. Stanisic et al[293] proposed a grading system, in which the strongest predictors for recurrence were isodense or hyperdense lesions and laminar or separated lesions, as well as a postoperative CSDH cavity volume greater than 200 ml.

The Danish CSDH study[13] proposed nomograms to assess the risk of recurrence. The preoperative model included hematoma size, hematoma density, and history of hypertension. The postoperative model included drain type, drainage time, and surgical complications. It concluded that the size of the CSDH represented the most consistent risk factor and predictor of recurrence and that subdural drain placement is superior to passive subgaleal placement.

In the case of bilateral CSDH, unilateral or bilateral operation is a decision made on the basis of hematoma volume and clinical symptoms[95, 207]. Bilateral surgical intervention significantly lowered the risk of retreatment compared with unilateral intervention (29% versus 14%) in a Danish series of 291 bilateral CSDH patients[14]. On the contrary, unilateral evacuation resulted in hematoma resolution for both sides in most cases (91%) among 128 consecutive bilateral CSDH cases, of which 60% were operated unilaterally during a 10-year periods in Boston, Massachusetts[207]. Accordingly, bilateral evacuation seems to be unnecessary in bilateral CSDHs when one side is small and asymptomatic.

Recurrence is mainly a concern in the first two months after surgery[252, 271]. Despite this, it may take up to six months to observe complete radiological resolution of a CSDH[194]. In a German study, the median time-to-cure after primary surgery was 65 days, and neuroimaging proven cure of CSDH could be documented in 90% of cases within five months[252]. Accordingly, CSDH healing takes time, which argues for the importance of pathophysiological mechanisms other than mere hematoma volume reduction.

2.1.10 Embolization of the Middle Meningeal Artery

The CSDH outer membrane and newly formed capillaries are fed through the dura mainly by distal branches of the middle meningeal artery (MMA)[301]. Recently, several case reports and two prospective studies have suggested that embolization of the MMA could inhibit the influx of blood into this membrane and thus prevent the accumulation of the hematoma in the subdural space[25, 182]. Most studies report the use of polyvinyl alcohol (PVA) particles for embolization, but coils and other substances have also been used.

Embolization of the MMA has mostly been applied to recurrent CSDH. The technique has also been proposed as an adjunct postoperative treatment after burr-hole surgery in patients operated for a CSDH with an independent recurrence risk factor, including antithrombotic therapy, coagulation disorder, hepatopathy, or chronic alcoholism[278]. However, systematic reviews of studies with up to 193 patients have concluded that the level of evidence supporting embolization of the MMA is currently too low to routinely recommend this procedure in clinical practice[65, 141, 290, 321]. Further studies are needed, as reflected by two ongoing RCTs[45, 58].

2.1.11 Non-Operative Treatment

"Wait and watch" or "wait and scan" management is indicated in patients with no or minor symptoms, or in patients with a premorbid condition not allowing surgical evacuation of CSDH[287]. Small CSDHs and many residual CSDHs after surgery will resolve without any intervention. In addition, the presence of a persistent fluid collection and outcome is uncorrelated[200]

An understanding of the underlying pathophysiological processes has been applied to develop potential drug treatments[287]. Pharmacological interventions have been used as adjunctive therapies to surgery, with the aim of reducing the risk of recurrence or serving as an alternative to surgery[287]. The premise requires ceasing the inflammatory and angiogenic disease processes leading to control and resolution of CSDH[287]. Additionally, improved access to medical care and imaging means that patients will probably be diagnosed earlier in their clinical course, making pharmacological treatment options more viable, with surgery potentially reserved for the more severely affected or comatose patients[157]. Drugs of interest have been dexamethasone, tranexamic acid, angiotensin-converting enzyme inhibitors, and statins[287].

Corticosteroids are known to be anti-inflammatory and inhibit the formation of new blood vessels[119]. Therefore, previous research has postulated that corticosteroids reduce the inflammation-induced angiogenic reaction in CSDH through the inhibition of inflammatory and angiogenetic factors[263]. Downsides of dexamethasone use include complications such as diabetes, infections, and (temporary) mental changes[119]. A systematic review by Soleman et al.[287] observed that corticosteroids might play a role in the conservative treatment of CSDH, but the ideal dosage, duration of treatment and the ideal group of patients for this particular treatment remains unclear. A recent meta-analysis by Holl et al.[121] suggested that the addition of corticosteroids to surgery might be effective in the treatment of CSDH. Seven ongoing trials are currently assessing the efficacy of corticosteroids, most commonly dexamethasone, as treatment for CSDH[18, 48, 51, 53, 85, 86, 87].

Tranexamic acid (TXA) reduces bleeding by inhibiting the breakdown of fibrin blood clots (fibrinolysis). TXA is hypothesized to potentially inhibit the hyperfibrinolytic activity and the increased vascular permeability in CSDH, leading to a gradual absorption of the hematoma[142, 302]. TXA has been shown to reduce the risk of hematoma expansion in patients with traumatic brain injury[326] and the risk of head injury related death in patients with mild-to-moderate head injury[67]. TXA might

represent a valid conservative treatment for CSDH in a selected patient population, but its role remains uncertain to date and will be evaluated in larger studies[287]. Currently five trials are assessing the role of TXA as both a conservative treatment and an adjunct to surgery[49, 50, 57, 59, 60].

Angiotensin-converting enzyme (ACE) inhibitors decrease vascular endothelial growth factor (VEGF) production, which reduces new immature vascularization[323]. ACE inhibitors might thus lower the risk for developing a CSDH and for its recurrence[323]. However, studies have shown contradictory results on CSDH patients[215, 238, 323], thus warranting further studies[287].

Atorvastatin has been investigated in the management of CSDH, because it also has anti-inflammatory and antiangiogenic effects[177, 319, 335]. Although one RCT on the effect of atorvastatin on CSDH volume found a significant difference compared with the placebo, the volume only differed by 12 ml in eight weeks, and the CSDHs included were small with a high spontaneous resolution rate[139]. Also, mannitol[155] and a platelet activating factor receptor antagonists (etizolam)[118] have been shown, with a low level of evidence, to promote the resolution of CSDH.

In conclusion, several RCTs examining the management of CSDH are currently ongoing and will hopefully provide strong evidence in either direction on the pharmacological treatment of CSDH[82]. Significant benefits will need to be demonstrated in these trials for widespread adoption of these drugs in the routine treatment of CSDH. At present, no evidence-based medical treatment for CSDH exists.

2.1.12 Follow-up

No guidelines on how and for how long patients should be followed-up after CSDH exist. Follow-up head CT scan has been used to assess possible recurrence, as well as when to restart antithrombotic therapy or provide the patient with permission to start exercise or to drive. Some centers routinely perform head CT scans after surgery and during follow-up, while others use CT only in cases of clinical deterioration[19, 248, 264, 284]. The differences in healthcare financing and medicolegal climate with associated defensive practices could play a role in the differences between countries[125].

Due to a lack of evidence on the best postoperative imaging policy, practices also vary between institutions and even between individual surgeons[264]. When CT scan is performed, patients may be reoperated on in the case of a residual hematoma even

when clinically asymptomatic. However, residual subdural fluid collections after treatment of CSDH are common, and previous studies have shown that up to six months may be required to observe complete resolution of a CSDH[192]. Recent studies suggest that the follow-up CT scan may not be indicated for patients with no neurological symptoms[92, 125, 229, 271].

2.1.13 Neurological Outcome

The natural progression of CSDH remains unknown[287]. A number of studies have examined the postoperative course and outcomes of CSDH[4, 36, 37, 42, 204, 250, 253, 254]. Age, GCS score or clinical state at admission and during discharge, presence of comorbidities, and coagulopathy have been identified as important prognostic factors. Again, the absence of standardized nomenclature complicates comparisons between studies[41]. Markwalder et al.[194] have developed a grading system, the Markwalder Grading Scale, for evaluating the neurologic status of a patient presenting with a CSDH; it also serves as a functional outcome assessment scale. The most common functional assessment scales used are the Glasgow Outcome Scale, and Glasgow Outcome Scale Extended (GOS, and GOS-E)[136, 137], which were originally developed for traumatic brain injury, and modified Rankin Scale (mRS)[315], which was developed for stroke.

In general, the surgical outcomes after CSDH are usually favorable, often with rapid relief of symptoms[270]. Complete neurological recovery is documented in 60-90% of operated patients[175]. In an observational cohort study from the United Kingdom with 1205 patients, 78% of patients displayed a favorable mRS score (0–3) upon discharge[37]. 86% of patients treated with BHC (n=1,481) displayed positive outcomes in a meta-analysis by Ducruet et al. (2012)[76]. Of course, the outcome should be always evaluated in relation to the premorbid functional status, as many patients have not been independent in their daily activities before a CSDH.

A delay between the initial diagnosis of CSDH and surgical evacuation did not negatively affect the outcome in patients with preoperatively favorable GCS scores (≥ 13) in a Swedish study[342]. The average time from CT to surgery was 76 hours, and 49 of 179 (27%) patients were operated at 96 hours or more from diagnosis.

Dementia has been shown to represent a negative prognostic factor for the outcome of CSDH[1, 15, 342]. This negative correlation could be explained by a delay in diagnosis and dementia's association with brain atrophy[15]. Brain atrophy independently increases the risk of unfavorable outcome after CSDH[11]. The clinical

status of CSDH patients with dementia or parkinsonism at admission and at discharge was worse and did not improve like those patients with no neurodegenerative disease, as reported by Arca et al.[15]. The same finding has been noted in patients with dementia and ischemic stroke[1].

Higher age has been associated with poor outcomes after CSDH surgery[36, 78, 140, 202, 294]. However, recent studies show that surgery is safe and allows complete recovery also in the over 90-year-old age group[28, 75, 299]. In a Singaporean series of 101 patients aged 90 years and older, the overall length of survival was longer in surgical patients than those receiving conservative treatment[174]. In a Scandinavian multicenter population-based study, patients 90 years or older (n=75) displayed similar rates of recurrence, perioperative morbidity, and 30-day mortality to younger patients (n=1,179)[28]. However, the 90-day mortality increased among patients ≥90 years old, which may indicate that more patients in this subgroup are too frail to recover from a CSDH.

Advanced age alone does not seem to lead to a poor outcome in patients surgically treated for CSDH[28, 69, 75, 299]. Instead, multiple comorbidities have been associated with increased risk of complications, with a worse clinical outcome and higher six-month mortality[1, 27, 174, 277]. Previous studies have postulated that CSDH in the very old may exacerbate underlying medical conditions, thus leading to poor long-term outcome; as such, CSDH has been called a sentinel health event[28, 78, 202].

2.1.14 Mortality and Long-Term Excess Mortality

Reported mortality rates after CSDH vary widely across studies. A one-year mortality rate of up to 32% has been reported[202]. In a meta-analysis by Ducruet et al.[76], mortality after BHC was 3.7%. Perioperative mortality during neurosurgical clinic admission was 2% (n=15) in a UK study among 798 CSDH patients[37]. Causes of death included pneumonia (10), sepsis (2), and stroke (3).

In general, CSDH patients are from an age group with high baseline expected mortality. Drawing reliable conclusions on the excess mortality related to CSDH is thus impossible without comparing these patients to a matched sample from the general population. To date, only four studies have compared mortality after CSDH with anticipated survival, all which showed a variation in excess mortality (Table 2) [78, 110, 189, 202].

Miranda et al.[202] observed excess mortality up to one year beyond diagnosis, but beyond that life expectancy was equivalent with the general population. Treatment

group (non-operative/operative), size or laterality (bilateral/unilateral) of subdural hematoma, and antithrombotic medication use were not associated with the mortality rate. Dumont and colleagues[78] showed that patients with CSDH demonstrated worse survival rates than expected in every age group, but patients undergoing surgical drainage of CSDH (median survival 5.5 years) had significantly longer survival than those who were treated non-operatively (2.3 years). The authors speculated that the finding may have arisen due to selection bias, because the patients most likely to improve from surgery were the ones offered surgical treatment. Mortality after CSDH was highest in the oldest patients over 85 years old, but the standardized mortality ratio was lower than in any other age group. Manickam et al.[189] reported excess mortality continuing throughout a prolonged follow-up (median 5.2 years) as peers lived 12.4 years longer.

A prospective, randomized study by Santarius et al.[262] revealed that among operatively treated patients, CSDH drainage significantly reduced six-month mortality from 18% to 9%. Additionally, a recent five-year follow-up analysis of the aforementioned study showed a significant survival advantage for drainage as the relative survival rate in the no-drain group was 77.6% compared to 89.8% in the drain group[110].

However, comorbidities play a significant role; it has been theorized that the increased mortality rates in patients with CSDH indicate that it represents a sentinel health event, or a marker of other underlying chronic diseases that supersede its significance as a solitary entity[28, 78, 202].

2.1.15 Financial Impact

Reports that include costs of CSDH are scarce. Moreover, comparing costs between different countries is difficult. Most importantly, the financing and configuration of health systems, key drivers of care, vary widely[260]. Higher cost for CSDH patients treated via craniotomy than via BHC due to longer operating time, higher number of additional procedures, and longer length of hospital stay have been reported from the USA[251]. The length of hospital stay represented the main predictor for costs of SDH patients in Fontera et al.'s study from the USA[93]. As the CSDH incidence among elderly is increasing[339], and the global population of people aged 80 and older is expected to more than triple between 2015 and 2050[117], the heathcare burden related to CSDH will most likely continue to grow.

Table 2. Summary of studies on long-term excess mortality in CSDH patients.

Authors	Country	Time period	n	Age mean, y (range)	Follow-up period median, y (range for survivors)	Mortality (%) 6 m	Mortality (%) 1 y	Control data	Excess mortality
Miranda et al. 2011[202]	USA	2000-2008	209	80.6 (65-96)	1.45 (N/A-8.3)	26.3	32	Center of Disease Control and Prevention data	• Excess mortality up to one year beyond diagnosis. • Median survival: ○ CSDH: 4.4y ○ Anticipated actuarial survival: 6y
Dumont et al. 2013[78]	USA	1996-2010	287	75 (55-N/A)	2.3 (0.5-14)	N/A	30	Center of Disease Control and Prevention data	• 1y standardized mortality ratio: ○ 55-64y: 17 ○ 65-74y: 8.1 ○ 75-84y: 3.4 ○ ≥85y: 2.9 • Median survival: 4.0±0.5y
Manickam et al. 2016[189]	Australia	2006-2011	155	69.3 (18-N/A)	5.2 (N/A-14.19)	14.19	20.35	Australian Bureau of Statistics, and the Registry of Births, Deaths and Marriages	• Excess mortality throughout follow-up. • Average long-term survival: ○ CSDH: 5.29±0.59y ○ Actuarial data: 17.74±1.8y

Table 2 continued

Authors	Country	Time period	n	Age mean, y (range)	Follow-up period median, y (range for survivors)	Mortality (%) 6 m	1 y	Control data	Excess mortality
Guilfoyle et al. 2017[110]	United Kingdom	2004-2007	215	78 (35-95)	N/A (8-10)	Drain group: 8.6 No drain group: 18.1	N/A	Cohorts of the general population with the same number of cases and identical age and sex profiles as the drain and no drain groups (Human Mortality Database)	• 5y cumulative excess mortality: ○ Drain group: 10.2% ○ No drain group: 22.4%
Present study	Finland	1990-2015	1,133	73 (22-99)	4.8 (2-27)	9.5	13.7	The population of Pirkanmaa region stratified by sex, age, and calendar year (Statistics Finland)	• Cumulative excess mortality: ○ 1y: 9% ○ 5y: 18% ○ 10y: 27% ○ 15y: 37% ○ 20y: 48%

CSDH = chronic subdural hematoma; N/A = not available

3 AIMS OF THE STUDY

The specific aims were:

1. To determine the population-based epidemiology of CSDH over a 26-year period. (Study I)

2. To assess possible long-term excess mortality and causes of death of patients with CSDH. (Study II)

3. To examine the incidence stratified by treatment groups, complications, and total direct hospital costs of CSDH treatment from hospital admission until the last follow-up visit in a neurosurgical clinic during the 26-year study period. (Study III)

4. To estimate the necessity of a prescribed postoperative follow-up head CT scan after CSDH. (Study III)

4 MATERIALS AND METHODS

4.1 Study Design and Ethical Aspects

The study was conducted in the Department of Neurosurgery at the Tampere University Hospital (Tampere, Finland). Patients had to meet all three of the following criteria: 1) resident in the Pirkanmaa region, 2) aged 18 years or over with no upper limit, and 3) diagnosed with CSDH between 1990 and 2015.

The cases were retrospectively identified using the hospital's patient administrative databases, including International Classification of Diseases (ICD) codes for traumatic and non-traumatic subdural hematomas (SDHs; ICD-10 codes: S06.5 and I62.0; ICD-9 codes: 432.1, 852.2 and 852.3). Verified cases were classified by SDH type (acute, subacute, chronic, and hygroma) by reviewing all the medical records. Cases were excluded if they contained acute or subacute SDH (< 3 weeks after head trauma), hygroma (a collection of subdural cerebrospinal fluid without any signs of blood), and any form of intracranial surgery within the 12 months preceding the CSDH diagnosis.

The study was approved by the Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (ethical code R12082). All the data was collected retrospectively without contacting the patients; therefore, no written informed consent was obtained or required.

4.1.1 Death Certificates

Postmortem cases with CSDH as the immediate, intermediate, main, or related cause of death were included in the study. The death certificates were obtained from the official Cause-of-Death Register, coordinated by Statistics Finland (Helsinki, Finland), which covers all deaths occurring in Finland. According to Finnish legislation, a medicolegal autopsy should be performed when death is caused or suspected to be caused by an accident. As a result, traumatic causes of death are identified with a high probability.

4.2 Study Population

The annual age-specific inhabitant number of the Pirkanmaa region (Finland) was obtained from Statistics Finland (Helsinki, Finland). The Pirkanmaa region is a geographically well-defined area with both rural and urban areas that contains one of Finland's five neurosurgical departments (Department of Neurosurgery, Tampere University Hospital, Tampere). All neurosurgical cases of the Pirkanmaa region are referred to the Tampere University Hospital. Over 9% of the Finnish population lives in the Pirkanmaa region. The population increased from 427,223 in 1990 to 506,114 in 2015. Furthermore, the number of inhabitants over 80 years old has almost doubled from 13,565 to 26,417 during the study period. The Pirkanmaa population of those over 90 years old increased 3.4 times, from 1,242 to 4,275.

4.3 Data Collection

A detailed and structured data collection was performed from medical records and death certificates. CT scans or MR images were not separately inspected. The data collection included the following details: comorbidities, medication, possible trauma, symptoms, neurological condition assessments based on both the Glasgow Coma Scale (GCS) and the mRS score at admission, as well as at discharge for group operated upon. An mRS score of 0 indicates no disability; a score of 1 or 2 indicates slight disability (i.e. the patient requires some help with daily activities, but can perform basic care for him- or herself), a score of 3 signals moderate disability (i.e. the patient requires some help in daily activity), a score of 4 or 5 denotes severe disability (i.e. the patient requires constant specific care or is bedridden), and a score of 6 indicates death. CSDH-related findings collected included localization (unilateral/bilateral) and hematoma thickness divided into three groups (<15 mm, 16-25 mm, and >25 mm). Operation details were collected. CSDH recurrence was defined as an ipsilateral hematoma needing reoperation within two years of the original operation.

Patients were stratified either into five age groups (Study I): (i) 18-59 years, (ii) 60–69 years, (iii) 70-79 years, (iv) 80–89 years, and (v) ≥ 90 years, or three groups (Studies II and III): (i) 18-59 years, (ii) 60–79 years, and (iii) ≥ 80 years. The study period was divided into five time periods: (i) 1990-1995, (ii) 1996-2000, (iii) 2001-2005, (iv) 2006-2010, and (v) 2011-2015. All patients were followed until death or the end of 2017.

4.4 Survival Analysis

The dates and causes of deaths were obtained from Statistics Finland (Helsinki, Finland). The Finnish official cause of death statistics is, in practice, 100% complete in relation to the cause and date of death. The entire Pirkanmaa population matched by sex, age, and calendar time was used for the excess mortality analysis. For the cause of death comparison, a separate reference group was formed by randomly choosing four control subjects for every CSDH patient, matched by sex, age (+/-6 months), and calendar time, from Pirkanmaa. The reference group (n=4,532) was obtained from Statistics Finland.

The variables chosen for survival analysis were sex, age groups, and variables known to be CSDH risk factors (trauma, chronic alcohol abuse, and antithrombotic medication). We analyzed the effect of neurological condition, treatment group (operative versus non-operative), and hematoma recurrence.

4.5 Cost Data

To estimate the direct, total hospital costs from admission until the last follow-up visit, we calculated all costs for the whole treatment period, including operations and number of days spent in the neurosurgical ward, recovery room or ICU, emergency department visits related to the CSDH, laboratory and radiologic costs, and neurosurgical follow-up visits. The unit costs were then multiplied by the number of cost factors of each patient. Due to the length of the study period, it was not possible to obtain all of the individual patient's costs directly from our hospitals' invoicing department. Instead, all costs were calculated from the latest 2018-2019 data from hospital administration and catalogues for in-hospital use.

When comparing the results to earlier studies, costs were first adjusted to their 2018 value using the Consumer Price Index (CPI) of the relevant country[303, 313], and then converted to FIN EUR using the most recent (2018) Purchasing Power Parities (PPP) of that country. PPP tries to equalize the purchasing power of different currencies by eliminating the differences in price levels between countries[224].

4.6 Statistical Analyses

We used SPSS (IBM SPSS Statistics for Windows, Versions 22.0-25.0, Armonk, NY, USA) for data analyses. Survival analyses were conducted using the statistical software R (version 3.6.0) with the popEpi package (version 0.4.7). Descriptive statistics [frequency (n), percentage, median, interquartile range (IQR), range] were used to describe variable and subgroup characteristics. The Chi square test was used to compare differences between groups. The statistical significance level was set at 5%.

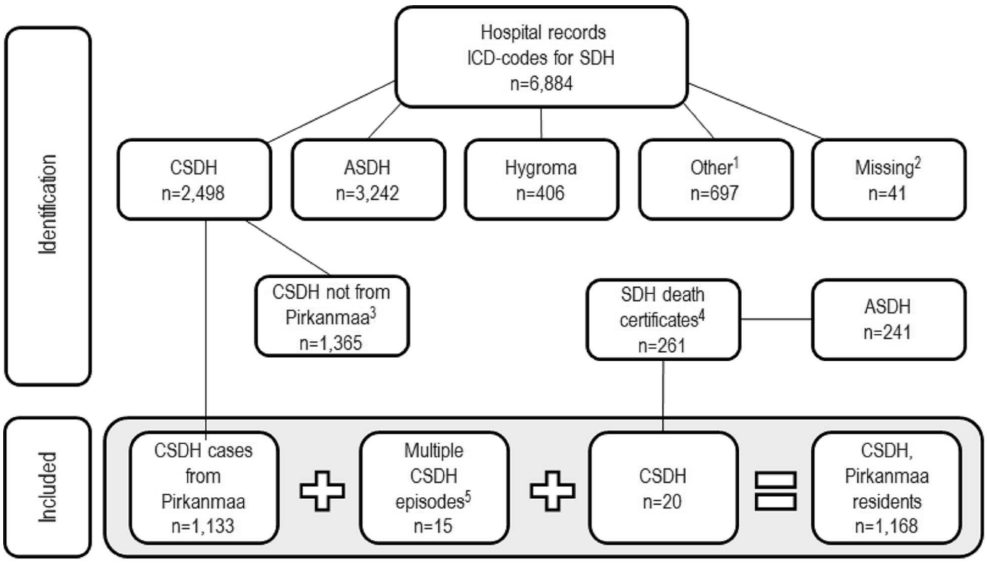
The cumulative relative survival ratio (CRSR) summarizes patients' excess risk of death due to the disease by comparing the survival of patients to that of the matched general population (the population of Pirkanmaa region stratified by sex, age, and calendar year). CRSRs were estimated with the Ederer II method[80, 273]. To compare differences in relative survival adjusted for age, sex, and follow-up time, we estimated relative excess risk (RER) of death by using Poisson regression[72]. Each model included sex, age at diagnosis (four groups: 0-59, 60-69, 70-79 and 80+ years), and five intervals of follow-up time after diagnosis (0 to <1 year, 1 to <5 years, and three 5-year intervals from 5 to 20 years) in addition to a risk factor.

A Kaplan–Meier analysis was used for the time of first surgery to recurrence and the hazard ratio was computed based on Cox regression. Observations for event-free patients were eliminated at the time of death. Univariable and multivariable forward stepwise binary logistic regression analysis was performed to assess which variables were associated with recurrence.

5 SUMMARY OF THE RESULTS

5.1 Study Sample

A total of 1,133 patients with CSDH were identified from the hospital records and an additional 20 from death certificates. The data collection process is shown in Figure 5.



SDH= subdural hematoma, CSDH=chronic subdural hematoma, ASDH=acute subdural hematoma

[1]Brain contusion intracerebral or subarachnoid hemorrhage or diagnosis due to clinically suspected subdural hematoma even though a subsequent brain scan ruled out that disorder.

[2]Medical records had been destroyed 20 years after patients' death before the data collection.

[3]The catchment area of Tampere Neurosurgical Department is approximately one million people.

[4]After excluding patients who had been found in the hospital records.

[5]Patients with recurrent CSDH were considered as new incidence cases after two years of primary treatment and if they had a new contralateral hematoma.

Figure 5. The data collection process for patients with CSDH between 1990-2015 in Pirkanmaa, Finland.

Patients with CSDH were considered new cases if two years had elapsed following primary treatment or if they had a new contralateral hematoma (n=15). During the study period, 14 patients underwent new contralateral CSDH evacuation and only one patient needed operative treatment for the same sided CSDH after five years of index CSDH. In terms of incidence, these 15 aforementioned cases were counted twice, and the total number of cases was 1,168 (Study I). For studies II and III, the cases found from death certificates were excluded. In terms of excess mortality, the total number of cases equalled 1,133 unique patients (Study II). In terms of financial impact, the total number of cases also included the 15 patients treated twice, and the total number was 1,148 (Study III).

The patient group aged 70-79 years represented the most common age group between 1990-2010, while those aged 80-89 became the largest group in 2011-2015 (Figure 6).

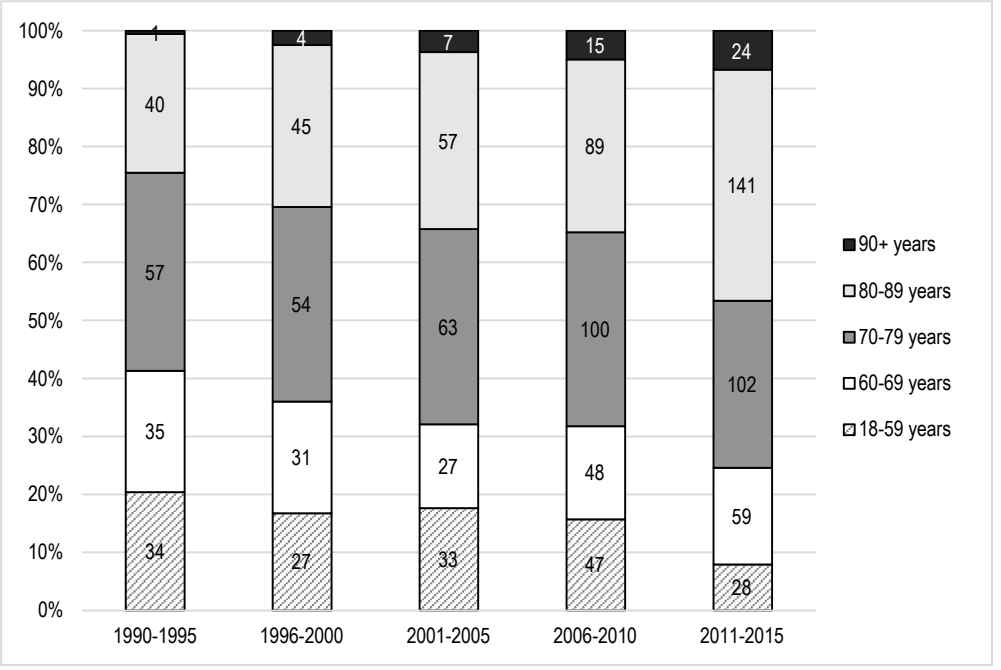


Figure 6. Patients with CSDH between 1990-2015 in Pirkanmaa, Finland. Proportions (%) of different age groups stratified by time periods.

5.2 Incidence of Chronic Subdural Hematoma

During the study period from 1990 to 2015, the overall incidence of CSDH in adults doubled from 8.2 to 17.6/100,000/year and nearly tripled for ≥ 80-year-olds from 46.9 to 129.5/100,000/year. The incidence rates stratified by age groups and time periods are presented in Figure 7. Among those under the age of 70, the incidence remained quite stable, whereas the incidence clearly increased among those aged 80 and older. The annual incidence increased from 32.3 to 52.1/100,000/year in patients in the age group 70-79, from 50.7 to 130.3/100,000/year in patients in the age group 80-89, and from 11.6 to 125/100,000/year in patients ≥ 90 years old.

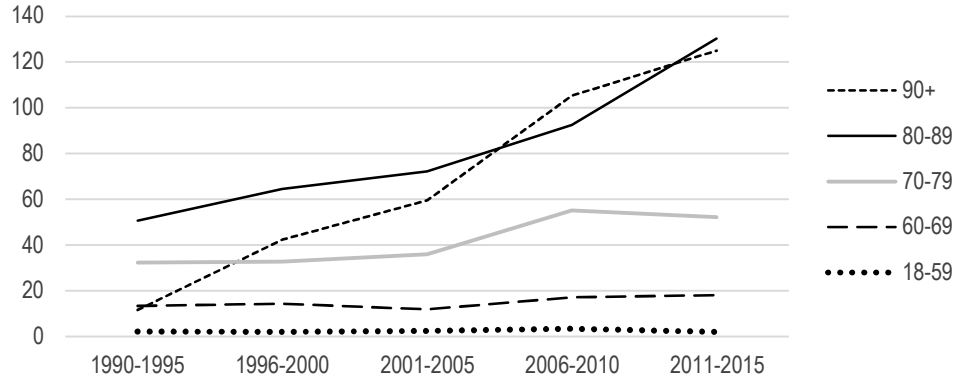


Figure 7. The incidence (n/100,000) of CSDH in different age groups during the study period between 1990-2015 in Pirkanmaa, Finland.

5.2.1 Incidence and Gender

The lowest, as well as the only comparable, incidence for men and women occurred in those between the ages of 18 and 59. Both men and women among this age group demonstrated an incidence of 2/100,000/year during the last five-year period (2011-2015). The highest rates of CSDH for both genders occurred in those aged 90 and older, and they increased from 56.6 to 231/100,000/year for men and from 0 to 94.2/100,000/year for women over the study period. The gender-stratified incidences by time periods are presented in Figure 8.

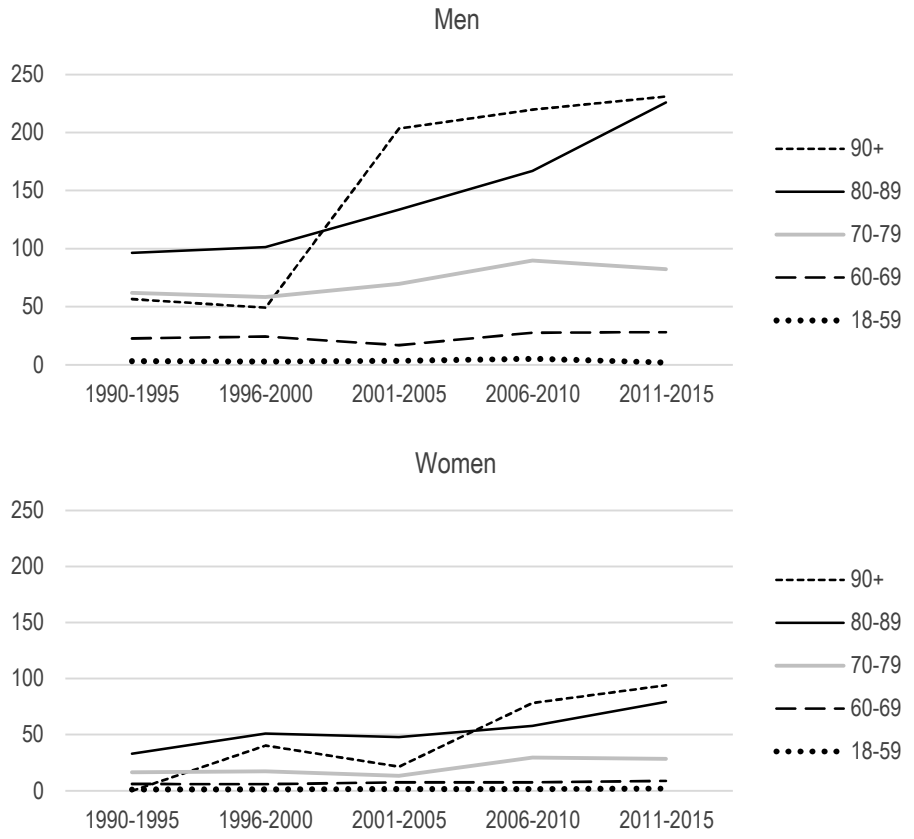


Figure 8. The incidence (n/100,000) of CSDH stratified by gender during the study period between 1990-2015 in Pirkanmaa, Finland.

5.2.2 Incidence and Treatment Group

From 1990 to 2015, the overall incidence of operatively treated CSDH in adults almost doubled from 7.2 to 13.4/100,000/year. The incidence remained quite stable among those under the age of 70 but increased 2.5 times for those over 80 from 36.6 to 91/100,000/year. Prior to the 2001-2005 period, only a small number of non-operatively treated patients were diagnosed. The incidence of non-operatively treated CSDH for those over 80 years increased from the beginning of the millennium, reaching 36.9/100,000/year in 2011-2015. CSDH cases identified from death certificates (n=20) represented less than 2% of all CSDH cases. These autopsy cases were distributed equally throughout the entire 26-year study period. The incidence rates without the autopsy-verified cases stratified by treatment groups are presented in Figure 9.

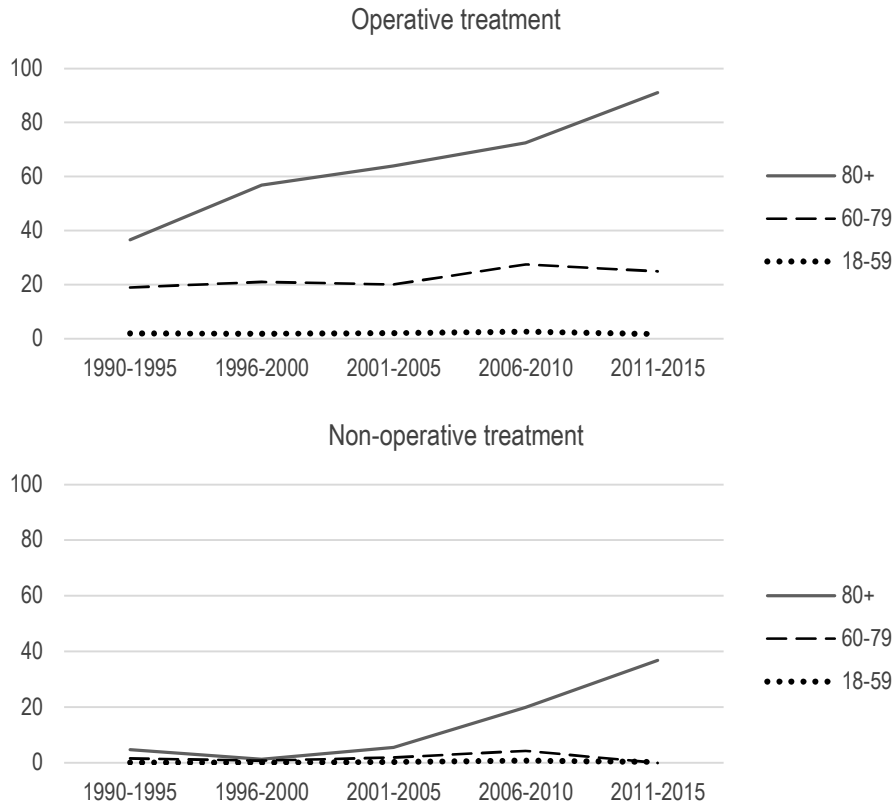


Figure 9. The incidence (n/100,000) of CSDH stratified by treatments groups during the study period between 1990-2015 in Pirkanmaa, Finland.

5.3 Etiology and Risk Factors

5.3.1 Head Trauma

Any type of preceding minor or major head trauma was retrospectively found in 690 of 1,168 CSDH cases (59%), most of which were ground-level falls (n=529; 77%) followed by bicycle accidents (n=23; 3.3%) and falls from a height of over one meter (n=23; 3.3%). There was no clear change over time or between genders in relation to the cause of injury. All age groups had similar overall incidence of trauma-related CSDHs, but the trauma mechanism profile varied. The mechanism of injury was more likely to be a ground-level fall in older patients [15-59 years: n=52/102 (51%) and ≥ 80 years old: n=228/258 (88%)]. In contrast, assault and battery was the cause in 16/102 (16%) among 15-59 years old, but only in 1/258 (1.4%) among those over 80 years old. Forty percent of both 15-59 years old and over 80 years old CSDH patients reported no trauma history.

5.3.2 Alcohol

The proportion of alcohol-related cases declined towards the end of the study period (1990-1995: 16% and 2011-2015: 7%, p=0.002), but the absolute number of chronic alcohol abusers did not change markedly (varying between 19 and 38 patients). The incidence of chronic alcohol abuse varied significantly between age groups (18-59 years: 44% and ≥ 80 years: 0.3%) and genders (men 14% and women 6%).

5.3.3 Antithrombotic Medication

Antithrombotic medication that was used by the patients included in the study cohort encompassed only one anticoagulant agent (warfarin) and three antiplatelet agents (acetylsalicylic acid, dipyridamole, and clopidogrel). None of the included patients were taking direct oral anticoagulant drugs.

The number of patients on antithrombotic medication increased over time (1990-1995: n= 45/167, 27% and 2011-2015: n=173/354, 49%; p<0.001), mostly due to an increase in anticoagulation medication (1990-1995: n=15/167, 9% and 2011-2015: n=98/354, 28%; p<0.001). Among the patients between 18 and 59 years old, the prevalence of antithrombotic medication usage was 10% (warfarin 3.6%,

antiplatelets 5.4%, and warfarin+antiplatelet 1.2%). In contrast, the prevalence was 58% (warfarin 22%, antiplatelets 34%, and warfarin+antiplatelet 2.4%) among patients aged 80 years or older ($p<0.001$). There was a higher prevalence of antithrombotic drug use in CSDH patients with no head trauma history (n=220/478 patients, 46%) compared to patients with a positive head trauma history (n=266/690, 39%; $p=0.011$). There was no significant difference in antithrombotic drug usage between men and women.

5.4 Clinical Characteristics

Of all the cases treated (n=1,148; cases identified from death certificates excluded), 748 (65%) were men. The proportion of men fell as age increased (Figure 10). The median age for CSDH diagnosis was 76 years, increasing from 73 to 79 years during the 26-year period. Women were older than men (79 vs. 75 years), with a median age at diagnosis rising from 76 to 81 years. The median follow-up time was 4.8 years, with a minimum of 0 days and maximum of 27 years. The median follow-up time for survivors was 6.6 years, with a minimum of 2 years. No patient data was lost during the follow-up period.

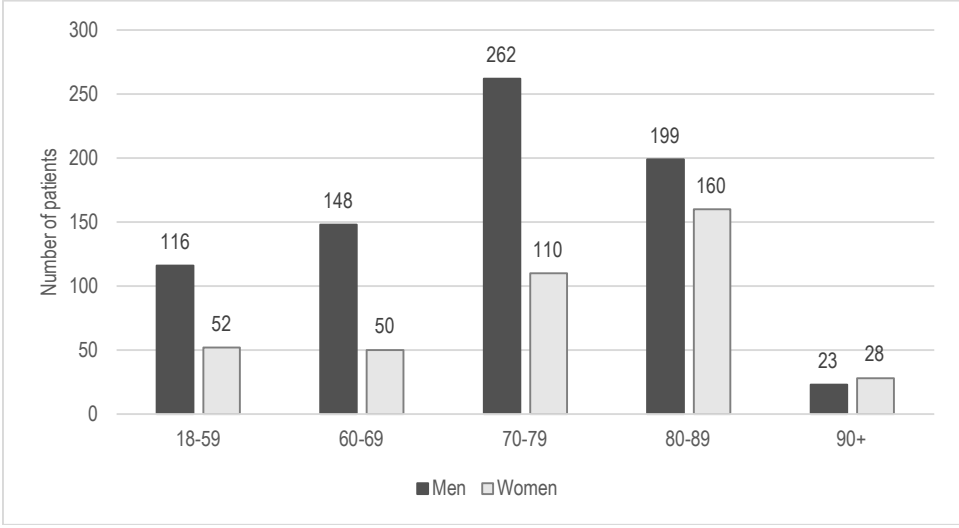


Figure 10. Age distribution of 748 men and 400 women with chronic subdural hematoma during the study period between 1990-2015 in Pirkanmaa, Finland.

Of the patients, 82% had at least one comorbidity. The comorbidities stratified by age groups are presented in Figure 11. The likelihood of comorbidities increased with age ($p<0.001$); two or more comorbidities were reported by 29% of the 18-59-year-old age group, by 36% of the 60-79-year-old age group, and by 50% of the over 80-year-old age group. Three or more comorbidities were reported by 11%, 13% and 15% of each age group respectively. When separated by treatment group, two or more comorbidities were reported by 38% of the operative group patients and 48% of the non-operative group patients ($p=0.015$), versus three or more by 13% and 15% ($p=0.052$) respectively. Non-operatively treated CSDH patients were more likely to report previously diagnosed dementia (16% vs. 8%, $p=0.001$). The overall average prevalence of dementia in CSDH patients aged 70 years or older was 12%; it increased from 4.6% (1990-1995) to 17% (2010-2015) during the study period.

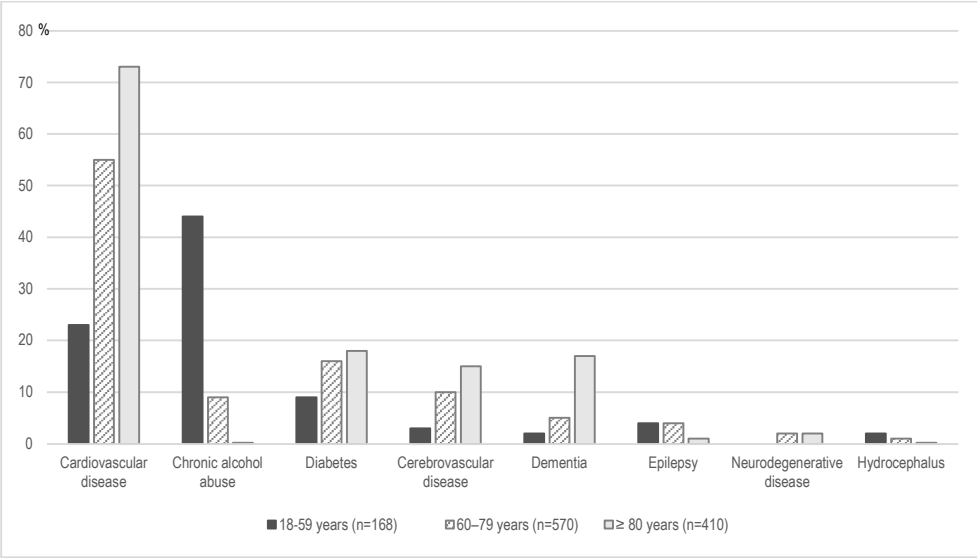


Figure 11. Comorbidities of the patients with CSDH stratified by age groups.

At hospital presentation, patients under 60 years more often reported headaches (50% vs. 16%, $p<0.001$) and nausea (10% vs. 3.3%, $p=0.008$) than those over 80 years old. Elderly patients over 80 years old, compared to patients under 60 years old, displayed disorientation or memory impairment more often (43% vs. 22%, $p<0.001$). General malaise was twice as common in patients over 80 years compared to patients under 60 years (42% vs. 21%, $p<0.001$). The symptoms stratified by age groups are presented in Figure 12. The patients' clinical status on admission was somewhat worse in the early 1990s, compared to the recent years, on both the GCS

(GCS<13,1990-1995: 18% and 2011-2015: 7%; p<0.001) and the mRS (mRS=0-2, 1990-1995: 8% and 2011-2015: 19%; p<0.001). Characteristics of all CSDH patients and treatment subgroups are presented in Table 3. Patients with CSDH stratified by time periods are presented in Table 4.

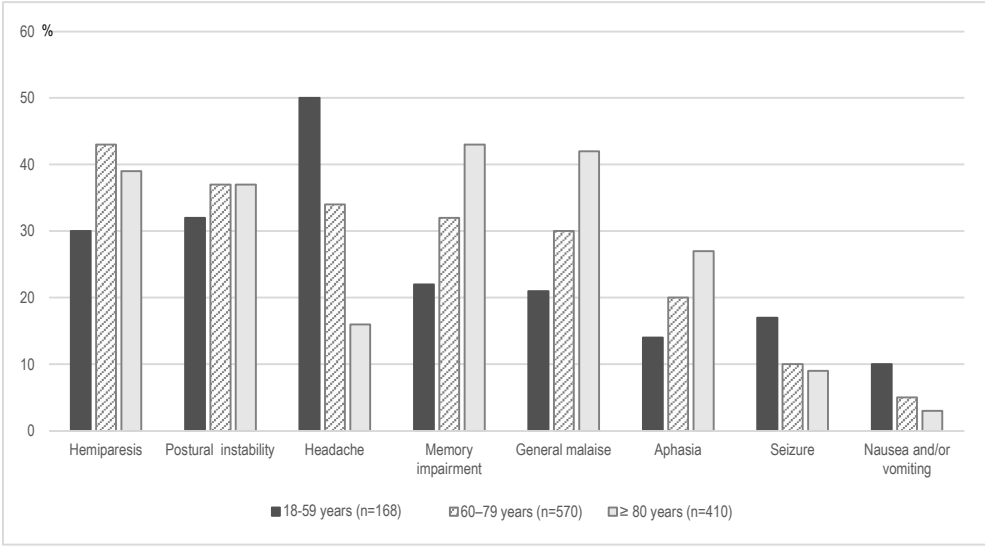


Figure 12. Symptoms of the patients with CSDH stratified by age groups.

Table 3. Characteristics of all CSDH patients and treatment subgroups.

	Total sample n=1,148		Non-operative treatment n=170		Operative treatment n=978		p-value
	n	%	n	%	n	%	
Median age, IQR (years)	76	67-83	79	68-86	76	66-82	**0.005**
Men	748	65.2	104	61.2	644	65.8	0.24
Traumatic etiology	679	59.1	109	64.1	570	58.3	0.15
Comorbidity	880	76.7	132	77.6	748	76.5	0.74
Cardiovascular disease	653	56.9	98	57.6	555	56.7	0.83
Diabetes	178	15.5	27	15.9	151	15.4	0.88
Chronic alcohol abuse	126	11.0	20	11.8	106	10.8	0.72
Cerebrovascular disease	125	10.9	24	14.1	101	10.3	0.13
Dementia	102	8.9	27	15.9	75	7.7	**0.001**
Epilepsy	34	3.0	3	1.8	31	3.2	0.44
Neurodegenerative disease	20	1.7	7	4.1	13	1.3	**0.013**
Hydrocephalus	9	0.8	0	0	9	0.9	0.21
Medication							
Antiplatelet	270	23.5	36	21.2	234	23.9	0.34
Warfarin	191	16.6	27	15.9	164	16.8	0.57
Antiplatelet AND warfarin	23	2.0	2	1.2	21	2.1	0.36
Admission GCS							
13-15	1,020	88.9	159	93.5	861	88.0	**0.04**
9-12	91	8.0	8	4.8	85	8.7	0.91
3-8	35	3.1	3	1.8	32	3.3	0.29
Admission mRS 0-2	172	15.0	59	34.7	113	11.6	**<0.001**
Symptoms							
Hemiparesis	455	39.6	10	5.9	445	45.5	**<0.001**
Vertigo or postural instability	415	36.1	37	21.8	378	38.7	**<0.001**
Disorientation/memory impairment	395	34.4	55	32.4	340	34.8	0.54
General malaise	374	32.6	51	30.0	323	33.0	0.44
Headache	342	29.8	28	16.5	314	32.1	**<0.001**
Aphasia	248	21.8	10	5.9	238	24.3	**<0.001**
Seizure	119	10.4	28	16.5	91	9.3	**0.005**
Nausea and/or vomiting	61	5.3	7	4.1	54	5.5	0.45

Note: Cases identified from death certificates have been excluded. Abbreviations: IQR, interquartile range; GCS=Glasgow Coma Scale, mRS= modified Rankin Scale

Table 4. Characteristics of patients with CSDH stratified by time periods.

	1990-1995 n=159		1996-2000 n=156		2001-2005 n=185		2006-2010 n=296		2011-2015 n=352	
	n	%	n	%	n	%	n	%	n	%
Median age, IQR (years)	73	62-80	75	64-81	75	67-82	76	66-84	79	70-85
Men	111	66.5	99	61.5	125	66.8	199	66.6	224	63.3
Traumatic etiology	97	58.1	97	60.2	115	61.5	176	58.9	205	57.9
Comorbidity										
Cardiovascular disease	74	46.5	82	52.6	97	52.4	174	58.8	226	64.2
Diabetes	20	12.6	25	16.0	20	10.8	43	14.5	70	19.9
Chronic alcohol abuse	25	15.7	18	11.5	21	11.4	37	12.5	25	7.1
Cerebrovascular disease	16	10.1	14	9.0	18	9.7	35	11.8	42	11.9
Dementia	5	3.1	6	3.8	16	8.6	34	11.5	41	11.6
Epilepsy	4	2.5	8	5.1	5	2.7	9	3.0	8	2.3
Neurodegenerative disease	1	0.6	0	0	0	0	10	3.4	9	2.5
Hydrocephalus	3	1.9	1	0.6	1	0.5	3	1.0	1	0.3
Medication										
Antiplatelet	30	18.9	39	25.0	53	28.6	73	24.7	75	21.3
Warfarin	15	9.4	14	9.0	26	14.1	44	14.9	92	26.1
Antiplatelet AND warfarin	0	0	1	0.6	2	1.1	14	4.7	6	1.7
Admission GCS										
13-15	131	82.4	133	85.3	167	90.3	262	88.5	327	92.9
9-12	17	10.7	17	10.9	15	8.1	28	9.5	16	4.5
3-8	11	6.9	6	3.8	3	1.6	6	2.0	9	2.6
Admission mRS 0-2	13	8.2	23	14.7	24	13.0	44	14.9	68	19.3
Symptoms										
Hemiparesis	78	49.1	75	48.1	91	49.2	101	34.1	110	31.3
Vertigo or postural instability	67	42.1	73	46.8	62	33.5	108	36.5	105	29.8
Disorientation or memory impairment	66	41.5	54	34.6	68	36.8	102	34.5	105	29.8
General malaise	57	35.8	53	34.0	48	25.9	83	28.0	133	37.8
Headache	72	45.3	63	40.4	58	31.4	66	22.3	83	23.6
Aphasia	44	27.7	41	26.3	46	24.9	54	18.2	63	17.9
Seizure	17	10.7	18	11.5	18	9.7	28	9.5	38	10.8
Nausea and/or vomiting	18	11.3	13	8.3	10	5.4	10	3.4	10	2.8

Note: Cases identified from death certificates have been excluded. Abbreviations: IQR, interquartile range; GCS=Glasgow Coma Scale, mRS= modified Rankin Scale

5.4.1 Hematoma Characteristics

The CSDHs occurred on the right side of the brain in 413 of 1,148 patients (36%), on the left side in 478 (42%), and on both sides in 257 patients (22%). Bilateral hematomas occurred more often in recent years compared to the early 1990s (1990-1995: 16% and 2011-2015: 26%, p=0.013) as well as in those over the age of 80 (18-59 years: 15% and ≥80 years: 24%, p=0.016).

A previous acute or subacute SDH was diagnosed in 47 patients (4.1%) with a mean time of 50 days (median 30 days) before CSDH diagnosis. A previous hygroma was diagnosed in 10 patients (0.9%) with a mean time of 58 days (median 38 days) before CSDH diagnosis. The CSDHs were related to arachnoid cysts in only 7 cases (0.6%).

The mean hematoma thickness was 22 ± 6 mm (maximal diameter) among patients who were operatively treated, and 10 ± 4 mm among patients with non-operative treatment. The hematoma thickness was divided into three groups: (i) <15 mm, (ii) 15-25 mm, and (iii) >25 mm. Among patients who were operatively treated, 31% fell into the first group, 51% in the second, and 17% in the third (with 1% missing data). Among those whose CSDH was not treated operatively, 95% fell into the first group and 3.7% in the second group (missing 1.3%). Midline shift was not reported constantly and hence was not used in our analysis.

5.5 Operative Treatment

For the total sample (n=1,148), 978 (85%) were treated operatively and 170 (15%) non-operatively. The indication for surgery was based on imaging and symptoms attributable to the mass effect of the hematoma. 223 (87%) of those with a bilateral CSDH (n=257) were operated on. Of these, 137 (61%) initially underwent a bilateral and 86 (39%) a unilateral operation. The contralateral side needed evacuation at a later stage in five (5.8%) of the latter group of patients.

The median time from CT to surgery was zero days: 588 of patients (60%) were operated on the same day, 294 (30%) on day one, and 50 (5%) on day two after diagnosis. Only 5% of patients were operated three days or more after diagnosis. Among the patients treated operatively, 53 patients (4.6%) were first treated non-operatively, but then underwent surgery when the CSDH increased in size (median time from first CT to surgery was 24 days).

Possible antithrombotic medication was discontinued, and preoperative methods to counteract the effects of these medications when needed were implemented. Most operations were performed under local anesthesia (n=839; 86%) via one burr hole (BHC) and the hematoma was evacuated through irrigation with body temperature saline solution. A subdural drain was inserted in 59 patients (6%). The drain was kept below the head level with no suction for 24-48 hours. Only one patient underwent craniotomy as the primary surgery. Surgery was performed in 610 (62%) of cases by residents. The patients were actively mobilized directly after the operation.

The median length of hospital stay was three days (min-max=1-33 days) for surgically treated patients and four days (min-max=1-46 days) during readmission for patients with a recurrent hematoma. The mean number of days the surgically treated patients spent in our neurosurgical ward decreased during the study period from five days (1990-1995) to three days (2011-2015).

The share of patients discharged home did not change significantly, declining slightly from 49% in 1990-1995 to 43% in 2011-2015 ($p=0.25$). By age group, rates varied: 64% of those aged 18-59 years, 50% of those in the 60-79 age group and 19% of those over 80 were discharged home ($p<0.001$).

Most patients (72%) were seen in an outpatient clinic and underwent follow-up CT four to six weeks after the operation. In the case of residual hematoma needing no reoperation, patients were followed monthly until the hematoma resolved significantly. A median of three head CT scans were performed (min-max=1-13), with a total number of scans of 3,043. The median number of outpatient follow-up visits was one (min-max=0-11), and the total number of visits was 1,463.

5.5.1 Complications

Seizures represented the most common complication, occurring in 4.8% of the total sample of patients undergoing surgery. Acute intracranial hemorrhage was rare, with only 11 cases of acute subdural hematoma (1.1%) and six cases of intracerebral hematoma (0.6%). Nine (0.9%) of these 17 intracranial hemorrhages required emergency craniotomies, and two (0.2%) patients died. Postoperative infection at the site of surgery was diagnosed in 29 (3.0%) patients; 20 (2.0%) patients were operated on because of an empyema.

Pneumonia represented the only complication whose frequency significantly differed between the age groups, occurring more often among the oldest patients (≥80-years, $p=0.02$). Patients undergoing a second surgery suffered more often from

seizures (10%, n=28 versus 3.9%, n=27; p<0.001), empyema (4.3%, n=12 versus 1.1%, n=8; p=0.002), and pneumonia (4.7%, n=13 versus 1.4%, n=12; p=0.008) compared to patients with no recurrence. The complications are shown in Table 5.

Table 5. Comorbidity, perioperative complications, and discharge to home in patients with an operatively treated CSDH.

	All n=978		Age group						p-value	Recurrence				p-value
			18-59y n=145		60-79y n=502		≥80y n=331			No n=700		Yes n=278		
	n	%	n	%	n	%	n	%		n	%	n	%	
Comorbidity	748	76.5	74	51.0	377	75.1	297	89.7		534	76.3	214	77.0	0.82
Complications														
Seizures	55	5.6	5	3.4	33	6.6	17	5.1	0.32	27	3.9	28	10.1	**<0.001**
Acute subdural hematoma	11	1.1	1	0.6	8	1.4	2	0.5	0.30	6	0.9	5	1.8	0.21
Intracerebral haemorrhage	6	0.6	0	0	5	0.9	1	0.2	0.24	3	0.4	3	1.1	0.24
Cerebrovascular infarction	6	0.6	1	0.6	3	0.5	2	0.5	1.0	3	0.4	3	1.1	0.24
Surgical site infection	29	3.0	1	0.7	20	4.0	8	2.4	0.92	15	2.1	14	5.0	**0.016**
Empyema	20	2.0	1	0.7	16	3.2	3	0.9	0.05	8	1.1	12	4.3	**0.002**
Pulmonary embolus	2	0.2	0	0	1	0.2	1	0.3	0.80	1	0.1	1	0.4	0.50
Pneumonia	25	2.6	0	0	11	2.2	14	4.2	**0.020**	12	1.7	13	4.7	**0.008**
Discharge to home	409	41.8	93	64.1	253	50.4	63	19.0	**<0.001**	291	41.6	118	42.4	0.80

5.5.2 Recurrence

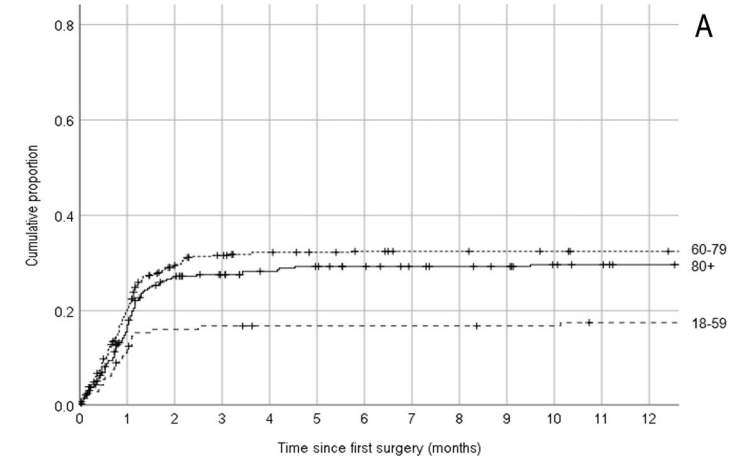
A CSDH was defined as recurrent if the CSDH was re-diagnosed within two years of the previous operation and treated surgically. 28% of total cases and 35% of the bilateral cases recurred (n=278; median age 76 years). Patients aged between 18 and 59 (17%) and those over the age of 90 (19%) had the lowest rate of recurrence. The highest recurrence rate occurred in the 70-79-year-old age group (32%). The recurrence rate between men and women differed significantly (men: 31% and women: 25%; p=0.017). Hematoma thickness was significantly associated with recurrence (p>0.001), with the following recurrence rates: 11% of <15 mm, 28% of 16-25 mm, and 37% of those >25 mm.

Eighty-six patients (7.5%) were operated on for re-recurrence, 10 (12%) via craniotomy. Thirty-two patients (2.8%) underwent a fourth (31% via craniotomy), and 13 (1.1%) a fifth surgery (38% via craniotomy). The highest number of operations due to a CSDH recurrence was six (two patients). One patient was operated on eight times, but the case was complicated by a subdural empyema.

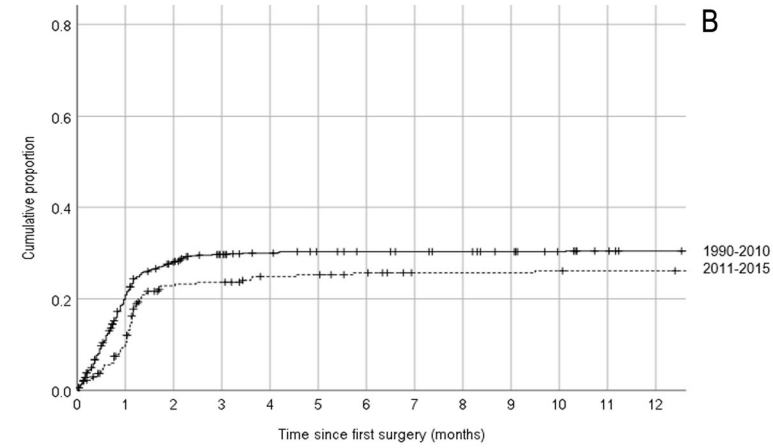
The first recurrent hematoma was symptomatic in 229 (82%) of the cases and operated on because follow-up CT revealed a large CSDH in 49 of patients (18%). Twenty-two patients (8% of the recurrences) underwent a second surgery during the primary admission. A reoperation was performed on 114 symptomatic patients (41% of the recurrences) before their scheduled outpatient clinic visit. The first scheduled outpatient visit with a head CT scan led to a reoperation in 108 patients (39% of the recurrences). Of these 108 patients, 70 (65%) demonstrated symptoms while 38 (35%) were symptom-free. The median time to recurrence was 25 days (min-max=0-304 days, IQR=14-35). Most of the recurrences were treated operatively within 30 days (63%) or two months (92%) after the primary operation. Only two patients underwent surgery after six months (285 days and 304 days) from their primary operation.

The cumulative proportion of first recurrences is shown in Figure 13. These shares differed significantly between the age group of 18-59 years versus both the age groups of 60-79 years (HR=2.02; 95% CI=1.32-3.08, p=0.001) and ≥80 years (HR=1.79; 95% CI=1.15-2.77, p=0.01). The recurrence rate among patients treated with drains fell significantly below those patients with no drain (17% versus 29%, p=0.04). Almost all patients with a drain (48/59; but still only 18% of all surgically treated patients) were from the last study period (2011-2015). During this period, the

recurrence rate was 25%, which was non-significantly lower than the rate of previous years combined (HR=0.79; 95% CI=0.60-1.04, p=0.10).



Age group (years)	No at Risk (two months' intervals)						
18-59	145	119	116	116	116	115	113
60-79	502	337	315	309	306	304	302
80+	331	227	211	203	197	190	185



Time period (years)	No at Risk (two months' intervals)						
1990-2010	707	489	458	449	445	436	428
2011-2015	271	194	184	179	174	173	172

Figure 13. Cumulative proportion of recurrences shown as Kaplan-Meier analysis in different age groups (A) and time periods (B). Observations for event-free patients were censored at the time of death.

Table 6. Factors associated with recurrence of CSDH requiring reoperation.

Primary Admission	No recurrence n=700		Recurrence n=278		Univariable logistic regression analysis		
	n	%	n	%	OR	95% CI	p-value
Age, median, IQR, years	76	64-82	76	69-82			
Age group, years							**0.004**
18-59	120	17.1	25	9.0	1	Ref	
60-79	343	49.0	159	57.2	2.23	1.39-3.56	**0.001**
≥80	237	33.9	94	33.8	1.90	1.16-3.12	**0.010**
Men	448	64.0	196	70.5	1.35	1.0-1.8	0.053
Traumatic etiology	414	59.1	156	56.1	0.88	0.67-1.17	0.39
Comorbidity	534	76.3	214	77.0	1.04	0.75-1.46	0.82
Chronic alcohol abuse	82	11.7	24	8.6	0.71	0.44-1.15	0.16
Medication							0.45
Antiplatelet	170	24.3	64	23.0	1.0	0.71-1.41	1.0
Warfarin	111	15.9	53	19.1	1.27	0.87-1.85	0.22
Warfarin AND antiplatelet	13	1.9	8	2.9	1.63	0.66-4.02	0.29
Neurological deficit (hemiparesis or dysphasia)	383	54.7	172	61.9	1.34	1.01-1.78	**0.042**
Admission mRS							0.82
0-3	333	47.6	130	46.8	1	Ref	
4-5	367	52.4	148	53.2	1.03	0.78-1.37	
Hematoma characteristics							
Unilateral	555	79.3	200	71.9	1	Ref	
Bilateral	145	20.7	78	28.1	1.49	1.09-2.05	**0.014**
Width, mean, mm (missing n=21)							
≤15 mm	200	29.1	41	15.1	1	Ref	
16-25	323	46.9	133	49.1	2.01	1.36-2.97	**<0.001**
≥25	165	24.0	97	35.8	2.87	1.89-4.36	**<0.001**
Subdural drain	49	7.0	10	3.6	0.50	0.25-1.0	**0.048**

5.5.2.1 Factors Associated with Recurrence

In the univariable regression model for factors associated with recurrence (Table 6), significant factors included age over 60 years (p=0.004), neurological deficit (hemiparesis or dysphasia; p=0.042), bilateral hematoma (p=0.014), hematoma thickness 15 mm or over (p<0.001), and a subdural drain (p=0.048). In the forward stepwise (likelihood ratio) multivariable regression model, patient's age (60-79 years: OR 2.21, 95% CI 1.37-3.56, p=0.001; 80 years and over: OR 1.67, 95% CI 1.01-2.76, p=0.045), thickness of the hematoma (16-24 mm: OR 2.12, 95% CI 1.43-3.16, P<0.001; 25 mm and over: OR 3.09, 95% CI 2.01-4.75, p<0.001), and a subdural drain (OR 0.39, 95% CI 0.19-0.79, p=0.009) were significantly associated with CSDH recurrence. Use of antithrombotic medication was not associated with increased CSDH recurrence.

5.6 Non-operative Treatment

Non-operative treatment included discontinuation of possible antithrombotic medication, active mobilization, and follow-up CT-scans (routinely or only for emerging new symptoms). For most cases, operative treatment was not pursued because the CSDH did not cause significant neurological signs or symptoms. A very small number of patients were not offered surgery because they presented in a moribund state (n=7). Most non-operatively treated patients were not treated in our neurosurgical ward, in which case they only consulted with (and not treated by) the neurosurgeon. As a result, the median length of hospital stay in neurosurgery was zero days (min-max=0-4 days). The median number of CT-scans performed was 1.5 (min-max=1-5). The median number of outpatient clinic follow-up visits was zero (min-max=0-4). These patients were treated by neurologists, geriatricians, and primary health care doctors (e.g., general practitioners).

5.7 Mortality

By the end of the follow-up period, 710 (63%) of the 1,133 patients had died, 449 of men (61%) and 261 of women (66%). Median age at death was 84 years (IQR 76-89 years), with 83 years for men and 86 years for women. Similarly, the median age at death was 84 years in the operative group and 85 years in the non-operative group. The 30-day and six-month mortalities after diagnosis of CSDH were 3.4% and 9.5%

respectively. The overall one- and two-year mortality rates were 14% and 22% respectively. Mortality did not differ significantly between men and women.

The mortality after diagnosis of CSDH remained quite stable during the study period. The 30-day mortality varied between 2.5-4.6%, six-month mortality between 7.5-11%, one-year mortality between 11-17%, and two-year mortality between 20-24%.

One-year mortality was 12% in the operative group (n=965) and 21% in the non-operative group (n=168; p=0.003). After the patients (n=7) not offered surgery because they presented in a moribund state were withdrawn from the non-operative group, the non-operative one-year mortality was 18% (operative vs. non-operative: p=0.053). One-year mortality was 4.8% among the patients under the age of 60 and 22% among those aged 80 and older (p<0.001).

A subgroup of patients with no comorbidities demonstrated a one-year mortality rate of only 2.9% (n=206, median age 72 years, IQR 61-78 years). On the contrary, 34% of CSDH patients with dementia died within one year (n=99, median age 84 years, IQR 77-87 years). Mortality rates are presented in Table 7, with the reference group mortality rates reported for comparison.

Table 7. Mortality after diagnosis of CSDH along with the mortality of the reference group.

Cumulative mortality	Total sample n=1,133		Men n=736		Women n=397		Age group 18-59y n=167		Age group 60-79y n=565		Age group ≥ 80y n=401	
	n	%	n	%	n	%	n	%	n	%	n	%
30 days	38	3.4	26	3.5	12	3.0	3	1.8	15	2.7	20	5.0
90 days	75	6.6	51	6.9	24	6.0	3	1.8	34	6.0	38	9.5
6 months	108	9.5	74	10.1	34	8.6	5	3.0	45	8.0	58	14.4
1 year	155	13.7	107	14.5	48	12.1	8	4.8	59	10.4	88	22.0
2 year	254	22.4	168	22.8	86	21.7	20	12.0	97	17.1	137	34.2

Cumulative mortality	Operative n=965		Non-operative n=168		Non-operative n=161*		No comorbidity n=206		Dementia n=99		Reference group n=4,532	
	n	%	n	%	n	%	n	%	n	%	n	%
30 days	25	2.6	13	7.7	8	5.0	3	1.5	6	6.1	16	0.4
90 days	54	5.6	21	12.5	15	9.3	4	1.9	15	15.2	61	1.3
6 months	82	8.5	26	15.5	20	12.4	6	2.9	23	23.2	125	2.8
1 year	120	12.4	35	20.8	29	18.0	6	2.9	34	34.3	248	5.5
2 year	200	20.7	54	32.1	47	29.2	19	9.2	47	47.5	486	10.7

* The patients (n=7) who were not offered surgery (because they presented in a moribund state) were not included.

5.8 Long-term Excess Mortality

The one-year cumulative relative survival ratio (CRSR) for all CSDH patients was 0.91 (95% CI: 0.89-0.94), implying 9% excess mortality compared to the matched general population. The cumulative excess mortality was 18% in five years (CRSR 0.82; 95% CI: 0.78-0.86), 27% in 10 years (CRSR 0.73; 95% CI: 0.67-0.80), 37% in 15 years (CRSR 0.63; 95% CI: 0.54-0.73), and 48% in 20 years (CRSR 0.52; 95% CI: 0.40-0.66). The excess mortality rate was highest during the first year of follow-up after diagnosis of CSDH, declining to 2-4% per year during the rest of the follow-up period.

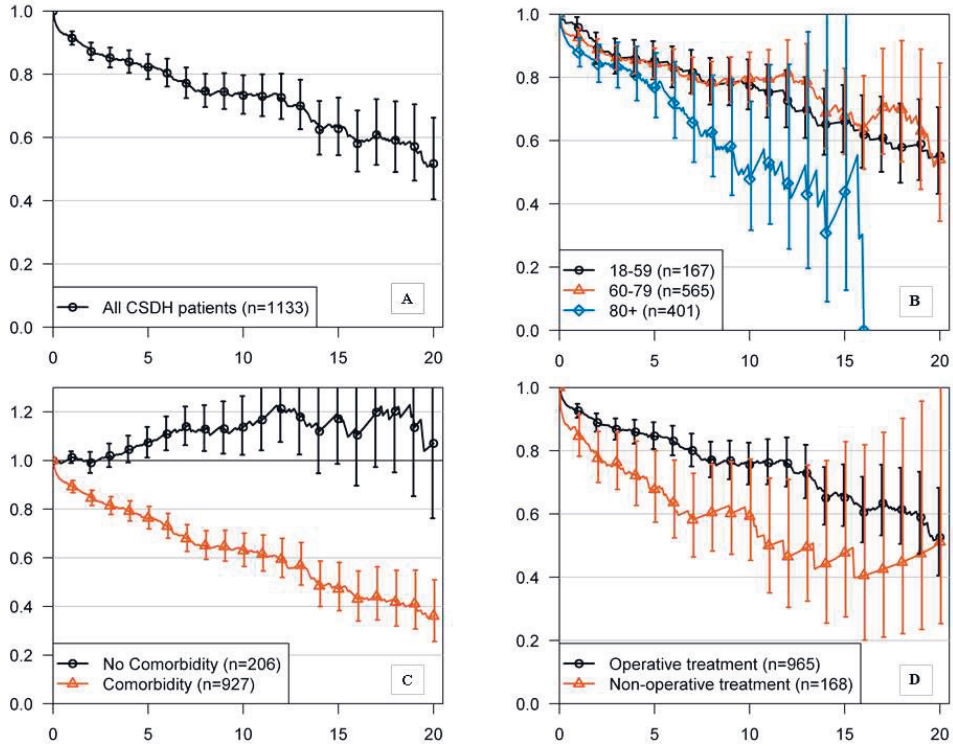


Figure 14. Excess mortality of CSDH patients. Cumulative relative survival ratios (with 95% confidence intervals) illustrating excess mortality of the CSDH patients compared with the matched general population: entire cohort (A), stratified by age groups (B), by prevalence of comorbidity (C), and by treatment group (D). The horizontal line at 1.0 represents the survival of the matched general population and curves below that line represent excess mortality of the study population. The vertical line shows follow-up time (years).

The excess mortality seemed to be more pronounced in women, but the difference was not statistically significant. Although CSDH patients demonstrated excess mortality in every age group, it was more pronounced in those aged 80 years and over as well as in the non-operatively treated patients. A subgroup of patients with no comorbidities survived at higher rates than the matched general population. The CRSR with 95% confidence intervals are shown in Figure 14.

5.8.1 Relative Excess Risk of Death

In the age-, gender-, and follow-up-time-adjusted regression model for RER, excess mortality was significantly related to (i) poor mRS (RER=4.93) at admission and especially (ii) at discharge (RER=8.31), (iii) chronic alcohol abuse (RER=4.47), (iv) warfarin medication (RER=2.94), (v) age ≥80y (RER=1.83), (vi) non-operative treatment (RER=1.77), and (vii) non-traumatic etiology (RER=1.69). Hematoma localization (unilateral/bilateral), thickness, or recurrence were not related to the excess mortality. Detailed RER results are presented in Table 8.

Table 8. Relative excess risk of death (RER) estimates and 95% confidence intervals for each subgroup of the 1,133 CSDH patients adjusted for age, gender, and follow-up time.

	Total sample n=1,133			RER	95% CI
	n	%			
Sex					
Men	736	65.0		1	Ref
Women	397	35.0		1.17	0.82-1.65
Age at CSDH diagnosis, y					
18-59	167	14.7		1	Ref
60-79	565	49.9		1.05	0.68-1.61
≥80	401	35.4		**1.83**	1.11-3.02
Chronic alcohol abuse					
No	1,007	88.9		1	Ref
Yes	126	11.1		**4.47**	2.88-6.95
Traumatic etiology					
Yes	672	59.3		1	Ref
No	461	40.7		**1.69**	1.20-2.38
Antithrombotic medication					
None	655	57.8		1	Ref
Antiplatelet	268	23.7		1.20	0.72-2.01
Warfarin	187	16.5		**2.94**	1.91-4.54
Warfarin AND antiplatelet	23	2.0		**3.24**	1.35-7.75
Admission GCS					
13-15	1,007	88.9		1	Ref
9-12	91	8.0		**3.53**	2.35-5.32
3-8	35	3.1		**5.71**	3.47-9.41
Admission mRS					
0-3	580	51.2		1	Ref
4-5	553	48.8		**4.93**	3.12-7.80
Hematoma Localization					
Unilateral	876	77.3		1	Ref
Bilateral	257	22.7		0.74	0.46-1.18
Hematoma thickness, mm (missing n=23)					
≤15 mm	376	33.2		1	Ref
16-25	474	41.8		0.69	0.48-1.01
>25	260	22.9		0.59	0.34-1.01
Operative treatment					
Yes	965	85.2		1	Ref
No	168	14.8		**1.77**	1.18-2.65
No[1]	161	14.2		**1.56**	1.01-2.41
Discharge GCS[2]					
13-15	942	97.6		1	Ref
9-12	9	0.9		**14.84**	6.64-33.18
3-8	14	1.5		**98.30**	39.35-245.56
Discharge mRS[2]					
0-3	727	75.3		1	Ref
4-5	238	24.7		**8.31**	5.48-12.58
Recurrent hematoma[2]					
No	692	71.7		1	Ref
Yes	273	28.3		0.78	0.48-1.26

RER = relative excess risk of death; CI = confidence interval; Ref = reference; GCS = Glasgow Coma Scale score; mRS = modified Rankin Scale score. [1]The patients (n=7) who were not offered surgery because they presented in a moribund state were not included. [2]Includes only operatively treated patients.

5.9 Causes of Death

The most frequent causes of death for women included dementia (29%), ischemic cardiac disease (15%), and cerebral ischemia (12%). The most common causes of death for men were ischemic cardiac disease (23%), dementia (16%), and cancer (14%). SDH represented the cause of death in 42 of 710 patients (6%). The hematoma type (chronic, subacute, acute) could not be verified due to the nature of the cause of death data.

In the matched reference group (n=4,532), the most common causes of death included ischemic cardiac disease (25%; women 22% and men 26%), cancer (19%; women 15% and men 22%), and dementia (15%; women 18% and men 13%). As a cause of death, dementia was more commonly represented in patients with CSDH than in the reference group (21% vs. 15%, $p<0.001$). These proportions differed significantly among women (29% vs. 18%, $p<0.001$), but not among men (16% vs. 13%, $p=0.12$). The cause of death was traumatic in 11% of the CSDH patients and 3% in the reference group ($p<0.001$). SDH represented the cause of death in 6% and in 0.5% of each group, respectively ($p<0.001$). Causes of death among the CSDH patients and the reference group are presented in Table 9.

When stratifying the causes of death by survival time, the incidence of trauma-related death was significantly higher among CSDH patients compared to the reference group during the first five years ($p<0.001$). In contrast, dementia represented the cause of death in more CSDH patients than in the reference group after the first year; this difference increased over time, reaching statistically significance from one to 10 years ($p<0.001$; Figure 15).

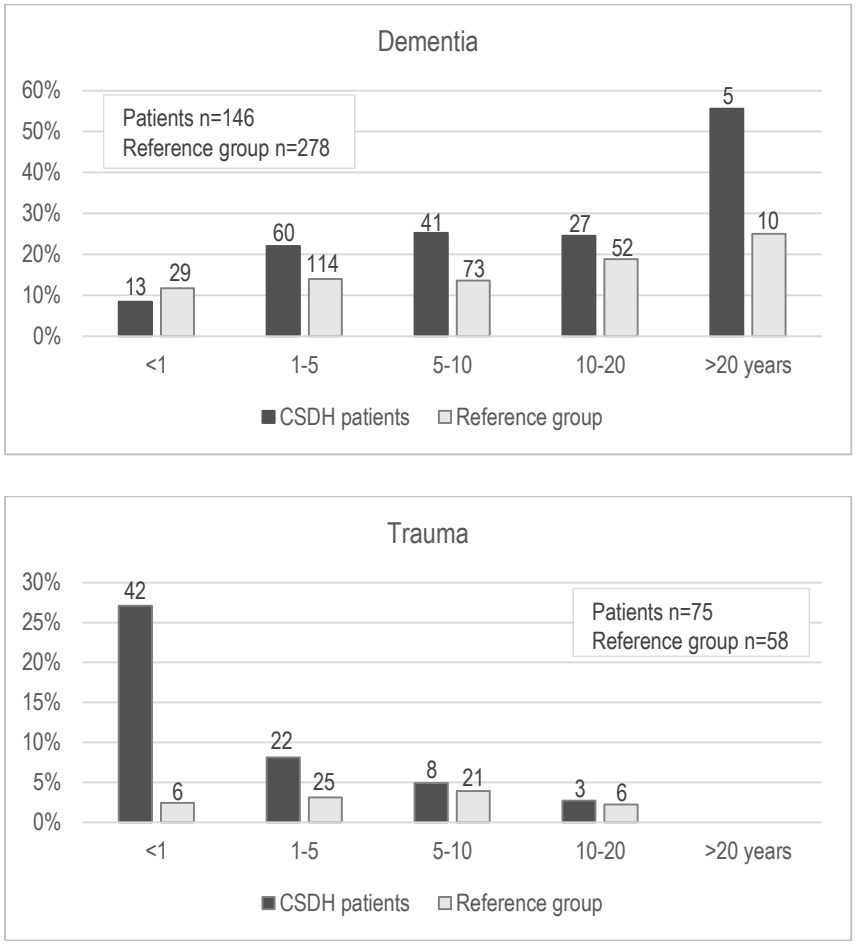


Figure 15. Dementia and trauma as a cause of death stratified by survival time. The CSDH patients are compared to the matched reference group. The percentages represent all the deaths during the time period. The number of deaths: 710 among CSDH patients, and 1,918 among the reference group.

Table 9. The causes of death until the end of 2017 of the 1,133 patients with CSDH between 1990-2015 in Pirkanmaa, Finland. The causes of death in the matched reference group between 1990-2015 are presented for comparison.

	Total sample n=1,133		Men n=736		Women n=397		Operative treatment n=965		Non-operative treatment n=168		Causes of death in the matched reference group n=4,532	
	n	%	n	%	n	%	n	%	n	%	n	%
Age, years (median, IQR)	76	67-83	75	65-81	79	70-85	76	66-82	79	68-86	76	67-83
Follow-up time, years												
Median	4.8		5.1		4.6		5.2		3.3		6.4	
Range	0-27		0-26		0-27		0-27		0-21		0-28	
No. of deaths	710	62.7	449	61.0	261	65.7	609	62.3	101	60.1	1918	42.3
Age at death, median, IQR	84	76-89	83	74-88	86	80-91	84	76-89	85	79-90	84	78-88
Ischemic cardiac disease	143	20.1	103	22.9	40	15.3	122	20.0	21	20.8	473	24.7
Cerebrovascular disease	90	12.7	54	12.0	36	13.8	80	13.1	10	9.9	216	11.3
Cerebral haemorrhage	18	2.5	13	2.9	5	1.9	13	2.1	5	5.0	23	1.2
Cerebral ischemia	72	10.1	41	9.1	31	11.9	67	11.0	5	5.0	167	8.7
Cancer	91	12.8	64	14.3	27	10.3	80	13.1	11	10.9	370	19.3
Dementia and Alzheimer's disease	146	20.6	70	15.6	76	29.1	121	19.9	25	24.8	278	14.5
Pulmonary disease	34	4.8	24	5.3	10	3.8	29	4.8	5	5.0	119	6.2
Pneumonia	16	2.3	9	2.0	7	2.7	15	2.5	1	1.0	45	2.3
Trauma	75	10.6	50	11.1	25	9.6	65	10.7	10	9.9	58	3.0
Accidental falls	41	5.8	25	5.6	16	6.1	36	5.9	5	5.0	33	1.7
Subdural hematoma, traumatic	38	5.4	25	5.6	13	5.0	33	5.4	5	5.0	9	0.5
Subdural hematoma, non-traumatic	4	0.6	4	0.9	0		3	0.5	1	1.0	1	0.05
Unknown	0		0		0		0		0		20	1.0

5.10 Hospital Costs

The mean total cost from the first hospital admission until the last follow-up visit per patient treated surgically was 5,250 € (median 3,810 €; IQR=2,930-5,900 €, min-max=2,170-33,420 €). This cost dropped to 3,820 € (median 3,370 €; IQR=2,870-4,100 €, min-max=2,170-28,977 €) per patient for those with no recurrence versus 8,850 € (median 7,110 €; IQR=5,840-9,820 €, min-max=3,637-33,420 €) per patient for those whose CSDH recurred. This 5,030 € difference in mean treatment costs means costs were 132% for the patients with recurrence. The mean cost for patients with drains was 4,100 € (median 3,370 €; IQR=2,930-4,670 €, min-max=2,170-19,280 €) as compared to 5,320 € for those with no drains (median 3,930 €; IQR=2,930-6,050 €, min-max=2,170-33,420 €), meaning patients with drains cost on average 1,220 € and 30% more.

Among surgically-treated patients, the 60-79 years old age group cost the most; their mean costs were 5,710 € (median 4,050 €; IQR=3,130-6,570 €, min-max=2,170-32,397 €), while the cost for those in the 18-59 years group (mean 4,640 €; median 3,690 €; IQR=2,930-5,060 €, min-max=2,170-29,606 €), and over 80 years old group (mean 4,810 €; median 3,660 €; IQR=2,930-5,600 €, min-max 2,170-33,420 €) were similar. The mean hospital cost per non-operatively treated patient was 580 € (median 455 €; IQR=310-630 €, min-max=310-2,710 €).

The length of hospital stay plays a large role in total costs. However, during the last ten years (2006-2015), while the duration of hospital treatment in the neurosurgical unit has decreased, the cost of operative treatment has become approximately equal with the hospital stay. The total costs related to treatment for CSDH are presented in Table 10 and Figure 16, which also shows a breakdown of mean hospital costs per patient stratified by time periods.

The lowest cost period for total hospital costs was 1990-1995, with a mean total of 140,000 € per year. The greatest total hospital costs per year occurred during 2006-2010, with a mean total of 248,000 €. The mean cost per patient reached its peak during 1996-2000, when it was 5,840 € (median 4,040 €; IQR=3,250-6,730 €, min-max=310-33,420 €). The period with the lowest costs per patient was 2011-2015 (mean 3,310 €; median 2,930 €; IQR=2,170-4,170 €, min-max=310-30,100 €). Due to this decline, even though the number of patients has increased, total costs have decreased in the more recent years of the study period.

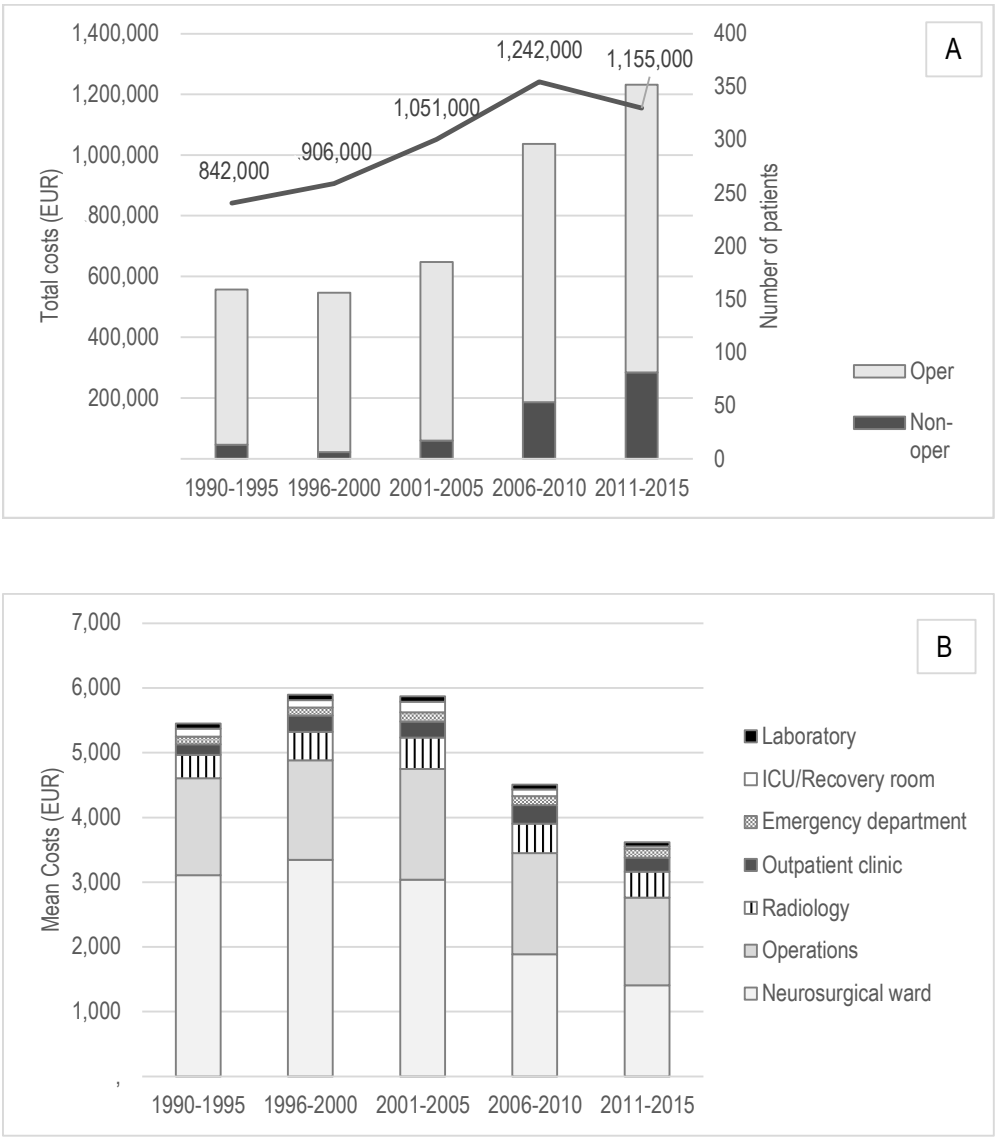
During the latest study period of 2011-2015, the mean cost per patient treated surgically was 4,140 € (median 3,250 €; IQR=2,610-4,980 €, min-max=2,170-30,100 €), but only 510 € (median 310 €, IQR=310-630 €, min-max=310-1,360 €) per patient treated non-operatively. Hospital costs totaled 231,000 € per year in 2011-2015, of which 4% (8,300 €) were non-operatively treated patients. The share of patients given head CT scans was 12% (28,100 €) during 2011-2015.

Table 10. Costs related to treatment of CSDH in Tampere University Hospital during the study period between 1990-2015.

	Non-operative treatment	Operative treatment	Cost
No of operations	0	1 (1-8)	982 €/hour*
Recovery room stay 2 h in the case of general anaesthesia	NA	0 (0-3)	290 €/2 h
ICU stay in the case of craniotomy	NA	0 (0-2)	1,376 €/day
Hospital stay in neurosurgical unit during primary admission, days	0 (0-4)	3 (1-33)	440 €/day
IQR	0	3-5	
Hospital stay in neurosurgical clinic during re-admission, days	NA	4 (1-46)	440 €/day
IQR	NA	3-8	
CT scans, median, n	1.5 (1-5)	3 (1-13)	147 €
Laboratory tests taken at the time of diagnosis, re-admission and/or complication	1	1 (1-10)	50 €
Emergency department visits, n**	1 (1-2)	1 (1-5)	111 €
Outpatient follow-up visits, n	0 (0-4)	1 (0-11)	174 €
Costs in Euros per patient, min-max	310-2,710	2,170-33,420	
Mean	580	5,250	
Median	455	3,810	
IQR	310-630	2,930-5,900	
No recurrence	NA	2,170-28,980	
Mean	NA	3,820	
Median	NA	3,370	
IQR	NA	2,870-4,100	
Recurrence	NA	3,640-33,420	
Mean	NA	8,850	
Median	NA	7,110	
IQR	NA	5,840-9,820	

Data are shown as median (min-max); IQR interquartile range; NA not applicable

*The mean operation theatre time for evacuation of CSDH via burr hole trephination was 1 h, and via craniotomy 3 h **Patients were assumed to be diagnosed in emergency department



Note: The analyzed CSDH patients living in Pirkanmaa region accounted for approximately half of all the CSDH patients treated in Tampere University Hospital with a catchment population of one million.

Figure 16. Direct costs of CSDH in Tampere University Hospital. Total hospital costs per 5-year time periods, and the number of operatively and non-operatively treated patients (A). A breakdown of mean hospital costs per patient stratified by time groups (B).

6 DISCUSSION

6.1 Summary of the Key Findings

Our study comprised a large consecutive series of CSDH cases (n=1,148) from a defined population during a 26-year period. Furthermore, we reviewed the death certificates for clinically undiagnosed CSDH (n=20) from this period. Although retrospective in nature, the population-based setting and non-register-based nature lowers its vulnerability to selection bias. Moreover, the author of this thesis (M.R.) collected all the data.

We observed six key findings related to CSDH: increased incidence, increased use of antithrombotics, a sufficient follow-up period of two-month, continuous excess mortality, possible relation to dementia, and stable hospital costs.

From 1990 to 2015, the overall incidence of CSDH in Pirkanmaa doubled. Among the over 80-year old population, the incidence nearly tripled. The use of antithrombotics has increased (27%-49%), but the ratio between a traumatic and a spontaneous CSDH etiology has not changed.

Routine four-to-six weeks' postoperative follow-up CT increased the number of reoperations, because asymptomatic patients were operated on based on radiological recurrence. Almost all (92%) of the recurrences occurred within 60 days. A two-month follow-up period after CSDH seems sufficient for most, and CT controls are advocated only for symptomatic patients.

Patients with CSDH demonstrated excess mortality rates, which cumulated over time from 9% at one year to 48% at 20 years after CSDH diagnosis. A subgroup of patients with no comorbidities displayed no excess mortality. Patient-related characteristics were strongly associated with excess mortality, whereas specific CSDH-related findings were not.

CSDH patients have an increased risk for dementia-related mortality. As a cause of death, dementia occurred later in CSDH patients than in the reference group. Brain atrophy appears to be a risk factor for CSDH, which in turn accelerates neurodegeneration and increases the risk of dementia.

Despite the increased number of cases, direct hospital costs declined during the most recent study period. This occurred in large part due to shortened hospital stays and fewer recurrences related to use of subdural drains.

6.1.1 Incidence

From 1990 to 2015, the overall incidence of CSDH doubled from 8 to 18/100,000/year. Among adults under 70 years old, the incidence remained quite stable, whereas it nearly tripled among the over 80-year old population, from 47 to 130/100,000/year. The incidence was higher for men than women after the age of 60. The incidence has increased in both operatively and non-operatively treated patients.

The incidence of CSDH has been reported to increase in the most recent decades[5, 24, 97, 147]. However, the few population based studies published to date have examined small patient cohorts[5, 16, 89, 161] and national registries[97, 147] (Table 1). No previous studies have distinguished between the incidence in operatively and non-operatively treated patients.

By comparing our results with the prior Finnish findings by Fogelholm and Waltimo[89], we find that the Finnish overall incidence of CSDH has increased 10-fold from 1.7 to 17.6/100,000/year since the late 1960s. Similarly, among the 70-79 years old age group, the incidence has increased from 7.4 to 52.1/100,000/year.

Our incidence rates are in line with the recent Japanese registry study[147] and somewhat higher than the estimated rates from Denmark[97]. The most recent numbers from the United Kingdom are close to ours[5]. The incidence differences between studies most likely occur due to the differences in case ascertainment, study design, health care systems, and cultural issues.

The reasons for higher incidence among the elderly include age-related general brain atrophy[184, 338], risk for multiple falls[116, 159, 180], and the frequent use of antithrombotic medication[63, 70, 97, 214]. In addition, improved awareness of CSDH among the medical profession and the wide availability of CT scanners have been proposed as influences on increasing incidence rates[9, 280].

In our study, the autopsy-verified CSDH rate was less than 2%, and these cases were distributed equally throughout the entire 26-year study period. However, the availability of CT likely contributes to the increase in non-operatively treated patients; asymptomatic CSDHs are found when the threshold for ordering imaging is low. A systematic review (including 16 studies from Asia, Europe and the USA

during 1989-2008) of incidental findings on brain MRI revealed only four extra-axial collections among 19,559 people, and the number needed to scan was 2,500[206]. However, a study from the USA concentrating on patients older than 90 years old (n=177) found incidental CSDH in three patients (2%)[7].

Interestingly, the CSDH patients in our study began to be diagnosed in a better clinical condition (fewer symptoms and higher GCS scores) towards the end of the study period. This could reflect the fact that diagnosis in more recent years has occurred relatively earlier than in the 1990s.

The next few chapters discuss the risk factors (head trauma, alcohol, and antithrombotic medication) that could contribute to the increase in the CSDH incidence.

6.1.2 Risk Factors Contributing to the Increase in Incidence

6.1.2.1 Head Trauma

Previous head trauma was reported by 59% of patients in our study (58% of men and 62% of women), which supports the findings of previous reports[44]. The proportion of ground-level falls among trauma events increased with advanced age (51% among 15-59 years versus 88% of those ≥ 80 years old). One reason for the greater incidence of CSDH among the elderly may be attributed to a higher number of falls in this population[180]. A Finnish study by Palvanen et al. estimated that approximately 30% of home-dwelling people aged 65 years or older fall every year, while about half of those who fall do so repeatedly[226].

A Finnish follow-up study by Kannus et al. of patients aged over 80 years showed that the age-adjusted incidence of fall-induced brain injury increased five-fold from 1970 to 2017 and was higher for men than for women[146]. The incidence of traumatic brain injury related hospitalizations also increased among Finnish patients ≥70 years of age during 2004-2014, as reported by Posti et al.[235]. Increasing hospitalization rates for traumatic brain injury have also been observed among the elderly population in Australia (1998-2011), where males similarly demonstrated a consistently higher hospitalization rate[116].

Forty percent of our CSDH patients aged ≥ 80 years did not recall a trauma history. However, in the elderly with brain atrophy, even a trivial head trauma may represent a causal event sufficient to produce CSDH. This link may be explained by the theory that the catalyst for the chain of events leading to a CSDH with mass

effect is likely to be represented by a minor traumatic event that triggers a cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis[120]. Brain atrophy, chronic health conditions, and polypharmacy might contribute to fall-related brain injuries in the elderly [159].

6.1.2.2 Alcohol

In our series, the percentage of cases with a history of chronic alcohol abuse decreased during the study period (from 16% to 7%) because alcohol abuse was particularly infrequent among the growing group of elderly. Alcohol overuse occurred more frequently in men (14%) than women (6%). In Finland, alcohol consumption increased between 1990 and 2007, but the subsequent consumption trend has declined[217]. Alcohol consumption has remained stable among the Finnish population over 80 years of age. Alcohol represents a considerable risk factor of CSDH for the younger patient population but does not seem to explain the increase in incidence of CSDH among the elderly.

6.1.2.3 Antithrombotic Medication

In our study, the number of CSDH patients on antithrombotic medication increased from 27% (1990-1995) to 49% (2011-2015). This is mostly due to the increase in warfarin usage (9%-28%). Among those aged 80 years or older, 57% were using antithrombotic drugs, including warfarin, which was used by 24% in 2011-2015 with no gender difference. The usage of warfarin was 4% among the Finnish adult population in 2011-2015[219]. Accordingly, the proportion was 23% (men: 26%, women: 22%) among residents 80 years or older.

Antithrombotic medication has been shown to represent a risk factor for CSDH[63, 70, 97, 115, 181, 214], and the association appears to be even stronger in the absence of trauma[17, 70, 280]. The rate of antithrombotic drug use in our study was modestly greater (46%) in those who had no documented history of head trauma compared to those with a documented history of head trauma (39%). Similarly, a study from Denmark reported a higher prevalence of antithrombotic drug use in patients without head trauma (63%) compared to patients with head trauma (42%)[17]. Additionally, a Korean study reported that antithrombotic drugs were associated with non-traumatic CSDH (i.e., no trauma was reported in 67% of antithrombotic drug users and 33% of non-users)[280].

In the most recent decades, the use of antithrombotic drugs has particularly increased among elderly patients[3] after these medications have been proven to represent effective primary and secondary prevention measures of cardio-cerebrovascular disease[32, 168]. Accordingly, antithrombotics are contributing to the increasing incidence of CSDH.

However, we found no change in the ratio between traumatic and spontaneous CSDH etiology even though the use of antithrombotic drugs has increased significantly. Moreover, the proportion of CSDH patients using warfarin did not differ from the proportion of the overall Finnish population on warfarin.

The role of antithrombotic medication in CSDH recurrence remains unclear, as contradictory findings have been reported[46, 181, 233, 256]. In our study, the use of antithrombotic medications, were not associated with increased CSDH recurrence.

6.1.3 Follow-up

In our neurosurgical practice, an outpatient clinic follow-up visit with a head CT scan four to six weeks after the operation has been routine. However, a routine follow-up CT reveals large recurring hematomas in some clinically asymptomatic patients, leading to the decision for a second surgery. Our CSDH recurrence rate (n=278/978; 28%) is toward the high end of what is reported in the literature[185, 230, 325]. Of the total sample of 978, 5% (n=49) of the patients undergoing a second surgery were asymptomatic. Among the 278 who had a recurrence, 18% were asymptomatic.

Correspondingly, asymptomatic patients were operated on based on head CT scan findings in the TOSCAN (To Scan or Not to Scan) trial[271]. In the TOSCAN study, 27% of the CSDH patients with follow-up CT underwent a second surgery versus 19% with no prescribed CT. However, some of the asymptomatic patients with radiological recurrence could have developed symptoms had they not been operated on.

In addition, the use of subdural drains during our study period was uncommon (6%). Insertion of an external drain after evacuation of CSDH decreases the rate of recurrence in most of the reported series by up to 50%[185, 230, 325]. The evidence supporting drain placement cumulated towards the end of our study period, and we also started to insert drains more often. For example, at Helsinki University Hospital, standard practice changed from no drain to subdural drain for 48 hours after burr

hole craniostomy for CSDH in April 2017[307]. Consequently, the six-month recurrence rate decreased from 18 % to 6 %.

In a Danish retrospective study of 202 patients with CSDHs, recurrence of neurological symptoms preceded the planned postoperative follow-up CT (four to six weeks after primary surgery) in all patients undergoing a second surgery[229]. A Swiss TOSCAN trial with 361 randomized patients showed that routine CT scans did not improve clinical outcome but instead led to unnecessary operations and increased costs[271]. A comparative study[125] between two hospitals with different imaging strategies, one in the USA (Boston, Massachusetts) and the other in the Netherlands (Utrecht), demonstrated no differences in CSDH recurrence or outcome, even though the former hospital had a median of four follow-up CT scans per patient versus zero in the latter hospital.

In conclusion, a routine follow-up head CT scanning of asymptomatic patients after their CSDH operation seems to demonstrate little clinical value. In our study, however, during the first follow-up visit, 70 patients of 108 (65%) with recurrence visible on CT were slightly symptomatic but still waited for the scheduled outpatient clinic visit to bring up their concerns. For this reason, patients should be informed to contact healthcare when suffering from new or persistent neurological deficits.

Additionally, the post-CSDH resumption of antithrombotic drugs is not straightforward[231]. The median time of 25 days to reoperation is in line with previous studies[188, 204, 229, 252]. Nine of ten (92%) recurrences occurred within 60 days, which compares favorably with the literature's findings[252, 271]. This information may help inform when to resume antithrombotics, even with no follow-up CT. Notably, early resumption has also been advocated [231], and not all the patients can wait for two months due to a high risk of thromboembolic events.

Furthermore, medicolegal issues arise from providing permission to drive, fly abroad, or return to work. For these reasons, in selected cases, a planned follow-up CT may be necessary. However, it seems that in the majority of the cases, clinical follow-up and CT only for symptomatic patients results in similarly favorable outcomes. When clinically indicated, a two-month follow-up period after CSDH is likely sufficient for most asymptomatic patients.

6.1.4 Long-term Excess Mortality

The high mortality rate after the diagnosis of CSDH has been proposed as reflecting high age, comorbidities and frailty[78, 202]. No conclusions can be drawn without a

matched sample from the general population. Previous studies[78, 110, 189, 202] have shown varied excess mortality, but the follow-up periods have extended only up to eight years. We followed patients up to 27 years, and the median follow-up time was 4.8 years. None of our patients were lost from follow-up.

Patients with CSDH displayed continuous excess mortality up to at least 20 years after diagnosis. The excess mortality rate was highest (9%) during the first year of follow-up after diagnosis of CSDH, declining to 2-4% per year during the rest of the follow-up period. As a result, the cumulative excess mortality was 48% at 20 years after CSDH.

Every age group of patients demonstrated excess mortality in our study. The excess mortality was more pronounced in those aged 80 years or over. The risk of excess mortality was higher in the non-operative group than in the operative group (RER 1.56) even though the neurological condition at admission was better among non-operatively treated patients, who were not predisposed to surgical complications. This observation probably occurred due to the higher burden of comorbidities among the elderly as well as non-operatively treated patients.

In contrast to the study by Santarius et al.[262], CSDH recurrence did not represent a risk factor for excess mortality among our study patients. In fact, the patients with recurrence died at lower rates during at least the first two years. We speculate that this difference might be explained by more frequent medical attention (follow-ups and reoperations) for patients that are in better general health before their first CSDH. Patients with more comorbidities are less likely to undergo a second operation. Even so, our six-month overall mortality rate (10%) and relative survival rate at five years (82%) were comparable to the findings by Santarius and colleagues[110, 262] in the UK. The mortality differences between studies most likely arise due to differences in case ascertainment, healthcare systems, and population-related life expectancies.

Our study reflects the findings of the previous studies demonstrating that neurological disability at discharge is strongly associated with long-term survival[78, 189, 202]. This finding comes as no surprise because neurological disability at discharge correlates to functional status, which has been recognized as greatly impacting life expectancy in general[150]. However, differentiating the effects of underlying comorbidities from the effects of CSDH on long-term survival is difficult. A subgroup of our patients (n=206) with no comorbidities survived at higher rates than the matched general population. In addition, hematoma bilaterality, thickness, or recurrence did not represent relative mortality risk factors. Accordingly, even a large recurring CSDH may not by itself affect long-term survival rates. Therefore, the

patient-related variables probably play a more important role in survival than the CSDH itself. Based on this data, comorbidities rather than the CSDH itself seem likely to represent the cause of excess mortality. Some patients are frail due to age-associated brain atrophy and other comorbidities; for this group of patients, CSDH seems to represent a sentinel health event, a harbinger of subsequent morbidity and mortality[28, 78, 202]. In contrast, patients with no comorbidities are probably healthier than the matched general population.

Hence, the excess mortality after diagnosis of CSDH might be reduced by more assertively treating the comorbidities, of which the most common included vascular diseases, diabetes, and chronic alcohol abuse. Furthermore, the hospitalization of older people is known to decrease daily living functioning[66]. For this reason, it has been proposed that already perioperative care should be optimized by using a multidisciplinary approach and promoting early rehabilitation[274]. The health care team should aim to allow the patients to return to their previous daily life at home or other living arrangements.

Antithrombotic drug use is common among CSDH patients and is speculated to contribute to the greater incidence of CSDH among elderly[63, 70, 97, 181, 214]. In our study, the use of warfarin, but not the use of antiplatelets, represented a relative risk factor for excess mortality. This finding could reflect the increased risks of warfarin in the context of CSDH or be explained by the fact that the baseline diseases treated with antiplatelet drugs do not represent as significant burdens as those treated with warfarin do.

Similarly, chronic alcohol abuse represented a relative risk factor for excess mortality after CSDH, in addition to also being a risk factor for general excess mortality independently[71, 327]. Moreover, non-traumatic etiology was a relative risk factor for excess mortality among CSDH patients. This could be at least partly explained by the more common use of antithrombotic medication by patients with non-traumatic than traumatic etiology (47% vs. 39%) as well as the underlying medication-related comorbidities. Additionally, CSDH might represent a manifestation of degenerative or inflammatory disease rather than trauma[81]. In other words, aging, worse baseline general and neurological health, and longstanding and ongoing alcohol abuse all appear to contribute to greater mortality following CSDH.

6.1.5 CSDH and Dementia

The global incidence of dementia has increased significantly during the last decades and will most likely continue to do so[242]. Dementia is considered a malignant disorder that carries an excess risk of death[21, 23, 149]. As a result, dementia is a major contributor to disability and healthcare costs[243]. In our study, the proportion of CSDH patients aged 70 years or older with a pre-existing diagnosis of dementia increased from 4.6% (1990-1995) to 17% (2010-2015). This is in line with a recent registry study from Finland by Tommiska et al.[306]

In our study, the one-year CSDH patient mortality was 14% overall but 34% for CSDH patients with dementia. Similarly, in a study from Lund, Sweden[342] (n=179), the one-year mortalities after CSDH were 12% and 40% respectively. In a Finnish registry study by Tommiska et al.[306] (n=7,621 operated CSDH patients aged ≥60 years), 16% of the overall pool of patients died within a year. In their case-control analysis, the one-year mortality increased to 26% among the CSDH patients with dementia (n=885) compared to 16% among controls with dementia and no CSDH (n=2,633).

Brain atrophy with an enlarged potential subdural space has been speculated to serve as the most important reason for the greater incidence of CSDH among the elderly [170, 184, 338]. Brain atrophy has also been linked to dementia[39]. At the time of diagnosis of CSDH, the prevalence of dementia in our CSDH patients (12% in patients aged 70 years or older) was comparable to the prevalence in Western Europe as reported by the 2015 World Alzheimer report[241]. However, as a cause of death, dementia occurred more frequently in patients with CSDH than in our reference group. The difference was seen after the first year and was more pronounced in the later years following CSDH diagnosis.

Our results support the idea that CSDH may represent a risk factor for dementia. This could be explained by Bin Zahid and colleagues' observation that CSDH is related to a significant increase in the degree of subsequent brain atrophy [34]. Brain atrophy seems to represent a risk factor for CSDH, which in turn accelerates neurodegeneration and increases the risk of dementia. If this is the case, CSDH can result in significant socio-economic consequences; patients therefore need long-term follow-up.

In previous literature, traumatic brain injury (TBI) has been associated with an increased risk of future dementia (RR 1.7-1.9)[105, 178, 249], but this report is the first to reveal the possible association of plain CSDH and dementia. TBI has been hypothesized to not itself cause dementia but rather accelerate an underlying process

of developing dementia in those with predisposing factors[322]. Furthermore, another brain insult, stroke, doubles the risk of dementia in the elderly population[268]. In addition, decreased physical activity[35], as well as comorbidities such as hypertension[247], diabetes[187] and depression[148] have been found to be significantly associated with the risk of dementia. These findings emphasize the importance of active rehabilitation and effective treatment of the comorbidities after CSDH. Furthermore, preventive interventions should be implicated to minimize the risk of head trauma.

6.1.6 Cost Comparison with Previous CSDH Studies

The literature on CSDH-related costs is scarce. In the Swiss TOSCAN trial[271] (conducted between 6/2012 – 8/2016), the mean cost per patient from hospital admission until the last follow-up visit was 21,298 CHF (15,927 €) in the CT-arm and 18,047 CHF (13,497 €) in the no-CT-arm, with a difference of 18%. The median length of hospital stay was six days. The investigators pointed out that the imaging strategy in the CT-arm probably increased the costs by triggering further follow-up visits, hospitalizations, and surgeries.

A financial impact study from the USA[93] collected all SDH cases (acute 14%, subacute 44%, chronic 12%, mixed 30%; n=216) admitted to a tertiary care center between January of 2001 and December of 2008. Surgery was performed in 64% of the cases. Patients stayed in the hospital for a median of eight days (min-max=1–99), which represented the largest contributor to total costs. The median total direct cost for hospitalization was $10,670 (10,820 €). Frontera and colleagues conducted a registry study between 1998 and 2007 showing that the national costs of SDH increased by 60% over the decade in the USA[94].

Our direct hospital costs (mean 5,250 € for operatively treated patient) were notably lower than the costs reported previously from Switzerland and the USA. However, the costs are difficult to compare between countries due to differences in case ascertainment, study design, health care systems, and economic issues. In Finland, virtually all neurosurgical care is publicly funded, with a heavy emphasis on evidence-based care and cost-effectiveness. On the contrary, countries in which health care is financed by the insurance companies and doctors compete for cases might emphasize patient satisfaction more than the strict necessity of procedures[125]. Furthermore, the medicolegal climate may differ between countries, and the concern

about malpractice liabilities can lead to additional potentially unnecessary interventions (including CT scans) and increased cost[216].

The most important predictor of costs in both previous studies as well as our own was the length of hospital stay, which was longer in previous studies than ours (with a median of three days). In our study, the annual total costs of CSDH increased over time until the 2006-2010 period (77% increase from 1990-1995) due to the increase in number of CSDH patients treated. However, towards the end of the study period (2011-2015), total costs declined, despite the greater number of patients treated, due to the decrease in the length of hospital stay and fewer recurrences.

6.2 Strengths and Limitations

Our series represents the most extensive non-register-based study of consecutive CSDH cases from a defined population treated in one neurosurgical department. Although retrospective in nature, the population-based setting decreases its vulnerability to selection bias. Moreover, all the data were collected by one of the authors (M.R.).

This study has several limitations. ICD-codes were used to retrospectively identify all the patients of interest. However, some cases may not have been recognized due to incomplete or incorrect ICD coding. All the patients undergoing surgery were most likely identified, but ICD coding can remain incomplete among the non-operatively treated patients, as a neurosurgeon was only consulted on these cases. Radiological images were not separately inspected, which could have resulted in incorrect measurements. Furthermore, midline shift was not reported constantly and hence was not used in our analysis. Moreover, head CT scans were rarely performed at the beginning of the study period, thus meaning that incidental CSDHs were almost never identified. Head CT scans became widely used in the late 1990s after the discovery of thrombolytic agents for ischemic stroke.

In addition, the distinction in terms of time or neuroradiological characteristics between subacute and chronic SDH is not always obvious. No definition of CSDH is universally accepted [129]. Subacute SDHs were excluded from this study, because this hematoma subtype is considered to represent an entity of its own[10, 79, 160]. Also, definitions used for recurrences differ[41]. Our definition is quite liberal and included second surgeries during the primary treatment. Due to the more common use of subdural drains after the study period, the recurrence rate has possible decreased during the latest years. This may also impact the long-term results in the future.

Moreover, the cost analysis was performed retrospectively and probably underestimates total costs, but this limitation applies to all our study periods equally. The costs are estimates based on the latest costs and do not consider temporal changes in prices. The costs reported include only the costs in the Tampere University Hospital; they do not take into account any costs of treatment outside our hospital. Considering that only half of those among the age group of 60-79 and one-fifth of those 80 years or older could be discharged to their home or previous living arrangements, the costs of, for example, rehabilitation and continuing care, are noteworthy.

6.3 Future Perspectives

The number of publications on CSDH has considerably increased in recent years (Figure 17). Twenty-six RCTs on CSDH are currently ongoing, with the most common topics including application of steroids (7), surgical techniques (5), and tranexamic acid (5). In addition, other trials' topics include other pharmacological agents (4), middle meningeal artery (MMA) embolization (2), and peri-operative management (3).[82]

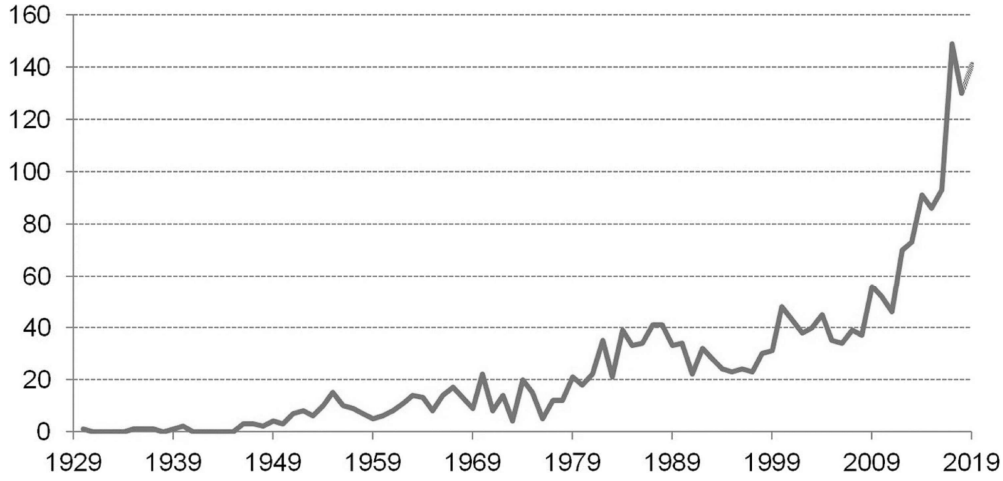


Figure 17. Evolution of the number of publications per year on CSDH over 90 years. Reprinted with permission from Edlmann et al. 2020.

The heterogeneity of CSDH presents a challenge for all of these trials, thus drawing attention to the need for a more collaborative approach in the future. The majority

of previous CSDH studies are small, retrospective, and occur in a single setting. Two reviews (2016) performed as part of the CODE-CSDH project on the reporting of data elements and outcomes in the CSDH literature highlighted wide heterogeneity in definitions, scales, and time points[41, 42].

The first international symposium on CSDH occurred at the EANS 2018 meeting (Brussels, Belgium, Oct 21-25). Following this meeting, a collaboration of specialists interested in CSDH (International COllaborative Research Initiative on CSDH; iCORIC) was formed[82]. This initiative aims to support the development of future collaborative trials in this field. The iCORIC group plans to publish a clear definition for CSDH, including an International Classification of Diseases (ICD) code, which does not currently exist, to improve classification and registry research. Following this publication, clinically important data elements (such as demographic data, classification of admission status, and preoperative and intraoperative variables) and outcome measures will be recommended for all future CSDH research, so that comparison between studies and systematic reviews will be easier and more reliable. This would improve the ability to reach consensus on high-grade evidence-based recommendations.

Due to the increasing burden of CSDH, further studies elaborating on the natural history and pathophysiology of CSDH, exploring the factors affecting its growth and its clinical evolution, and evaluating conservative treatment modalities are essential. Based on pathophysiologic mechanisms, animal experiments, and small patient studies, medical treatment (dexamethasone, atorvastatin, tranexamic acid, or angiotensin-converting enzyme inhibitors) may play a role in the treatment of CSDH in the future[120]. Many of the ongoing RCTs examining the role of medical management as adjuvant therapy or as compared to surgery are nearing completion. These studies may provide evidence that will significantly alter practice in this domain.

CSDH has been treated with trepanation since prehistoric times[165]. However, multiple questions on the optimal treatment of this patient category remain unanswered. The current consensus is that symptomatic CSDH is best treated by surgical evacuation, and BHC is generally accepted as the first-line option for surgical treatment worldwide. Postoperative drainage has been shown to reduce recurrences, but the optimal location of drain placement and duration of drainage requires further study. Additionally, the use of saline irrigation and postoperative ambulation still need to be further explored. Further work to define indications for the least invasive (minimally invasive hollow screws) and the most invasive (craniotomy) procedures

should be performed. Moreover, the utility and indications of MMA embolization need to be evaluated.

Many CSDH patients have comorbidities indicating the use of antithrombotic medication. Nonetheless, the published data on the risks and benefits of temporary withdrawal of these drugs is limited. These limitations have led to great variations in practice[284]. Better evidence and guidelines, including the timing of antithrombotic medication resumption, which may provide one of the topics of future collaborative work, are necessary. Furthermore, the increasing use of direct oral anticoagulants needs to be considered in future studies, since cardiologists and neurologists report positive preventive effects of these agents, whose usage is increasing.

Patients with CSDH come from different age groups, and their comorbidities and medications differ. Moreover, CSDH itself is not a homogenous condition, as different patterns of bleeding and/or membranes may indicate the need for different approaches. Accordingly, the treatment strategies will probably be more individualized in the future. Whether to use operative or non-operative management and the need for adjuvant therapies, as well as follow-up, will be more precisely tailored for each patient.

The number of elderly patients is growing as CSDH incidence as well as average age of the population increases. For this reason, future studies should specifically focus on the treatment of elderly patients with CSDH and multiple comorbidities. In addition to short-term perioperative outcomes, long-term outcomes are important. Optimizing perioperative care and rehabilitation to improve long-term functional outcomes is essential.

Future CSDH research should also focus on preventive measures, considering prior health conditions and fall-related injury risk factors that predispose one to CSDH. Frailty, functionality, dependency, and comorbidity should be of special interest as these issues are prognosticators of general disability, hospital readmission, and mortality. Considering the growing group of elderly patients, it is apparent that a multidisciplinary treatment approach of this common neurological condition is required.

Further studies are needed to investigate the actual overall costs on healthcare and society (e.g., rehabilitation, post-CSDH nursing facility dwelling, medication, and social security reimbursements). Finally, health-economic analyses are crucial and should be incorporated in all CSDH studies to ensure sustainable evidence-based decision-making.

7 CONCLUSIONS

We studied the population-based epidemiology of CSDH from 1990 to 2015 in the Pirkanmaa region, Finland. The main outcomes of the thesis can be summarized as follows:

1. The overall incidence of CSDH doubled from 8 to 18/100,000/year. Among the adults under 70 years old, the incidence remained quite stable, whereas the incidence nearly tripled among the over 80-year old population, from 47 to 130/100,000/year. The use of antithrombotics has increased but the ratio between a traumatic and a spontaneous CSDH etiology has not changed.

2. Patients with CSDH displayed excess mortality, which cumulated over time from 9% at one year to 48% at 20 years after CSDH diagnosis. A subgroup of patients with no comorbidities demonstrated no excess mortality. Patient-related characteristics are strongly associated with excess mortality, whereas specific CSDH-related findings are not. CSDH patients have an increased risk for dementia-related mortality.

3. The number of cases has increased as both the CSDH incidence and the elderly population have grown. Nonetheless, direct hospital costs have declined in recent years, as a result of shortened hospital stays and fewer recurrences related to use of subdural drains. The oldest group of patients, 80 years or older, did not have higher costs than the others, nor did this group have more complications other than pneumonia.

4. Routine four to six weeks' postoperative follow-up head CT scans increased the number of reoperations, because asymptomatic patients were operated based on radiological recurrence. Almost all (92%) of the recurrences occurred within two months. A two-month follow-up period after CSDH seems sufficient for most, and CT controls are advocated only for symptomatic patients.

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PUBLICATIONS

PUBLICATION I

The incidence of chronic subdural hematomas from 1990 to 2015 in a defined Finnish population

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JNS

CLINICAL ARTICLE

The incidence of chronic subdural hematomas from 1990 to 2015 in a defined Finnish population

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OBJECTIVE The aim of this study was to determine the population-based epidemiology of chronic subdural hematoma (CSDH) over a 26-year period.

METHODS A retrospective study was conducted of all adult patients (≥ 18 years and residents of Pirkanmaa [Finland]) with a diagnosis of CSDH between 1990 and 2015. The cases were identified using ICD codes. Detailed data collection was performed using medical records and death certificates. All patients were monitored until death or the end of year 2017. The annual number of inhabitants in the Pirkanmaa region was obtained from Statistics Finland (Helsinki, Finland).

RESULTS A total of 1168 patients with CSDH were identified from hospital records and death certificates; patients were considered as new-incidence cases if 2 years had elapsed following primary treatment and in cases involving a new contralateral CSDH. From 1990 to 2015, the overall incidence of CSDH doubled from 8.2 to 17.6/100,000/year. Among adults younger than 70 years, the incidence remained quite stable, whereas the incidence clearly increased among the ≥ 80-year-old population, from 46.9 to 129.5/100,000/year. The median age for a CSDH diagnosis increased from 73 to 79 years during the 26-year period. Head trauma was documented in 59% of cases. A ground-level fall was related to the CSDH in 31% of patients younger than 60 years and in 54% of those 80 years or older. The proportion of alcohol-related cases decreased toward the end of the study period (1990–1995: 16% and 2011–2015: 7%), because alcohol abuse was less frequent among the growing group of elderly patients. In contrast, the percentage of patients receiving anticoagulant or antiplatelet medication almost doubled toward 2015 (1990–1995, 27%; and 2011–2015, 49%). The patients' neurological condition on admission, based on both Glasgow Coma Scale score (score < 13: 1990–1995, 18%; and 2011–2015, 7%; $p < 0.001$) and the modified Rankin Scale score (score 0–2: 1990–1995, 8%; and 2011–2015, 19%; $p < 0.001$), was better in recent years than in the early 1990s.

CONCLUSIONS From 1990 to 2015, the incidence of CSDH has increased markedly. The incidence of CSDH among the population 80 years or older has nearly tripled since 1990. The use of anticoagulants has increased, but there has been no change regarding the ratio between a traumatic and a spontaneous CSDH etiology. As the world population becomes progressively older, the increasing incidence of CSDH will be a burden to patients and a future challenge for neurosurgical clinics.

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KEYWORDS hematoma; subdural; epidemiology; aged; risk factors; vascular disorders

Chronic subdural hematoma (CSDH) is a common disease in neurosurgical practice, particularly among elderly patients.[2,6,10,36] The reported annual incidence of CSDH has ranged widely from 1.7 to 20.6 per 100,000 across studies.[50] Although a time-related increase in the incidence of CSDH has been noted for decades, no large-scale population-based studies have been published.[50] The few studies published to date have examined small patient cohorts[3,6,17,29] and national registries.[18,24] Moreover, the published epidemiology of CSDH has

ABBREVIATIONS CSDH = chronic SDH; GCS = Glasgow Coma Scale; mRS = modified Rankin Scale; SDH = subdural hematoma.

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been predominantly based on surgical series, where the conservatively/nonoperatively treated patients are missing.[8,12,19,25,38,44,45] Furthermore, postmortem studies examining undiagnosed CSDH cases are lacking. Therefore, true incidence rates are unknown.

The incidence of CSDH increases with age, and there seems to be a clear incidence peak among the over-70-years-old.[17,18,29] The age-related incidence increase combined with the growing elderly population[22] causes a major challenge for neurosurgical clinics because a large proportion of these patients are managed operatively.[26] The underlying reason for the greater incidence of CSDH among the elderly is not completely understood. The reasons have been speculated to be attributed to brain atrophy,[31,34,49] a high risk of falls,[19,43,48] and broad use of antithrombotic medication within this population.[1,14,15,18,33,40]

Men are at greater risk for CSDH.[50] Higher risk for head trauma and also chronic alcohol abuse are some of the explanations that have been suggested for the sex difference, but the reasons underlying this difference are not well studied;[13] few reports have examined sex-related incidences in different age groups.[17,18]

The objective of this study was to determine the population-based epidemiology of CSDH over a 26-year period from 1990 to 2015 in a defined Finnish population. A specific interest was in the temporal trends in CSDH incidence and patient characteristics among different age groups and between sexes.

Methods

Material and Ethical Aspects

The study was conducted in the Department of Neurosurgery at the Tampere University Hospital (Tampere, Finland). All adult patients (≥ 18 years old and residents of Pirkanmaa) with a diagnosis of CSDH between 1990 and 2015 were retrospectively identified using the hospital's patient administrative databases. The death certificates were obtained from the official Cause of Death Register, coordinated by Statistics Finland (Helsinki, Finland), which covers all deaths occurring in Finland. According to Finnish legislation, a medicolegal autopsy should be performed when death is caused or suspected to be caused by an accident. As a result, traumatic causes of death are identified with a high probability. The cases were identified using ICD codes for traumatic and nontraumatic subdural hematomas (SDHs). The applied ICD codes for the 9th revision (ICD-9, 1990–1995) included the following: 432.1, 852.2, and 852.3. For the 10th revision (ICD-10, 1996–2015) the following codes were included: S06.5 and I62.0. Verified cases were classified by SDH type (acute, subacute, chronic, and hygroma) by reviewing all the medical records and death certificates.

Exclusion criteria were acute or subacute SDH (< 3 weeks after head trauma), hygroma (a collection of subdural cerebrospinal fluid without any signs of blood), and any form of intracranial surgery within 12 months preceding the CSDH diagnosis. Postmortem cases with CSDH as the immediate, intermediate, main, or related cause of death were included in the study. The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland. All data were collected retrospectively without contacting the patients; therefore, no written informed consent was obtained or required.

Data Collection

A detailed and structured data collection was performed using medical records and death certificates. The data collection included sociodemographics, comorbidities, antithrombotic medication, clinical history related to CSDH, treatment of CSDH, CSDH recurrence, and mortality (30 and 90 days from diagnosis of CSDH). Antithrombotic medication that was used by the patients included in the study cohort encompassed only 1 anticoagulant agent (warfarin) and 3 antiplatelet agents (acetylsalicylic acid, dipyridamole, and clopidogrel). None of the included patients were on direct oral anticoagulant drugs.

Patients were stratified into 5 groups according to age: 1) 18–59 years, 2) 60–69 years, 3) 70–79 years, 4) 80–89 years, and 5) ≥ 90 years. The study period was divided into 5 time epochs: 1) 1990–1995, 2) 1996–2000, 3) 2001–2005, 4) 2006–2010, and 5) 2011–2015. All patients were followed until death or the end of year 2017. The annual age-specific inhabitant number of the Pirkanmaa region (Finland) was obtained from Statistics Finland (Helsinki, Finland).

The Pirkanmaa region is a geographically well-defined area with both rural and urban areas that holds one of Finland's 5 neurosurgical departments (Department of Neurosurgery, Tampere University Hospital, Tampere, Finland). All neurosurgical cases in the Pirkanmaa region are referred to the Tampere University Hospital. Over 9% of the Finnish population lives in the Pirkanmaa region. The population increased from 427,223 in 1990 to 506,114 in 2015. The population 80 years or older has almost doubled from 13,565 to 26,417 during the study period.

Statistical Analysis

IBM SPSS Statistics for Windows (versions 22.0–24.0, IBM Corp.) was used for data analyses. Descriptive statistics (frequency [n], percentage, median, interquartile range, range) were used to describe variable and subgroup characteristics. The chi-square test was used to compare differences between groups. The statistical significance level was set at $p < 0.05$.

Results

The Incidence of CSDH

A total of 1133 patients with CSDH were identified from university hospital records and an additional 20 from death certificates. The data collection process is shown in Fig. 1. Patients with a CSDH were considered as new-incidence cases if 2 years had elapsed following primary treatment and in cases involving a new contralateral hematoma (n = 15). Only 1 patient required operative treatment for the same-sided CSDH 5 years after the primary CSDH operation. During the study period, 14 patients underwent new contralateral CSDH evacuation. In terms of incidence, these 15 aforementioned cases were counted twice. Two more patients underwent surgery after the study period (1990–2015) during the follow-up time

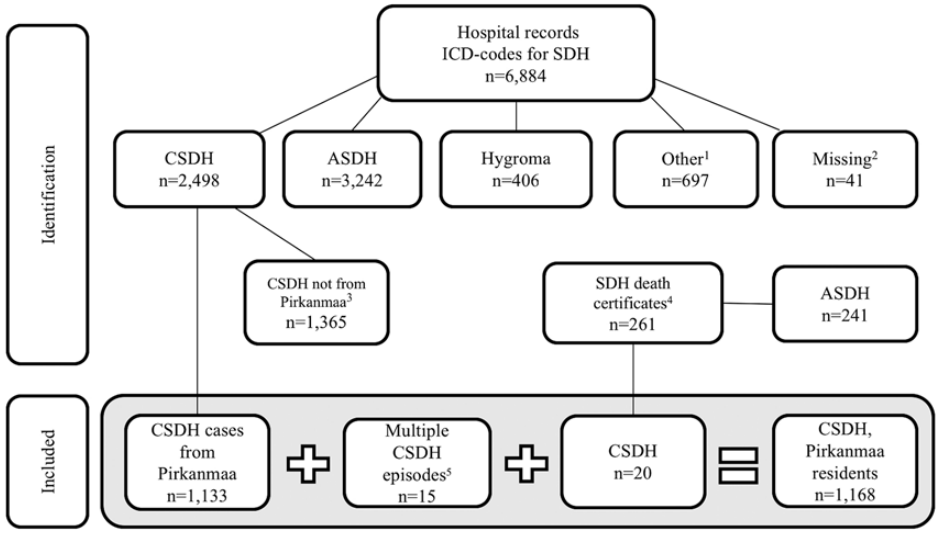
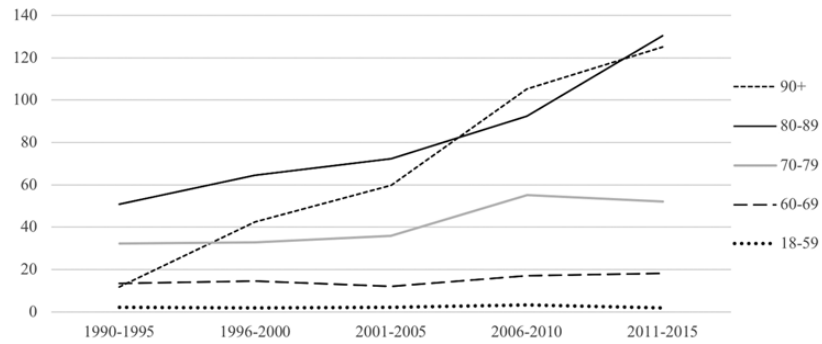


FIG. 1. Data collection process for patients with CSDHs between 1990 and 2015 in Pirkanmaa, Finland. ASDH = acute SDH. [1]Brain contusion, intracerebral or subarachnoid hemorrhage, or diagnosis due to clinically suspected SDH even though a subsequent brain scan ruled out that disorder. [2]Medical records had been destroyed 20 years after patients' deaths before data collection. [3]The catchment area of the Tampere Neurosurgical Department is approximately 1 million people. [4]After excluding patients who had been found in the hospital records. [5]Patients with recurrent CSDH were considered as new-incidence cases 2 years after primary treatment and if they had a new contralateral hematoma.

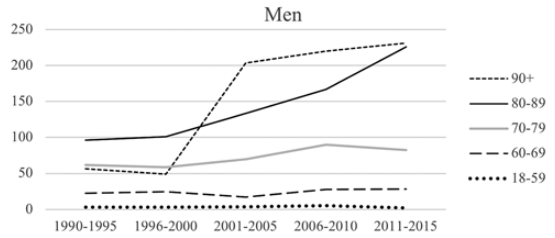
(2015–2017). Thus, the total number of cases was 1168, and 758 (65%) were men.

From the time period of 1990–1995 to 2010–2015, the overall incidence of CSDH in adults doubled from 8.2 to 17.6/100,000/year and nearly tripled for those ≥ 80 years from 46.9 to 129.5/100,000/year. The incidence rates stratified by age groups and time epochs are presented in Fig. 2. Among those younger than 70 years, the incidence remained quite stable, whereas the incidence clearly increased among those 80 years and older. The annual inci-



	Year				
Age	1990-1995	1996-2000	2001-2005	2006-2010	2011-2015
90+	11.6	42.4	59.6	105.4	125.0
80 - 89	50.7	64.5	72.2	92.5	130.3
70 - 79	32.3	32.7	36.0	55.2	52.1
60 - 69	13.4	14.4	11.9	17.1	18.2
18 - 59	2.3	2.1	2.5	3.5	2.1

FIG. 2. Incidence (n/100,000) of CSDHs in different age groups during the study period between 1990 and 2015 in Pirkanmaa, Finland.



Age	Year 1990-1995	1996-2000	2001-2005	2006-2010	2011-2015
90+	56.6	49.2	203.3	219.7	231.0
80 - 89	96.4	101.2	133.3	166.8	226.0
70 - 79	61.9	58.3	69.5	89.8	82.3
60 - 69	22.6	24.3	17.0	27.6	28.2
18 - 59	3.3	2.9	3.4	5.2	2.0

Age	Year 1990-1995	1996-2000	2001-2005	2006-2010	2011-2015
90+	0	40.6	21.6	78.3	94.2
80 - 89	33.3	51.0	47.8	57.8	79.3
70 - 79	16.5	17.4	13.4	29.7	28.3
60 - 69	6.2	6.0	7.5	7.5	8.9
18 - 59	1.2	1.3	1.5	1.7	2.1

FIG. 3. The incidence (n/100,000) of CSDH in men and women in different age groups during the study period between 1990 and 2015 in Pirkanmaa, Finland.

dence increased from 32.3 to 52.1/100,000/year in patients in the age group 70–79 years, from 50.7 to 130.3/100,000/year in patients in the age group 80–89 years, and from 11.6 to 125/100,000/year in patients 90 years or older.

The lowest, and also the only comparable, incidence for men and women was in those between the ages of 18 and 59 years. Men and women during the last 5-year period (2011–2015) had incidences of 2/100,000/year. The highest incidences for both sexes were in those aged 90 and older, and they increased from 56.6 to 231/100,000/year for men and from 0 to 94.2/100,000/year for women over the study period. The sex-stratified incidences by time periods are presented in Fig. 3.

The median age for a CSDH diagnosis increased from 73 years (1990–1995) to 79 years (2011–2015) during the 26-year study period. Women were older than men, with a median age increasing from 76 to 81 years. The characteristics of the entire sample, subgroups during the time epochs, and sex subgroups are presented in Tables 1–3. The 70- to 79-year age group was the most common age group between 1990 and 2010. The 80- to 89-year age group became the largest group in 2011–2015 (Fig. 4). At the same time, the 80- to 89-year-old population almost doubled, from 12,323 to 22,142, in Pirkanmaa. The percentage of CSDH patients ≥ 90 years increased from 0.6 to 6.8 during (increased 11.3 times) the study period, while the Pirkanmaa population ≥ 90 years increased from 1242 to 4275 (increased 3.4 times).

Etiology and Risk Factors

Any type of preceding minor or major head trauma were retrospectively found in 690 cases (59%), most of which were ground-level falls (n = 529, 77%), followed by bicycle accidents (n = 23, 3%) and falls from a height of over 1 m (n = 23, 3%). There was no clear change over time or between sexes in relation to the cause of injury. All age groups had a similar overall incidence of trauma-related CSDHs, but the trauma mechanism profile varied. The mechanism of injury was more likely to be a ground-level fall in older patients (18–59 years, 52/102 [51%]; and ≥ 80 years, 228/258 [88%]).

The proportion of alcohol-related cases was lower toward the end of the study period (1990–1995, 16%; vs 2011–2015, 7%; $p = 0.002$), but the absolute number of chronic alcohol abusers did not change markedly (varied between 19 and 38 patients). Concerning chronic alcohol overuse, there was a significant difference ($p < 0.001$) between age groups (18–59 years, 44% vs ≥ 80 years, 0.3%), and between sexes (men 14% vs women 6%).

The number of patients on antithrombotic medication increased over time (1990–1995, 45/167 [27%]; and 2011–2015, 173/354 [49%]; $p < 0.001$), mostly due to an increase in anticoagulation (1990–1995, 15/167 [9%]; and 2011–2015, 98/354 [28%]; $p < 0.001$). Among the patients between 18 and 59 years old, the prevalence of antithrombotic medication usage was 10%. In contrast, the prevalence was 57% among patients 80 years or older ($p < 0.001$). There was a higher prevalence of antithrombotic drug use in CSDH patients with no head trauma history (220/478 patients [46%]) than in those with a positive head trauma history (266/690 [39%], $p = 0.011$). There was not a significant difference in antithrombotic drug use between men and women.

Clinical Characteristics, Treatment, and Recurrence of CSDH

At hospital presentation, patients younger than 60 years more often had headache (50% vs 16%, $p < 0.001$) and nausea (10% vs 0.03%, $p = 0.002$) than patients ≥ 80 years. Elderly patients 80 years or older, compared with patients younger than 60 years, more often had disorientation or memory impairment (43% vs 22%, $p < 0.001$). General malaise was twice as common in patients 80 years or older than in those younger than 60 years (42% vs 21%, $p < 0.001$). The patients' clinical status on admission was somewhat worse in the early 1990s than in recent years, on both the Glasgow Coma Scale (GCS score < 13, 1990–1995: 18% and 2011–2015: 7%; $p < 0.001$) and the modified Rankin Scale (mRS score 0–2, 1990–1995, 8%; and 2011–2015, 19%; $p < 0.001$).

The CSDHs were right-sided in 413 of 1148 cases (36%), left-sided in 478 cases (42%), and bilateral in 257 cases (22%). Bilateral hematomas were more common in recent years than in the early 1990s (1990–1995, 16%; and 2011–2015, 26%; $p = 0.013$) and also more common

TABLE 1. Characteristics of patients with CSDH stratified by time periods

	1990–1995 (n = 167)	1996–2000 (n = 161)	2001–2005 (n = 187)	2006–2010 (n = 299)	2011–2015 (n = 354)
Median age, yrs (IQR)	73 (62–80)	75 (64–81)	75 (67–82)	76 (66–84)	79 (70–85)
Sex					
Men	111 (66.5)	99 (61.5)	125 (66.8)	199 (66.6)	224 (63.3)
Traumatic etiology	97 (58.1)	97 (60.2)	115 (61.5)	176 (58.9)	205 (57.9)
Ground-level fall	78 (80.4)	73 (75.3)	80 (71.3)	132 (75.0)	166 (81.0)
Comorbidity					
Cardiovascular disease	78 (46.7)	86 (53.4)	99 (52.9)	177 (59.2)	227 (64.1)
Diabetes	20 (12.0)	25 (15.5)	20 (10.7)	44 (14.7)	71 (20.1)
Epilepsy	4 (2.4)	8 (5.0)	5 (2.7)	9 (3.0)	8 (2.3)
Dementia	5 (3.0)	9 (5.6)	16 (8.6)	38 (12.7)	45 (12.7)
Neurodegenerative disease	2 (1.2)	0 (0)	0 (0)	10 (3.3)	9 (2.5)
Cerebrovascular disease	17 (10.2)	15 (9.3)	19 (10.2)	35 (11.7)	42 (11.9)
Hydrocephalus	3 (1.8)	1 (0.6)	1 (0.5)	3 (1.0)	1 (0.3)
Chronic alcohol abuse	26 (15.6)	19 (11.8)	21 (11.2)	38 (12.7)	25 (7.1)
Medication					
Antiplatelet	30 (18.0)	39 (24.2)	53 (28.3)	73 (24.4)	75 (21.2)
Warfarin	15 (9.0)	15 (9.3)	27 (14.4)	44 (14.7)	92 (26.0)
Warfarin & antiplatelet	0 (0)	1 (0.6)	2 (1.1)	14 (4.7)	6 (1.7)
No. of cases w/ clinical data available*	159	156	185	296	352
Admission GCS score					
13–15	131 (82.4)	133 (85.3)	167 (90.3)	262 (88.5)	327 (92.9)
9–12	17 (10.7)	17 (10.9)	15 (8.1)	28 (9.5)	16 (4.5)
3–8	11 (6.9)	6 (3.8)	3 (1.6)	6 (2.0)	9 (2.6)
Admission mRS score 0–2	13 (8.2)	23 (14.7)	24 (13.0)	44 (14.9)	68 (19.3)
Symptoms					
Headache	72 (45.3)	63 (40.4)	58 (31.4)	66 (22.3)	83 (23.6)
Nausea &/or vomiting	18 (11.3)	13 (8.3)	10 (5.4)	10 (3.4)	10 (2.8)
Aphasia	44 (27.7)	41 (26.3)	46 (24.9)	54 (18.2)	63 (17.9)
Hemiparesis	78 (49.1)	75 (48.1)	91 (49.2)	101 (34.1)	110 (31.3)
Vertigo or postural instability	67 (42.1)	73 (46.8)	62 (33.5)	108 (36.5)	105 (29.8)
Disorientation or memory impairment	66 (41.5)	54 (34.6)	68 (36.8)	102 (34.5)	105 (29.8)
General malaise	57 (35.8)	53 (34.0)	48 (25.9)	83 (28.0)	133 (37.8)
Seizure	17 (10.7)	18 (11.5)	18 (9.7)	28 (9.5)	38 (10.8)
Hematoma localization					
Rt	53 (33.3)	56 (35.9)	75 (40.5)	111 (37.5)	118 (33.5)
Lt	80 (50.3)	66 (42.3)	76 (41.1)	115 (38.9)	141 (40.1)
Bilat	26 (16.4)	34 (21.8)	34 (18.4)	70 (23.6)	93 (26.4)
Op treatment	146 (91.8)	150 (96.2)	168 (90.8)	243 (82.1)	271 (77.0)
Recurrent hematoma†	38 (26.0)	42 (28.0)	54 (32.1)	76 (31.3)	68 (25.1)
Mortality 30 days‡	4 (2.5)	7 (4.6)	4 (2.2)	9 (3.1)	14 (4.0)
Mortality 90 days‡	7 (4.4)	11 (7.2)	10 (5.5)	24 (8.3)	23 (6.6)

Values are presented as no. (%) unless otherwise indicated.
* Cases identified from death certificates were excluded.
† Accounts for operatively treated patients.
‡ Patients with multiple CSDH episodes were excluded (n = 15).

in those ≥ 80 years (18–59 years, 15%; and ≥ 80 years, 24%; p = 0.016). The hematoma side was not documented on the death certificates (n = 20). In relation to treatment, 978 (85%) patients were treated operatively and 170 (15%) conservatively. A CSDH was defined as recurrent if the CSDH was diagnosed again within 2 years of the previous operation. The overall recurrence rate for the first recurrence was 28%. The lowest recurrence rates were for those between the ages of 18 and 59 years (17%) and those 90 years or older (19%). The highest recurrence rate was in

TABLE 2. Age-stratified characteristics of patients with CSDHs

	18–59 Yrs (n = 169)	60–69 Yrs (n = 200)	70–79 Yrs (n = 376)	80–89 Yrs (n = 372)	≥ 90 Yrs (n = 51)
Sex					
Male	117 (69.2)	149 (74.5)	263 (69.9)	206 (55.4)	23 (45.1)
Traumatic etiology	102 (60.4)	123 (61.5)	207 (55.1)	225 (60.5)	33 (64.7)
Ground-level fall	52 (51.0)	83 (67.5)	166 (80.2)	198 (88.0)	30 (90.9)
Comorbidity					
Cardiovascular disease	38 (22.5)	92 (46.0)	228 (60.6)	273 (73.4)	36 (70.6)
Diabetes	15 (8.9)	28 (14.0)	62 (16.5)	69 (18.5)	6 (11.8)
Epilepsy	6 (3.6)	8 (4.0)	14 (3.7)	6 (1.6)	0 (0)
Dementia	5 (3.0)	5 (2.5)	26 (6.9)	66 (17.7)	11 (21.6)
Neurodegenerative disease	0 (0)	2 (1.0)	13 (3.5)	6 (1.6)	0 (0)
Cerebrovascular disease	5 (3.0)	18 (9.0)	41 (10.9)	58 (15.6)	6 (11.8)
Hydrocephalus	4 (2.4)	2 (1.0)	2 (0.5)	1 (0.3)	0 (0)
Chronic alcohol abuse	75 (44.4)	41 (20.5)	12 (3.2)	1 (0.3)	0 (0)
Medication					
Antiplatelet	9 (5.3)	40 (20.0)	82 (21.8)	123 (33.1)	16 (31.4)
Warfarin	6 (3.6)	20 (10.0)	77 (20.5)	76 (20.4)	14 (27.5)
Warfarin & antiplatelet	2 (1.2)	3 (1.5)	8 (2.1)	9 (2.4)	1 (2.0)
Cases w/ clinical data available*	168	198	372	359	51
Admission GCS score					
13–15	147 (87.5)	178 (89.9)	343 (92.2)	309 (86.1)	43 (84.3)
9–12	11 (6.5)	16 (8.1)	19 (5.1)	41 (11.4)	6 (11.8)
3–8	10 (6.0)	4 (2.0)	10 (2.7)	9 (2.5)	2 (3.9)
Admission mRS score 0–2	49 (29.2)	46 (23.2)	46 (12.4)	29 (8.1)	2 (3.9)
Symptoms					
Headache	84 (50.0)	85 (42.5)	108 (29.0)	64 (17.8)	1 (2.0)
Nausea &/or vomiting	16 (9.5)	14 (7.1)	17 (4.6)	12 (3.3)	2 (3.9)
Aphasia	24 (14.3)	32 (16.2)	81 (21.8)	91 (25.3)	20 (39.2)
Hemiparesis	51 (30.4)	90 (45.5)	154 (41.4)	148 (41.2)	12 (23.5)
Vertigo or postural instability	53 (31.5)	61 (30.8)	151 (40.6)	129 (35.9)	21 (41.2)
Disorientation or memory impairment	37 (22.0)	49 (24.7)	133 (35.8)	150 (41.8)	26 (51.0)
General malaise	35 (20.8)	45 (22.7)	123 (33.1)	142 (39.6)	29 (56.9)
Seizure	28 (16.7)	25 (12.6)	31 (8.3)	29 (8.1)	6 (11.8)
Hematoma localization					
Rt	71 (42.3)	79 (39.9)	133 (35.8)	120 (33.4)	10 (19.6)
Lt	72 (42.9)	73 (36.9)	151 (40.6)	157 (43.7)	25 (49.0)
Bilat	25 (14.9)	46 (23.2)	88 (23.7)	82 (22.8)	16 (31.4)
Op treatment	145 (86.3)	174 (87.9)	328 (88.2)	295 (82.2)	36 (70.6)
Recurrent hematoma†	25 (17.2)	54 (31.0)	105 (32.0)	87 (29.5)	7 (19.4)
Mortality 30 days‡	3 (1.8)	5 (2.5)	10 (2.7)	16 (4.5)	4 (8.3)
Mortality 90 days‡	3 (1.8)	12 (6.1)	22 (6.0)	29 (8.2)	9 (18.8)

Values are presented as no. (%) unless otherwise indicated.
* Cases identified from death certificates have been excluded.
† Accounts for operatively treated patients.
‡ Patients with multiple CSDH episodes excluded (n = 15).

the 70- to 79-year-old age group (32%). The recurrence rate between men and women differed significantly (men, 30%; and women, 25%; p = 0.017). The 30-day and 90-day mortality after diagnosis of CSDH remained quite stable during the study period. The 30-day mortality varied between 2.5% and 4.6%. Similarly, the 90-day mortality varied between 4.4% and 8.3%.

Discussion

Summary of the Key Findings

Between 1990 and 2015, the incidence of CSDH in adults ≥ 80 years nearly tripled, from 46.9 to 129.5 per 100,000. The incidence was higher for men than women after the age of 60 years, and highest in recent years (i.e.,

2011–2015) for both sexes in those older than 90 years (i.e., 231 per 100,000 for men and 94.2 per 100,000 for women). The admission GCS score was 13–15 in most cases, ranging from 86% to 92% across the age groups. In the total sample, across all years combined, head trauma was documented in 59% of cases. The number of patients on antithrombotic medications increased over time, from 27% to 49%.

Comparison of the Current Findings to Prior Literature

Epidemiological studies have reported a significant increase in the incidence of CSDH in the elderly compared with other age cohorts.[50] However, only a few of these studies were population-based in design (Table 4). According to a former study from Finland by Fogelholm and Waltimo with 64 patients (1967–1973) that also included death certificates, the annual incidence of CSDH was 1.7/100,000 in the general population, and the highest incidence was 7.4/100,000 in the age group of 70–79 years.[17] At that time, the authors speculated that one-third of the patients with a CSDH would die with an undiagnosed hematoma. Kudo and colleagues found 66 CSDH patients (1986–1988) on Awaji Island in Japan and reported an overall incidence of 13.1/100,000/year.[29] They calculated an incidence of 3.4/100,000/year and 58.1/100,000/year in the population younger and older than 65 years, respectively. In a case series of 40 patients (1996–1999) from North Wales (United Kingdom), Asghar and colleagues estimated an annual incidence of only 8.2/100,000 among patients older than 65 years.[6] The incidence in North Wales was updated after 15 years. The authors concluded that the annual incidence of CSDH in patients older than 65 years had increased to 48/100,000.[3]

Based on a Japanese registry of 1445 patients (2005–2007), Karibe and coauthors reported an annual CSDH incidence of 20.6/100,000. The incidences in the 70- to 79-year age group and those ≥ 80 years were 76.5/100,000/year and 127.1/100,000/year, respectively.[24] A study from the United States by Balser and colleagues (2000–2012), focusing on the veteran population (median age 64 years), observed an overall incidence rate of 79.4/100,000/year for subacute or chronic SDH.[9] In a case-control registry study from Denmark that included 10,010 patients with any SDH during the study period from 2000 to 2015, Gaist and colleagues found an increase in the incidence rate of SDH from 10.9 to 19.0/100,000/year.[18] The largest increase in the incidence of SDH occurred among older patients (aged 75–89 years) from 55.1 to 99.7/100,000/year. They estimated that 55% of all the SDH cases were subacute or chronic and that the incidence rates were probably underestimated by 22% due to the registry-based nature of the study.[18]

By comparing our results with the prior Finnish findings,[17] the Finnish overall incidence of CSDH has increased 10-fold from 1.7 to 17.6/100,000/year since the late 1960s. Similarly, among the 70- to 79-year age group, the incidence has increased from 7.4 to 52.1/100,000/year. Our incidence rates are in line with those from a recent Japanese study[24] and somewhat higher than the estimated rates from Denmark.[18] In the United Kingdom, the recent numbers are close to ours.[3] The incidence differences be-

TABLE 3. Characteristics of all CSDH patients and sex subgroups

	Men (n = 758)	Women (n = 410)	Total Sample (n = 1168)
Median age, yrs (IQR)	75 (65–82)	79 (70–85)	76 (67–83)
Traumatic etiology	436 (57.5)	254 (62.0)	690 (59.1)
Ground-level fall	317 (72.7)	212 (83.5)	529 (76.7)
Comorbidity			
Cardiovascular disease	420 (55.4)	247 (60.2)	667 (57.1)
Diabetes	115 (15.2)	65 (15.9)	180 (15.4)
Epilepsy	23 (3.0)	11 (2.7)	34 (2.9)
Dementia	62 (8.2)	51 (12.4)	113 (9.7)
Neurodegenerative disease	13 (1.7)	8 (2.0)	21 (1.8)
Cerebrovascular disease	79 (10.4)	49 (12.0)	128 (11.0)
Hydrocephalus	5 (0.7)	4 (1.0)	9 (0.8)
Chronic alcohol abuse	104 (13.7)	25 (6.1)	129 (11.0)
Medication			
Antiplatelet	175 (23.1)	95 (23.2)	270 (23.1)
Warfarin	120 (15.8)	73 (17.8)	193 (16.5)
Warfarin & antiplatelet	20 (2.6)	3 (0.7)	23 (2.0)
Cases w/ clinical data available*	748	400	1148
Admission GCS score			
13–15	668 (89.3)	352 (88.0)	1020 (88.9)
9–12	63 (8.4)	30 (7.5)	93 (8.1)
3–8	17 (2.3)	18 (4.5)	35 (3.0)
Admission mRS 0–2 score	121 (16.2)	51 (12.8)	172 (15.0)
Symptoms			
Headache	235 (31.4)	107 (26.8)	342 (29.8)
Nausea &/or vomiting	25 (3.3)	36 (9.0)	61 (5.3)
Aphasia	160 (21.4)	88 (22.0)	248 (21.6)
Hemiparesis	319 (42.6)	136 (34.0)	455 (39.6)
Vertigo or postural instability	274 (36.6)	141 (35.3)	415 (36.1)
Disorientation or memory impairment	250 (33.4)	145 (36.3)	395 (34.4)
General malaise	221 (29.5)	153 (38.3)	374 (32.6)
Seizure	80 (10.7)	39 (9.8)	119 (10.4)
Hematoma localization			
Rt	271 (36.2)	142 (35.5)	413 (36.0)
Lt	311 (41.6)	167 (41.8)	478 (41.6)
Bilat	166 (22.2)	91 (22.8)	257 (22.4)
Op treatment	644 (86.1)	334 (83.5)	978 (85.2)
Recurrent hematoma†	196 (30.4)	82 (24.6)	278 (28.4)
Mortality 30 days‡	26 (3.5)	12 (3.0)	38 (3.4)
Mortality 90 days‡	51 (6.9)	24 (6.0)	75 (6.6)

Values are presented as no. (%) unless otherwise indicated.
* Cases identified from death certificates have been excluded.
† Accounts for operatively treated patients.
‡ Patients with multiple CSDH episodes excluded (n = 15).

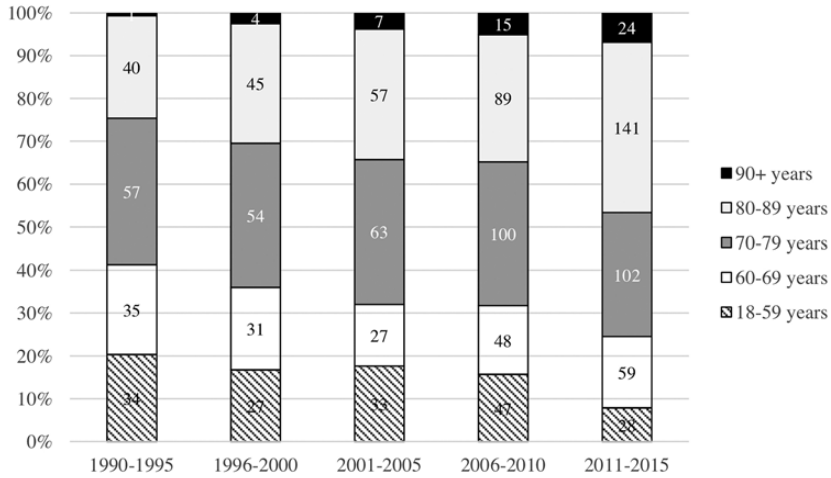


FIG. 4. Patients with CSDH between 1990 and 2015 in Pirkanmaa, Finland. Proportions (%) of different age groups stratified by time periods.

tween studies are most likely due to differences in case ascertainment, study design, healthcare systems, and cultural issues.

Head trauma is considered to be the most important risk factor of CSDH and, in most large series, 50% to 80% of the patients have a history of trauma.[13] Previous head trauma was reported by 59% of patients in our study (58% of men and 62% of women). One reason for the greater incidence of CSDH among the elderly may be attributed to a higher number of falls in this population.[32] It has been estimated that approximately 30% of home-dwelling people 65 years or older fall every year and about half of those who fall do so repeatedly.[42] A Finnish follow-up study (1970–2011) of patients 80 years or older showed that the number and age-adjusted incidence of fall-induced brain injury increased considerably and was higher for men than for women.[27] Brain atrophy, chronic health conditions, and polypharmacy might contribute to fall-related brain injuries in the elderly.[27]

One well-known risk factor for CSDH is alcohol overuse by inducing brain atrophy and coagulation dysfunction and by increasing the risk of head trauma.[35] Reported rates of CSDH with chronic alcoholism range from 6% to 35%.[47] In our series, the percentage of patients with a history of chronic alcohol abuse decreased during the study period (from 16% to 7%), because alcohol abuse was particularly infrequent among the growing group of elderly patients. Alcohol overuse was more common among men (14%) than women (6%). In Finland, alcohol consumption increased between 1990 and 2007, but subsequently the consumption trend has been decreasing.[41] Alcohol is a considerable risk factor for the younger patient population but does not explain the increase in incidence of CSDH in those 80 years or older.

Antithrombotic medication is an undisputable risk factor for CSDH.[14,15,18,21,33,40] During the past decades, the use of antithrombotic drugs has increased, especially among elderly patients,[1] after a number of studies have shown effective primary and secondary prevention of cardiocerebrovascular disease.[11,30] A Danish nationwide register study (1999–2014) showed that anticoagulation usage was more common among men than women, and it was most frequent in age categories above 65 years.[1]

In our study, the number of patients on antithrombotic medication increased from 27% to 49% during the study period, mostly due to the increase in anticoagulant medication usage (9%–28%). In patients 80 years or older, 57% were using antithrombotic drugs and almost half of these were anticoagulants. The rate of antithrombotic drug use in the total sample was modestly greater (46%) in those who had no documented history of head trauma than in those with a documented history of head trauma (39%). Similarly, Aspegren et al.[7] reported a higher prevalence of antithrombotic drug use in patients without head trauma (63%) than in patients with head trauma (42%), and Sim et al.[47] reported that antithrombotic drugs were associated with nontraumatic CSDH (i.e., no trauma was reported in 67% of antithrombotic drug users and 33% of nonusers).

It has been suggested that improved awareness of CSDH among the medical profession and the wide availability of CT scanners have led to sensitive diagnostics and higher incidence rates.[4,46] This idea is supported by a Finnish pre-CT era study in which one-third of the CSDH cases were found during autopsy.[17] In our study, the autopsy-verified CSDH rate was less than 2%. These autopsy cases were distributed equally throughout the entire 26-year study period. A systematic review (including studies from 1989 to 2008) of incidental findings on brain MRI revealed only 4 extra-axial collections among 19,559 people, and the number needed to scan was 2500.[39] Therefore, better access to neuroimaging is an unlikely explanation for the increasing CSDH incidence rates. Nevertheless, our CSDH patients were diagnosed in a better clinical condition (fewer symptoms and higher GCS scores) toward the end of the study period. This could reflect the

TABLE 4. Summary of population-based studies on chronic subdural hematoma incidence

Authors & Year	Country	Time Period	No. of Patients	Incidence (n/100,000/yr)			
				Overall	>65 Yrs	70–79 Yrs	>80 Yrs
Foelholm & Waltimo, 1975	Finland	1967–1973	64	1.7		7.4	6.4
Kudo et al., 1992	Japan	1986–1988	66	13.1	58.1		
Asghar et al., 2002*	United Kingdom	1996–1999	40		8.2		
Karibe et al., 2011*	Japan	2005–2007	1445	20.6		76.5	127.1
Adhiyaman et al., 2017†	United Kingdom	2014–2015	66		48		
Present study‡	Finland	1990–2015	1168	12.2	45.6	42.1	85.4
		1990–1995	167	8.2	28.5	32.3	46.9
		2011–2015	354	17.6	64.3	52.1	129.5

* Registry study.
† Included patients > 65 years.
‡ Included patients ≥ 18 years.

fact that diagnosis in more recent years is accomplished earlier than in the 1990s.

Strengths and Limitations

Our series represents the most extensive non–register-based study of consecutive CSDH cases treated in one neurosurgical department, and, although retrospective in nature, the population-based setting makes it less prone to selection bias. Moreover, all data were collected by one of the authors (M.R.). Our study gives a reliable population-based estimate of the CSDH incidence and its progress in time. This study has several limitations. There is a possibility that some cases were not recognized due to incomplete or incorrect ICD coding. In addition, the distinction between subacute and chronic SDH is not always obvious, both in relation to time and neuroradiological characteristics. No definition of CSDH is universally accepted.[23] The recent register-based studies reporting CSDH incidence have also included subacute SDHs. Subacute SDHs were excluded from this study because this hematoma subtype is considered to represent an entity of its own.[5,16,28]

Age-related brain degeneration with an enlarging potential subdural space is an important risk factor for CSDH.[31,34,49] Of the other well-known risk factors for CSDH (trauma, alcohol overuse, antithrombotic therapy), only the use of anticoagulant drugs has increased among the study population during the 26-year study period from 1990 to 2015. The present results are thus in line with those of previous studies, indicating that the increased incidence of CSDH appears to be associated with the incremental use of anticoagulants among older patients. The combination of age-related general brain atrophy, risk for multiple falls, and the frequent use of anticoagulants results in increased risk for CSDH. National guidelines with multifactorial interventions for preventing falls among elderly are important and should be implemented widely.[37] The risk/benefit equation of anticoagulation for elderly, stroke-prone patients is complex. The benefits of these drugs should outweigh possible harm from a risk of CSDH. The global population of people 80 years or older is expected to more than triple between 2015 and 2050.[22] Therefore, the number of elderly patients with CSDH will likely greatly increase all over the world.

Conclusions

From 1990 to 2015, the incidence of CSDH has increased markedly. The incidence in CSDH among the population 80 years or older has nearly tripled since 1990. The use of anticoagulants has increased, but there has been no change regarding the ratio between traumatic and spontaneous CSDH etiology. As the world population becomes progressively older, the increasing incidence of CSDH will be a burden to patients and a future challenge for neurosurgical clinics.

Acknowledgments

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Conception and design: Rauhala, Luoto, Niskakangas, Öhman, Helén. Acquisition of data: Rauhala. Analysis and interpretation of data: Rauhala, Luoto. Drafting the article: Rauhala, Luoto. Critically revising the article: Luoto, Iverson, Helén. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Rauhala. Statistical analysis: Rauhala, Huhtala. Study supervision: Luoto, Öhman, Helén.

Supplemental Information

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ORIGINAL ARTICLE - BRAIN TRAUMA

Long-term excess mortality after chronic subdural hematoma

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Abstract

Objective To assess possible long-term excess mortality and causes of death of patients with chronic subdural hematoma (CSDH).

Methods A retrospective study (1990–2015) of adult patients ($n = 1133$, median age = 76 years old, men = 65%) with CSDH identified by ICD-codes and verified by medical records. All patients were followed until death or the end of 2017. Cumulative relative survival ratios and relative excess risks of death (RER) were estimated by comparing patients' mortality with that in the entire regional matched population. The causes of death were compared with a separate reference group formed by randomly choosing sex, age, and calendar time matched controls (4 controls per each CSDH patient).

Results The median follow-up time was 4.8 years (range = 0–27 years), and 710 (63%) of the patients died (median age at death = 84 years old). The cumulative excess mortality was 1 year = 9%, 5 years = 18%, 10 years = 27%, 15 years = 37%, and 20 years = 48%. A subgroup of CSDH patients ($n = 206$) with no comorbidity had no excess mortality. Excess mortality was related to poor modified Rankin score at admission (RER = 4.93) and at discharge (RER = 8.31), alcohol abuse (RER = 4.47), warfarin (RER = 2.94), age ≥ 80 years old (RER = 1.83), non-operative treatment (RER = 1.56), and non-traumatic etiology (RER = 1.69). Hematoma characteristics or recurrence were unrelated to excess mortality. Dementia was the most common cause of death among the CSDH patients (21%) and the third most common cause in the reference group (15%, $p < 0.001$).

Conclusions Patients with CSDH have continuous excess mortality up to 20 years after diagnosis. Patient-related characteristics have a strong association with excess mortality, whereas specific CSDH-related findings do not. CSDH patients have an increased risk for dementia-related mortality.

Keywords Subdural hematoma, chronic · Mortality, excess · Causes of death · Survival · Mortality, excess

Introduction

Chronic subdural hematoma (CSDH) is a common disease in neurosurgical practice among elderly patients [1, 3, 27]. The reported annual incidence of CSDH has ranged widely across studies, from 1.7 to 20.6 per 100,000—and the overall incidence is increasing as the global population becomes progressively older [38]. In a prior study using this same patient

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cohort, we reported that during a 26-year period between 1990 and 2015, the overall incidence doubled from 8.2 to 17.6/100,000/year in the Pirkanmaa region, Finland [32]. The incidence per 100,000 person-years remained quite stable among adults younger than 70 years, whereas the incidence nearly tripled among the population 80 years or older. The global population of people aged 80 and older is expected to more than triple between 2015 and 2050 [17]. Consequently, CSDH is a condition of growing importance.

CSDH has been considered to be relatively benign, but during the last years, it has been recognized to have worse outcome than earlier assumed [11, 25, 29]. It has been speculated that CSDH may be a sentinel health event, and a harbinger of subsequent morbidity and mortality [3, 11, 29]. Age-related brain degeneration with an enlarging potential subdural space is assumed to be an important risk factor for CSDH [22, 24, 37]. Conversely, CSDH itself has been associated with a significant increase in the degree of brain atrophy post-CSDH [4]. Other well-known risk factors for CSDH are trauma [26], alcohol overuse [28], and antithrombotic therapy [6, 15, 23, 30].

Reported mortality rates after CSDH vary widely across studies, and a 1-year mortality rate of up to 32% has been reported [29]. In general, CSDH patients are from an age group with high baseline expected mortality. It is not possible to draw reliable conclusions on the excess mortality related to CSDH without comparing these patients to a matched sample from the general population. To date, only four studies (Table 1) have compared mortality after CSDH with anticipated survival [11, 16, 25, 29]. All of these studies have shown varied excess mortality, but the follow-up periods have extended only up to 8 years. Furthermore, there are no prior studies reporting long-term mortality in CSDH patients compared with a matched sample from the general population in an unselected, population-based series. Additionally, only two studies have previously reported the causes of death after a diagnosis of CSDH [19, 25].

The objective of this study was to examine the possible long-term excess mortality related to CSDH, and the causes of death after a diagnosed CSDH. A large unselected, population-based CSDH patient cohort was compared with the general population from the same region, matched by sex, age, and calendar time. The causes of death of the CSDH patients were compared with a separate matched reference group.

Methods

Material and ethical aspects

The study was conducted in the Department of Neurosurgery at the Tampere University Hospital (Tampere, Finland). All adult patients (≥ 18 years old Pirkanmaa residents) with a diagnosis of CSDH between 1990 and 2015 were retrospectively identified using the hospital's patient administrative databases. The cases were identified using International Classification of Diseases (ICD) codes for traumatic and non-traumatic subdural hematomas (SDHs). Verified cases were classified by SDH type (acute, subacute, chronic, and hygroma) by reviewing all the medical records. Exclusion criteria were acute or subacute SDH (< 3 weeks after head trauma), hygroma (a collection of subdural cerebrospinal fluid without any signs of blood), and any form of intracranial surgery within 12 months preceding the CSDH diagnosis.

The dates and causes of deaths were obtained from Statistics Finland (Helsinki, Finland). The Finnish official cause of death statistics are, in practice, 100% complete in relation to the cause and date of death. The entire Pirkanmaa population matched by sex, age, and calendar time was used for the excess mortality analysis. For the cause of death comparison, a separate reference group was formed by randomly choosing 4:1 sex, age (± 6 months), and calendar time–matched control subjects from Pirkanmaa for each CSDH patient. The reference group ($n = 4532$) was obtained from the Statistics Finland.

The Pirkanmaa region is a geographically well-defined area with both rural and urban areas that holds one of Finland's five neurosurgical departments (Department of Neurosurgery, Tampere University Hospital, Tampere, Finland). All neurosurgical cases of the Pirkanmaa region are referred to the Tampere University Hospital. Over 9% of the Finnish population lives in the Pirkanmaa region. The population increased from 427,223 in 1990 to 506,114 in 2015. The population over 80 years old has almost doubled from 13,565 to 26,417 during the study period.

Data collection

A detailed and structured data collection was performed from medical records. CT scans or MR images were not separately inspected. Patients were stratified into three groups according to age:(1) 18–59 years, (2) 60–79 years, and (3) ≥ 80 years. The age categories were formed a priori on the basis of previous literature, convenience and the ease of presenting the results. The data collection included the following: comorbidities, medication, possible trauma, symptoms, neurological condition assessments based on both the Glasgow Coma Scale (GCS) and the modified Rankin Scale (mRS) score at admission, and for the operative group also at discharge. CSDH-related findings collected were localization (unilateral/bilateral) and hematoma thickness divided into three groups (≤ 15 mm, 16–25 mm, and > 25 mm) selected before the data collection was started. Operation details were collected. CSDH recurrence was defined as an ipsilateral hematoma

Table 1 Summary of studies on long-term excess mortality in chronic subdural hematoma patients

Authors	Country	Time period	*n*	Age mean, y (range)	Follow-up period median, y (range for survivors)	Mortality (%)		Control data	Excess mortality
						6 months	1 year		
Miranda et al. 2011[7]	USA	2000–2008	209	80.6 (65–96)	1.45 (N/A-8.3)	26.3	32	Center of Disease Control and Prevention data	• Excess mortality up to 1 year beyond diagnosis • Median survival: o CSDH 4.4 year o Anticipated actuarial survival 6 year
Dumont et al. 2013[8]	USA	1996–2010	287	75 (55-N/A)	2.3 (0.5–14)	N/A	30	Center of Disease Control and Prevention data	• 1 year standardized mortality ratio: o 55–64 years:17 o 65–74 years:8.1 o 75–84 years:3.4 o ≥ 85 years:2.9 • Median survival: 4.0 ± 0.5y
Manickam et al. 2016[9]	Australia	2006–2011	155	69.3 (18-N/A)	5.2 (N/A-14.19)	14.19	20.35	Australian Bureau of Statistics, and the Registry of Births, Deaths and Marriages	• Excess mortality throughout follow-up. • Average long-term survival: o CSDH: 5.29 ± 0.59 year o Actuarial data: 17.74 ± 1.8 year
Guilfoyle et al. 2017[19]	UK	2004–2007	215	78 (35–95)	N/A (8–10)	Drain group: 8.6 No drain group: 18.1	N/A	Cohorts of the general population with the same number of cases and identical age and sex profiles as the drain and no drain groups (Human Mortality Database)	• 5 year cumulative excess mortality: o Drain group: 10.2% o No drain group: 22.4%
Present study	Finland	1990–2015	1133	73 (22–99)	4.8 (2–27)	9.5	13.7	The population of Pirkanmaa region stratified by sex, age, and calendar year (Statistics Finland)	• Cumulative excess mortality: o 1 year: 9% o 5 years: 18% o 10 years: 27% o 15 years: 37% o 20 years: 48%

CSDH = chronic subdural hematoma; N/A = not available

needing re-operation within 2 years of the original operation. All patients were followed until death or the end of year 2017.

Survival analysis

The variables chosen for survival analysis were sex, age groups, and variables known to be CSDH risk factors (trauma, chronic alcohol abuse, and antithrombotic medication). The effect of neurological condition, treatment group (operative versus non-operative), and hematoma recurrence were analyzed.

Statistical analyses

SPSS (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, USA) was used for data analyses. Survival analyses were conducted using the statistical software R (version 3.6.0) with popEpi package (version 0.4.7). Descriptive statistics [frequency (*n*), percentage, median, interquartile range, range] were used to describe variable and subgroup characteristics. The Chi square test was used to compare differences between groups. The statistical significance level was set at $p < 0.05$.

The cumulative relative survival ratio (CRSR) summarizes patients' excess risk of death due to the disease by comparing the survival of patients to that of the matched general population (the population of Pirkanmaa region stratified by sex, age, and calendar year). CRSRs were estimated by using the Ederer II method [13, 34]. To compare differences in relative survival adjusted for age, sex, and follow-up time, we estimated relative excess risk (RER) of death by using Poisson regression [10]. Each model included sex, age at diagnosis (4 groups: 0–59, 60–69, 70–79, and 80+ years), and 5 intervals of follow-up time after diagnosis (0 to < 1 year, 1 to < 5 years, and three 5-year intervals from 5 to 20 years) in addition to a risk factor.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Characteristics

A total of 1133 patients with CSDH were identified, 736 (65%) were men. The median age for CSDH diagnosis was 76 years, and women were older than men (79 vs. 75 years). Median follow-up time was 4.8 years, with a minimum of 0 days and maximum of 27 years. Median follow-up time for survivors was 6.6 years, with a minimum of 2 years. No patients were lost from follow-up.

Of all the patients, 965 (85%) were operated. The indication for surgery was based on imaging and symptoms attributable to the mass effect of the hematoma. Operatively treated patients were slightly younger than non-operatively treated (median age 76 vs. 79 years, $p = 0.001$). At least one comorbidity was reported by 82% of the patients in both treatment groups. Antithrombotic medication was used by 42% of the patients. Two or more comorbidities were reported by 38% of operative group patients and 48% of non-operative group patients ($p = 0.015$), three or more by 13% and 15% ($p = 0.052$), respectively. Non-operatively treated CSDH patients more often had previously diagnosed dementia (16% vs. 8%, $p = 0.001$). The overall prevalence of dementia in CSDH patients aged 70 years or older was 12%. Significant differences were also noted in admission mRS; operatively treated patients had worse neurological disability [mRS scores of 4–5 were found in 52% of the operative group ($n = 506/965$) versus 28% of the non-operative group ($n = 47/168$), $p < 0.001$]. Operatively treated patients more often had headache or localizing neurological deficits. The characteristics of the entire sample and treatment subgroups are presented in Table 2. We have previously published the details of CSDH patients from this same patient cohort stratified by gender, age groups, and time periods [32].

Most operations used local anesthesia ($n = 828$; 86%) via one burr hole, and the hematoma was removed through irrigation. A subdural drain was inserted in 59 patients (6%). The drain was kept below the head level with no suction for 24–48 h. Subgaleal drains were not used. Only one patient underwent craniotomy as the primary surgery. The patients were actively mobilized directly after the operation. Recurrent hematoma was treated surgically for 273 cases (28%, median age 76 years). The reason for non-operative treatment for majority of the cases was that the CSDH did not cause neurological signs or significant symptoms. Only 7 patients were not offered surgery because they presented in a moribund state, and the analyses have been done also by excluding these patients. Most non-operatively treated patients were not admitted to a neurosurgical clinic. Non-operative treatment included discontinuation of possible antithrombotic medication, active mobilization, and follow-up CT-scans (routinely or for emerging new symptoms).

Mortality after diagnosis of CSDH

By the end of the follow-up period, 710 (63%) of the 1133 patients had died, 449 of men (61%), and 261 of women (66%). Median age at death was 84 years (IQR 76–89 years), 83 years for men, and 86 years for women. Similarly, the median age at death was 84 years in the operative group and 85 years in the non-operative group. The 30-day and 6-month mortalities after diagnosis of CSDH were 3% and 10%, respectively. The overall 1-year and 2-year mortality rates were 14% and 22%, respectively. There was no significant difference in mortality between men and women. One-year mortality was 12% in the operative group ($n = 965$) and 21% in the non-operative group ($n = 168$; $p = 0.003$). After the patients ($n = 7$) who were not offered surgery, because they presented in a moribund state, were withdrawn from the non-operative group, the non-operative 1-year mortality was 18% (operative vs. non-operative: $p = 0.053$). One-year mortality was 5% among the patients under the age of 60, and 22% among those aged 80 and older ($p < 0.001$). A subgroup of patients with no comorbidities had a 1-year mortality of only 3% ($n = 206$, median age 72 years, IQR 61–78 years). Mortality rates are presented in Table 3. For comparison, the reference group mortality rates also are reported in Table 3.

Long-term excess mortality

The 1-year cumulative relative survival ratio (CRSR) for all CSDH patients was 0.91 (95% CI 0.89–0.94), implying 9% excess mortality compared with the matched general population. The cumulative excess mortality was 18% in 5 years (CRSR 0.82; 95% CI 0.78–0.86), 27% in 10 years (CRSR

Table 2 Characteristics of all chronic subdural hematoma patients and treatment subgroups

	Total sample $n = 1133$		Non-operative treatment $n = 168$		Operative treatment $n = 965$		p value
	n	%	*n*	%	*n*	%	
Median age, years, IQR	76	67–83	79	68–86	76	66–82	0.001
Sex							
Men	736	65.0	102	60.7	634	65.7	0.21
Traumatic etiology	672	59.3	107	63.7	565	58.5	0.21
Comorbidity							
Cardiovascular disease	644	56.8	96	57.1	548	56.8	0.93
Diabetes	178	15.7	27	16.1	151	15.6	0.89
Chronic alcohol abuse	126	11.1	20	11.9	106	11.0	0.73
Cerebrovascular disease	124	10.9	24	14.3	100	10.4	0.13
Dementia	99	8.8	26	15.7	73	7.6	0.001
Pulmonary disease	68	6.0	16	9.5	52	5.4	0.05
Epilepsy	32	2.8	3	1.8	29	3.0	0.38
Neurodegenerative disease	20	1.8	7	4.2	13	1.3	0.01
Hydrocephalus	9	0.8	0	0	9	0.9	0.21
Medication							
Antiplatelet	268	23.7	36	21.4	232	24.0	0.46
Warfarin	187	16.5	26	15.5	161	16.7	0.69
Warfarin AND antiplatelet	23	2.0	2	1.2	21	2.2	0.40
Admission GCS							
13–15	1007	88.9	157	93.5	850	88.1	0.04
9–12	91	8.0	8	4.8	83	8.6	0.91
3–8	35	3.1	3	1.8	32	3.3	0.29
Admission mRS 0–3	580	51.2	121	72.0	459	47.6	< 0.001
Symptoms							
Hemiparesis	444	39.2	9	5.4	435	45.1	< 0.001
Vertigo or postural instability	408	36.0	35	20.8	373	38.7	< 0.001
Disorientation/memory impairment	390	34.4	54	32.1	336	34.8	0.50
General malaise	367	32.4	50	29.8	317	32.8	0.43
Headache	340	30.0	28	16.7	312	32.3	< 0.001
Aphasia	245	21.6	9	5.4	236	24.5	< 0.001
Seizure	117	10.3	28	16.7	89	9.2	0.003
Nausea and/or vomiting	60	5.3	7	4.2	53	5.5	0.48

IQR Interquartile range; *GCS* Glasgow Coma Scale; *mRS* Modified Rankin Scale

0.73; 95% CI 0.67–0.80), 37% in 15 years (CRSR 0.63; 95% CI 0.54–0.73), and 48% in 20 years (CRSR 0.52; 95% CI 0.40–0.66). The excess mortality rate was highest during the first year of follow-up after diagnosis of CSDH, and it was 2–4% per year during the rest of the follow-up period. The excess mortality seemed to be more pronounced in women, but the difference was not statistically significant. CSDH patients had excess mortality in every age group, and it was more pronounced in the age group of ≥ 80 years and in the non-operatively treated patients. A subgroup of patients with no comorbidities had better survival than the matched general population. The CRSR with 95% confidence intervals are shown in Fig. 1.

Relative excess risk of death

In the age-, gender-, and follow-up time–adjusted regression model for RER, excess mortality was significantly related to (i) poor mRS 4–5 (RER = 4.93) at admission and especially (ii) at discharge (RER = 8.31), (iii) chronic alcohol abuse (RER = 4.47), (iv) warfarin medication (RER = 2.94), (v) age ≥ 80 years old (RER = 1.83), (vi) non-operative treatment

Table 3 Mortality after diagnosis of CSDH stratified by sex, age, treatment group, and prevalence of comorbidity. Also shown the mortality of the reference group

	Total sample $n = 1133$		Men $n = 736$		Women $n = 397$		Age group 18–59 years $n = 167$		Age group 60–79 years $n = 565$		Age group ≥ 80 years $n = 401$		Operative $n = 965$		Non-operative $n = 168$		Non-operative $n = 161$*		No comorbidity $n = 206$		Reference group $n = 4532$	
Cumulative mortality	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
30 days	38	3.4	26	3.5	12	3.0	3	1.8	15	2.7	20	5.0	25	2.6	13	7.7	8	5.0	3	1.5	16	0.4
90 days	75	6.6	51	6.9	24	6.0	3	1.8	34	6.0	38	9.5	54	5.6	21	12.5	15	9.3	4	1.9	61	1.3
6 months	108	9.5	74	10.1	34	8.6	5	3.0	45	8.0	58	14.4	82	8.5	26	15.5	20	12.4	6	2.9	125	2.8
1 year	155	13.7	107	14.5	48	12.1	8	4.8	59	10.4	88	22.0	120	12.4	35	20.8	29	18.0	6	2.9	248	5.5
2 year	254	22.4	168	22.8	86	21.7	20	12.0	97	17.1	137	34.2	200	20.7	54	32.1	47	29.2	19	9.2	486	10.7

*The patients ($n = 7$) who were not offered surgery (because presenting in a moribund state) were not included

(RER = 1.56; moribund patients $n = 7$ excluded), and (vii) non-traumatic etiology (RER = 1.69). Hematoma localization (unilateral/bilateral), thickness, or recurrence were not related to the excess mortality. Detailed RER results are presented in Table 4.

Causes of death after CSDH

The most frequent causes of death for women were dementia (29%), ischemic cardiac disease (15%), and cerebral ischemia (12%), and the most common causes for men were ischemic cardiac disease (23%), dementia (16%), and cancer (14%). SDH (the hematoma type (chronic, subacute, acute) could not be verified due to the nature of the cause of death data) was the cause of death in 42/710 patients (6%). In the matched reference group ($n = 4532$), the most common causes of death were ischemic cardiac disease (25%; women 22% and men 26%), cancer (19%; women 15% and men 22%), and dementia (15%; women 18% and men 13%). As a cause of death, dementia was more common in patients with CSDH than in the reference group (21% vs. 15%, $p < 0.001$). The difference was significant for women (29% vs. 18%, $p < 0.001$), but not for men (16% vs. 13%, $p = 0.12$). The cause of death was traumatic in 11% of the CSDH patients, and 3% in the reference group ($p < 0.001$). SDH was the cause of death in 6% and in 0.5%, respectively ($p < 0.001$). Causes of death among the CSDH patients and the reference group are presented in Table 5. When stratifying the causes of death by survival time, the incidence of trauma-related death was significantly higher among CSDH patients compared with the reference group during the first 5 years ($p < 0.001$). In contrast, the incidence of dementia as the cause of death was higher among CSDH patients compared with the reference group after the first year, and increased over time reaching statistical difference from 1 to 10 years ($p < 0.001$; Fig. 2).

Discussion

Summary of the key findings

In our large population-based cohort, patients with CSDH had excess mortality, which increased over time from 9% at 1 year to 48% at 20 years after CSDH diagnosis. A subgroup of patients with no comorbidities had no excess mortality. The most important factors related to excess mortality were neurological disability at admission and at discharge. Age over 80 years almost doubled, warfarin almost tripled, and chronic alcohol abuse almost quintupled the risk of death after CSDH. Hematoma localization (unilateral/bilateral) or thickness were not relative risk factors nor was hematoma recurrence. In the median follow-up time of 4.8 years, there were 710 deaths, of which 6% were caused by SDH. The most common cause of

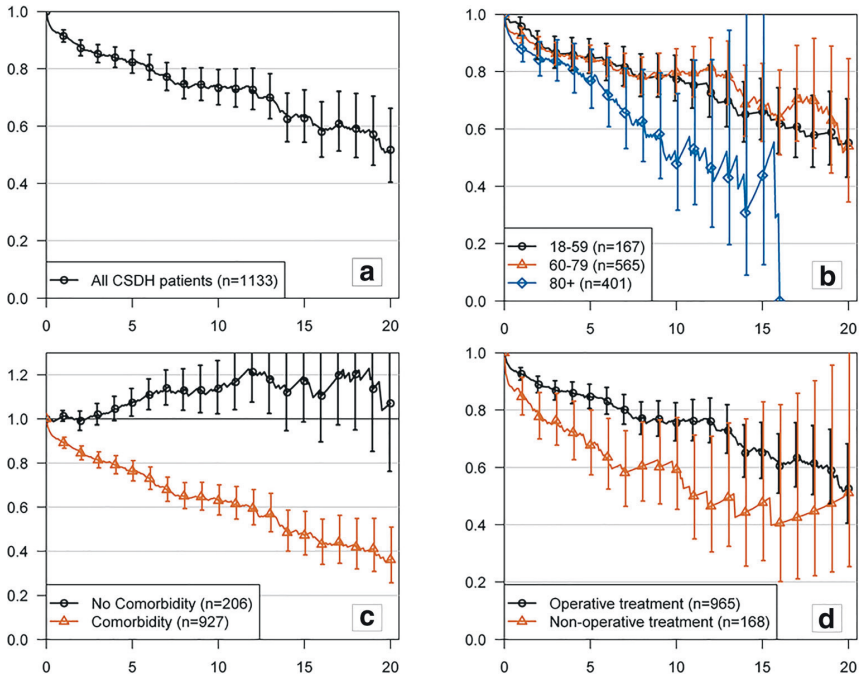

Fig. 1 Excess mortality of chronic subdural hematoma patients. Cumulative relative survival ratios (with 95% confidence intervals) illustrating excess mortality of the CSDH patients compared with the matched general population; entire cohort (**a**), stratified by age groups (**b**), by prevalence of comorbidity (**c**), and by treatment group. The horizontal line at 1.0 represents the survival of the matched general population and curves below that line represent excess mortality of the study population. The vertical line shows follow-up time (years)

death was dementia, which was significantly more common as a cause of death among the CSDH patients than in the reference group. As a cause of death, dementia occurred later in CSDH patients than in the reference group.

Comparison of the current findings to prior literature

Miranda et al. observed excess mortality up to 1 year beyond diagnosis, but after that, life expectancy was equivalent with the general population [29]. Treatment group, size or laterality of subdural hematoma, and antithrombotic medication use were not associated with the mortality rate. Dumont and colleagues showed that patients with CSDH had worse survival than expected in every age group, and patients undergoing surgical drainage of CSDH (median survival 5.5 years) had significantly longer survival compared with patients not undergoing surgical drainage (2.3 years) [11]. The authors speculated that there can be selection bias, because the patients most likely to improve from surgery were offered surgical treatment. Mortality after CSDH was highest in the oldest patients over 85 years old, but the standardized mortality ratio was lower than in any other age group. Manickam et al. reported excess mortality continuing throughout a prolonged follow-up (median 5.2 years) as peers lived 12.4 years longer [25]. A prospective, randomized study by Santarius et al. revealed that among operatively treated patients, CSDH drainage significantly reduced 6-month mortality from 18 to 9% [33]. Additionally, a recent 5-year follow-up analysis of the aforementioned study showed a significant survival advantage for drainage as the relative survival in the no drain group was 77.6% compared with 89.8% in the drain group [16].

In our study, CSDH patients had excess mortality in every age group. The excess mortality was more pronounced in the age group of ≥ 80 years. The risk of excess mortality was higher in the non-operative group than in the operative group (RER 1.56) even though the neurological condition at admission was better among non-operatively treated patients, and they were not predisposed to surgical complications. The reason behind this is probably that the burden of comorbidities was somewhat higher among non-operatively treated patients.

In contrast to the study by Santarius, CSDH recurrence was not a risk factor for excess mortality among our study patients. In fact, the patients with recurrence had a lower mortality at least during the first 2 years. We speculate that this might be explained by more frequent medical attention (follow-ups and re-operations) for patients that are in better general health before their first CSDH. Patients with more comorbidities are less likely to undergo a second operation. Even so, our 6-month overall mortality rate (10%) was comparable with the findings by Santarius and colleagues [33]. Also, our relative survival at 5 years was similar (82%) than analyzed by Guilfoyle [16]. The mortality differences between studies are most likely due to differences in case ascertainment, healthcare systems, and population-related life expectancies.

Our study is in line with the previous studies demonstrating that neurological disability at discharge is strongly associated

Table 4 Relative excess risk of death (RER) estimates and 95% confidence intervals for each subgroup of the 1133 chronic subdural hematoma patients adjusted for age, gender, and follow-up time

	Total sample n = 1133		RER	95% CI
	n	%		
Sex				
Men	736	65.0	1	Ref
Women	397	35.0	1.17	0.82–1.65
Age at CSDH diagnosis, years				
18–59	167	14.7	1	Ref
60–79	565	49.9	1.05	0.68–1.61
≥ 80	401	35.4	1.83	1.11–3.02
Chronic alcohol abuse				
No	1007	88.9	1	Ref
Yes	126	11.1	4.47	2.88–6.95
Traumatic etiology				
Yes	672	59.3	1	Ref
No	461	40.7	1.69	1.20–2.38
Antithrombotic medication				
None	655	57.8	1	Ref
Antiplatelet	268	23.7	1.20	0.72–2.01
Warfarin	187	16.5	2.94	1.91–4.54
Warfarin AND antiplatelet	23	2.0	3.24	1.35–7.75
Admission GCS				
13–15	1007	88.9	1	Ref
9–12	91	8.0	3.53	2.35–5.32
3–8	35	3.1	5.71	3.47–9.41
Admission mRS				
0–3	580	51.2	1	Ref
4–5	553	48.8	4.93	3.12–7.80
Hematoma localization				
Unilateral	876	77.3	1	Ref
Bilateral	257	22.7	0.74	0.46–1.18
Hematoma thickness, mm (missing $n = 23$)				
≤ 15 mm	376	33.2	1	Ref
16–25	474	41.8	0.69	0.48–1.01
> 25	260	22.9	0.59	0.34–1.01
Operative treatment				
Yes	965	85.2	1	Ref
No	168	14.8	1.77	1.18–2.65
No[1]	161	14.2	1.56	1.01–2.41
Discharge GCS[2]				
13–15	942	97.6	1	Ref
9–12	9	0.9	14.84	6.64–33.18
3–8	14	1.5	98.30	39.35–245.56
Discharge mRS[2]				
0–3	727	75.3	1	Ref
4–5	238	24.7	8.31	5.48–12.58
Recurrent hematoma[2]				
No	692	71.7	1	Ref
Yes	273	28.3	0.78	0.48–1.26

RER Relative excess risk of death, *CI* Confidence interval, *Ref* Reference, *GCS* Glasgow Coma Scale score, *mRS* Modified Rankin Scale score

[1] The patients ($n = 7$) who were not offered surgery because they presented in a moribund state were not included

[2] Includes only operatively treated patients

to long-term survival [11, 25, 29]. This is no surprise because it correlates to functional status, which has been recognized to have a great impact on life expectancy in general [20]. However, it is difficult to differentiate the effects of underlying comorbidities from the effects of CSDH on long-term survival. A subgroup of patients ($n = 206$) with no comorbidities

survived better than the matched general population. In addition, hematoma bilaterality, thickness, or recurrence were not relative risk factors. Accordingly, even a large recurring CSDH may not affect the long-term survival by itself. Therefore, the patient-related variables are probably more important than the CSDH itself. Based on this data, it seems likely that the comorbidities are the cause of excess mortality rather than CSDH itself. Some patients are frail due to age-associated brain atrophy and other comorbidities, and CSDH seems to be a sentinel health event, a harbinger of subsequent morbidity and mortality, for this group of patients [3, 11, 29]. In contrast, patients with no comorbidities are probably healthier than the matched general population.

Hence, the excess mortality after diagnosis of CSDH might be reduced by more assertively treating the comorbidities, of which the most common were vascular diseases, diabetes, and chronic alcohol abuse. It is also known, that the hospitalization of older people decreases daily living functioning [7]. For this reason, it has been proposed that already perioperative care should be optimized by a multidisciplinary approach and by promoting early rehabilitation [35].

Antithrombotic drug use is common among CSDH patients and is speculated to attribute to the greater incidence of CSDH among elderly [6, 8, 15, 23, 30]. In our study, the use of warfarin, but not the use of antiplatelets, was a relative risk factor for excess mortality. This could reflect the increased risks of warfarin in the context of CSDH or be explained by the fact that the baseline diseases treated with antiplatelet drugs are not as severe as with warfarin. Similarly, chronic alcohol abuse was a relative risk factor for excess mortality after CSDH, but it is a risk factor for excess mortality also independently [9, 36]. Moreover, non-traumatic etiology was a relative risk factor for excess mortality among CSDH patients. This could be at least partly explained by the more common use of antithrombotic medication by patients with non-traumatic than traumatic etiology (47% vs. 39%), and the underlying medication-suggesting comorbidities. Additionally, CSDH might be a manifestation of degenerative or inflammatory disease rather than trauma [14]. In other words, aging, longstanding and ongoing alcohol abuse, and worse baseline general and neurological health all appear to contribute to greater mortality following CSDH.

The most important reason for the greater incidence of CSDH among the elderly has been speculated to be attributed to brain atrophy [22, 24, 37]. Dementia has been linked to brain atrophy [5]. At the time of diagnosis of CSDH, the prevalence of dementia in our CSDH patients (12% in patients aged 70 years or older) was similar as the prevalence in

Table 5 The causes of death until the end of 2017 of the 1133 patients with chronic subdural hematomas between 1990 and 2015 in Pirkanmaa, Finland. The causes of death in the matched reference group between 1990 and 2015 are presented for comparison

	Total sample $n = 1133$		Men $n = 736$		Women $n = 397$		Operative treatment $n = 965$		Non-operative treatment $n = 168$		Causes of death in the matched reference group $n = 4532$	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age, years (median, IQR)	76	67–83	75	65–81	79	70–85	76	66–82	79	68–86	76	67–83
Follow-up time, years												
Median	4.8		5.1		4.6		5.2		3.3		6.4	
Range	0–27		0–26		0–27		0–27		0–21		0–28	
No. of deaths	710	62.7	449	61.0	261	65.7	609	62.3	101	60.1	1918	42.3
Age at death, median, IQR	84	76–89	83	74–88	86	80–91	84	76–89	85	79–90	84	78–88
Ischemic cardiac disease	143	20.1	103	22.9	40	15.3	122	20.0	21	20.8	473	24.7
Cerebrovascular disease	90	12.7	54	12.0	36	13.8	80	13.1	10	9.9	216	11.3
Cerebral hemorrhage	18	2.5	13	2.9	5	1.9	13	2.1	5	5.0	23	1.2
Cerebral ischemia	72	10.1	41	9.1	31	11.9	67	11.0	5	5.0	167	8.7
Cancer	91	12.8	64	14.3	27	10.3	80	13.1	11	10.9	370	19.3
Dementia and Alzheimer's disease	146	20.6	70	15.6	76	29.1	121	19.9	25	24.8	278	14.5
Pulmonary disease	34	4.8	24	5.3	10	3.8	29	4.8	5	5.0	119	6.2
Pneumonia	16	2.3	9	2.0	7	2.7	15	2.5	1	1.0	45	2.3
Trauma	75	10.6	50	11.1	25	9.6	65	10.7	10	9.9	58	3.0
Accidental falls	41	5.8	25	5.6	16	6.1	36	5.9	5	5.0	33	1.7
Subdural hematoma, traumatic	38	5.4	25	5.6	13	5.0	33	5.4	5	5.0	9	0.5
Subdural hematoma, non-traumatic	4	0.6	4	0.9	0		3	0.5	1	1.0	1	0.05
Unknown	0		0		0		0		0		20	1.0

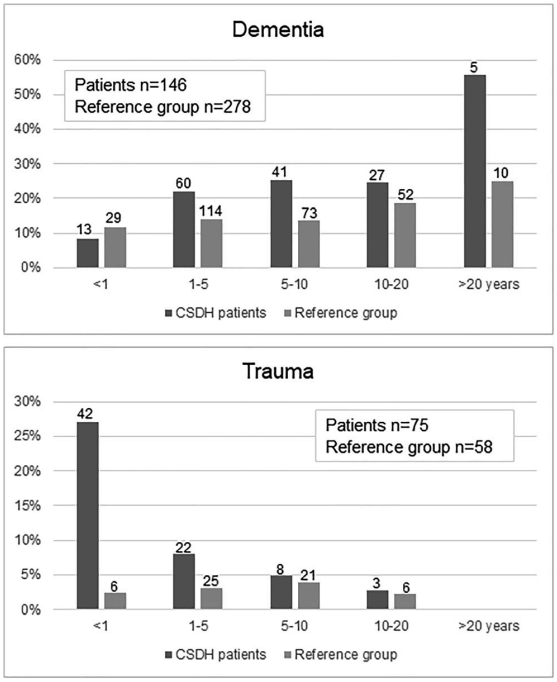

Fig. 2 Dementia and trauma as a cause of death stratified by survival time. The CSDH patients are compared with the matched reference group. The percentages represent all the deaths during the time period. The number of deaths 710 among CSDH patients, and 1918 among the reference group

Western Europe reported by the World Alzheimer report 2015 [31]. As a cause of death, dementia was more prevalent in patients with CSDH than in our reference group. The difference was seen after the first year and was more pronounced in the later years. Additionally, the excess mortality related to CSDH increases with time. Our results support the idea that CSDH may be a risk factor for dementia. This could be explained by Bin Zahid and colleagues' observation that CSDH is related to a significant increase in the degree of subsequent brain atrophy [4]. It seems that brain atrophy is a risk factor for CSDH, which in turn accelerates neurodegeneration and increases the risk of dementia. Further long-term prospective studies are needed to verify this association.

Strengths and limitations

Our series represents the most extensive non-register-based study of consecutive CSDH cases treated in one neurosurgical department. Although retrospective in nature, the population-based setting makes it less prone to selection bias. Moreover, all the data was collected by one of the authors (M.R.). Our study gives a reliable population-based estimate of the CSDH-associated excess mortality based on the comparison with a matched general population.

This study has several limitations. ICD-codes were used to retrospectively identify all the patients of interest. There is a possibility that some cases were not recognized due to incomplete or incorrect ICD-coding. It is likely that all the patients undergoing surgery were identified, but the ICD-coding can be incomplete among the non-operatively treated patients, as a neurosurgeon has only been consulted on these cases. Neuroimaging was not reviewed, and there can be inconsistencies in reporting the hematoma thickness. In addition, the distinction between subacute and chronic SDH is not always obvious, both in relation to time and neuroradiological characteristics. No definition of CSDH is universally accepted [18]. Subacute SDHs were excluded from this study, because this hematoma subtype is considered to represent an entity of its own [2, 12, 21]. Additionally, autopsies were not performed on all of the deceased patients, and some of the causes of deaths might not be correct. Also, adjustments to the statistical analyses were limited because we did not have access to comorbidity data from the matched general population. However, it is reasonable to assume that controls and patients had similar comorbidities.

Future CSDH research should focus on preventive measures that take into account prior health conditions and fall-related injury risk factors that predispose to CSDH. Frailty, functionality, dependency, and comorbidity should be of special interest as these issues are prognosticators of general disability, hospital readmission, and mortality.

Conclusions

Patients with CSDH have long-term excess mortality, which is evident up to at least 20 years after diagnosis. Patient-related characteristics, especially chronic alcohol abuse, antithrombotic medication use, and neurological disability both at admission, and at discharge, have a strong association with excess mortality, whereas specific CSDH-related findings do not. A subgroup of patients with no comorbidities had no excess mortality. The most common cause of death was dementia, which was more common as a cause of death in patients with CSDH than in the reference group after the first year. Consequently, there can be a two-way correlation between CSDH and dementia.

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Compliance with ethical standards

Conflict of interest Dr. Luoto has received funding from the Government's Special Financial Transfer tied to academic research in Health Sciences (Finland), the Emil Aaltonen Foundation, and Finnish Medical SocietyDuodecim. Dr. Iverson acknowledges unrestricted

philanthropic support from the Mooney-Reed Charitable Foundation, Heinz Family Foundation, ImPACT Applications, Inc., and Spaulding Research Institute. He serves as a strategic scientific advisor for BioDirection, Inc. The other authors report nothing to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (the Ethics Committee of the Pirkanmaa Hospital District, approval code R12082) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All data was collected retrospectively without contacting the patients. For this type of study formal consent is not required.

Disclaimer The sponsors had no role in the design or conduct of this research.

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PUBLICATION III

Chronic Subdural Hematoma - Incidence, Complications, and Financial Impact

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ORIGINAL ARTICLE - NEUROSURGERY GENERAL

Chronic subdural hematoma—incidence, complications, and financial impact

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Abstract

Objective To examine the population-based incidence, complications, and total, direct hospital costs of chronic subdural hematoma (CSDH) treatment in a neurosurgical clinic during a 26-year period. The aim was also to estimate the necessity of planned postoperative follow-up computed tomography (CT).

Methods A retrospective cohort (1990–2015) of adult patients living in Pirkanmaa, Finland, with a CSDH was identified using ICD codes and verified by medical records (n = 1148, median age = 76 years, men = 65%). Data collection was performed from medical records. To estimate the total, direct hospital costs, all costs from hospital admission until the last neurosurgical follow-up visit were calculated. All patients were followed until death or the end of 2017. The annual number of inhabitants in the Pirkanmaa Region was obtained from the Statistics Finland (Helsinki, Finland).

Results The incidence of CSDH among the population 80 years or older has increased among both operatively (from 36.6 to 91/100,000/year) and non-operatively (from 4.7 to 36.9/100,000/year) treated cases. Eighty-five percent (n = 978) underwent surgery. Routine 4–6 weeks' postoperative follow-up CT increased the number of re-operations by 18% (n = 49). Most of the re-operations (92%) took place within 2 months from the primary operation. Patients undergoing re-operations suffered more often from seizures (10%, n = 28 vs 3.9%, n = 27; $p < 0.001$), empyema (4.3%, n = 12 vs 1.1%, n = 8; $p = 0.002$), and pneumonia (4.7%, n = 13 vs 1.4%, n = 12; $p = 0.008$) compared with patients with no recurrence. The treatment cost for recurrent CSDHs was 132% higher than the treatment cost of non-recurrent CSDHs, most likely because of longer hospital stay for re-admissions and more frequent outpatient follow-up with CT. The oldest group of patients, 80 years or older, was not more expensive than the others, nor did this group have more frequent complications, besides pneumonia.

Conclusions Based on our population-based study, the number of CSDH patients has increased markedly during the study period (1990–2015). Reducing recurrences is crucial for reducing both complications and costs. Greater age was not associated with greater hospital costs related to CSDH. A 2-month follow-up period after CSDH seems sufficient for most, and CT controls are advocated only for symptomatic patients.

Keywords Chronic subdural hematoma · Recurrence · Follow-up · Health care costs · Excess mortality · Causes of death · Survival

This article is part of the Topical Collection on *Neurosurgery general*

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Introduction

Chronic subdural hematoma (CSDH) is a common disease in neurosurgical practice among elderly patients and it is associated with substantial morbidity and mortality [5, 10, 25, 27, 41]. The incidence of CSDH has increased during the last decades [1, 4, 14, 18]. We have previously published the epidemiological findings of our Finnish CSDH cohort (1990–2015), in which the overall incidence doubled from 8.2 to 17.6/100,000/year [33], and nearly tripled among the population 80 years or older. The global population of people aged 80 and older is expected to more than triple between 2015 and 2050 [16]. Consequently, there is a growing healthcare burden related to CSDH. Only a few studies have described the financial impact of CSDH [12, 13, 35].

Surgical treatment is recommended in CSDH patients with neurological symptoms, and the preferred surgical technique is burr-hole drainage [26, 37]. Recurrence is common, ranging from approximately 5 to 30%, and a reduced recurrence rate is observed with external subdural drains [22, 31, 40]. Routine postoperative CT can potentially detect recurrent CSDH before clinical deterioration occurs [9]. A concern has been raised, however, that unnecessary revision surgery and increased costs may outweigh this benefit [30]. The usefulness of routine follow-up CT to predict symptomatic recurrence is questionable [35]. There are no guidelines on how, or for how long, CSDH patients should be followed. In our neurosurgical unit, an outpatient clinic follow-up visit with a head CT 4 to 6 weeks after the operation is a routine.

The objective of this study was to examine the incidence, complications, and total, direct hospital costs of CSDH treatment from hospital admission until the last follow-up visit in a neurosurgical clinic during a 26-year study period. The aim was also to evaluate the necessity of pre-scheduled routine follow-up CT after CSDH. A large unselected, population-based CSDH patient cohort from 1990 to 2015 was analyzed. We hypothesized that costs are high and increasing because the incidence of CSDH is increasing, re-operations are frequent, and the duration of overall treatment (including follow-up visits) is long. We also hypothesized that there would be a substantial percentage of patients that would have asymptomatic post-operative recurrence of their hematomas visible on follow-up CT.

Methods

Material and ethical aspects

The study was conducted in the Department of Neurosurgery at the Tampere University Hospital (Tampere, Finland). Patients included were (1) residents in the Pirkanmaa Region, (2) aged 18 years or over with no upper limit, and (3) diagnosed with CSDH between 1990 and 2015. The cases were retrospectively identified using the hospital's patient administrative databases, including International Classification of Diseases (ICD) codes for traumatic and non-traumatic subdural hematomas (SDHs; ICD-10 codes: S06.5 and I62.0; ICD-9 codes: 432.1, 852.2 and 852.3). Verified cases were classified by SDH type (acute, subacute, chronic, and hygroma) by reviewing all the medical records. Exclusion criteria were acute or subacute SDH (< 3 weeks after head trauma), hygroma (a collection of subdural cerebrospinal fluid without any signs of blood), and any form of intracranial surgery within 12 months preceding the CSDH diagnosis.

The Pirkanmaa Region is a geographically well-defined area with both rural and urban areas that holds one of Finland's five neurosurgical departments (Department of Neurosurgery, Tampere University Hospital, Tampere, Finland). All neurosurgical cases from this area are referred to the Tampere University Hospital, with a catchment population of one million inhabitants. To investigate the population-based burden of CSDH, we collected data on patients with CSDHs who were residents of the Pirkanmaa Region. Over 9% of the Finnish population lives in the Pirkanmaa Region. The population increased from 427,223 in 1990 to 506,114 in 2015. The population over 80 years old almost doubled from 13,565 to 26,417 during the study period. The annual number of inhabitants in the Pirkanmaa Region was obtained from the Statistics Finland (Helsinki, Finland).

The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (ethical code: R12082). All data was collected retrospectively without contacting the patients; therefore no, written informed consent was obtained or required.

Data collection

A detailed and structured data collection was performed from medical records. Results from imaging reports were coded; CT scans or MR images were not examined directly. Patients were stratified into three groups according to age: (i) 18–59 years, (ii) 60–79 years, and (iii) ≥ 80 years. The study period was divided into five time periods: (i) 1990–1995, (ii) 1996–2000, (iii) 2001–2005, (iv) 2006–2010, and (v) 2011–2015. CSDH recurrence was defined as an ipsilateral hematoma needing re-operation within 2 years of the original operation. All patients were followed until death or the end of year 2017.

Cost data

To estimate the direct, total hospital costs from admission until the last follow-up visit, we calculated all costs for the

whole treatment period, including operations and number of days spent in the neurosurgical ward, recovery room or ICU, emergency department visits related to the CSDH, laboratory and radiologic costs, and follow-up visits. The possible period of rehabilitation following treatment in the neurosurgical ward was not included the financial calculations. The unit costs (presented in Table 3) were then multiplied by the number of cost factors of each patient. Because of the long study period, it was not possible to get all of the individual patient's costs directly from our hospitals' invoicing department. Instead, all costs were calculated from the latest 2018–2019 data from hospital administration and catalogues for in-hospital use.

When comparing the results from earlier studies, costs were first adjusted to year 2018 value by consumer price index of the relevant country [38, 39], and then converted to FIN EUR using the latest year 2018 Purchasing Power Parities (PPP) of that country. PPP tries to equalize the purchasing power of different currencies, by eliminating the differences in price levels between countries.

Statistical analyses

SPSS (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, USA) was used for data analyses. Descriptive statistics [frequency (n), percentage, median, interquartile range, range] were used to describe variable and subgroup characteristics. The chi-square test was used to compare differences between groups. The statistical significance level was set at $p < 0.05$. A Kaplan–Meier analysis was used for the time of first surgery to recurrence, and the hazard ratio was computed based on a Cox regression. Observations for event-free patients were censored at the time of death.

Results

Characteristics

A total of 1133 unique patients with CSDH were identified. Patients with CSDH were considered new cases if 2 years had elapsed following primary treatment or if they had a new contralateral hematoma (n = 15). During the study period, 14 patients (1.2%) underwent new contralateral CSDH evacuation and only one patient (0.09%) needed operative treatment for the same sided CSDH after 5 years of index CSDH. Therefore, the total number of cases was 1148, and 748 (65%) were men. The median age for CSDH diagnosis was 76 years, increasing from 73 to 79 years during the 26-year period. Mortality was 3.4% in 30 days and 14% in 1 year. The characteristics of the whole sample and treatment subgroups are presented in Table 1 and Fig. 1. We have previously published the details of CSDH patients from this same patient cohort stratified by gender, age groups, and time periods [33].

Incidence of CSDH stratified by treatment groups

From the time period of 1990–1995 to 2011–2015, the overall incidence of operatively treated CSDH in adults almost doubled from 7.2 to 13.4/100,000/year. The incidence remained quite stable among those under the age of 70 but increased 2.5 times for ≥ 80-year olds from 36.6 to 91/100,000/year. Prior to the 2001–2005 time period, only a small number of non-operatively treated patients were diagnosed. The incidence of non-operatively treated CSDH for those 80 years and older increased from the beginning of the millennium reaching 36.9/100,000/year (2011–2015). The incidence rates stratified by treatment groups are presented in Fig. 2.

Non-operatively treated patients

Fifteen percent of cases (n = 170) were treated non-operatively. For most cases, the reason for non-operative treatment was that the CSDH did not cause significant neurological signs or symptoms. A very small number of patients were not offered surgery because they presented in a moribund state (n = 7). Non-operative treatment included discontinuation of possible antithrombotic medication, active mobilization, and follow-up CT scans (routinely or for emerging new symptoms). The median number of CT scans performed was 1.5 (min–max = 1–5). The median number of outpatient clinic follow-up visits was 0 (min–max = 0–4).

Operatively treated patients

For the total sample, 978 (85%) were treated operatively. Median time from CT to surgery was 0 days, and 588 of patients (60%) were operated on the same day, 294 (30%) on day 1, and 50 (5%) on day 2 from diagnosis. Only 5% of patients were operated on day 3 or more from diagnosis. There were 53 patients (5%) who were first treated non-operatively but then underwent surgery when the CSDH increased in size (median time from first CT to surgery was 24 days). The operative treatment strategy has remained practically unchanged during the 26-year study period. The only evolution in the treatment has been the more frequent use of subdural drains during the last years of the study period. Most operations were performed under local anesthesia (n = 839; 86%) via one burr hole, and the hematoma was evacuated through irrigation. A subdural drain was inserted in 59 patients (6%). The drain was kept below the head level with no suction for 24–48 h. Only one patient underwent craniotomy as the primary surgery. The patients were actively mobilized directly after the operation. Antiepileptic drugs were not prescribed routinely. Most patients (72%) were seen in an outpatient

Table 1 Characteristics of all patients with chronic subdural hematoma in Pirkanmaa that were treated at the Tampere University Hospital between 1990-2015.

	Total sample n = 1148		Non-operative treatment *n* = 170		Operative treatment *n* = 978		*p* value
	n	%	*n*	%	*n*	%	
Age, median, IQR (years)	76	67–83	79	68–86	76	66–82	0.005
Men	748	65.2	104	61.2	644	65.8	0.24
Traumatic etiology	679	59.1	109	64.1	570	58.3	0.15
Comorbidity	880	76.7	132	77.6	748	76.5	0.74
Chronic alcohol abuse	126	11.0	20	11.8	106	10.8	0.72
Medication							0.63
Antiplatelet	270	23.5	36	21.2	234	23.9	0.34
Warfarin	191	16.6	27	15.9	164	16.8	0.57
Warfarin AND antiplatelet	23	2.0	2	1.2	21	2.1	0.36
Neurological deficit (hemiparesis or dysphasia)	573	49.9	18	10.6	555	56.7	< 0.001
Admission mRS 0–3	585	51.0	122	71.8	463	47.3	< 0.001
Hematoma characteristics							
Left sided	478	41.6	71	41.8	407	41.6	0.67
Bilateral	257	22.4	34	20.0	223	22.8	0.42
Mortality*							
30 days	38	3.4	13	7.7	25	2.6	0.001
6 months	108	9.5	26	15.4	82	8.5	0.005
1 year	155	13.7	35	20.7	120	12.4	0.004
2 years	254	22.4	54	32.0	200	20.7	0.001

IQR interquartile range, *mRS* modified Rankin scale

* Patients with multiple CSDH episodes were excluded (*n* = 15)

clinic and underwent follow-up CT 4 to 6 weeks after the operation. In the case of residual hematoma needing no re-operation, patients were followed monthly until the hematoma resolved significantly. The median number of CT scans performed was 3 (min–max = 1–13), and the total number was 3043. The median number of outpatient follow-up visits was 1 (min–max = 0–11), and the total number was 1463.

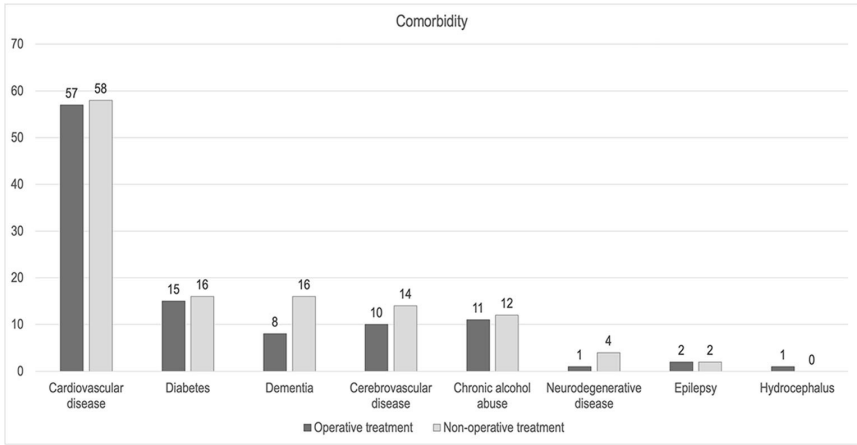
Recurrence

A recurrent hematoma was treated surgically in 278 cases (28%, median age 76 years). The recurrent hematoma was symptomatic in 229 (82%) of the cases, and operated because follow-up CT revealed a large CSDH in 49 of patients (18%). Twenty-two patients (8% of the recurrences) underwent a second surgery during the primary admission. A re-operation was done on 114 symptomatic patients (41% of the recurrences) before their scheduled outpatient clinic visit. The first scheduled outpatient visit with CT led to a re-operation in 108 patients (39% of the recurrences). Of these 108 patients, 70 (65%) had symptoms and 38 (35%) were symptom free. The median time to recurrence was 25 days (min–max = 0–304 days, IQR = 14–35). Most of the recurrences were treated operatively within 30 days (63%) or within 2 months (92%) after the primary operation. Only two patients underwent surgery after 6 months (285 days and 304 days) from their primary operation.

The cumulative proportion of recurrences is shown in Fig. 3. The differences between the age group of 18–59 years, and both the age groups of 60–79 years (HR = 2.02; 95% CI = 1.32–3.08, $p = 0.001$) and ≥ 80 years (HR = 1.79; 95% CI = 1.15–2.77, $p = 0.01$), were significant. The recurrence rate among patients treated with drains was significantly lower than for patients with no drain (17% vs 29%, $p = 0.04$). Almost all patients with a drain (48/59; but still only 18% of all surgically treated patients) were from the last study period (2011–2015). During this period, the recurrence rate was 25%, which was non-significantly lower than the rate of previous years combined (HR = 0.79; 95% CI = 0.60–1.04, $p = 0.10$).

Complications related to operative treatment of CSDH

The most common complication was a seizure occurring in 4.8% of the total sample of patients undergoing surgery. Acute intracranial hemorrhage was rare; there were 11 cases of acute subdural hematoma (1.1%) and 6 cases of



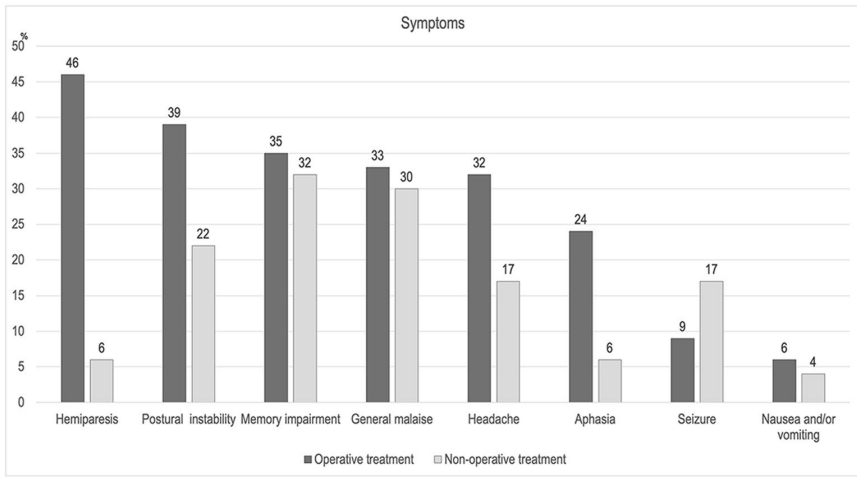
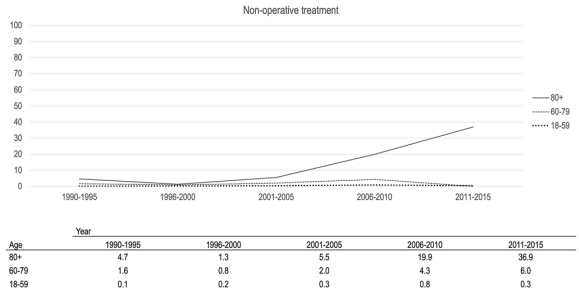


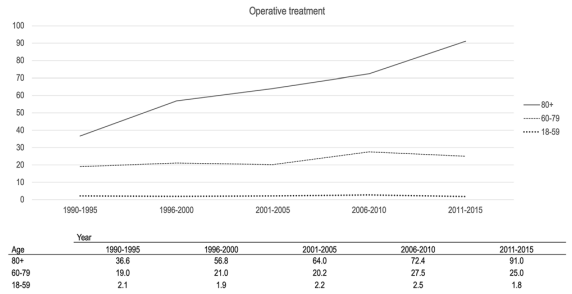
Fig. 1 Comorbidities and symptoms of patients with chronic subdural hematoma stratified by treatment group

intracerebral hematoma (0.6%). Nine (0.9%) out of these 17 required emergency craniotomies, and two (0.2%) patients died. Postoperative infection at the site of surgery was diagnosed in 29 (3.0%), and 20 (2.0%) patients underwent a second surgery because of an empyema.

The only complication with a significant difference between the age groups was pneumonia occurring more often among the oldest patients (≥ 80-years, $p = 0.02$). Patients undergoing a second surgery suffered more often from seizures (10%, $n = 28$ vs 3.9%, $n = 27$; $p < 0.001$), empyema (4.3%, $n = 12$ vs 1.1%, $n = 8$; $p = 0.002$), and pneumonia (4.7%, $n = 13$ vs 1.4%, $n = 12$; $p = 0.008$) compared with patients with no recurrence. The complications are shown in Table 2.



Age	Year 1990-1995	1996-2000	2001-2005	2006-2010	2011-2015
80+	4.7	1.3	5.5	19.9	36.9
60-79	1.6	0.8	2.0	4.3	6.0
18-59	0.1	0.2	0.3	0.8	0.3



Age	Year 1990-1995	1996-2000	2001-2005	2006-2010	2011-2015
80+	36.6	56.8	64.0	72.4	91.0
60-79	19.0	21.0	20.2	27.5	25.0
18-59	2.1	1.9	2.2	2.5	1.8

Fig. 2 Incidence (n/100,000) of chronic subdural hematoma stratified by treatment group in different age groups during the study period between 1990–2015 in Pirkanmaa, Finland

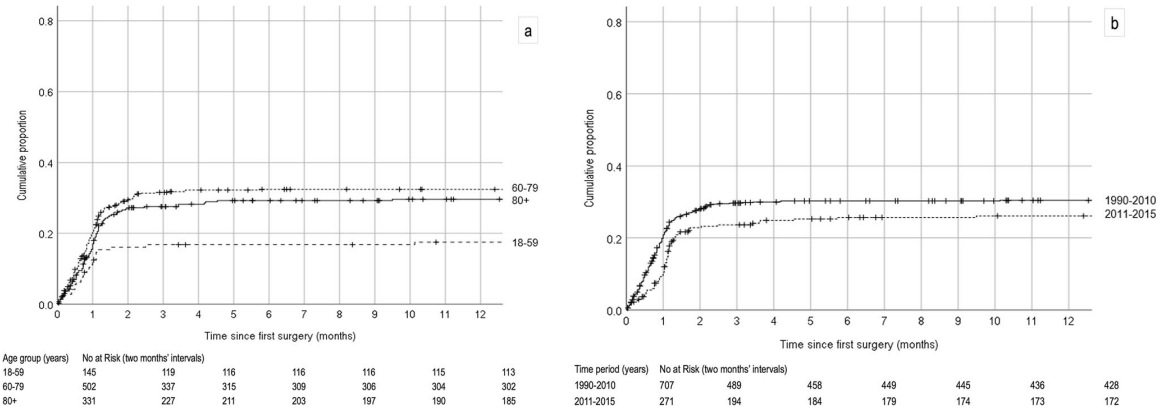


Fig. 3 Cumulative proportion of recurrences shown as Kaplan–Meier analysis in different age groups (**a**) and time periods (**b**). Observations for event-free patients were censored at the time of death

Length of hospital stay and discharge

Most non-operatively treated patients were not treated in our neurosurgical ward, so the median length of hospital stay was 0 days (min–max = 0–4 days). The median length of hospital stay for surgically treated patients was 3 days (min–max = 1–33 days), and 4 days (min–max = 1–46 days) during the re-admission for patients with a recurrent hematoma. The number of days the surgically treated patients spent in our neurosurgical ward decreased during the study period from 5 days (1990–1995) to 3 days (2011–2015). The proportion of patients discharged home did not change significantly; it was 49% in 1990–1995 and 43% in 2011–2015 ($p = 0.25$). The rate of home discharge was as follows: 18–59 years, 64%; 60–79 years, 50%, and ≥ 80 years, and 19% ($p < 0.001$).

Hospital costs

The mean total cost from the first hospital admission until the last follow-up visit per patient treated surgically was 5250 € (median 3810; €; IQR = 2930–5900 €) (Table 3). It was 3820 € (median 3370 €; IQR = 2870–4100 €) per patient for those with no

Table 2 Morbidity, perioperative complications, and mortality in patients with an operatively treated chronic subdural hematoma

	Total $n = 978$		Age group						p value	Recurrence				p value
			18–59 $n = 145$		60–79 $n = 502$		≥ 80 $n = 331$			No $n = 700$		Yes $n = 278$		
	n	%	n	%	n	%	n	%		n	%	n	%	
Comorbidity	748	76.5	74	51.0	377	75.1	297	89.7	< 0.001	534	76.3	214	77.0	0.82
Complications														
Seizures	55	5.6	5	3.4	33	6.6	17	5.1	0.32	27	3.9	28	10.1	< 0.001
Acute subdural hematoma	11	1.1	1	0.6	8	1.4	2	0.5	0.30	6	0.9	5	1.8	0.21
Intracerebral hemorrhage	6	0.6	0	0	5	0.9	1	0.2	0.24	3	0.4	3	1.1	0.24
Cerebrovascular infarction	6	0.6	1	0.6	3	0.5	2	0.5	1.0	3	0.4	3	1.1	0.24
Surgical site infection	29	3.0	1	0.7	20	4.0	8	2.4	0.92	15	2.1	14	5.0	0.016
Empyema	20	2.0	1	0.7	16	3.2	3	0.9	0.05	8	1.1	12	4.3	0.002
Pulmonary embolus	2	0.2	0	0	1	0.2	1	0.3	0.80	1	0.1	1	0.4	0.50
Pneumonia	25	2.6	0	0	11	2.2	14	4.2	0.020	12	1.7	13	4.7	0.008
Discharge to home	409	41.8	93	64.1	253	50.4	63	19.0	< 0.001	291	41.6	118	42.4	0.80
Mortality														
30 days	25	2.6	2	1.4	12	2.4	11	3.4	0.43	23	3.3	2	0.7	0.022
6 months	82	8.5	4	2.8	38	7.6	40	12.3	0.002	66	9.5	16	5.9	0.06
1 year	120	12.4	6	4.2	50	10.1	64	19.8	< 0.001	92	13.3	28	10.3	0.20
2 years	200	20.7	14	9.7	84	16.9	102	31.5	< 0.001	145	21.0	55	20.1	0.77

Table 3 Costs related to treatment of chronic subdural hematoma in Tampere University Hospital during the study period between 1990-2015

	Non-operative treatment	Operative treatment	Cost á
No of operations	0	1 (1–8)	982 €/h*
Recovery room stay 2 h in the case of general anesthesia	NA	0 (0–3)	290 €/2 h
ICU stay in the case of craniotomy €/day	NA	0 (0–2)	1376
Hospital stay in neurosurgical unit during primary admission, days €/day	0 (0–4)	3 (1–33)	440
IQR	0	3–5	
Hospital stay in neurosurgical clinic during re-admission, days €/day	NA	4 (1–46)	440
IQR	NA	3–8	
CT scans, median, *n*	1.5 (1–5)	3 (1–13)	147 €
Laboratory tests taken at the time of diagnosis, re-admission and/or complication	1	1 (1–10)	50 €
Emergency department visits, *n***	1 (1–2)	1 (1–5)	111 €
Outpatient follow-up visits, *n*	0 (0–4)	1 (0–11)	174 €
Costs in Euros per patient, min–max	310–2,710	2,170–33,420	
Mean	580	5,250	
Median	455	3,810	
IQR	310–630	2,930–5,900	
No recurrence	NA	2,170–28,980	
Mean	NA	3,820	
Median	NA	3,370	
IQR	NA	2,870–4,100	
Recurrence	NA	3,640–33,420	
Mean	NA	8,850	
Median	NA	7,110	
IQR	NA	5,840–9,820	

Data are shown as median (min–max); *IQR* interquartile range; *NA* not applicable

*The mean operation theatre time for burr hole trephination of CSDH was 1 h, and for craniotomy 3 h

**Patients were assumed to be diagnosed in emergency department

recurrence, and 8850 € (median 7110 €; IQR = 5840–9820 €) per patient for those with recurrence. The difference in mean hospital costs of 5030 € reflects 132% higher costs for the patients with recurrence. The mean cost for patients with drains was 4100 € (median 3370 €; IQR = 2930–6050 €) and for those with no drains 5320 € (median 3930 €; IQR = 2610–5500 €). The difference in mean treatment costs of 1220 € reflects 30% higher costs for patients with no drains compared with patients with drains.

Among surgically treated patients, the 60–79 years old age group had the greatest costs; the mean cost was 5710 € (median 4050 €; IQR = 3130–6570 €), while the cost for those in the 18–59 years group (mean 4640 €; median 3690 €; IQR = 2930–5060 €), and over 80-year old group (mean 4810 €; median 3660 €; IQR = 2930–5600 €) were similar. The mean hospital cost per non-operatively treated patient was 580 € (median 455 €; IQR = 310–630 €).

The length of hospital stay is a large contributor to total costs. However, during the last 10 years (2006–2015), while the duration of hospital treatment has decreased, the cost of operative treatment has become approximately equal with the hospital stay. The total, direct hospital costs for CSDH are presented in Table 3 and Fig. 4, and a breakdown of mean hospital costs per patient stratified by time period is presented in Fig. 4.

The mean cost per patient was greatest during 1996–2000, when it was 5840 € (median 4040 €; IQR = 3250–6730 €). The greatest total hospital costs 1,242,000 € were during 2006–2010. The period with the lowest costs per patient was 2011–2015 (mean 3310 €; median 2930 €; IQR = 2170–4170 €). Because of this, even though the number of patients has increased, the total costs have decreased during the more recent years of the study period. Considering total hospital costs, the lowest cost period was 1990–1995, and the total costs were 842,000 €.

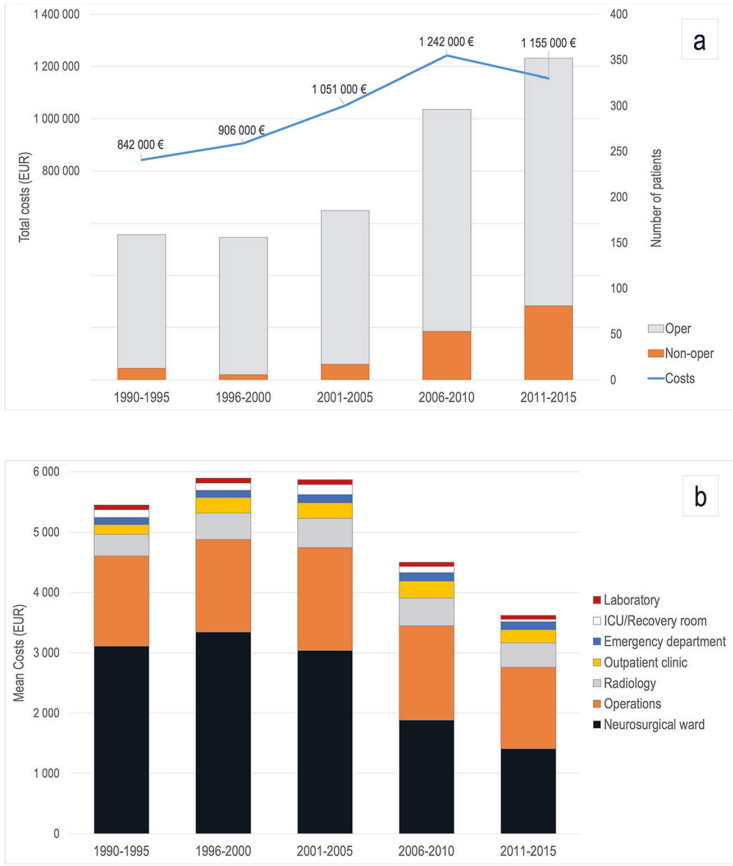


Fig. 4 Direct costs of chronic subdural hematoma in Tampere University Hospital. Total hospital costs per 5-year time periods, and the number of operatively and non-operatively treated patients (**a**). A breakdown of mean hospital costs per patient stratified by time groups (**b**). The analysed CSDH patients living in Pirkanmaa Region accounted approximately half of all the CSDH patients treated in Tampere University Hospital with a catchment population of one million

Discussion

Summary of the key findings

During the study period from 1990 to 2015, the incidence of CSDH among those 80 years and older has increased in both operatively (from 36.6 to 91/100,000/year) and non-operatively (from 4.7 to 36.9/100,000/year) treated patients. Patients prescribed routine post-operative head CT scans were more likely to undergo a second surgery, and 18% of those with a second surgery were asymptomatic during the follow-up visit in which the CT was conducted. Most of the second surgeries took place within 30 days (63%) or 2 months (92%) from the primary operation. Those undergoing a second surgery suffered more often from seizures (10% vs 3.1%), empyema (4.3% vs 0.9%), and pneumonia (4.7% vs 1.4%). The treatment cost for recurrent CSDHs was 132% higher than the treatment cost of non-recurrent CSDHs, most likely because of longer hospital stay for re-admissions and more frequent outpatient follow-up with CT. The costs were 30% higher for patients with no drain compared with patients with a drain, perhaps due in large part to more frequent recurrences needing second surgeries.

The mean cost per patient was greatest for the 60–79-year old age group, in large part because they were more likely to undergo a second surgery than patients in younger and older groups. The oldest group, 80 years and older, did not have greater costs than the others, nor did patients in this group have more complications, besides pneumonia. The mean cost per patient has decreased over the past two time periods (i.e., 2006–2015). This is explained mostly by reduced hospital stay and fewer recurrences requiring surgery. There were also more frequently diagnosed non-operatively treated patients, but their share of the costs was modest. The total costs increased through the 2006–2010 period, but then decreased during the 2011–2015 period, despite greater numbers of patients being treated. This relates to the decrease in the mean cost per patient.

Comparison of the current findings to prior literature

The incidence of CSDH has increased among the elderly during the last decades [1, 4, 14, 18, 33]. The reasons for this include age-related general brain atrophy [23, 42], risk for multiple falls [15, 19, 21], and the frequent use of antithrombotic medication [7, 8, 14, 29]. In addition,

improved awareness of CSDH among the medical profession and the wide availability of CT scanners have been proposed to have an influence [2, 36]. The availability of CT likely contributes to the increase in non-operatively treated patients; asymptomatic CSDHs are found when the threshold for ordering imaging is low. There are no previous reports separating the incidence between the operatively and non-operatively treated patients.

Routine follow-up head CT reveals large recurring hematomas in some clinically asymptomatic patients, leading to the decision for a second surgery. In a Danish retrospective study of 202 patients with CSDHs, recurrence of neurological symptoms preceded the planned postoperative follow-up CT (4 to 6 weeks after primary surgery) in all patients undergoing a second surgery [30]. The Swiss TOSCAN trial with 361 randomized patients showed that routine CT scans did not improve clinical outcome but led to increased costs [35].

Our data support some previous findings. Our recurrence rate (n = 278/978; 28%), is toward the high end of what is reported in the literature [22, 31, 40]. Of the total sample of 978, 5% (n = 49) of the patients undergoing a second surgery were asymptomatic. Considering the 278 who had a recurrence, 18% were asymptomatic. Correspondingly, asymptomatic patients were operated on based on CT findings in the TOSCAN trial [35]. In the TOSCAN study, 27% of the CSDH patients with follow-up CT underwent a second surgery vs 19% with no prescribed CT. In our study, however, during the first follow-up visit, 70 patients of 108 (65%) with recurrence visible on CT were slightly symptomatic, but waited for the scheduled outpatient clinic visit. In addition, the use of subdural drains during the study period was uncommon (6%). Insertion of an external drain after evacuation of CSDH decreases the rate of recurrence in most of reported series by up to 50% [22, 31, 40].

The median time to re-operation, 25 days, is in line with previous studies. Mori et al. [28] reported a median time to re-operation of 24.5 days, Lutz et al. [24] 22.5 days, Pedersen et al. [30] 22 days, although Ridwan et al. [34] only 17 days. In our study, most of the second surgeries took place within 30 days (63%) or 2 months (92%) from the primary operation. Results from the TOSCAN trial were similar (68% within 30 days and 93% within 2 months) [35]. In addition, in a German study of 208 patients with a recurrence rate of 18%, the majority (92%) of recurrences occurred within 60 days [34].

Many patients with CSDHs are on antithrombotic medication, and this medication is paused at the time of diagnosis. The post-CSDH resumption of these drugs is not straightforward [32]. Nine of ten recurrences occur within 60 days. This information may help inform when to resume antithrombotics when needed, even with no follow-up CT. Notably, early resumption has also been advocated [32], and not all the patients can wait for 2 months due to a high risk of thromboembolic events. Further studies are warranted to investigate if early resumption of antithrombotics is safe without prescribing follow-up CT. In addition, there is a medico-legal issue of permission to drive. For these reasons, in selected cases, a planned follow-up CT may be necessary. However, it seems that in the majority of the cases, clinical follow-up and CT only for symptomatic patients, is just as good. When clinically indicated, a 2-month follow-up period after CSDH is likely sufficient for most asymptomatic patients.

Cost comparison with previous CSDH studies

The literature on CSDH-related costs is scarce. In the TOSCAN trial (conducted June 2012–August 2016), the mean cost per patient from hospital admission until the last follow-up visit was 21,298 CHF (15,927 €) in the CT-arm and 18,047 CHF (13,497 €) in the no-CT-arm, the difference being 18% [35]. Median length of hospital stay was 6 days. The investigators pointed out that the imaging strategy in the CT-arm probably increased the costs by triggering further follow-up visits, hospitalizations, and surgeries.

A financial impact study from the USA collected all SDH cases (acute 14%, subacute 44%, chronic 12%, mixed 30%; n = 216) admitted to a tertiary care center between January 2001 and December 2008 [12]. Surgery was performed in 64% of the cases. Median hospital length of stay was 8 days (min–max = 1–99), which was the most important predictor of costs. The median total direct cost for hospitalization was $10,670 (10,820 €). Frontera and colleagues [13] conducted a registry study between 1998 and 2007 showing that the national costs of SDH increased by 60% over the last decade in the USA.

Our costs (mean 5250 € for operatively treated patient) were notably lower than the costs reported previously from Switzerland and the USA. However, the costs are difficult to compare between countries due to differences in case ascertainment, study design, health care systems, and economic issues. The most important predictor of costs has been the length of hospital stay, which was longer in previous studies compared with ours (median 3 days). In our study, the total costs of CSDH increased over time until the 2006–2010 period (50% increase from 1990 to 1995) because of the increase in number of patients treated. However, towards the end of the study period (2011–2015), there was a decline in total costs, despite a greater number of patients treated, in association with a decrease in hospital stay and fewer recurrences. Inpatient time in our neurosurgery clinic decreased during the study period from 5 days (1990–1995) to 3 days (2011–2015) meaning earlier discharge to home or transfer to rehabilitation. The proportion of patients discharged home did not change significantly during the 26-year period. Correspondingly, it can be assumed that the rehabilitation periods after CSDH treatment have become longer towards the end of the study period. In conclusion, while the total direct neurosurgical hospital costs have temporally decreased, there might have been an increase in the rehabilitation costs.

Strengths and limitations

Our series represents the most extensive non-register-based study of consecutive CSDH cases treated in one neurosurgical department. Although retrospective in nature, the population-based setting makes it less prone to selection bias. Moreover, all the data were collected by one of the authors (M.R.).

This study has several limitations. ICD-codes were used to retrospectively identify all the patients of interest. However, there is a possibility that some cases were not recognized due to incomplete or incorrect ICD-coding. It is likely that all the patients undergoing surgery were identified, but the ICD-coding can be incomplete among the non-operatively treated patients, as the neurosurgeon has only been consulted on these cases. Also, head CT was done only rarely early in the study period; thus, incidental CSDHs were almost never identified. Head CT became widely used in the late 1990s after discovery of thrombolytic agents for ischemic stroke. In addition, the distinction between subacute and chronic SDH is not always obvious, both in relation to time and neuroradiological characteristics. No definition of CSDH is universally accepted [17]. Subacute SDHs were excluded from this study, because this hematoma subtype is considered to represent an entity of its own [3, 11, 20]. Also, definitions used for recurrences differ [6]. Our definition is quite liberal and included second surgeries during the primary treatment.

Moreover, the cost analysis was performed retrospectively and probably underestimates total costs, but this applies to all our study periods equally. The costs are estimates based on the latest costs and do not take into account temporal changes in prices. The costs reported include only the costs in Tampere University Hospital; they do not take into account any costs of treatment outside our hospital. Considering that only half of those among the age group of 60–79 and one-fifth of those 80 years and older could be discharged home, the costs of, for example, rehabilitation and continuing care are noteworthy. Further studies are needed to investigate the actual overall costs on healthcare and society (e.g., rehabilitation, post-CSDH nursing facility dwelling, medication, and social security reimbursements).

Conclusions

The population-based incidence of CSDH increased markedly during the study period from 1990 to 2015. The number of cases has increased as the CSDH incidence and the aging population is increasing. Nonetheless, in more recent years, the direct hospital costs declined, perhaps due in large part to shortened hospital stays and fewer recurrences related to use of subdural drains. Reducing recurrences is critical for reducing complications and costs. The oldest group of patients, 80 years or older, did not have higher costs than the others, nor did this group have more frequent complications, besides pneumonia. The majority (92%) of recurrences occurred within 60 days. A 2-month follow-up period after CSDH seems sufficient for most, and CT controls are advocated only for symptomatic patients.

Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (the Ethics Committee of the Pirkanmaa Hospital District, approval code R12082) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All data was collected retrospectively without contacting the patients. For this type of study formal consent is not required.

Conflict of interest Dr. Luoto has received funding from the Government's Special Financial Transfer tied to academic research in Health Sciences (Finland), the Emil Aaltonen Foundation, and the Finnish Medical Society Duodecim. Dr. Iverson acknowledges unrestricted philanthropic support from the Mooney-Reed Charitable Foundation, Heinz Family Foundation, ImPACT Applications, Inc., and Spaulding Research Institute. He serves as a strategic scientific advisor for BioDirection, Inc. The other authors have nothing to disclose.

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