IMPROVING OUTCOMES IN HIP FRACTURE PATIENTS

PhD Thesis

Christian Thomas Pollmann

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Institute of Clinical Medicine
Campus Akershus University Hospital
University of Oslo
Norway

Department of Orthopaedic Surgery
Akershus University Hospital
Lørenskog
Norway

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The beautiful thing about knowledge is that you can give it away and still have it.

Andy Weir. *Project Hail Mary*. New York: Random House Inc.; 2021.

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Abbreviations

AHUS	Akershus University Hospital
ASA	American Society of Anaesthesiologists
A & E	Accident and emergency
CI	Confidence interval
CSF	Cerebrospinal fluid
DAG	Directed acyclic graph
DAIR	Debridement, antibiotics, and implant retention
EQ-5D-3L	Three-level Euro-Qol five-dimension index
EQ-VAS	EQ-5D visual analogue scale
HOOS	Hip Disability Osteoarthritis Score
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
MCII	Minimally Clinically Important Improvement
NAR	Norwegian Arthroplasty Register
NHFR	Norwegian Hip Fracture Register
NNH	Number needed to harm
NNT	Number needed to treat
OR	Odds ratio
OSLA	Observational Scale for Level of Arousal
PASS	Patient Acceptable Symptom State
PJI	Prosthetic joint infection
RASS	Richmond Agitation Sedation Scale
REC	Regional Ethics Committee
RR	Risk ratio
SPAIRE	Save Piriformis and Internus, Repairing Externus
Sqrt	Square root
SSD	Subsyndromal delirium
SSI	Surgical site infection
THA	Total hip arthroplasty
WOMAC	Western Ontario and McMaster Universities osteoarthritis index
4AT	4 ‘A’s test (delirium screening test)

Articles in the Thesis

1. Pollmann CT, Røtterud JH, Gjertsen JE, Dahl FA, Lenvik O, Årøen A: **Fast track hip fracture care and mortality - an observational study of 2230 patients.** *BMC Musculoskelet Disord* 2019, **20:**248.

2. Pollmann CT, Dahl FA, Røtterud JHM, Gjertsen JE, Årøen A: **Surgical site infection after hip fracture - mortality and risk factors: an observational cohort study of 1,709 patients.** *Acta Orthop* 2020, **91:**347-352.

3. Pollmann CT, Gjertsen JE, Dale H, Straume-Næsheim TM, Dybvik E, Hallan G: **Operative approach influences functional outcome after DAIR for infected total hip arthroplasty.** *Bone Joint J* 2020, **102-b:**1662-1669.

4. Pollmann CT, Mellingsæter MR, Neerland BE, Straume-Næsheim T, Årøen A, Watne LO: **Orthogeriatric co-management reduces incidence of delirium in hip fracture patients.** *Osteoporos Int* 2021, **32:**2225-2233.

Thesis Summary

Hip fractures typically occur in the frail and elderly. They result in considerable morbidity and in increased mortality comparable to acute myocardial infarction. Deep surgical site infection after hip fracture surgery can worsen the functional outcome and seems to be associated with a further increase in mortality. Approximately every other hip fracture patient develops delirium.
The aim of this thesis was to investigate possibilities to improve mortality, the incidence of surgical site infection, functional outcome after revision for deep surgical site infection, and delirium in hip fracture patients.

Fast track hip fracture care and mortality

In study 1, we investigated the effect of fast track hip fracture care on mortality. Secondary outcome measures were reoperations, surgical site infection, acute readmissions, admission time, time to surgery, and length of hospital stay. We compared a cohort of 1090 hip fracture patients treated before with a cohort of 1140 hip fracture patients treated after the introduction of a comprehensive fast track hip fracture care pathway in a single centre observational study. Data were obtained from the electronic hospital records, the Norwegian Hip Fracture Register, the Central Population Register, and the Norwegian Surveillance System of Antibiotic Use and Hospital-Acquired Infections.
Mortality rates were similar in both groups. Median admission time and median time to surgery were shorter, and the 30-day reoperation rate was lower in the fast track group. The remaining secondary outcome measures only showed a trend towards improvement in the fast track group.

Surgical site infection and mortality

In study 2, we investigated the contribution of deep surgical site infection to mortality after hip fracture surgery. In addition, we analysed the role of the duration of surgery as a risk factor for deep surgical site infection. All patients from the cohort in study 1, who were operated with a hemiarthroplasty of the hip (n = 884) or with a sliding hip screw (n = 825), were included in study 2. After adjusting for several confounders, deep surgical site infection more than doubled the risk of 90-day mortality (relative risk = 2.4, 95%CI: 1.6 – 3.5). A sensitivity analysis indicated quite robust evidence for a causal association. Duration of surgery was positively correlated with the risk of deep surgical site infection in univariable analysis. After adjusting for observed confounders, this association was no longer statistically significant.

Surgical approach and functional outcome

In study 3, we investigated the effect of the surgical approach on the functional outcome after debridement, antibiotics, and implant retention (DAIR) for treating infected total hip arthroplasties. Patients, who had been treated with a single DAIR procedure and in whom both the primary total hip

arthroplasty and the DAIR procedure were performed through either the transgluteal or the posterior surgical approach, were identified in the Norwegian Arthroplasty Register. Eligible patients received a questionnaire concerning functional outcome, health-related quality of life, patient satisfaction, infection eradication, limping, nerve injury, and prosthesis dislocation. With a response rate of 62 %, a total of 189 patients were included in the study. Median follow-up after DAIR was 2.5 years in the posterior approach group (n = 102) and 5.5 years in the transgluteal approach group (n = 87). The patients in the posterior approach group reported better functional outcome, less limping, better health-related quality of life, and were more satisfied with their hip arthroplasty. The differences in all these outcome measures were clinically relevant. Multivariable analysis of the association of patient satisfaction and of the functional outcome with the surgical approach confirmed the results.

Orthogeriatric co-management and delirium

In study 4, we investigated the effect of orthogeriatric co-management as an integrated care model on the incidence of subsyndromal delirium and delirium in hip fracture patients. We compared a cohort of 94 hip fracture patients treated before with a cohort of 103 hip fracture patients treated after the introduction of orthogeriatric co-management in a single centre observational study. Delirium was assessed daily applying the DSM-5 criteria. The incidence of subsyndromal delirium and delirium was lower in the orthogeriatric group. With a dichotomized outcome ('no delirium' vs. 'subsyndromal delirum or delirium'), the number needed to treat was 5.3 (95%CI: 3.1 – 19.7). Orthogeriatric co-management remained a significant predictor for a lower incidence of subsyndromal delirium / delirium (odds ratio = 0.46, 95%CI: 0.23 – 0.89) in a multivariable ordinal logistic regression model adjusted for several variables including pre-existing cognitive impairment.

Conclusions

'Fast-tracking' hip fracture patients to the orthopaedic ward is safe. However, in light of our study and other available evidence, the effect of fast track hip fracture care on mortality seems to be limited.

Deep surgical site infection after hip fracture surgery is an independent risk factor for mortality and preventive measures against surgical site infection should be taken. The role of the duration of surgery as a risk factor for surgical site infection is unclear. Our data, in conjunction with other reports, may indicate that the elapsed time during surgery could be less important than the reason for a prolonged operation.

When a deep surgical site infection after total hip arthroplasty is treated with a DAIR procedure, the use of the posterior approach is associated with better function, better health-related quality of life, and increased patient satisfaction compared to the use of the transgluteal approach. However, most

patients in our study had other indications for their total hip arthroplasty than an acute hip fracture. Therefore, it is unclear if this result can be extrapolated to hip fracture patients.

Orthogeriatric co-management reduced the incidence of subsyndromal delirium / delirium in our cohort of hip fracture patients. In conjunction with previous evidence, a clinically relevant effect of orthogeriatric co-management on the incidence of delirium in hip fracture patients seems probable.

Sammendrag på Norsk [Thesis Summary in Norwegian]

Hoftebrudd, som typisk rammer gamle og ofte skrøpelige mennesker, medfører betydelig morbiditet og en økning i mortalitet på linje med et akutt hjerteinfarkt. En dyp postoperativ infeksjon etter hoftebruddkirurgi kan forverre det funksjonelle resultatet og synes å være assosiert med en ytterligere økning i mortalitet. Omtrent annenhver hoftebruddpasient utvikler delir.
Dette forskningsprosjektet hadde som mål å se på muligheter å forbedre og forebygge noen av de viktigste komplikasjonene etter hoftebruddkirurgi, nemlig mortalitet, delir, postoperativ infeksjon og nedsatt funksjonelt resultat etter bløtdelsrevisjon for dyp infeksjon.

Fast track for hoftebruddpasienter og mortalitet

I studie 1 undersøkte vi effekten av et akselerert ('fast track') pasientforløp for hoftebruddpasienter på mortalitet. Sekundære utfallsmål var reoperasjoner, postoperative infeksjoner, akutte reinnleggelser, tid fra ankomst sykehus til ankomst sengepost, ventetid til operasjon og oppholdstid på sykehus. Vi sammenlignet en kohort på 1090 hoftebruddpasienter, som ble behandlet før, med en kohort på 1140 hoftebruddpasienter, som ble behandlet etter innføring av et tverrfaglig 'fast track' pasientforløp ved sykehuset vårt. Som datakilder brukte vi det elektroniske pasientjournal, det Nasjonale Hoftebruddregisteret, Folkeregisteret og det Norske Overvåkingssystemet for Antibiotikabruk og Helsetjenesteassosierte Infeksjoner.
Mortaliteten var lik i begge grupper. Den mediane tiden fra ankomst sykehus til ankomst sengepost og den mediane ventetiden til operasjon var kortere og 30-dagers reoperasjonsraten var lavere i fast track gruppen. De øvrige sekundære utfallsmålene viste bare en trend til forbedring i fast track gruppen.

Dyp postoperativ infeksjon og mortalitet

I studie 2 undersøkte vi sammenhengen mellom en dyp postoperativ infeksjon og mortalitet etter hoftebruddkirurgi. I tillegg så vi på sammenhengen mellom operasjonstid og risiko for en dyp postoperativ infeksjon. Alle pasienter fra studie 1, som ble operert med enten hemiprotese (n = 884) eller glideskrue (n = 825), ble inkludert i studie 2. Dyp postoperativ infeksjon mer enn doblet risikoen for å dø innen 90 dager (relativ risiko = 2,4; 95%KI: 1,6 – 3,5). En sensitivitetsanalyse viste nokså robust evidens for en kausal sammenheng. Operasjonstiden var positivt korrelert med risikoen for dyp postoperativ infeksjon i univariabel analyse. I en multivariabel analyse derimot var sammenhengen mellom operasjonstid og dyp postoperativ infeksjon ikke statistisk signifikant lenger.

Kirurgisk tilgang og funksjonelt resultat

I studie 3 undersøkte vi om den kirurgiske tilgangen til hofteleddet har effekt på det funksjonelle resultatet etter bløtdelsrevisjon for behandling av infisert totalprotese. Fra det Nasjonale Register for

Leddproteser ble det identifisert pasienter, som hadde blitt operert med én bløtdelsrevisjon for infisert primærprotese og som hadde fått begge inngrep gjennomført med den samme operative tilgangen, enten transgluteal eller bakre tilgang. Disse pasientene fikk tilsendt et spørreskjema med spørsmål angående det funksjonelle utfallet, livskvalitet, tilfredshet, helbredelse av infeksjonen, halting, nerveskade og eventuelle proteseluksasjoner. Svarprosenten var på 62 % og 189 pasienter ble inkludert i studien. Median oppfølgingstid etter bløtdelsrevisjonen var 2,5 år i gruppen operert med bakre tilgang (n = 102) og 5,5 år i gruppen operert med transgluteal tilgang (n = 87). Pasientene, som ble operert med bakre tilgang, rapporterte et bedre funksjonelt resultat, mindre halting, bedre livskvalitet og var oftere fornøyde med hofteprotesen. Forskjellene mellom gruppene var klinisk relevante. Multivariabel analyse av sammenhengen mellom det funksjonelle resultatet og kirurgisk tilgang og mellom pasient tilfredshet og kirurgisk tilgang bekreftet funnene.

Ortogeriatri og delir

I studie 4 undersøkte vi effekten av ortogeriatri på forekomst av delir blant hoftebruddpasienter. Vi sammenlignet en kohort på 94 hoftebruddpasienter, som ble behandlet før med en kohort på 103 hoftebruddpasienter, som ble behandlet etter innføring av ortogeriatri ved sykehuset vårt. Delir ble definert etter DSM-5 kriteriene og delir screening ble gjennomført daglig. Forekomst av subsyndromalt delir og delir var lavere i ortogeriatri gruppen. Med et dikotomisert utfall ('ingen delir' vs. 'subsyndromalt delir eller delir'), var antall som må behandles for å forebygge et tilfelle (NNT) 5,3 (95%KI: 3,1 – 19,7). Ortogeriatri forble en signifikant prediktor for lavere forekomst av subsyndromalt delir / delir (odds ratio = 0,46; 95%KI: 0,23 – 0,89) også i en multivariabel analyse justert for flere variabler, inkludert kjent kognitiv svikt.

Konklusjoner

Vi konkluderer at et akselert 'fast track' forløp for hoftebruddpasienter er trygt. Men, effekten av et fast track pasientforløp på mortalitet, tatt vår studie og annen evidens i betraktning, synes å være begrenset.

En dyp postoperativ infeksjon etter hoftebruddkirurgi er en uavhengig risikofaktor for mortalitet. Infeksjonsforebyggende tiltak er derfor en viktig del av hoftebruddkirurgien. Hvilken rolle operasjonstiden har som risikofaktor for postoperativ infeksjon er uavklart. Våre funn, sammenholdt med annen evidens, kan tyde på at selve operasjonstiden er mindre viktig enn den underliggende årsaken for et forlenget operativt inngrep.

Ved behandling av en infisert hoftetotalprotese med bløtdelsrevisjon, fører bruk av den bakre tilgangen til hofteleddet til et bedre funksjonelt resultat, bedre livskvalitet og flere fornøyde pasienter sammenlignet med bruk av den transgluteale tilgangen. De fleste pasienter i vår studie hadde en annen indikasjon enn et akutt hoftebrudd for å bli operert med en hoftetotalprotese. Det er således uklart hvorvidt funnene våre kan direkte overføres til hoftebruddpasienter.

Ortogeriatri reduserte forekomsten av subsyndromalt delir / delir i vår kohort av hoftebruddpasienter. Sammenholdt med tidligere publiserte studier anses det som sannsynlig at ortogeriatri har en klinisk relevant effekt på forekomst av delir blant hoftebruddpasienter.

Preface

I have worked as a consultant in the Hip Division of the Department of Orthopaedic Surgery at Akershus University Hospital since 2011. The Hip Division is responsible for all primary and revision hip arthroplasties, for periprosthetic fractures, and for the treatment of intracapsular hip fractures. In addition, I have a special interest in the treatment of orthopaedic infections, especially of prosthetic joint infections of the hip.

In December 2012, I was commissioned to develop a standardized fast track patient pathway for our hip fracture patients. A project that required stamina. When the pathway finally was implemented, I became interested to see if we could demonstrate an effect on outcomes in hip fracture patients. Thus, the first study of this thesis came into being.

The second study, which focused on surgical site infections after hip fracture surgery, was based on the same cohort of patients as the first study.

The idea for the third study was based on my personal impression that revision for prosthetic joint infection resulted in abductor insufficiency in a large proportion of patients operated with the transgluteal approach. This led us to investigate the influence of the surgical approach on functional outcome after debridement, antibiotics, and implant retention (DAIR) for prosthetic joint infection of the hip.

The fourth study was a result of a collaboration with Leiv Otto Watne, a geriatrician and delirium researcher, and of my involvement in setting up orthogeriatric co-management at our hospital. Leiv Otto Watne has established the world's largest biobank with cerebrospinal fluid samples from hip fracture patients operated in spinal anaesthesia. Incidentally, approximately half of the patients in his study from Akershus University Hospital were included before and approximately half of the patients were included after the introduction of orthogeriatric co-management at our hospital. This enabled us to investigate the effect of orthogeriatric co-management on delirium in hip fracture patients.

Background

Hip fractures

Hip fractures (fractures of the femoral neck, trochanteric, and subtrochanteric fractures) typically affect frail, older individuals and lead to substantial morbidity and mortality. Only about 50 % of hip fracture patients recover their pre-fracture level of mobility [1, 2]. The rate of return to pre-fracture level of independence is reported to be between 36 % and 70 % with older and frailer patients being less likely to recover their level of independence [2, 3]. The 30-day mortality rates after hip fracture vary between 6 % and 11 % [4-7], which is comparable to the 30-day mortality rate after myocardial infarction [8]. One-year mortality rates after hip fracture typically lie between 20 % and 30 % [5, 9, 10]. Scandinavia has the highest hip fracture rates worldwide [11] and Norwegian hospitals perform approximately 8000 primary hip fracture operations annually [12, 13]. Approximately 8 % of all primary hip fracture operations in Norway are performed at Akershus University Hospital [12, 13], which makes our institution an ideal place to study different aspects of hip fracture treatment. The hip fracture incidence is expected to increase further in the western world during the next decades [14].

Improving outcomes in hip fracture patients

Orthopaedic research has often focused on surgical techniques in the treatment of hip fracture patients [15-17]. However, mortality rates after hip fracture have remained high [9, 18] and improvements in the perioperative care of hip fracture patients are warranted [19]. While mortality is the hardest and most crucial endpoint, other outcomes, which are associated with both morbidity and mortality, are also relevant to hip fracture patients, namely surgical site infection, functional outcome, and delirium. This thesis will address aspects of all of these outcomes.

Norwegian Hip Fracture Register and Norwegian Arthroplasty Register

Both registers are owned by the Norwegian Orthopaedic Association. They are based in Bergen, Norway, and are maintained by the Orthopaedic Department, Haukeland University Hospital.

The Norwegian Hip Fracture Register was established in 2005 and records all primary and revision hip fracture operations [20]. The completeness of the Norwegian Hip Fracture Register for primary operations is 88 % for osteosyntheses, 94 % for hemiarthroplasties, and 91 % for total hip

arthroplasties (for fracture) [12]. For revision surgeries the completeness is 80 % for osteosyntheses, 73 % for hemiarthroplasties, and 84 % for total hip arthroplasties [12].

The Norwegian Arthroplasty Register was established in 1987. Among other arthroplasties, it records all primary and revision total hip arthroplasties. The completeness of the Norwegian Arthroplasty Register is 97 % for primary total hip arthroplasties [12, 21] and 93 % for revision hip arthroplasties [12].

Data from the Norwegian Hip Fracture Register were used in **articles 1** and **2**; data from the Norwegian Arthroplasty Register were used in **article 3**.

Fast track surgery

The term 'fast track surgery' as a term for an enhanced postoperative recovery program was coined by Professor Kehlet [22], a Danish gastrointestinal surgeon. It is a multimodal concept based on evidence-based medicine rather than traditions. It addresses different aspects of the stress response in surgical patients with the goal to reduce morbidity and shorten convalescence [22, 23]. The basic pillars of the fast track surgery concept are preoperative information, stress reduction (preoperative glucocorticoids, regional anaesthesia, less invasive surgical procedures), multimodal pain management, prophylaxis against postoperative nausea and vomiting, early mobilisation, and adequate nutrition [22, 23]. Subsequently, fast track surgery principles were successfully applied in other surgical fields, including elective arthroplasty surgery [24].

Fast track surgery for hip fracture patients

'Fast track surgery' is not a protected trademark and hence, the first reports on 'fast tracking' hip fracture patients used the term 'fast track' in a different sense [25-27]. These authors did not describe a comprehensive, multimodal treatment concept, but focused on the logistics of the admission pathway. They aimed to reduce the time spent in the emergency department or bypass it altogether in order to minimize the number of interactions with different health care workers and to minimize the time spent on a gurney rather than in a hospital bed with the goal of preventing delirium, pressure sores, and other complications. The second goal was to reduce the time to surgery, which, although not unequivocally [28, 29], is considered a risk factor for negative outcomes [7, 30-33]. Admission time (time from arrival at the hospital to arrival on the orthopaedic ward) and time to surgery were significantly reduced in these studies [25-27]. In addition, Larsson and Holgers found a significant reduction in postoperative complications [26] while Eriksson et al. saw a trend towards fewer postoperative complications [27]. No reduction in mortality was observed.

The focus on logistics in hip fracture patients coupled with the fact that the term 'fast track' is somewhat of a misnomer for the multimodal treatment concept may have contributed to "uninitiated" health care personnel often misinterpreting 'fast track' to indicate a focus on short hospital stays due to economic incentives. However, while short admission times and short waiting times to surgery are part of the concept for hip fracture patients, a short hospital stay is a consequence of the enhanced recovery rather than a primary goal of fast track surgery.

Other authors have reported on more comprehensive fast track surgery concepts for hip fracture patients, which included both improved preoperative logistics and a multimodal treatment concept [34, 35]. While Pedersen et al. found a reduced incidence of postoperative complications and a reduced 1-year mortality in a subgroup of community dwellers in the fast track surgery group [34], Haugan et al. found no difference in mortality or readmissions [35].

In summary, fast track surgery for hip fracture patients should include improved logistics with reduced admission time and time to surgery as well as a standardized, multimodal treatment concept based on evidence-based medicine. However, the effect of such a comprehensive fast track surgery concept for hip fracture patients on the most important outcome, namely mortality, remains unclear [34, 35].

The aim of **study 1** of this thesis was to investigate the effect of such a comprehensive fast track surgery concept on mortality, reoperations, surgical site infections, 30-day readmissions, and benchmarking times in a large 'before and after' single centre observational study. Data were obtained from the electronic hospital records, the Norwegian Hip Fracture Register, the Central Population Register, and the Norwegian Surveillance System of Antibiotic Use and Hospital-Acquired Infections [36].

Surgical site infection after hip fracture surgery

Reported rates for deep surgical site infection (SSI) after hip fracture surgery vary between 0.5 % and 2.9 % after internal fixation [37-39] and between 1.3 % and 9 % after hemiarthroplasty [31, 37-43]. A deep SSI constitutes a serious complication for this frail group of patients leading to revision surgery [44], increased morbidity [31], and increased mortality [38].

Several studies have shown a significant increase in 1-year mortality rates in hip fracture patients with deep SSI compared to patients without SSI [31, 38, 44]. However, these studies did not address the question if this increased mortality is caused by the infection itself or if it is caused by an increased frailty which predisposed these patients to SSI in the first place [45].

Risk factors for surgical site infection

Identified risk factors for SSI after hip fracture surgery vary from study to study. Reported risk factors include obesity [46], cognitive impairment [41], surgical delay [31, 47], type of surgery [37], surgeon's experience [37, 42], short duration of surgery [42, 43], long duration of surgery [37, 42, 46], and intraoperative hypothermia [48].

Long duration of surgery is often focused upon as a risk factor for SSI by surgeons and other theatre staff. This notion is supported by a multitude of publications from different surgical specialties as reviewed by Cheng et al. [49]. Accordingly, some authors have advocated expeditious surgical technique as a means to reduce SSI [50]. However, one should bear in mind that also a short duration of surgery represents a risk factor for SSI [42, 43]. In addition, it is notoriously difficult to distinguish if a long duration of surgery is a risk factor in itself or and indicator for a different, underlying cause for SSI. A long duration of surgery could increase infection risk by prolonging the exposure to possible bacterial contamination [51] and/or it could represents an indicator for a more complex procedure, an inexperienced surgeon, or an intraoperative complication as the principal aetiology of SSI.

In **study 2** of this thesis, using data from the electronic hospital records, the Norwegian Hip Fracture Register, the Norwegian Surveillance System for Antibiotic Use and Hospital-Acquired Infections [36], and the Central Population Register, we aimed to determine the contribution of deep SSI to mortality after hip fracture surgery. In addition, we aimed to identify risk factors for SSI with emphasis on the role of duration of surgery.

Arthroplasty for femoral neck fractures

Femoral neck fractures constitute between 50 % and 60 % of all hip fractures [12, 52]. The choice of surgical management of these fractures (internal fixation or arthroplasty) depends on the age and physical condition of the patient as well as on the displacement of the fracture [53]. Non-displaced femoral neck fractures (Garden I and II [54]) are mostly treated with internal fixation [53]. However, in older patients there is a trend towards arthroplasty also for non-displaced fractures [12, 55], which is corroborated by evidence of fewer re-operations and a somewhat better functional outcome after hemiarthroplasty compared to internal fixation [56].

Displaced fractures (Garden III and IV [54]) are typically treated with internal fixation in younger patients and with arthroplasty in older patients [53]. At what age we become elderly in this context is not quite clear, but the cut off is generally set somewhere between 60 and 70 years of age [17, 53, 57].

If fitter, community-dwelling patients among the elderly should be treated with a total hip

arthroplasty (THA) rather than a hemiarthroplasty is still up for debate [19]. While some authors have reported higher revision rates [58], more hip-related complications [59], and a higher rate of dislocation after THA [58], others have reported fewer revisions after THA [60-63]. Concerning patient reported outcomes, a large randomized controlled trial found that THA conveyed no relevant improvement in functional outcome or quality of life over hemiarthroplasty after short term follow-up [64]. However, the length of follow-up is important for the comparison of outcomes after THA and hemiarthroplasty, since acetabular erosion after hemiarthroplasty usually does not occur before medium to long term follow-up [65, 66]. Accordingly, a recent meta-analysis of randomized controlled trials found improved quality of life and better functional outcome after THA, especially with follow-up longer than 4 years [62]. The proportion of THAs among all arthroplasties performed for a femoral neck fracture in 2019 was approximately 16 % in Norway and 32 % in Sweden [12, 55].

Surgical approach

If arthroplasty is selected as operative management, the next question that arises is which surgical approach to the hip joint one should choose. All major surgical approaches to the hip joint, an anterior approach, the transgluteal (direct lateral) approach, and the posterior approach can be used in arthroplasty for a femoral neck fracture [67]. Although some evidence suggests superior outcomes with an anterior approach [68, 69], the transgluteal and the posterior approach are most commonly used for fracture related hip arthroplasty [12, 55, 67, 70]. The transgluteal approach is favoured over the posterior approach in Norway and Sweden [12, 55]. This choice is mostly motivated by several reports of an increased risk of dislocation and re-operations for fracture related hip arthroplasties performed with the posterior compared to the transgluteal approach [67, 70-75]. In addition, in the only contemporary randomized controlled trial comparing the transgluteal to the posterior approach in hemiarthroplasty of the hip, Parker found no difference in pain or mobility [76]. On the other hand, in a large register study, Kristensen et al. reported better quality of life, higher satisfaction, less pain, and a similar risk of re-operation after the posterior compared to the transgluteal approach for hemiarthroplasty [77]. Ugland et al. also found poorer functional outcome with the transgluteal approach for hemiarthroplasty, although compared to the anterior Watson Jones approach, not the posterior approach [69]. In elective total hip arthroplasty, worse patient reported outcomes with the transgluteal compared to the posterior approach have been reported by several authors [78-80]. Hence, it would seem that the debate on the best surgical approach for fracture related hip arthroplasty is not finished yet.

DAIR for prosthetic joint infection of the hip

The risk of prosthetic joint infection (PJI) is increased after fracture related compared to elective hip arthroplasty [43, 81]. Treatment options for PJI of the hip range from debridement, antibiotics, and implant retention (DAIR) to one-stage revision, two-stage revision, multi-stage revision, chronic suppressive therapy, and, in rare cases, hip disarticulation [82]. DAIR is the treatment modality of choice in acute PJI with a stable implant [82, 83]. The infection eradication rate with a DAIR procedure is good after elective THA with approximately 75 % [84]. In PJI after hemiarthroplasty for a femoral neck fracture, the success rate after DAIR is lower [85, 86] with reported rates as low as 20 % to 40 % [87-89]. The eradication rate in PJI after fracture related THA is probably higher, since these patients are, on average, less frail than patients treated with hemiarthroplasty [53]. In accordance with this, Mellner et al. reported a success rate of 82 % for DAIR after fracture related arthroplasty in a population with a relevant, although unspecified, proportion of THAs. However, since patients treated with DAIR for a PJI after fracture related THA represent a small population and are typically reported together with hemiarthroplasties [85, 90], the success rate for DAIR after fracture related THA is unknown.

Besides infection eradication, functional outcome after DAIR is also important. Grammatopoulos et al. reported that patients treated with a single, successful DAIR procedure for PJI after elective THA had a mean Oxford hip score comparable to a control group of patients who had undergone an uneventful primary THA [91]. However, the functional outcome after DAIR might be influenced by the surgical approach. Blackburn et al. reported better functional outcome after revision hip arthroplasty for aseptic loosening with the posterior compared to the transgluteal approach [92], a finding which can probably be explained by progressive muscle damage with repeated use of the transgluteal approach [93].

As mentioned above, a significant proportion of fracture related hip arthroplasties are THAs, and the optimal surgical approach for fracture related THA is still debated. As a contribution to this debate, in **study 3** of this thesis, we investigated if the surgical approach influences the functional outcome after DAIR for an infected THA. To this effect, we conducted a nationwide observational study based on the Norwegian Arthroplasty Register. We compared patient reported outcomes between patients who had both their primary THA and a single, successful DAIR procedure performed through the same surgical approach, either the transgluteal or the posterior approach. In order to attain a meaningful sample size, the indication for the primary THA was not restricted to acute femoral neck fractures and the overwhelming majority of study participants had been operated for osteoarthritis.

Orthogeriatric co-management

Another approach to improving outcomes in hip fracture patients is the co-management by both an orthopaedic surgeon and a geriatrician, orthogeriatric co-management. Orthogeriatric co-management is recommended by the Norwegian guidelines for the interdisciplinary treatment of hip fracture patients [94] and is the standard of care in the United Kingdom [95].

Orthogeriatric co-management can be provided in different organizational settings. In their review, Kammerlander et al. defined four different organizational models [96]:

1) The patients are treated on the orthopaedic ward with geriatric consultation on request.
2) The patients are treated on the orthopaedic ward with daily geriatric consultations.
3) The patients are treated on the geriatric ward with orthopaedic consultations.
4) An integrated care model where the patients are admitted to the orthopaedic ward and are treated by an interdisciplinary team consisting of an orthopaedic surgeon, a geriatrician, nurses, physiotherapists and possibly other health care professionals such as occupational therapists.

Positive effects of orthogeriatric co-management compared to standard care include better mobility 4 months after hip fracture in home-dwelling patients [97, 98], and reduced mortality [99-101]. With respect to mortality, some evidence suggests that the integrated care model is superior to models with geriatric consultations [96, 100, 102].

Evidence also suggests that orthogeriatric co-management reduces the incidence of delirium in hip fracture patients [103-105]. However, the evidence is not consistent and other reports were inconclusive [99, 106] or showed no effect of orthogeriatric co-management on delirium [97, 107].

Delirium in hip fracture patients

Delirium is an acute confusional state, which is common in hospitalized older patients with an average incidence of about one in four acute medical inpatients [108]. Delirium is defined as an acute onset of a disturbance in attention, awareness, and cognition, which tends to fluctuate and is a direct physiologic consequence of another medical condition other than a pre-existing neurocognitive disorder [109]. As frailty predisposes patients to delirium [110], the incidence of delirium in hip fracture patients is high with reported rates of up to 50 % [97, 111]. Delirium is not only distressing for the patient, their family, and the hospital staff, but is also associated with negative outcomes such as institutionalization, an increased risk of dementia, further decline of pre-existing cognitive impairment, and increased mortality [112-115]. Thus, the prevention of delirium is an important aspect in the management of hip fracture patients.

Subsyndromal delirium

Subsyndromal delirium (SSD) is a condition that does not progress to full delirium and which falls between having no signs of delirium and fulfilling all delirium criteria [116]. Consequently, the frequency and severity of negative outcomes in patients with SSD lie somewhere between the outcomes in patients with delirium and without delirium [117].

In **study 4** of this thesis, we investigated the effect of orthogeriatric co-management as an integrated care model on the incidence of delirium and SSD in hip fracture patients in a 'before and after' single centre observational study.

Thesis Aims

Elderly patients with a fracture of the hip represent one of the largest groups of patients in orthopaedic surgery. While the literature on hip fractures is vast ('hip fractures' as MESH term in PubMed gives 25169 results [accessed 21 May 2021]), outcomes after hip fracture surgery still have room for improvement [19]. The overall aim of this thesis was to investigate possibilities to ameliorate some of the most important outcomes in hip fracture treatment, namely mortality, surgical site infection, functional outcome, and delirium.

Specific Aims of the Studies

Study 1

To investigate if the introduction of 'fast track surgery' for hip fracture patients could reduce mortality, the incidence of reoperations, surgical site infections, readmissions, and benchmarking times (admission time, time to surgery, and length of hospital stay).

Study 2

To determine the effect of deep surgical site infection after hip fracture surgery on mortality. To identify risk factors for deep surgical site infection after hip fracture surgery with an emphasis on the duration of surgery.

Study 3

To investigate if the choice of either the transgluteal or the posterior surgical approach had an influence on the functional outcome, health-related quality of life, and patient satisfaction after debridement, antibiotics, and implant retention (DAIR) for infected total hip arthroplasty.

Study 4

To investigate if the introduction of orthogeriatric co-management could reduce the incidence of delirium and subsyndromal delirium in hip fracture patients.

Patients and Methods

Study design

Study 1 and **4** were single centre, 'before and after', observational studies. In **study 1**, we investigated the effect of fast track hip fracture care on mortality. A cohort of hip fracture patients treated 'conventionally' was compared to a cohort of hip fracture patients treated after the introduction of 'fast track care'. In **study 4**, we investigated the effect of orthogeriatric co-management on the incidence of delirium in hip fracture patients. A cohort of hip fracture patients under 'usual care' (here fast track hip fracture care) was compared to a cohort of hip fracture patients treated after the introduction of orthogeriatric co-management.

Study 2 was a single centre, observational study, analysing the contribution of early (≤ 30 days) deep surgical site infection after hip fracture surgery to mortality. We also investigated risk factors for early and delayed (> 30 days ≤ 1 year) surgical site infection with focus on the role of duration of surgery.

Study 3 was a nationwide observational study investigating the influence of the surgical approach on patient reported outcomes after DAIR for infected total hip arthroplasty. Potential study participants were identified in the Norwegian Arthroplasty Register and were sent questionnaires.

Patients

Study 1

All adult hip fracture patients operated at Akershus University Hosptital (AHUS) during the study period (January 2012 to December 2015) were eligible for study 1. Patients who sustained two hip fractures during the study period were only included with their first hip fracture. The only exclusion criteria were a pathologic fracture (reported as such to the Norwegian Hip Fracture Register (NHFR)) and lack of reporting to the NHFR. Fast track care was introduced in October 2013. The conventional treatment group comprised 1090 patients; the fast track group comprised 1140 patients. **Figure 1** shows a flow chart of patient inclusion.

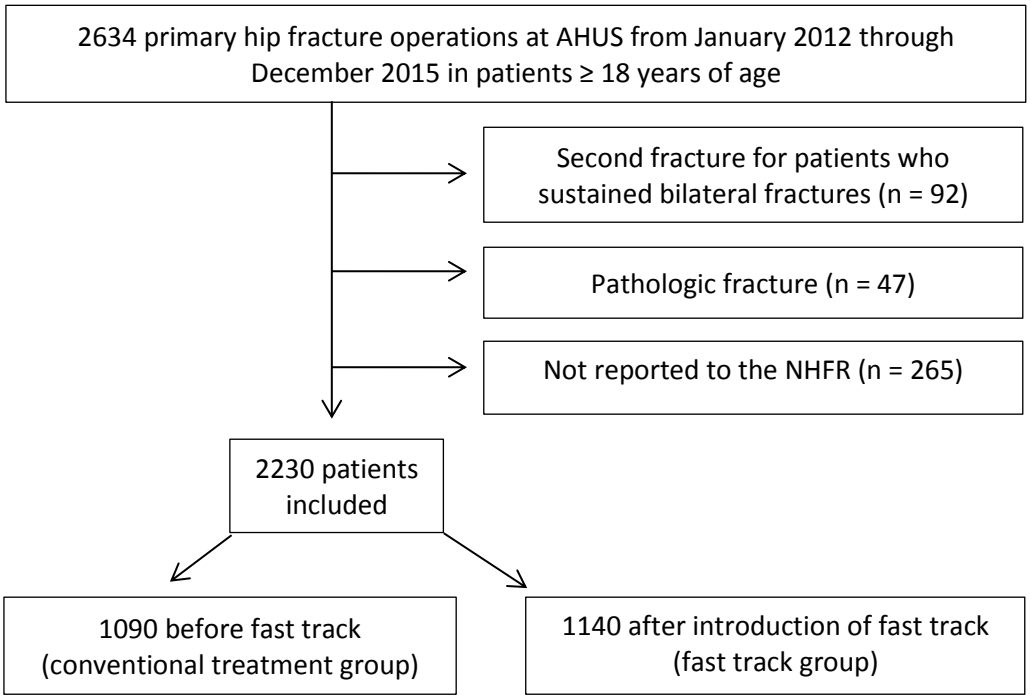


Figure 1. Flow chart of patient inclusion, study 1. AHUS, Akershus University Hospital. NHFR, Norwegian Hip Fracture Register.

Study 2

The patients in study 2 were a subgroup of the study population from study 1. Patients operated with either a screw osteosynthesis or an intramedullary nail are not routinely surveyed for surgical site infection and were thus excluded (n = 426). No surgical site infection was recorded in patients operated with a total hip arthroplasty and these patients were also excluded (n = 95). 884 patients operated with a hemiarthroplasty of the hip and 825 patients operated with a sliding hip screw were included in the study. **Figure 2** shows a flow chart of patient inclusion.

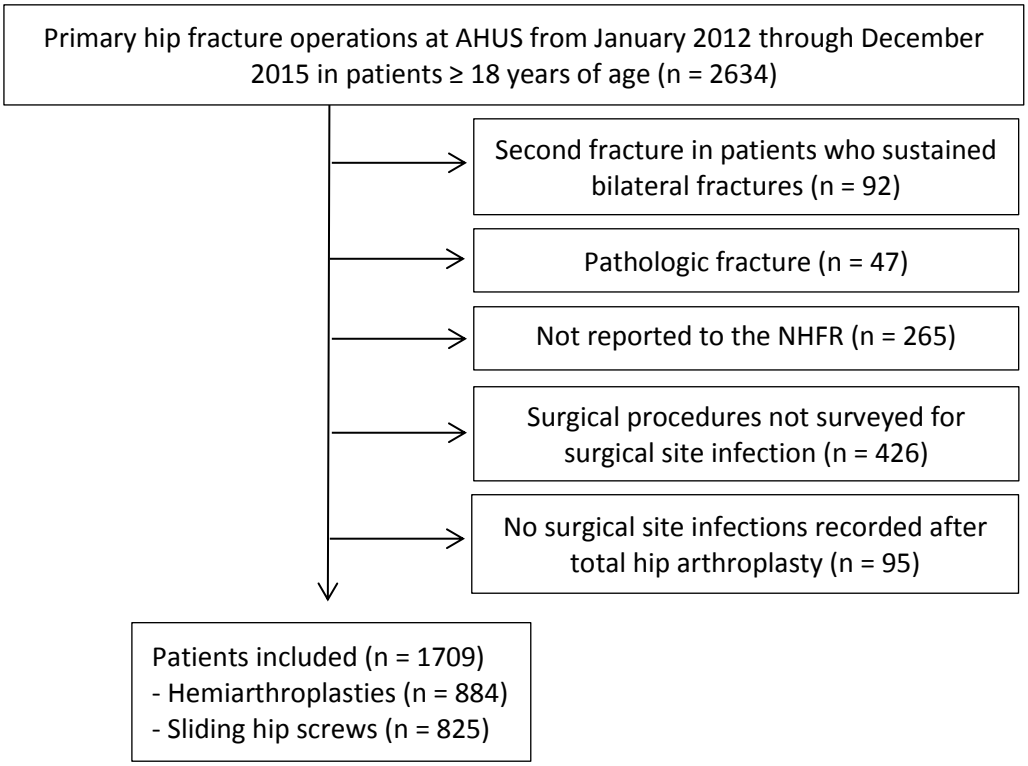


Figure 2. Flowchart of patient inclusion, study 2. AHUS, Akershus University Hospital. NHFR, Norwegian Hip Fracture Register.

Study 3

Patients who were registered in the Norwegian Arthroplasty Register with a single DAIR procedure for a deep infection after a primary total hip arthroplasty and in whom both procedures had been performed through the same surgical approach, either the transgluteal approach or the posterior approach, were eligible for the study. The study period was from June 1990 to December 2017. The eligible patients were asked by questionnaire to confirm the aforementioned criteria and that the infection was considered as eradicated. Patients who gave information to the contrary were excluded. Two patients who reported a repair of the gluteus medius tendon as a second revision procedure after the DAIR were not excluded. The study population comprised 189 patients, 87 patients in the transgluteal approach group and 102 patients in the posterior approach group. **Figure 3** shows a flowchart of the selection of eligible patients in the Norwegian Arthroplasty Register. **Figure 4** shows a flowchart of patient inclusion from the eligible patients.

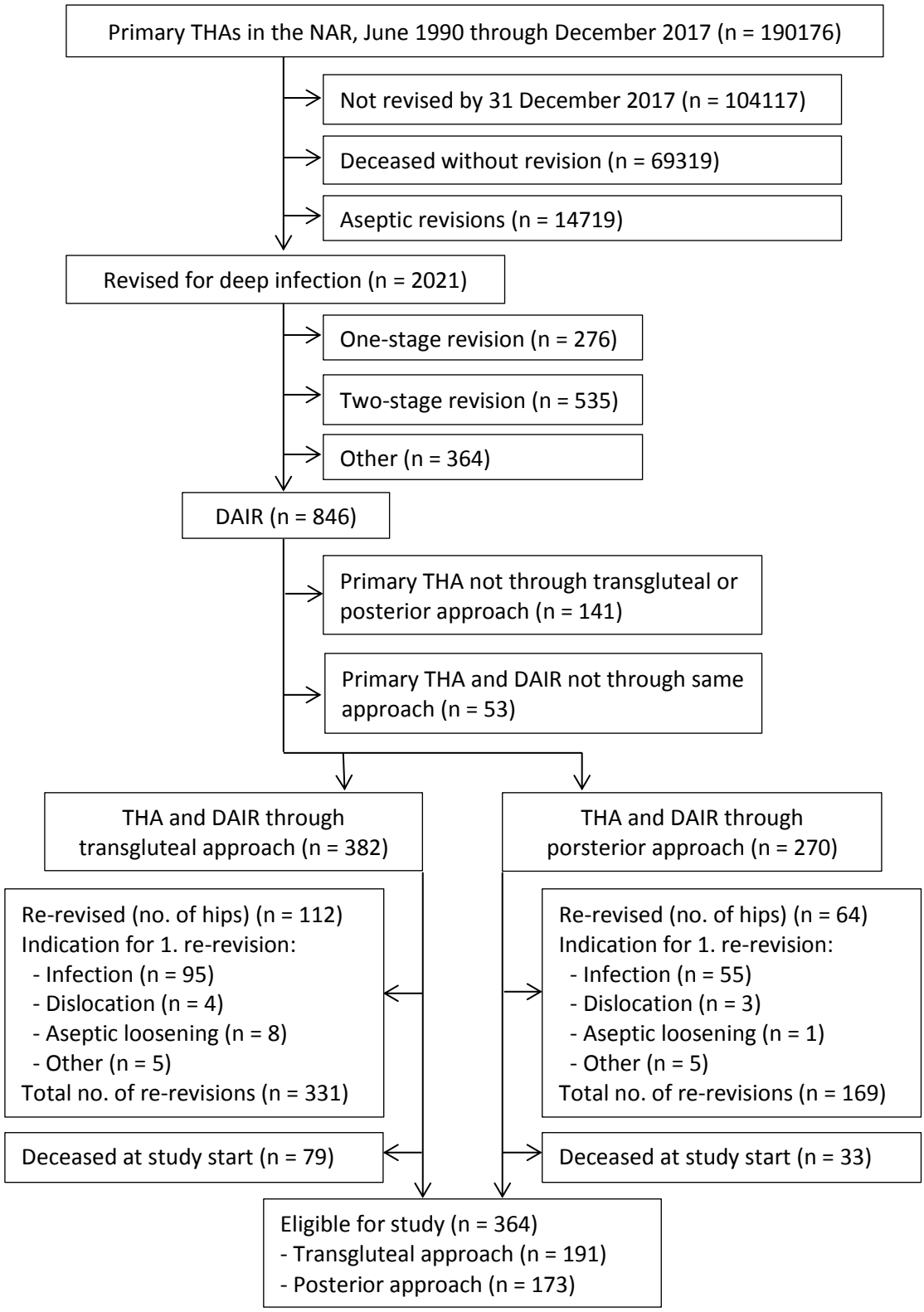


Figure 3. Flowchart of selection of eligible patients in the Norwegian Arthroplasty Register, study 3. NAR, Norwegian Arthroplasty Register. DAIR, debridement, antibiotics, and implant retention. THA, total hip arthroplasty.

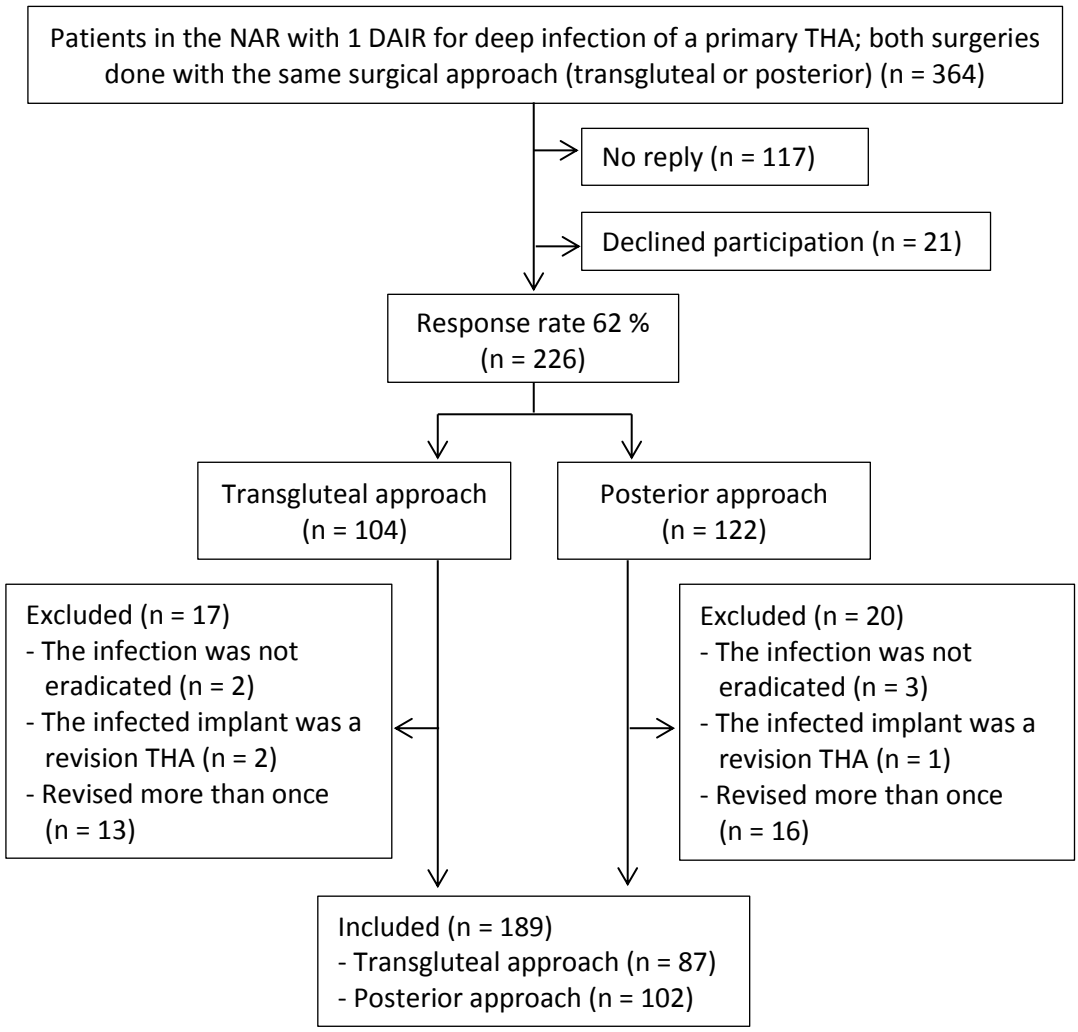


Figure 4. Flowchart of patient inclusion, study 3. NAR, Norwegian Arthroplasty Register. DAIR, debridement, antibiotics, and implant retention. THA, total hip arthroplasty.

Study 4

All patients in this study were initially recruited for a study of delirium pathophysiology. To this effect, cerebrospinal fluid was sampled from hip fracture patients operated in spinal anaesthesia at AHUS. All adult hip fracture patients were eligible and lack of informed consent, and failure to obtain cerebrospinal fluid were the only exclusion criteria for that study.

Incidentally, orthogeriatric co-management was introduced at our hospital in October 2018, approximately midway through the inclusion period of the original study, thus giving a 'ususal care group' and an 'orthogeriatric group'. Patients with delirium on hospital admission were excluded from the orthogeriatry study. **Figure 5** shows a flow chart of patient inclusion.

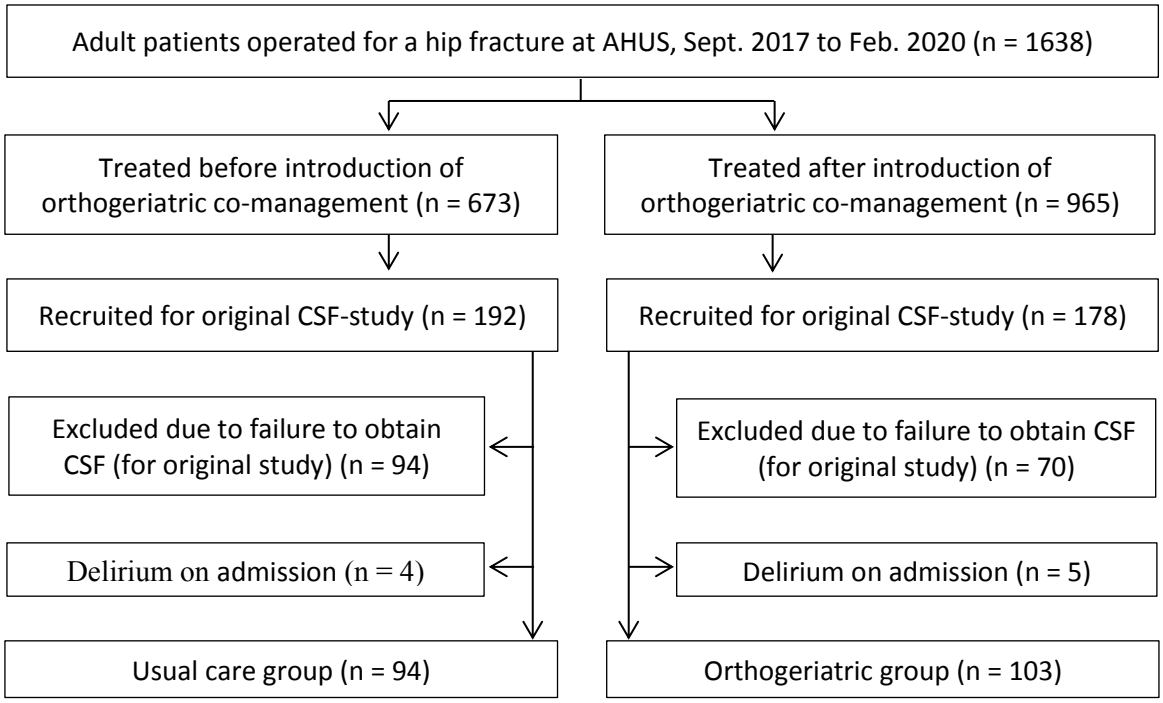


Figure 5. Flow chart of patient inclusion, study 4. AHUS, Akershus University Hospital. CSF, cerebrospinal fluid.

Data collection

Study 1

Data on the patients' baseline characteristics (age, sex, American Society of Anaesthesiologists (ASA) score, cognitive impairment, and type of fracture), on surgical treatment (type of operation, type of anaesthesia, surgeon's experience, and operating time), and on re-operations were collected from the Norwegian Hip Fracture Register.

Mortality data were obtained from the Central Population register. Hence, there was no missing data concerning mortality.

Data on surgical site infection were provided by the department of Microbiology and Infection Control, AHUS. The department surveys SSIs after sliding hip screws with a follow-up of 30 days and monitors SSIs after hemiarthroplasty and total arthroplasty of the hip with 30-day and 1-year follow-up under the Norwegian Surveillance System of Antibiotic Use and Hospital-Acquired Infections [36]. Until 2014, case definitions for surgical site infection from the American Centers for Disease Control and Prevention [118] were used. From 2014 and onwards, case definitions from the European Centre for Disease Prevention and Control [119] were employed.

Data on readmissions, admission time, time to surgery, and length of hospital stay were acquired from the electronic hospital records.

Study 2

The data sources were the same as for study 1.

As additional parameters, 'intraoperative complication' (recorded in the register as "no"/"yes" with optional free text) and 'time from fracture to surgery' were collected from the NHFR.

The completeness of follow-up for surgical site infection was 99 %.

Study 3

From the Norwegian Arthroplasty Register, we obtained data on the ASA-score at the time the patient was treated with a DAIR procedure, the time elapsed between the primary hip arthroplasty and the DAIR procedure, and the length of follow-up. In addition, the 2-year re-revision rate for all patients who were registered with a primary total hip arthroplasty and a DAIR, both either through the transgluteal or through the posterior approach, was determined from the Norwegian Arthroplasty Register for the study period.

All eligible patients received a reply-paid envelope with information about the study, a consent form, and a questionnaire. The questionnaire contained the three-level Euro-Qol five-dimension index (EQ-5D-3L), the EQ-5D visual analogue scale (EQ-VAS), and the Hip Disability Osteoarthritis Score (HOOS). The HOOS allows the calculation of the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) [120]. Participants were asked to confirm the inclusion criteria used for selection in the Norwegian Arthroplasty Register. Further, the questionnaire included questions concerning infection eradication, limping, nerve injury, prosthesis dislocation, and patient satisfaction (see Supplementary Material study 3 for details).

Study 4

Delirium was assessed daily until discharge or up to and including the fifth postoperative day by trained study nurses. The following instruments were used:

The 4'A's test (4AT) [121] was used as a screening tool. The level of arousal was evaluated using the Richmond Agitation Sedation Scale (RASS) [122] and the Observational Scale for Level of Arousal (OSLA) [123]. Attention was assessed with 'Months of the Year backwards', 'Days of the Week backwards', the vigilance A-task 'SAVEHAART', and counting backwards from 20 to 1 [124].

Two geriatricians, involved in the study, independently evaluated all available information applying the DSM-5 criteria for delirium [109]. The interrater agreement was excellent (kappa 0.97).

Delirium on admission was judged from the admission notes in the electronic patient records.

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was used to determine pre-admission cognitive status [125].

Treatment / Comparisons

Study 1

Conventional treatment group

The patients in the conventional treatment group were admitted to the accident and emergency (A & E) department, AHUS, for initial evaluation, radiologic examination, and further work-up. They received standardized antithrombotic and perioperative antibiotic prophylaxis. Otherwise, perioperative treatment was not standardized.

Fast track group

'Fast track care' for hip fracture patients was introduced as a multimodal treatment concept with improved admission logistics and standardized perioperative treatment. In short, fluid treatment, oxygen supplementation, and pain management are started by the ambulance personnel. In the A & E department, patients are only triaged using the Manchester triage system [126] and a checklist (no high-energy trauma, not previously operated in the hip in question, no sign of additional fractures) and are then prioritized for radiologic examination. If the radiology technician identifies an obvious hip fracture, the patient is transported directly to the orthopaedic ward. Fluid management, pain relief, blood sampling, premedication, transfusion triggers, and management of anticoagulants are standardized. Patients are mobilized on the first postoperative day. They are screened for delirium and nutritional status, and appropriate interventions are implemented.

Study 2

Comparisons in study 2 were made between survivors and deceased and between patients with and without deep surgical site infection.

Study 3

Comparisons in study 3 were made between patients who had been operated through either the transgluteal approach or the posterior approach with a primary total hip arthroplasty and a single, successful DAIR procedure (both surgeries performed through the same approach).

Study 4

Usual care

Usual care consisted of fast track hip fracture care described under study 1.

Orthogeriatric co-management

Orthogeriatric co-management was provided in addition to the existing fast track patient pathway. Orthogeriatric co-management was delivered on the orthopaedic ward as an integrated care model [96] by a multidisciplinary team consisting of orthopaedic surgeons, a geriatrician, nurses, physiotherapists, and occupational therapists. The goals of the team are to optimize pain and fluid management, nutrition, bowel function, and mobilization. The geriatrician reviews the patient's medications and adds expertise in the treatment of underlying comorbidities and arising medical complications. In addition, the geriatrician assists with discharge planning and includes her assessments in the discharge note.

Outcome measures

Study 1

The main outcome measure in the study of the effect of fast track care for hip fracture patients was 30-day mortality.

Secondary outcome measures were:

- 90-day mortality
- 1-year mortality
- any cause reoperation within 30 days
- any cause reoperation within 1 year
- surgical site infection within 30 days
- surgical site infection within 1 year
- 30-day non-elective readmissions
- composite 30-day outcome (at least one of the following: death, reoperation, surgical site infection)
- admission time (time from arrival at the hospital to arrival on the orthopaedic ward)
- waiting time to surgery (time from arrival at the hospital to skin incision)
- length of hospital stay

Study 2

Outcome measures for the effect of early, deep SSI were 30-day, 90-day and 1-year mortality.
The outcome measure for the analysis of risk factors for deep SSI was the occurrence of early (≤ 30 days; data available for both sliding hip screws and hemiarthroplasties) or delayed (> 30 days ≤ 1 year; data only available for hemiarthroplasties), deep SSI. Variables analysed as possible risk factors for SSI were age, time from fracture to surgery, ASA-score, cognitive impairment, the occurrence of an intraoperative complication, the surgeon's experience (at least one of the surgeons present with > 3 years' experience in hip fracture surgery), and duration of surgery.

Study 3

The main outcome measure was the function subscale of the WOMAC score. Its Minimally Clinically Important Improvement has been reported to be 8 points [127]. The Patient Acceptable Symptom State (PASS) for the WOMAC function subscale has been reported to be ≥ 69 [128].
Secondary outcome measures were self-reported limping, nerve injury, and dislocations, health-related quality of life (EQ-5D-3L index score, EQ-VAS, and HOOS quality of life subscale), and patient satisfaction.
PASS values for the quality of life measures have been reported as ≥ 0.92 for the EQ-5D-3L index score, ≥ 85 for the EQ-VAS, and ≥ 83 for the HOOS quality of life subscale [129].
Patient satisfaction was measured on a five point Likert scale with the choices 'not at all satisfied', 'not satisfied', 'somewhat satisfied', 'satisfied', and 'very satisfied'. In the analysis, patient satisfaction was dichotomized to 'not satisfied' (first three categories) and 'satisfied' (last two categories).
WOMAC and HOOS subscales are presented as normalized scores from 0 (worst) to 100 (best).

A difference in the risk for re-revision after DAIR between the two surgical approaches could alter the interpretation of the functional outcome. Therefore, the 2-year re-revision rate after DAIR was determined for the study period for all patients registered in the Norwegian Arthroplasty Register with a primary total hip arthroplasty and a subsequent DAIR, both through either the transgluteal or the posterior approach.

Study 4

The outcome measure was SSD or delirium. Delirium was defined according to the DSM-5 criteria [109]. SSD was defined as changed mental status in addition to any of the following: altered arousal,

attention deficit, delusions or hallucinations, or other cognitive change without fulfilling the DSM-5 criteria.

In the main analyses, the outcome was treated as an ordinal variable ('no delirium / SSD / delirium'). For the calculation of the number needed to treat and for the subgroup analysis, the outcome was dichotomized to 'no delirium' vs. 'SSD or delirium' and treated as a binary variable.

Statistics

Data were analysed with SPSS version 25.0.0.1 (IBM Corp., Armonk, NY, USA) in **studies 1**, **2** and **3** and with SPSS version 26.0.0.1 in **study 4**. A p-value < 0.05 was considered statistically significant. Confidence intervals for proportions and for differences in proportions were derived using the normal approximation and confidence intervals for the difference in medians are given as the Hodges-Lehmann median difference.

Sample size calculation

Sample size calculations were based on the standardized difference [130].

For **study 1**, the sample size was calculated based on a reduction of the 30-day mortality rate at AHUS in 2011 of 10.7 % to the lowest 30-day mortality rate in Norway in 2011 of 6.8 % [131]. With a power of 85 % and a significance level of 0.05 the required total sample size was estimated to 1800 patients. For **study 1**, we also performed a post hoc power analysis.

For **study 3**, the sample size was calculated based on the values for the Minimal Clinically Important Improvement (8 points) and the standard deviation (16.5) for the WOMAC function subscale reported by Tubach et al. [127]. With a power of 90 % and a significance level of 0.05 the required total sample size to detect a difference in the WOMAC function subscale between the study groups of at least 8 points was estimated to 185.

Sample size was not calculated for **study 2** or **study 4**.

Unadjusted analyses

For unadjusted comparisons we used Fisher's exact test (**studies 1** and **2**) or the Chi squared test (**studies 3** and **4**) for proportions, the Chi squared test for ordinal and nominal distributions, student's T test for continuous variables, and the Mann-Whitney U test for continuous variables with skewed distribution. In **study 2**, an unadjusted comparison of survival was presented as a Kaplan-Meier survival curve. The unadjusted analysis of risk factors for early and delayed deep surgical site infection in **study 2** was performed with univariable logistic regression.

Adjusted analyses

In **study 1**, other predictors than the main predictor of interest, 'fast track care', were included in the final regression model as confounders if they were statistically significant at the 0.05 level with the exception of age and sex, which were always included.

In **studies 2**, **3** and **4**, the inclusion of variables as confounders was based on directed acyclic graphs (DAG) [132]. DAGs were drawn using the online tool DAGitty [133]. **Figure 6** shows the unadjusted and the adjusted DAG for the association between duration of surgery and early and delayed deep SSI (**study 2**). **Figure 7** shows the unadjusted and the adjusted DAG for the association between surgical approach and functional outcome (**study 3**).

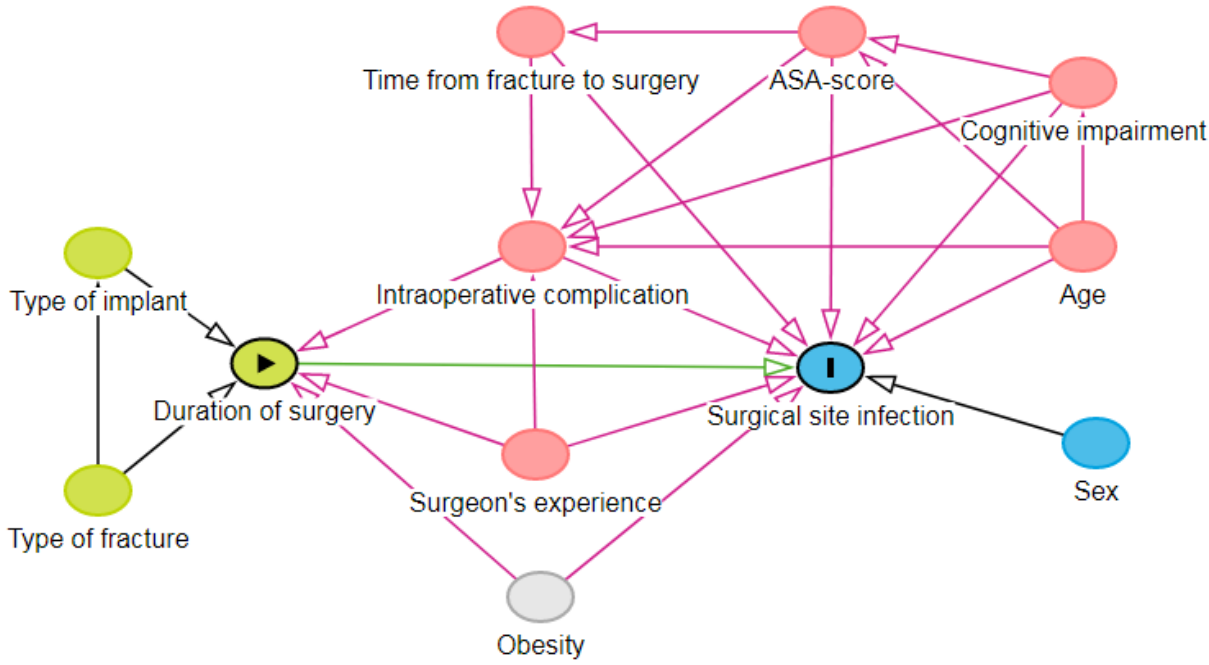
Some ordinal explanatory variables were included as binary variables. The ASA-score was dichotomized to ≤ 2 / ≥ 3 in **studies 2** and **3,** and time from fracture to surgery was dichotomized to ≤ 24 hours / > 24 hours in **study 2**.

For **studies 1** and **2**, survival analysis with Cox regression was considered for the outcome mortality, but the proportional hazard assumption was not fulfilled. Logistic regression was used for all multivariable analyses in **study 1** and for the multivariable analysis of the risk factors for early and delayed deep surgical site infection in **study 2**. Since no patients were lost to follow-up with respect to mortality, right-censoring was not an issue for the analysis of mortality with logistic regression in **study 1**. However, odds ratios overestimate the relative risk in situations with high initial risk (e.g. 1-year mortality rates after hip fracture) and large effect sizes (e. g. effect of deep surgical site infection on mortality) [134]. Therefore, the risk ratio (RR) was chosen as the statistical effect measure for the analysis of the effect of surgical site infection on mortality in **study 2** and for the analysis of the effect of the transgluteal approach on not being satisfied, and on not achieving a Patient Acceptable Symptom State for the WOMAC function score in **study 3**. In **study 2**, the risk ratio was estimated in a Poisson regression model with robust variance, as log-binomial regression did not converge [135]. Log-binomial regression was used to estimate the risk ratio in **study 3**.

Multiple linear regression was used for the adjusted analysis of the continuous outcome 'WOMAC function score' in **study 3**.

Proportional odds model multivariable ordinal logistic regression was used to analyse the ordinal outcome 'no delirium / subsyndromal delirium / delirium' in **study 4**.

A)



B)

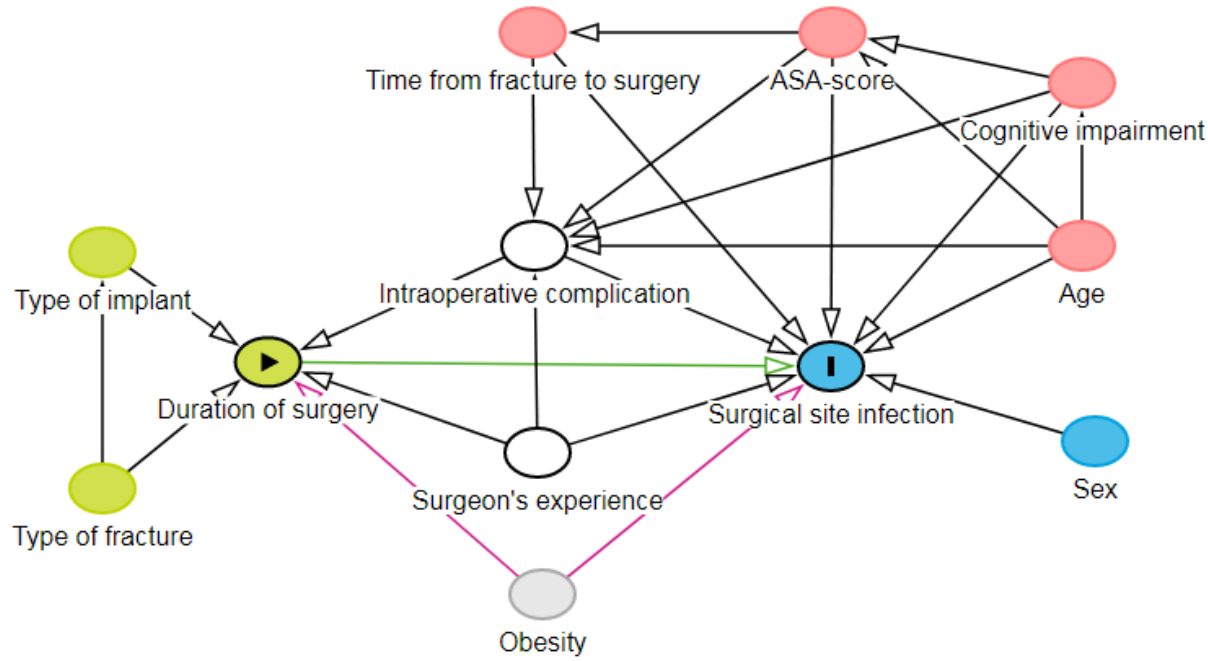
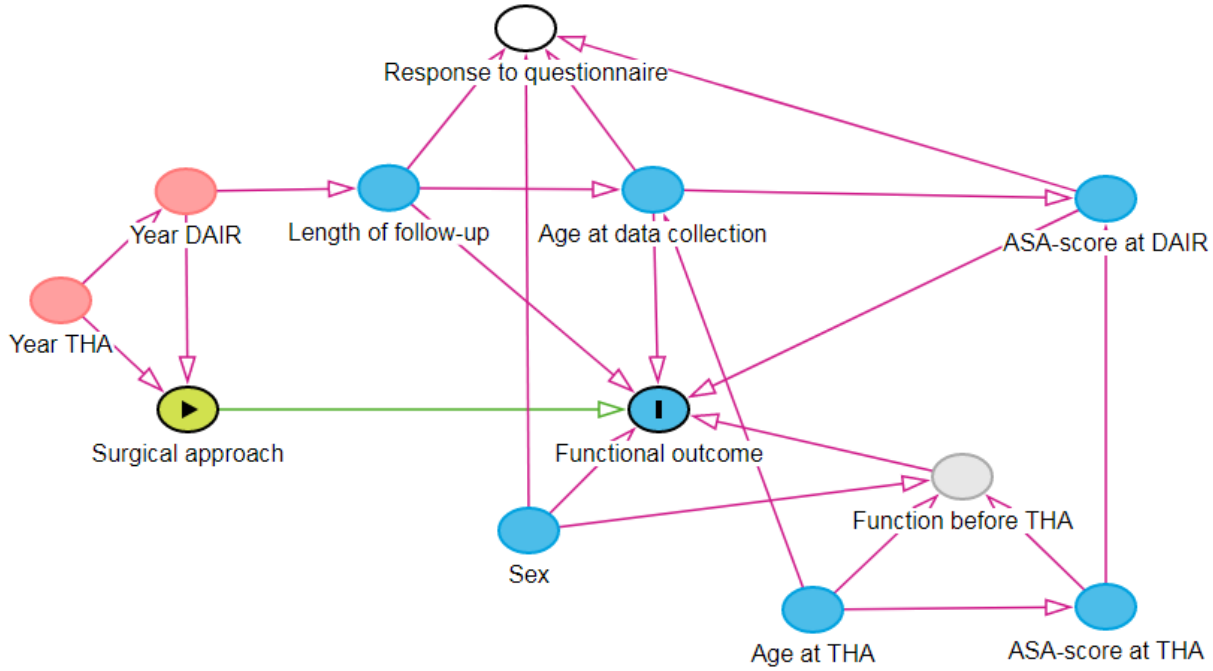


Figure 6. Directed acyclic graph depicting a causal model for the association between duration of surgery and early and delayed deep surgical site infection. exposure outcome ancestor of exposure ancestor of outcome ancestor of exposure *and* outcome (confounder) adjusted variable unobserved causal path biasing path. ASA, American Society of Anaesthesiologists. **A)** Before adjustment **B)** Adjustment for 'Intraoperative complication' and 'Surgeon's experience' controls for all observed confounders. Obesity is an unobserved confounder.

A)



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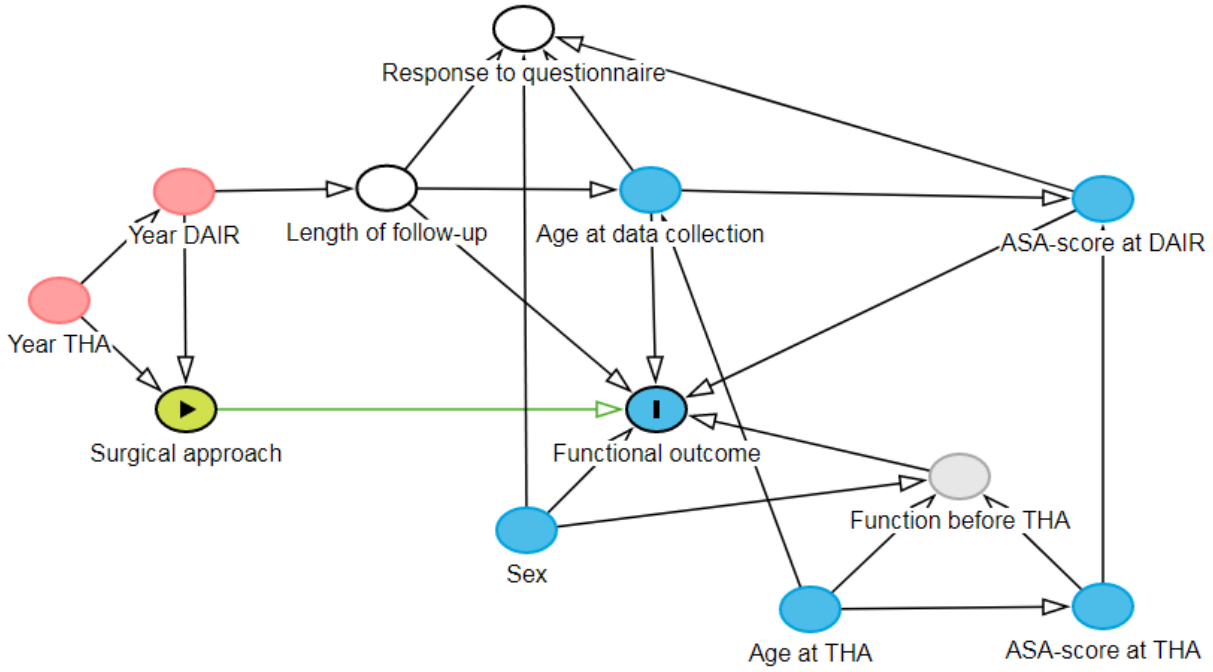

Figure 7. Directed acyclic graph depicting a causal model for the association between surgical approach and functional outcome. exposure outcome ancestor of exposure ancestor of outcome ancestor of exposure *and* outcome (confounder) adjusted variable unobserved causal path biasing path. DAIR, debridement, antibiotics, and implant retention; ASA, American Society of Anaesthesiologists; THA, total hip replacement. **A)** Before adjustment. 'Response to questionnaire' is an adjusted variable since only responders were included in the study. **B)** Adjusting for 'Length of follow-up' controls for selection bias ('Response to questionnaire'), observed, and some unobserved ('Function before THA') confounding.

Impact measures

As impact measures, the number needed to harm (NNH) was calculated in **study 3** and the number needed to treat (NNT) was calculated in **study 4**. Both measures are calculated as 1 divided by the absolute risk difference with the interpretation depending on the effect of the intervention (harmful -> NNH; beneficial -> NNT). Confidence intervals for the NNH and the NNT were derived using the Wald method.

Subgroup analysis

In **study 4**, a subgroup analysis was performed for patients with and for patients without pre-existing cognitive impairment.

Sensitivity analyses

An inherent problem with trying to establish a causal effect in observational studies is uncontrolled confounding. That is, the uncertainty if an association between an exposure and an outcome is causal or if this association is caused by an unmeasured confounder. While it is not possible to determine that an observed effect is a causal effect, one can try to quantify how much unmeasured confounding would have to be present to nullify such an observed effect. This can be achieved by calculating the E-value: “The E-value represents the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment‑outcome association, conditional on the measured covariates.” [136]

The E-value should not only be calculated for the point estimate of the effect measure (e.g. the risk ratio), but also for the limit of its confidence interval closest to 1. The latter gives the strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to move the limit of the confidence interval to 1, i.e. to render the observed association statistically non-significant.

For a risk ratio > 1 the formula is [136]:

E-value for the point estimate of the risk ratio = RR + sqrt[RR x (RR -1)]

For a risk ratio < 1 the formula is [136]:

E-value for the point estimate of the risk ratio = 1/RR + sqrt[1/RR x (1/RR -1)]

To calculate the E-value for the lower limit (RR > 1) or the upper limit (RR < 1) of the confidence interval, one simply substitutes the risk ratio by the value for the lower, respectively the upper limit of the confidence interval in the same formula [136].

Since the E-value is conditional on the measured covariates, the interpretation of the E-value not only depends on its size, but also on the covariates an analysis has been adjusted for. In other words, an E-value of the same size for the same exposure-outcome association from two different studies would be interpreted as more robust from the study, which adjusted for more relevant covariates. This is because the E-value characterizes the strength of association an *unmeasured* confounder would have to have with both exposure and outcome independent of the *measured* confounders [136].

The E-value was calculated for the effect of early deep SSI on mortality in **study 2**, for the effect of the transgluteal approach on the risk of having a WOMAC function score lower than the PASS in **study 3**, and for the effect of orthorgeriatric co-management on the incidence of SSD / delirium in **study 4**. Since the multivariable analysis in **study 4** modelled the odds ratio, the effect measure had first to be converted to an approximate risk ratio. This was achieved by a square root transformation (RR ≈ sqrt[OR]) [137].

In **study 3**, the continuous outcome measures (WOMAC function score, EQ-5D-3L-index, and EQ-VAS) showed ceiling effects and the data thus deviated somewhat from a normal distribution. Therefore, as a sensitivity analysis, all unadjusted comparisons were repeated with bootstrapping (1000 samples, bias corrected and accelerated intervals).

Summary of Results

Study 1

Mortality rates were similar in the fast track group and the conventional treatment group after 30 days (6.5 % vs. 7.9 %), 90 days (12.5 % vs. 13.5 %), and 1 year (22.8 % vs. 22.8 %). 30-day mortality decreased already before the introduction of fast track care and then levelled off (**Figure 8**).

In the fast track group, the 30-day reoperation rate was lower both in univariable (0.6 % vs. 1.7 %, p = 0.017) and in multivariable analysis adjusted for age and gender (OR = 0.35, 95% CI: 0.15 – 0.84). The reason for this, and hence the interpretation, is unclear.

While the occurrence of a 30-day composite outcome (reoperation and/or surgical site infection and/or death) was less frequent in the fast track group in univariable analysis (8.1 % vs. 10.7 %, p = 0.035), this was no longer the case in a multivariable analysis (OR = 0.85, 95% CI: 0.63 – 1.16).

In summary, while none of the outcome measures improved statistically significantly (except for the 30-day reoperation rate mentioned above), all outcome measures showed a trend towards improvement in the fast track group with the 95 % confidence intervals for the between group differences containing clinically meaningful values for all outcome measures.

The time from arrival at the hospital to arrival on the orthopaedic ward was both statistically and clinically significantly shorter in the fast track group (median 1.1 vs. 3.9 hours, p < 0.001). While waiting time to surgery was also statistically significantly shorter in the fast track group (median 23.6 vs. 25.7 hours, p < 0.001), a two-hour difference may not have been clinically relevant. The length of hospital stay was the same in both groups with a median length of stay just over 5 days.

One could speculate that the care given to hip fracture patients after hospital discharge might have an influence on 30-day mortality and that the quality of care in the primary health care sector may differ between municipalities. However, ‘municipality’, which was included as a random effect variable in the multivariable regression model, was not a significant predictor of mortality.

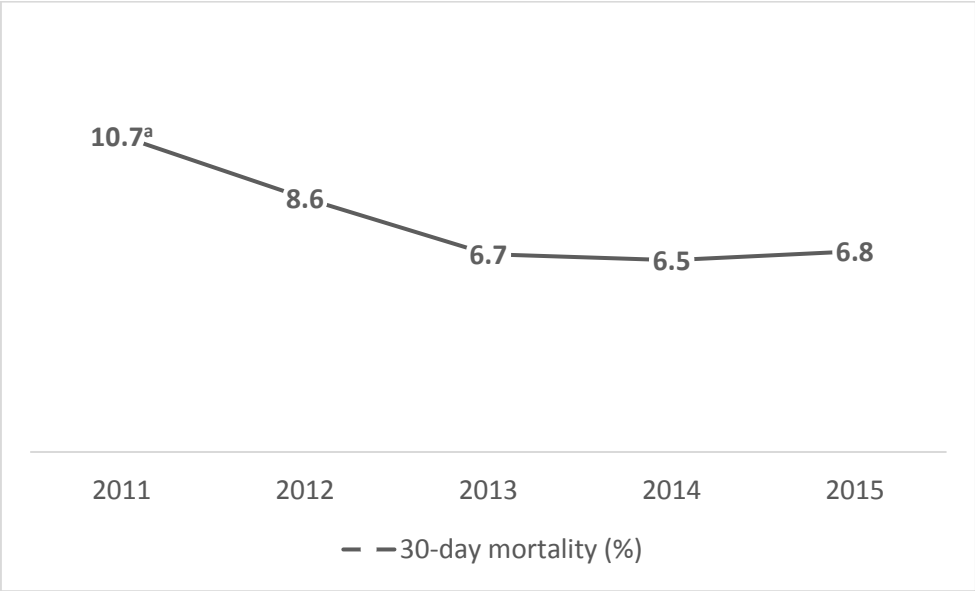

Figure 8. 30-day mortality decreased before fast track hip fracture surgery was introduced in October 2013. [a] from [131].

Study 2

The average rate of early (≤ 30 days) deep SSI during the study period was 2.2 % (38 of 1709) and was similar for hemiarthroplasties (2.4 %; 21 of 884) and sliding hip screws (2.1 %; 17 of 825).

Surgical site infection and mortality

90-day mortality increased three-fold in patients with an early deep SSI (42 % vs. 14 %; $p < 0.001$) and 1-year mortality more than doubled (55 % vs. 24 %; $p < 0.001$).

After adjusting for age, sex, cognitive impairment, ASA-score, intraoperative complications, and time from fracture to surgery, early deep SSI increased the risk of 90-day mortality by 2.4 (95%CI: 1.6 – 3.5) and of 1-year mortality by 1.8 (95%CI: 1.3 – 2.5). Hence, the excess mortality in the group of patients with early deep SSI is mostly caused by the infection itself and only to a much lesser degree by a more pronounced frailty.

The E-values were 4.2 for the point estimate of the risk ratio and 2.6 for the lower limit of its confidence interval. This indicates quite robust evidence for a causal association between early deep SSI and 90-day mortality. The corresponding E-values of 3.0 and 1.9 for the association with 1-year mortality indicate moderately robust evidence for a causal association.

Risk factors for deep surgical site infection after hip fracture surgery

Risk factors for deep SSI were analysed for early (≤ 30 days) and delayed (> 30 and ≤ 1 year) infections together. Information on delayed deep SSI was only available for hemiarthroplasties. Out of 1709 hip fracture patients, 45 patients experienced an early or delayed deep SSI.

A longer duration of surgery increased the risk of deep SSI in univariable analysis (OR = 1.9 for every 60 minutes, 95%CI: 1.1 – 3.5). However, after adjusting for observed confounders, the effect of duration of surgery was no longer statistically significant (OR = 1.5, 95%CI: 0.8 – 2.9). The absence of evidence for an association between duration of surgery and deep SSI is not evidence of absence of such an association. However, this finding underlines the uncertainty if there is a direct association between duration of surgery and deep SSI or if this association is, at least partly, due to the underlying cause for an increase in duration of surgery.

Study 3

Median follow-up after DAIR was 2.5 years in the posterior approach group and 5.5 years in the transgluteal approach group. Otherwise, the two groups were comparable.

The patients in the posterior approach group reported a better functional outcome, less limping, better health-related quality of life, and were more satisfied with their hip arthroplasty.

In an analysis adjusted for age, sex, ASA-score, and length of follow-up, the use of the posterior approach was associated with an increase in the WOMAC function score of 10.2 points (95%CI: 3.1 – 17.2), which is above the Minimal Clinically Important Improvement [127]. More patients in the posterior approach group had a WOMAC function score corresponding to a Patient Acceptable Symptom State (76 % vs. 55 %, p = 0.002). This translates into a number needed to harm of 4.8 (95%CI: 2.9 – 12.5) for the transgluteal approach. In an analysis adjusted for the length of follow-up, the transgluteal approach was associated with approximately double the risk of not achieving a Patient Acceptable Symptom State for the WOMAC function score (RR = 1.8, 95%CI: 1.2 – 3.0).

While the proportion of patients who reported that they were limping sometimes was similar in both groups (22 % posterior approach vs. 21 % transgluteal approach), the proportion of patients who reported no limping was significantly higher in the posterior approach group (61 % vs. 40 %, difference between groups: 21 %, 95%CI: 7 – 35 %).

The posterior approach group reported better hip related quality of life (mean HOOS-QoL: 74 vs. 64, p = 0.016; HOOS-QoL > PASS: 49 % vs. 33 %, p = 0.03) and better generic quality of life (mean EQ-5D-3L score: 0.79 vs. 0.71, p = 0.023). The difference in mean EQ-5D-3L score was above the Minimally Important Difference of 0.074 reported by Walters et al. [138].

75 % of patients in the posterior approach group were satisfied with their hip arthroplasty compared to 55 % in the transgluteal approach group (p = 0.001).

The E-values of 3.0 for the point estimate of the risk ratio and of 1.7 for the lower limit of its confidence interval indicate moderately robust evidence for a causal association between the

transgluteal approach and not achieving a Patient Acceptable Symptom State for the WOMAC function score.

Bootstrapping did not change the results of the unadjusted analyses of the continuous outcome measures.

Patients, who were re-revised after their DAIR procedure were excluded from this study. However, a potential difference in re-revision rates between the two surgical approaches could influence the interpretation of the difference in functional outcome. Therefore, we compared re-revision rates for the two surgical approaches in the Norwegian Arthroplasty Register. The 2-year all cause re-revision rates were similar for patients who were operated with a primary total hip arthroplasty and a subsequent DAIR through either the transglutealt approach (26 %) or the posterior approach (25 %) (p = 0.64). This indicates that the improved outcomes with the use of the posterior approach do not come at the expense of a higher re-revision rate.

Study 4

SSD and delirium were less common in the orthogeriatric group (no delirium: 59 % vs. 40 % / SSD: 6 % vs. 13 % / delirium: 35 % vs. 47 %; p = 0.021). With a dichotomized outcome ('no delirium' vs. 'SSD or delirium'), this corresponds to a NNT of 5.3 (95%CI: 3.1 – 19.7).

The patients in the usual care group and the patients in the orthogeriatric group were comparable except for a higher proportion of patients with pre-existing cognitive impairment in the usual care group (51 % vs. 37 %, p = 0.045). Pre-existing cognitive impairment is an important risk factor for the development of delirium. However, we performed a multivariable ordinal logistic regression analysis adjusted for pre-existing cognitive impairment, age, sex, ASA-score, time to surgery, type of surgery, and the occurrence of any type of complication. Also in this analysis, orthogeriatric co-management remained a significant predictor for a lower incidence of SSD/delirium (OR = 0.46, 95%CI: 0.23 – 0.89).

In a subgroup analysis, again with a dichotomized outcome, the difference in incidence of SSD or delirium was significantly lower in the orthogeriatric group for patients with pre-existing cognitive impairment (66 % vs. 85 %; p = 0.032), but not for patients without pre-existing cognitive impairment (26 % vs. 33 %, p = 0.46).

A square root transformation of the adjusted odds ratio for the incidence of SSD / delirium in the orthogeriatric group gave an adjusted risk ratio of 0.68. The E-values of 2.3 for the point estimate of the risk ratio and of 1.3 for the upper limit of its confidence interval indicate that the evidence for a

causal association between orthogeriatric co-management and a reduced incidence of SSD / delirium is not very robust.

Discussion of Main Findings

Fast track hip fracture care and mortality

Fast track hip fracture care did not significantly reduce mortality compared to conventional treatment. This is in agreement with other studies in which the focus was on fast-tracking patients to the orthopaedic ward [27, 139-141], as well as with another large observational study from Norway with a similar, comprehensive fast track system [35]. On the other hand, Pedersen et al., who also reported on a comprehensive fast track system, found a significantly reduced 1-year mortality with fast track care (12 % vs. 23 %) in a subgroup analysis of community-dwelling patients [34]. Our study had several limitations, which may have contributed to us not finding an effect of fast track surgery on mortality: Judging from the admission times, only about half of the patients followed the fast track admission pathway as intended. We do not know to what extent the other procedures of the fast track pathway were followed in individual patients. Preoperative waiting time, which probably is a risk factor for mortality in hip fracture patients [7, 28, 29, 32, 33], was only reduced by 2 hours, which may not have been clinically relevant. Finally yet importantly, the study was underpowered. The sample size calculation was based on the 30-day mortality rate at our hospital in 2011, the year preceding the study period. However, the 30-day mortality rate decreased already during the 'conventional treatment' period, before the introduction of fast track care. A post hoc analysis showed that, with a level of significance of 0.05, given the observed 30-day mortality rate of 7.9 % in the conventional treatment group and the sample size, the study had 80 % power to detect a decrease in 30-day mortality to 5.0 %. Given the observed 30-day mortality rates of 7.9 % in the conventional treatment group and of 6.5 % in the fast track group, the study would have needed a total sample size of roughly 8000 to have 80 % power to detect this difference as statistically significant at the 0.05 level.

On the other hand, this study also had some strengths. It is the largest study on the effect of fast track hip fracture care on mortality to date. In addition, the study had very limited exclusion criteria, which should convey high generalizability to the study's results. Furthermore, this was a 'real life' study using routinely collected health data and register data to investigate the effect of the introduction of fast track hip fracture care as a quality improvement measure. Thus, in contrast to interventional clinical trials, inclusion in this study should not have had any influence on the participants' outcomes [142].

In conclusion, our study seems to indicate, that the effect on mortality one can expect from introducing fast track hip fracture care as a quality improvement measure is somewhat limited. Although, one could speculate that, in a situation with a higher 30-day mortality rate under

conventional treatment, the effect of fast track care on mortality might become significant. In a situation with a 30-day mortality rate under conventional treatment in the lower range of reported rates [6, 7], fast track care might have to be combined with orthogeriatric co-management [143] and improved rehabilitation efforts [144] to significantly reduce mortality.

Surgical site infection and mortality after hip fracture surgery

Deep SSI increased mortality after hip fracture surgery. This is in accordance with findings from other studies [38, 44, 145]. The 1-year mortality rate for patients with early SSI of 55 % in our cohort was similar to the 1-year mortality rates reported by Merrer et al. [44] and by Edwards et al. [38]. While Duckworth et al. investigated risk factors for mortality in hip fracture patients with deep SSI [145], we asked if early deep SSI is an independent risk factor for mortality or if the increased mortality is due to common risk factors for both SSI and mortality. In univariable analysis, we found that early deep SSI tripled 90-day mortality and more than doubled 1-year mortality, while in multivariable analysis, early deep SSI more than doubled 90-day mortality and nearly doubled 1-year mortality. This indicates that the excess mortality after early deep SSI is mainly due to the infection itself and only to a lesser degree to factors that increase both the risk of mortality and SSI. This interpretation is also supported by the E-values for the association between early deep SSI and mortality, which indicate quite robust evidence for a causal association. Although it has to be mentioned, that the multivariable model could not be adjusted for some unobserved confounders, namely obesity [46], diabetes mellitus [145, 146] and smoking [147].

Duration of surgery and risk of surgical site infection

We found an increased risk of deep SSI with increasing duration of surgery in univariable analysis. This association has been reported in several other studies [37, 42, 49, 50] and Daley et al. have gone so far as to suggest expeditious surgical technique as a measure to reduce the risk of SSI [50]. However, De Jong et al. found an increased risk of SSI after hemiarthroplasty of the hip also for rapid surgery times (< 45 min.) [42]. This suggests that exposure time to possible bacterial contamination [51] might not be the only causative link in the association between duration of surgery and SSI. Careless tissue handling (short duration of surgery), intraoperative complications, or an inexperienced surgeon (long duration of surgery) might confound the association between duration of surgery and SSI. In a multivariable analysis of our cohort adjusted for surgeon's experience and the occurrence of any intraoperative complication, duration of surgery was no longer a significant

predictor of deep SSI. The absence of statistical significance is not straightforward to interpret and this finding cannot be taken to indicate that an association between duration of surgery and SSI does not exist. However, this result gives an indication that the association between duration of surgery and SSI may be more complex and might be partly confounded by the underlying reason(s) for a deviation in duration of surgery from the norm. This view is supported by two register studies on revisions due to deep infection of total knee arthroplasties, which both concluded that, after adjustment for confounders, the effect of duration of surgery in itself on the risk of deep SSI was weak [148, 149].

Surgical approach and functional outcome after DAIR for infected total hip arthroplasty

After a single, successful DAIR-procedure, patients operated with the posterior approach during both the primary arthroplasty and the revision procedure were more satisfied with their hip arthroplasty and reported a better functional outcome, less limping, and better health-related quality of life compared to patients in whom both surgeries were performed through the transgluteal approach. Other authors have reported similar findings when comparing the posterior to the transgluteal approach for primary total hip arthroplasty [78-80]. Of note, the differences in patient satisfaction [79], WOMAC function score [80], limping [78], and health-related quality of life [78, 79] between the two surgical approaches were more pronounced in our study. This is not surprising when one considers the probable causes for worse outcomes with the transgluteal approach, namely abductor insufficiency and heterotopic ossification. These are known complications already after primary hip arthroplasty through the transgluteal approach [150-155]. Revision surgery through the transgluteal approach has been shown to lead to progressive damage of the gluteus medius muscle [93] and deep SSI is an additional risk factor for heterotopic ossification [156, 157]. Thus, the more pronounced differences in patient reported outcomes between the posterior and the transgluteal approach after DAIR compared to primary hip arthroplasty are probably due to an increased incidence of gluteus medius insufficiency and heterotopic ossification after DAIR through the transgluteal approach.
The functional outcome, generic health-related quality of life, and patient satisfaction in the posterior approach group were comparable to reported outcomes after primary total hip arthroplasty [79, 128]. This is in accordance with findings by Grammatopoulos et al., who found that patients treated with a single, successful DAIR procedure through either a posterior or anterolateral (Watson-Jones) approach had an Oxford hip score comparable to patients after primary total hip arthroplasty [91].

Only 2 % of the patients in our study received their primary total hip arthroplasty to treat an acute femoral neck fracture. Nonetheless, the results of this study may have some implications for the surgical treatment of hip fracture patients. As elucidated in the background chapter, there is still some controversy over the best surgical approach for fracture related hip arthroplasty. While good evidence exists for a higher dislocation risk with the posterior approach [67, 70-75], some evidence suggests worse functional outcome with the transgluteal approach [69, 77]. Jobory et al. conducted a large register study comparing the use of a conventional with a dual-mobility acetabular cup in fracture related total hip arthroplasty [158]. The study included 9020 patients of whom three quarters had been operated through the posterior approach. The authors reported a significantly reduced risk of revision due to dislocation with the use of a dual mobility cup. One could speculate that fitter hip fracture patients, who are operated with a total hip arthroplasty by an arthroplasty surgeon [159], might fare better functionally with a posterior approach in combination with the use of a dual mobility cup to reduce the risk of dislocation. Since the risk of deep SSI is higher in hip fracture patients than in elective arthroplasty patients [43, 81], our findings of better outcomes after DAIR through the posterior approach add a little more weight to the balance in favour of the posterior approach for fracture related total hip arthroplasty.

However, for the majority of hip fracture patients, who are elderly and frail, the choice of surgical approach for hip arthroplasty will be governed by slightly different considerations. In these patients, both, the risk for gluteus medius insufficiency after the transgluteal approach, and the risk of dislocation after the posterior approach is probably increased. The direct anterior, Smith-Petersen approach could be an alternative [160], but this approach has a long learning curve [161]. Another alternative, at least for hemiarthroplasty, might be the SPAIRE approach [162], a modified posterior approach in which only the tendon of the obturator externus is released and subsequently reinserted. This approach might be able to combine the functional advantages of not releasing the gluteus medius tendon with a significantly increased stability compared to a traditional posterior approach. A randomized controlled trial comparing the SPAIRE approach to the transgluteal approach for hemiarthroplasty in hip fracture patients is ongoing [163].

Orthogeriatric co-management and delirium

After the introduction of orthogeriatric co-management as an integrated care model [96] at our institution, fewer hip fracture patients developed SSD or delirium with a NNT of 5.3 (95%CI: 3.1 – 19.7). The effect of orthogeriatric co-management remained significant after adjusting for several known confounders, including pre-existing cognitive impairment. Since delirium and SSD are

common in hip fracture patients and are associated with negative outcomes including cognitive decline [112-115], this is a clinically relevant finding. Of note, the effect of orthogeriatric co-management was seen although the usual care it was compared to consisted of the previously described comprehensive fast track hip fracture care pathway.

The evidence concerning the effect of orthogeriatric co-management on the incidence of delirium in hip fracture patients is somewhat ambiguous. Of four previously published randomized controlled trials, two showed a significant effect [103, 104], one was inconclusive [99], and one showed no effect [97]. Of three previously published observational studies, one showed a significant effect [105], one was inconclusive [106], and one showed no effect [107]. One also has to bear in mind that orthogeriatric co-management 'comes in different shapes and sizes', which makes the reproduction of results more difficult. On the other hand, a systematic review of the four abovementioned randomized controlled trials concluded that comprehensive geriatric assessment reduces the incidence of delirium in hip fracture patients (RR = 0.81, 95%CI: 0.69 – 0.94) [164]. Our findings give further support to this conclusion.

In our study, the effect of orthogeriatric co-management was most pronounced in patients with pre-existing cognitive impairment. In contrast, Marcantonio et al. reported a trend towards a more pronounced effect in patients without pre-existing cognitive impairment [103]. Thus, from the existing evidence one cannot conclude if certain subgroups of hip fracture patients are more probable to benefit from orthogeriatric co-management.

Methodological Considerations

General methodological considerations

P-values and probability of true research findings

The American Statistical Association published a "Statement on Statistical Significance and P-Values" in 2016 [165]. This statement sought to clarify that, while the p-value is a measure of the incompatibility of an observed set of data with a so-called null hypothesis under a specified statistical model, it does not measure the probability that the studied alternative hypothesis is true. The statement also specified that "scientific conclusions … should not be based only on whether a *p*-value passes a specific threshold" (such as $p < 0.05$).

In their 2019 editorial in The American Statistician, Wasserstein et al. recommended that the use of the term 'statistically significant' and its derivatives should be abandoned altogether [166]. However, the frequentist approach to medical statistics and the reliance on p-values is still predominant in the medical literature and the studies presented here are no exception. While we made efforts to avoid some of the pit-falls of relying on p-values by reporting exact p-values, confidence intervals, Minimally Clinically Important Improvement (**study 3**), Patient Acceptable Symptom State (**study 3**), and E-values (**studies 2**, **3**, and **4**), our conclusions were still largely influenced by the measured p-values.

In a special issue in the American Statistician entitled 'Statistical Inference in the 21st Century: A World Beyond $p < 0.05$' (with the abovementioned editorial by Wasserstein et al. [166]), Colquhoun proposed 'the false positive risk' as a possible supplement to the p-value [167]. Colquhoun explains how, by invoking Bayes' theorem, one can calculate the probability that the result of a single unbiased statistical test is based on chance (a false positive). Longstaff and Colquhoun provide a web calculator [168], which calculates the 'false positive risk' from the observed p-value, the prior probability of a real effect, the sample size, and the standardized effect size. As an example, using this calculator for the main outcome measure in **study 3** (mean (SD) WOMAC function score: 71 (26) vs. 80 (22), $p = 0.013$), postulating a 0.5 prior probability (50 : 50 chance that the hypothesized effect exists) the 'false positive risk' is 0.08. While this would not necessarily change the interpretation of the study, an 8 % risk of a false positive result is considerably larger than if one were to misinterpret the measured p-value of 0.013 in the same way. However, this 'false positive risk' does not consider possible bias and represents thus a 'minimum false positive risk'.

In his 2005 assay, Ioannidis claimed that "most published research findings are false" [169]. A humbling statement for everyone involved in research. Ioannidis went on to demonstrate that the

probability of a research finding being true increases with the pre-study probability of a true relationship, the study size, and the effect size, and decreases with the level of bias [169]. According to Ioannidis, the positive predictive value for a research finding from an adequately powered, well conducted, randomized controlled trial with a 0.5 prior probability is only about 85 %. Applying the examples given in his assay, the post study probabilities of a true effect for the studies presented in this thesis probably lie between 60 % and 80 % with the exception of the analysis of risk factors for SSI after hip fracture surgery, which might have a post study probability of a true effect as low as 20 %.

Interpreting confidence intervals

Not only p-values, but also confidence intervals have come under criticism. Morey et al. demonstrate that confidence intervals, which are derived by frequentist statistical methods, do not have the properties, which they are commonly ascribed [170]. The authors conclude: "Claims that confidence intervals yield an index of precision, that the values within them are plausible, and that the confidence coefficient can be read as a measure of certainty that the interval contains the true value, are all fallacies and unjustified by confidence interval theory". In contrast, the authors argue that Bayesian credible intervals do allow these inferences and should therefore be preferred to confidence intervals [170]. However, further discussion of this subject is beyond the scope of this thesis and the statistical expertise of its author.

Observational versus experimental study design

An experimental study design, that is a randomized controlled trial, would have been methodologically preferable to the employed observational designs in **studies 1**, **3**, and **4**. For **study 1**, the main reason for this shortcoming was that the fast track patient pathway already was well established when the study was conceived. It would thus have been challenging, both practically and ethically, to revert to 'conventional treatment' for half of our hip fracture patients. **Study 2** was an epidemiological study and an observational design was therefore warranted. Concerning **study 3**, a randomized controlled trial with the same research question would have had to be a multicentre, multinational trial in order to achieve sufficient power. Such a trial would have been difficult to conduct and would have required more resources than were available to us. For **study 4**, the research question was formulated after the data had been collected.

For **studies 2**, **3**, and **4**, we tried to address the higher risk of bias in observational studies by determining confounders to be adjusted for from causal graphs [132, 133] and by presenting E-values [136] (see also *Statistics, Adjusted analyses and Sensitivity analysis*).

There is also an argument to be made, that “real world data” from well-conducted observational studies have their place in evidence based medicine and are not necessarily inferior to randomized controlled trials [171].

Table 2 fallacy

The aim of a causal model for the effect of an exposure on an outcome is to control for confounding. However, even in a ‘correct’ causal model for the exposure-outcome relationship, the effect of covariates on the outcome might still be confounded [172]. Therefore, in a multivariable regression model, the effects of covariates on the studied outcome cannot readily be interpreted in the same way as the effect of the studied exposure on the outcome [172]. This misinterpretation of the effects of covariates has been termed ‘table 2 fallacy’ (since these data often are presented in a ‘table 2’) [172]. To avoid this confusion, it has been suggested that only the effect measure for the studied exposure should be presented, at least in the primary manuscript [132, 172].
Alas, we did not heed this advice in the first two studies. In **study 1**, we did not present a causal graph and did present a ‘table 2’ for mortality (table 4 in the article) with effect measures for several covariates. In **study 2**, we did present causal graphs, but did also present a ‘table 2’ for mortality (table 4 in the article). In **studies 3** and **4**, we presented causal graphs and only reported the effect measure for the studied exposure in the primary manuscript.

Specific methodological considerations

Study 1

We considered an interrupted time series analysis [173]. This would have been important if the mortality rate had clearly improved after introducing fast track hip fracture care. An interrupted time series analysis could then have determined if an improved mortality with fast track care could have been explained by a time trend or if fast track care had an additional, significant effect. However, since mortality improved before the introduction of fast track care and then levelled off, an interrupted time series analysis would not have provided additional information.
All outcome measures showed a “trend” towards improvement in the ‘fast track group’. However, talking about a “trend” in frequentist statistical hypothesis testing is unconvincing. A Bayesian instead of a frequentist statistical analysis might have helped with interpreting the study’s results since it would have allowed stating the probability of a specified effect of fast track care (for example the probability of a 1 % absolute reduction in mortality risk with fast track care is xy %) [174].

Study 2

The analysis of the influence of duration of surgery on the risk of SSI was hampered by several caveats. While information on early infections was available for patients operated with sliding hip screws as well as for patients operated with a hemiarthroplasty, information on delayed SSI was only available for the latter. Only 45 patients of our cohort experienced a deep SSI. This limited number of 'cases' confined the number of variables that could be included in the multivariable regression model and reduced the power of the analysis. In addition, information on at least one possible confounder of the association between duration of surgery and SSI, namely obesity, was unavailable. Further, as already mentioned in the discussion of the study's results, the fact that the association between duration of surgery and SSI was statistically significant in univariable analysis, but did not remain so in multivariable analysis has to be interpreted with caution. In light of these limitations, we tried to moderate our conclusion. However, one could argue that even the presented conclusion is still somewhat bold considering the data.

Study 3

As mentioned in the 'Discussion of Main Findings' section, only 2 % of the patients in this study had received their total hip arthroplasty for an acute hip fracture and hence, the results may not be directly transferable to arthroplasties performed in hip fracture patients. However, it would not have been feasible to include only hip fracture patients in this study. Compared to patients undergoing elective hip arthroplasty, the number of hip fracture patients operated with an arthroplasty is considerably lower [12], fewer hip fracture patients are operated through the posterior approach [12], and hip fracture patients have a higher mortality rate [175]. As the study already was nationwide and included patients operated as long ago as 1990, it would not have been possible to conduct a sufficiently powered study when restricting the study to hip fracture patients.

An important limitation of this study was the lack of baseline data for the patient reported outcomes. It was thus not possible to analyse any change in outcome measures from baseline to follow-up. On the other hand, according to the DAG, which we drew for this study, adjusting for 'length of follow-up' controlled for 'function before THA'. However, if 'function before THA' differed according to the 'year of THA' (which the DAG does not take into account), some confounding from 'function before THA' would still have been present. We also analysed the proportion of patients in each study group, who achieved a Patient Accepted Symptom State for the functional outcome and health-related quality of life, which can be determined without the need for baseline values [176]. However, baseline values may still influence the probability of achieving a Patient Accepted Symptom State.

The sample size calculation for this study was based on the Minimal Clinically Important Improvement (MCII) for the WOMAC function subscale as reported by Tubach et al. [127]. Tubach et al. used an anchor-based method to determine the MCII, which is methodologically preferable to distribution-based methods [177]. Terwee et al. analysed the variation of the Minimal Important Change (which is conceptually comparable to the MCII [178]) for the WOMAC function subscale and found a considerable variation between studies [177]. However, Tubach et al. showed that the variability in values for the Minimal Clinically Important Difference has little effect on the estimation of treatment effect values [179].

We related the difference in WOMAC function score between the study groups to the MCII. This is methodologically somewhat problematic since the MCII should be applied to individual changes, not to changes in group-means or to differences in group-means [178]. However, as mentioned above, we were not able to analyse change in outcome measures on an individual basis due to the lack of baseline data. Therefore, in lieu of not making a statement on the clinical relevance of our findings at all, we chose to relate the mean difference in WOMAC function score to the MCII.

Study 4

As detailed in the 'Patients and Methods' section, the patients in this study were originally recruited for a study of delirium pathophysiology which had sampling of cerebrospinal fluid as a prerequisite. Due to the somewhat difficult logistics of obtaining and processing cerebrospinal fluid, only about 13 % of eligible hip fracture patients were included in the original study and hence in study 4. This raises the question if our study sample was representative for the studied population. We found that the included and excluded patients were comparable with respect to age, sex, patients with ASA-score ≥ 3, and fracture types. However, some extent of selection bias may still have been present.

Study 4 was a 'before and after' study comparing a cohort of hip fracture patients under usual care with a cohort after the introduction of orthogeriatric co-management. However, after the introduction of orthogeriatric co-management, due to capacity limits, not all patients were treated by a multidisciplinary team. Our data suggest that approximately 70 % in the orthogeriatric group did receive a multidisciplinary intervention. Albeit, for two reasons we decided to treat all hip fracture patients after the introduction of orthogeriatric co-management as the 'orthogeriatric group': i) Since the orthopaedic surgeons and nurses rotated in and out of the orthogeriatric team, we postulated a considerable spill-over effect to patients not directly receiving multidisciplinary care [180]. ii) There was a certain selection of patients, who received orthogeriatric co-management, towards frailer and more complex patients, which would have introduced considerable bias.

Ethics

Ethical Approvals

Study	Institution	Type of approval	Date	Reference no.
1	Regional Ethics Committee South East	Deemed to not require REC approval	15.04.2015	2015/409
		Change study 1 – Deemed to not require REC approval	18.09.2015	2015/409
	Data Protection Officer, Akershus University Hospital	Approval study 1	07.10.2015	15-046
		Change study 1	11.04.2018	15-046
2	Regional Ethics Committee South East	Change to study 1 -> study 2 Deemed to not require REC approval	21.11.2018	2015/409
	Data Protection Officer, Akershus University Hospital	Change to study 1 -> study 2	11.03.2019	2015_046
3	Regional Ethics Committee South East	Deemed to not require REC approval	05.04.2017	2017/432
	Data Protection Officer, Akershus University Hospital	Approval study 3	05.05.2017	17-062
4	Regional Ethics Committee Central	Approval of original CSF-study	05.10.2016	2016/1368
		Change -> study 4	26.01.2017	2016/1368
		Change	19.06.2017	2016/1368
		Change	05.02.2018	2016/1368
	Data Protection Officer, Akershus University Hospital	Approval	23.03.2017	17-071

REC, Regional Ethics Committee.

Trial registration

Study 1 was registered retrospectively at ClinicalTrials.gov (ID: NCT02986399) 6 December 2016. **Study 3** was registered at ClinicalTrials.gov (ID: NCT03161990) 15 May 2017. **Studies 2** and **4** were not registered.

Ethical Considerations

Studies 1 and **2** were observational studies, using routinely collected health data and register data. Hence, data collection did not involve patient contact and the studies had no influence on treatment or follow-up.

Study 3 was also an observational study and had no influence on patient treatment or follow-up. However, potential participants received a consent form and a questionnaire by postal mail. Patients, who did not wish to participate, were asked to return the uncompleted questionnaire by reply-paid envelope. The questionnaire was posted once again to patients who did not respond at all. The possible disadvantages for the individual patient were the time used to read and complete the consent form and the questionnaire. In addition, if the patient had been traumatized by the surgical site infection and treatment thereof, being reminded of this through the study may have been stressful.

Study 4 was observational as well. The original study, for which these patients were recruited, required the sampling of cerebrospinal fluid during the spinal anesthesia before hip fracture surgery. This entailed a small increase in the risk of a post-tap spinal headache compared to spinal anesthesia alone. The Regional Ethics Committee considered this to be acceptable.

Participation in the study also involved daily cognitive tests conducted by the study nurses. This may have felt cumbersome to some patients. On the other hand, the study participants may also have profited from improved detection of subsyndromal delirium and / or delirium, which should have promoted adequate interventions.

The study required informed consent. However, the Regional Ethics Committee allowed the inclusion of cognitively impaired patients under the condition that informed consent was obtained from the patient's family. The inclusion of patients who lack the competency to consent can be ethically problematic. However, the possible risks and disadvantages of participation in this study were of minor character. Conversely, not including cognitively impaired patients in relevant studies is also ethically problematic. Up to 50 % of hip fracture patients are cognitively impaired [97, 111].

Excluding these patients from a study with a highly relevant research question for this group of patients could be considered unethical.

On a societal level, a possible disadvantage of conducting the presented studies would be the use of the required resources. However, this disadvantage should be weighed-up by the generated data and insights.

Data were handled in compliance with the requirements from the local data protection officer.

Competing interests

None of the authors of the four articles included in this thesis had any financial or other obvious competing interests. However, it might be judicious to mention the following facts, which had the potential to introduce involuntary bias:

Concerning study 1: I headed the task force responsible for developing and implementing fast track hip fracture care.

Concerning study 2: I am more a meticulous than a fast surgeon.

Concerning study 3: I initiated the switch from the transgluteal to the posterior surgical approach to the hip joint in our department.

Concerning study 4: I represented the orthopaedic department in the task force responsible for developing and implementing orthogeriatric co-management.

Conclusions

Room for improvement exists in hip fracture care. This is not only true for the operative treatment, including the choice of implants, but it is especially true for the perioperative treatment of hip fracture patients. The perioperative care should be standardized, multidisciplinary, and address a wide variety of aspects including opiate-sparing pain management, fluid homeostasis, bowel function, nutrition, medication review, prevention and detection of delirium, early mobilization, fall prevention, and discharge planning.

Fast-tracking hip fracture patients to the orthopaedic ward increased neither complications nor readmissions and seems to be safe. Although all outcome measures in our study showed a numerical trend towards improvement, we found no clear reduction in 30-day mortality. Thus, the effect of fast track hip fracture care on mortality seems to be limited, which is in accordance with previous studies. However, a post-hoc analysis showed that our study was underpowered.

Orthogeriatric co-management as an integrated care model reduced the incidence of subsyndromal delirium / delirium with a NNT of 5.3 (95%CI: 3.1 – 19.7) in our cohort. Considering this result in the context of previous evidence, a clinically relevant effect of orthogeriatric co-management on the incidence of delirium is probable, but not certain.

Surgical site infection is a potentially devastating complication after hip fracture surgery. In multivariable analysis, a deep surgical site infection increased 90-day mortality by 2.4-fold. Therefore, preventing surgical site infections should be considered an essential part of hip fracture care.

The role of the duration of surgery as a risk factor for surgical site infection is still up for debate. Our data, in conjunction with other reports, may indicate that the elapsed time during surgery could be less important than the reason for a prolonged operation.

When a deep surgical site infection after total hip arthroplasty is treated with debridement, antibiotics, and implant retention, the surgical approach to the hip joint is important for the functional result. Patients in whom the primary arthroplasty and the DAIR procedure were performed through the posterior approach had better function, better health-related quality of life, and were more likely to be satisfied with their hip arthroplasty compared to patients operated with the transgluteal approach. The observed differences were clinically relevant. The improved outcomes with the use of the posterior approach did not come at the expense of a higher re-revision rate.

However, since hip fracture patients operated with a total hip arthroplasty differ from elective total hip arthroplasty patients, it is unclear to what extent this finding can be extrapolated to hip fracture patients.

Future Perspectives

Well conducted, adequately powered, randomized controlled trials would be ideal to investigate the effect of fast track hip fracture care on mortality and of orthogeriatric co-management on the incidence of delirium after hip fracture. However, such trials would meet several challenges. It might be difficult to recruit patients for a trial if one possible outcome of participation is a four-hour wait in the emergency department (fast track) or to forego multidisciplinary treatment (orthogeriatric co-management). Along the same line of thought, this would also pose ethical dilemmas. Therefore, large, register-based, observational studies might be a more realistic alternative. Ideally, questions about fast track care and orthogeriatric co-management could be included in the questionnaires from national registers. Data analysis should make use of an appropriate matching technique [181] and Bayesian statistics.

Hansson et al. reported that only 30 % of a cohort of Swedish hip fracture patients were satisfied with their rehabilitation [141]. This indicates a need for improvement, and probably a need for more research into this topic.

Pharmacological secondary prophylaxis after hip fracture with antiresorptive drugs has been shown to be effective [182, 183]. Fracture liaison services are one way to assure that hip fracture patients receive secondary prophylaxis [184]. However, questions about logistics and timing remain, some of which might be answered by the ongoing NoFRACT study [185].

The best surgical approach for fracture related hip arthroplasty is still up for debate. For fracture related total hip arthroplasty, a posterior approach using a dual mobility cup might be a good solution. This could be investigated in large register studies. For hemiarthroplasty of the hip, a SPAIRE approach (Save Piriformis and Internus, Repairing Externus) might be superior to both the transgluteal and the classic posterior approach. While this is being investigated in an ongoing trial [163], a positive result would have to be confirmed by other investigators.

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Supplementary Material Articles 2, 3, and 4

Article 2

Supplementary data

Table 2. Surgical treatment. Values are n (%) unless otherwise specified

Factor	Entire cohort (n = 1,709)	Survivors at 90 days (n = 1,459)	Deceased at 90 days (n = 250)	No SSI (n = 1,664)	SSI (n = 45)
Hours from fracture to surgery					
0–6	11 (0.6)	9 (0.6)	2 (0.8)	11 (0.7)	–
>6–12	115 (6.7)	105 (7.2)	10 (4.0)	113 (6.8)	2 (4.4)
>12–24	514 (30)	449 (31)	65 (26)	504 (30)	10 (22)
>24–48	698 (41)	590 (40)	108 (43)	678 (41)	20 (44)
>48	302 (18)	248 (17)	54 (22)	290 (17)	12 (27)
Not reported	69 (4.0)	58 (4.0)	11 (4.4)	68 (4.1)	1 (2.2)
Type of anesthesia					
Spinal	1,476 (86)	1,258 (86)	218 (87)	1,435 (86)	41 (91)
General	152 (8.9)	131 (9.0)	21 (8.4)	149 (9.0)	3 (6.7)
Other	59 (3.5)	51 (3.5)	8 (3.2)	58 (3.5)	1 (2.2)
Not reported	22 (1.3)	19 (1.3)	3 (1.2)	22 (1.3)	–
Type of procedure					
Hemiarthroplasty	884 (52)	753 (52)	131 (52)	856 (51)	28 (62)
Sliding hip screw	825 (48)	706 (48)	119 (48)	808 (49)	17 (38)
Surgeon's experience					
≤ 3 years	209 (12)	176 (12)	33 (13)	203 (12)	6 (13)
> 3 years	1427 (84)	1219 (84)	208 (83)	1,388 (83)	39 (87)
Not reported	73 (4.3)	64 (4.4)	9 (3.6)	73 (4.4)	–
Intraoperative complication					
No	1,524 (89)	1,305 (89)	219 (88)	1,487 (89)	37 (82)
Yes	126 (7.4)	103 (7.1)	23 (9.2)	119 (7.2)	7 (16)
Not reported	59 (3.5)	51 (3.5)	8 (3.2)	58 (3.5)	1 (2.2)
Duration of surgery [a]					
median	64	65	60	64	65
range	16–241	16–241	19–144	16–209	30–241

Percentages are column percentages; SSI: early (sliding hip screws) and early and delayed (hemiarthroplasties) deep surgical site infection;
[a] Time from incision to skin closure in minutes.

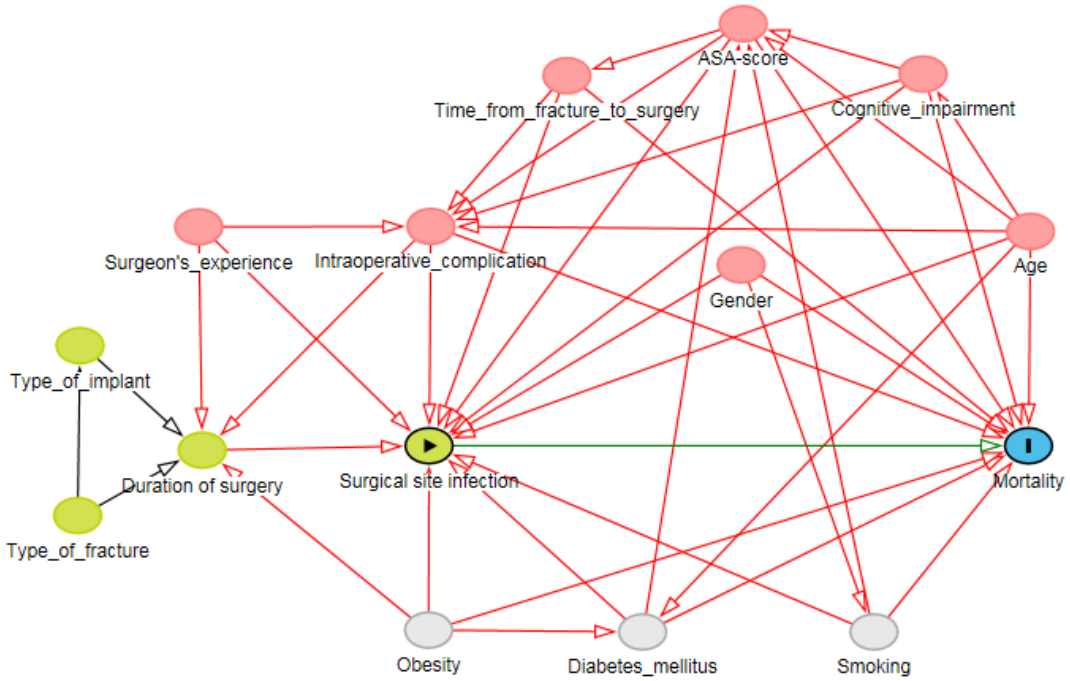

Figure 3a. Directed acyclic graph depicting a causal model for the association between early deep surgical site infection and mortality. exposure; outcome; ancestor of exposure; ancestor of exposure *and* outcome (confounder); unobserved; causal path; biasing path.

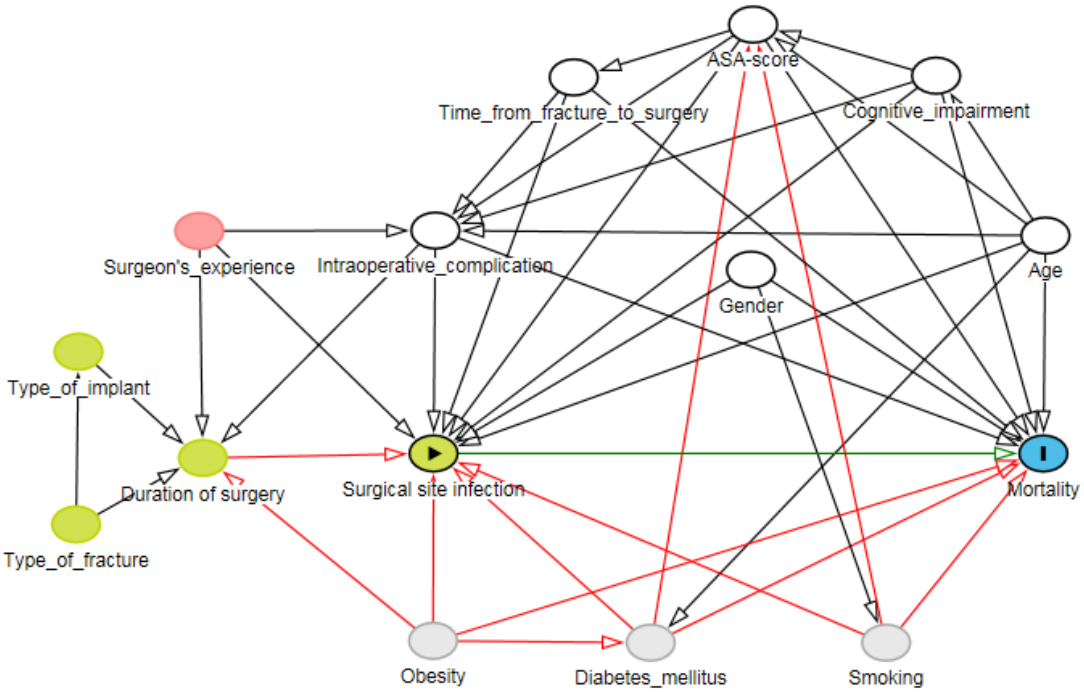

Figure 3b. Directed acyclic graph depicting the adjustment for observed confounding of the association between early deep surgical site infection and mortality. For symbols, see Figure 3a and adjusted variable.

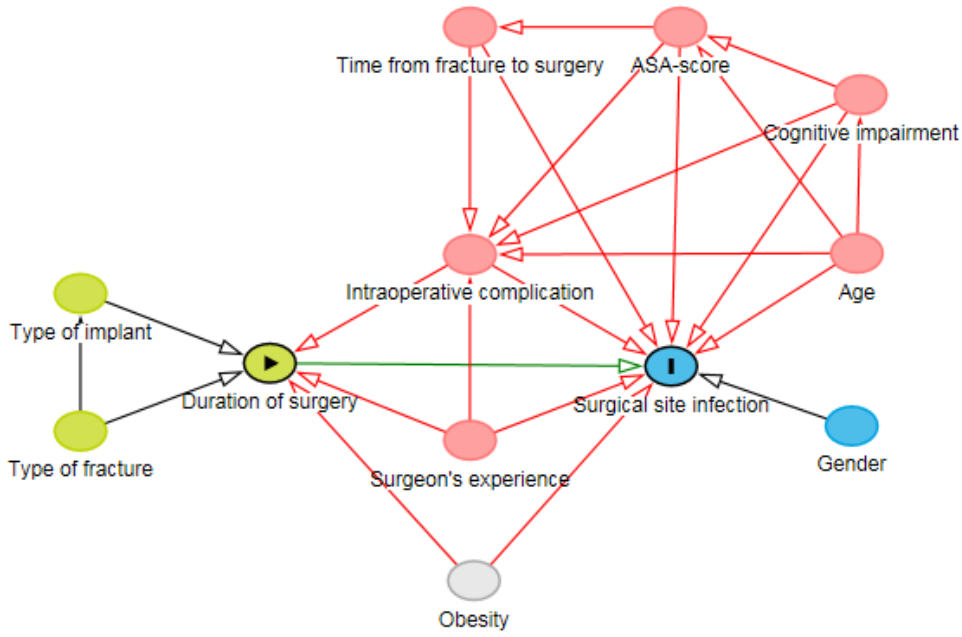

Figure 4a. Directed acyclic graph depicting a causal model for the association between duration of surgery and early and delayed deep surgical site infection. exposure; outcome; ancestor of exposure; ancestor of outcome; ancestor of exposure *and* outcome (confounder); unobserved; causal path; biasing path.

(This figure corresponds to **Figure 6 A** in the main text of this thesis.)

Table 5. Univariable binary logistic regression analysis of risk factors for early and delayed deep surgical site infection

Factor	Early and delayed deep SSI [a] Odds ratio (CI)	p-value	Missing (%)
Cognitive impairment		0.05	2.6
uncertain	2.6 (1.2–5.8)	0.02	
yes	1.6 (0.8–3.4)	0.2	
Intraoperative complication	2.4 (1.03–5.4)	0.04	3.5
Duration of surgery (hours)	1.9 (1.1–3.5)	0.04	–
ASA score ≥ 3	2.2 (0.98–5.0)	0.06	2.1

[a] Early (sliding hip screws) and early and delayed (hemiarthroplasties) deep surgical site infection.
ASA: American Society of Anesthesiologists.

Table 6. Multivariable binary logistic regression analysis of the association between duration of surgery and early and delayed deep surgical site infection

Factor	Early and delayed deep SSI [a] Odds ratio (CI)	p-value
Duration of surgery (hours)	1.5 (0.8–2.9)	0.2
Intraoperative complication	2.1 (0.9–4.9)	0.1
Surgeon's experience [b]	0.9 (0.4–2.2)	0.9

[a] Early (sliding hip screws) and early and delayed (hemiarthroplasties) deep surgical site infection.
[b] At least 1 surgeon with more than 3 years of experience in hip fracture surgery; 7.1% missing.

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Supplementary Material

<10.1302/0301-620X.102B12. BJJ-2020-0501.R1>

Non-standard questions in the questionnaire (translated from Norwegian)

1. According to the Norwegian Arthroplasty Register you have had a hip replacement and you have been reoperated once in this hip to treat a deep infection. Is this correct.

Possible answers: Yes / No; if not, what is incorrect? (free text field)

2. As far as you know, has the infection been eradicated?

Possible answers: Yes / No / Do not know

3. Has the hip in question been operated again for other reasons than infection?

Possible answers: Yes / No; if yes, do you remember what for? (free text field)

4. Were you limping (on the side in question) before you got the hip replacement?

Possible answers: Always / sometimes / never / do not remember

5. Were you limping between having had your hip replacement and being reoperated?

Possible answers: Always / sometimes / never / do not remember

6. Are you limping now (on the side in question)?

Possible answers: Always / sometimes / never

7. As far as you know, have you suffered nerve damage during one of your hip operations?

Possible answers: Yes / No / Do not know

8. Have you had a dislocation of your hip replacement such that the prosthesis had to actively be put back in place?

Possible answers: Yes / No

Online Resource 1 Comparison of patient characteristics by inclusion status

	Patients included in the study (n = 197)	**Patients not included in the study** (n = 1441)	**Difference between groups** (with 95%CI)	**p-value[b]**
Age, years, mean (SD)	78.2 (10.0)	79.4 (11.6)	1.2 (-0.4 to 2.7)	0.14
Female sex, n (%)	121 (61)	953 (66)	5 % (-2 to 12)	0.19
ASA-score ≥ 3, n (%)	91 (46)	663[a] (52)	6 % (-1 to 14)	0.10
Type of fracture, n (%)				0.79
Femoral neck	121 (61)	877 (61)	0 % (-8 to 7)	
Trochanteric	65 (33)	465 (32)	-1 % (-8 to 6)	
Subtrochanteric	11 (6)	99 (7)	1 % (-2 to 5)	

CI - confidence interval; ASA - American Society of Anesthesiologists; [a]of 1265 (11% missing); [b]Independent samples t-test or chi-squared test as appropriate

Online Resource 2 Multivariable ordinal logistic regression of the outcome 'no delirium / subsyndromal delirium / delirium'

	'no delirium / subsyndromal delirium / delirium'	
	Odds ratio (95%CI)	**p-value**
Orthogeriatric co-management	0.46 (0.23 – 0.89)	0.023
Pre-existing cognitive impairment	4.55 (2.31 – 9.13)	< 0.001
Age (years)	1.06 (1.02 - 1.11)	0.002
ASA-score		
1	1.41 (0.19 – 7.20)	0.70
2	1[a]	
3	3.62 (1.76 – 7.62)	0.001
4	9.85 (1.77 – 79.16)	0.014
Female sex	0.91 (0.46 - 1.79)	0.78
Time to surgery[b]	1.00 (0.98 – 1.02)	0.88
Type of surgery		
Screw osteosynthesis	0.90 (0.28 – 2.88)	0.86
Sliding hip screw / nail	1.21 (0.58 – 2.57)	0.61
Hemiarthroplasty	1[a]	
Total hip arthroplasty	0.30 (0.01 – 2.50)	0.33
Complication[c]	1.35 (0.68 – 2.70)	0.39

CI - confidence interval; ASA - American Society of Anesthesiologists; [a] Reference category [b] Time from hospital admission to skin incision; [c] Any type of medical (other than delirium) or surgical complication during hospital admission

Online Resource 3a Incidence of subsyndromal delirium and delirium by study group in patients **without** pre-existing cognitive impairment

	Usual care (n = 46)	**Orthogeriatric co-management** (n = 65)	**Difference between groups** (with 95%CI)
No delirium, n (%)	31 (67)	48 (74)	7 % (-11 to 24)
Subsyndromal delirium, n (%)	7 (15)	3 (5)	-10 % (-21 to 0.2)
Delirium, n (%)	8 (17)	14 (22)	5 % (-11 to 19)

p = 0.15 (chi-squared test); CI - confidence interval

Online Resource 3b Incidence of subsyndromal delirium and delirium by study group in patients **with** pre-existing cognitive impairment

	Usual care (n = 48)	**Orthogeriatric co-management** (n = 38)	**Difference between groups** (with 95%CI)
No delirium, n (%)	7 (15)	13 (34)	19 % (2 to 38)
Subsyndromal delirium, n (%)	5 (10)	3 (8)	-2 % (-15 to 10)
Delirium, n (%)	36 (75)	22 (58)	-17 % (-37 to 3)

p = 0.10 (chi-squared test); CI - confidence interval

Articles 1 – 4

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RESEARCH ARTICLE Open Access

Fast track hip fracture care and mortality – an observational study of 2230 patients

Christian Thomas Pollmann[1,2*], Jan Harald Røtterud[1], Jan-Erik Gjertsen[3,4], Fredrik Andreas Dahl[2,5], Olav Lenvik[6] and Asbjørn Årøen[1,2,7]

Abstract

Background: Hip fracture patients are frail and have a high mortality. We investigated whether the introduction of fast track care reduced the 30-day mortality after hip fractures.

Methods: Fast track hip fracture care was established at our institution in October 2013. Data from the Norwegian Hip Fracture Register and electronic hospital records were merged for 2230 hip fracture patients operated in our department from January 2012 through December 2015. 1090 of these patients were operated before (conventional treatment group) and 1140 patients were operated after the introduction of fast track care (fast track group). Data were analysed by univariate analysis and binary logistic regression.

Results: Mortality did not differ significantly between the conventional treatment group and the fast track group at 30 days (7.9% vs. 6.5%), 90 days (13.5% vs. 12.5%) and one year (22.8% vs. 22.8%). Median admission time and time to surgery were significantly shorter in the fast track group than in the conventional treatment group (1.1 h vs. 3.9 h and 23.6 h vs. 25.7 h, both $p < 0.0001$). The 30-day reoperation rate was significantly lower in the fast track group compared to the conventional treatment group (odds ratio = 0.35 (95% CI: 0.15–0.84), $p = 0.019$). A composite 30-day outcome (reoperation, surgical site infection and/or death) was significantly less frequent in the fast track group (8.1%) than in the conventional treatment group (10.7%) in unadjusted analysis ($p = 0.006$), but not after adjusting for age, gender, cognitive impairment and ASA score (odds ratio = 0.85 (95% CI: 0.63–1.16), $p = 0.31$, 8.0% missing). Reoperations within 1 year, surgical site infections, 30-day readmissions and length of hospital stay did not differ significantly between the conventional treatment group and the fast track group.

Conclusions: Fast track hip fracture care is safe. However, we observed no statistically significant change in 30-day, 90-day or 1-year mortality after the introduction of fast track hip fracture care.

Trial registration: The study was registered retrospectively at ClinicalTrials.gov (Protocol Record 284907) 6 December 2016.

Keywords: Hip fracture, Fast track, Mortality, Reoperation, Surgical site infection, Admission time, Time to surgery, Length of stay, Readmission, Norwegian hip fracture register

Background

Hip fracture patients represent one of the largest groups of patients in orthopaedic surgery. A hip fracture constitutes a serious injury for these typically frail and elderly patients. This is reflected in several studies reporting high mortality rates between 6 and 11% within 30 days [1–4] and between 20 and 30% within 1 year [2, 5, 6]. In addition to the individual fate, hip fractures pose a growing public health problem. Due to the increasing age of the population in the western world the hip fracture burden is predicted to increase substantially over the next decades [7].

Traditionally, orthopaedic research has focused on surgical techniques for the treatment of hip fractures [8, 9]. However, excess mortality after a hip fracture remains high [5, 10]. Therefore, a new approach is warranted to try to reduce the high mortality. One such approach is

* Correspondence: Christian.Pollmann@ahus.no
[1]Department of Orthopaedic Surgery, Akershus University Hospital, Lørenskog, Norway
[2]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway
Full list of author information is available at the end of the article

the development of standardized fast track care systems for hip fracture patients.

Fast track methodology refers to a comprehensive treatment concept for surgical patients which takes into account the patients' co-morbidities, cognitive impairment and polypharmacy, and which focuses on stress reduction, opioid sparing pain relief, nutrition and early mobilization to promote postoperative recovery [11]. Fast track patient care was initially developed for elective abdominal surgery [11], but the principles have subsequently been applied to elective orthopaedic surgery with good results [12]. More recently, fast track care systems have also been reported for hip fracture patients [13–17]. However, the effect on mortality is unclear. While one study reported lower 1-year mortality in community dwellers [18] several other studies found no effect of fast track care on mortality in hip fracture patients [14–17, 19].

The primary aim of this study was to investigate if the introduction of fast track care at our institution reduced the 30-day mortality rate after hip fracture surgery. Secondary outcome measures were 90-day and 1-year mortality, any cause reoperation, surgical site infection, a composite 30-day outcome (reoperation, surgical site infection or death), admission time, time to surgery, length of hospital stay and 30-day readmission.

Methods

This study is reported according to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [20].

Conventional hip fracture care

Patients with suspected hip fracture were admitted via the accident and emergency (A&E) department, Akershus university hospital (AHUS). The patients had to wait for an available examination room, an available physician and a slot in the radiology lab. After x-ray examination the patients were transported back to the A&E department where the admitting physician evaluated the x-rays and finished the work-up before the patient was transported to the orthopaedic ward.

Apart from antithrombotic and perioperative antibiotic prophylaxis, perioperative treatment was not standardized. There was no systematic focus on nutritional status and on prevention and treatment of delirium. The patients were not consistently mobilized on the first postoperative day.

Fast track hip fracture care

Fast track hip fracture care was introduced at AHUS in two steps. From 28 October 2013, guidelines concerning perioperative treatment were taken into practice. Secondly, 27 January 2014, the fast track pathway for hospital admission was implemented.

The ambulance personnel initiate first line treatment (intravenous fluids, oxygen, pain relief and electrocardiogram). Upon arrival at the A&E department a trained nurse triages all suspected hip fracture patients using the Manchester triage system [21]. If deemed necessary, additional intravenous opiates are administered in selected cases.

Patients without signs of other, more acute medical conditions (score of 3 or higher) continue in the fast track admission pathway if they fulfil the following criteria: Low energy trauma, hip/groin pain, shortened and/or externally rotated lower extremity and/or unable to bear weight, no sign of other fractures, no sign of neurovascular injury, not previously operated on the hip in question.

From the triage area the patient is brought directly to the radiology lab where fast track hip fracture patients are prioritized after any ongoing procedure.

The radiology technician evaluates the x-ray. If considered to have a hip fracture the patient is transported directly to the orthopaedic ward where a nurse performs standard procedures according to a check-list and gives the patient both oral and written information about hip fractures and the expected course of treatment.

The orthopaedic surgeon re-evaluates the x-ray, writes an admission note, administers a fascia iliaca compartment block and prescribes a set of standard medications, including oral and intravenous fluids and pain medication.

The fast track hip fracture care system includes written guidelines concerning standard blood sampling, premedication, pre- and postoperative pain relief with focus on opiate sparing, pre- and postoperative fluid treatment with focus on short periods of fasting, transfusion-triggers and management of anticoagulants. Patients are mobilized on the first postoperative day. The guidelines also advise on screening for and prevention and treatment of delirium, on screening of nutritional status and on appropriate interventions concerning nutrition.

Data collection

All primary and revision hip fracture operations in Norway should be reported to the Norwegian Hip Fracture Register (NHFR) [22]. This is done prospectively by the surgeon on a 1-page questionnaire which includes information on the type of fracture, American Society of Anaesthesiologists (ASA) score [23], cognitive impairment (possible choices: 'no', 'uncertain', 'yes'), type of anaesthesia, type of operation, surgeon's experience (at least one surgeon with > 3 years of experience in hip fracture surgery) and operating time (time from incision to skin closure).

We obtained the NHFR data for patients operated at AHUS from January 2012 through December 2015. For the same time period, hip fracture patients were identified from the electronic hospital records using the search strings main diagnosis S72.0, S72.1 or S72.2 (ICD-10), in-patient, operated during that hospital admission. The two databases were linked deterministically using the unique 11-digit Norwegian personal identification number. For patients who were only identified in one of the data sources or for whom the records did not match, the electronic hospital records were scrutinized to determine if there had occurred an error in coding or in reporting to the NHFR.

Patients

All patients 18 years of age or older who were operated for a fracture of the proximal femur (femoral neck, trochanteric or subtrochanteric) at a single institution (AHUS) from January 2012 through December 2015 were eligible for inclusion (Fig. 1). AHUS has a catchment area of approximately 500.000 inhabitants.

During the study period 2634 primary hip fracture operations were performed. For patients who sustained two hip fractures during the study period ($n = 92$), only the first fracture was included in the analysis. Patients with a pathologic fracture were excluded ($n = 47$). 265 patients were not reported to the NHFR, corresponding to an overall reporting rate from AHUS of 89.4% (87.9% before and 90.8% after the introduction of fast track hip fracture care). The remaining 2230 patients, who were reported to the NHFR, represent the study population. Of these 1090 patients were operated before (conventional treatment group) and 1140 patients were operated after the introduction of fast track hip fracture care (fast track group) with 28 October 2013 as cut-off. The available data do not allow us to determine to what extent the different components of the reported fast track care system were applied to an individual patient. Therefore, the analysis follows the intention to treat principle and hip fracture patients treated from 28 October 2013 and onwards are included in the fast track group, irrespective of length of admission time or other criteria.

Operative treatment

Patients with a femoral neck fracture were treated either with closed reduction and internal fixation with two screws, with a cemented bipolar hemiarthroplasty or with a cemented total hip arthroplasty, both with a taper slip stem using a direct lateral approach. Trochanteric fractures were treated with a sliding hip screw and subtrochanteric fractures with an intramedullary nail. Surgical treatment guidelines did not differ before and after the introduction of fast track hip fracture care.

Outcome measures

Mortality

Mortality data from the Central Population Register are routinely imported to the electronic hospital records and a last up-date of the database was performed on 14 September 2017 to allow for a delay in registration. There was no loss to follow-up. 30-day, 90-day and

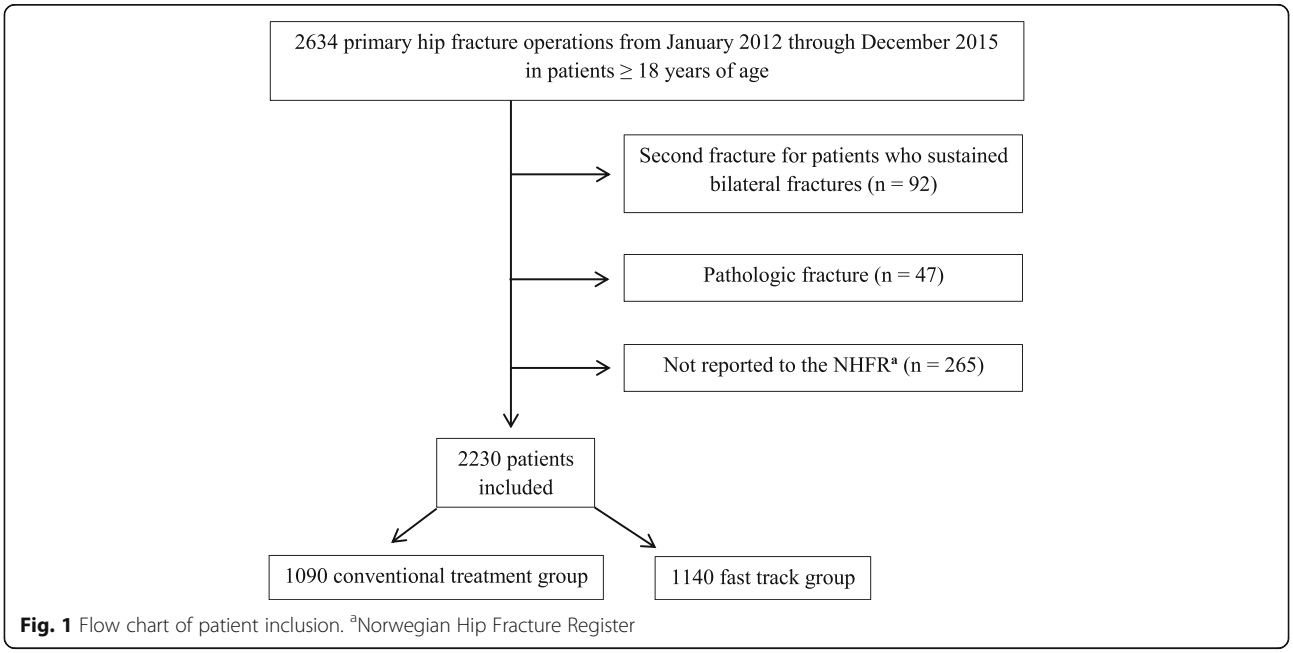

Fig. 1 Flow chart of patient inclusion. [a]Norwegian Hip Fracture Register

1-year mortality were calculated from time of arrival at the hospital. Survival was censored at 1 year.

Reoperations

Data on reoperations were obtained from the NHFR. Time to event was calculated from the index operation. In 2013 and 2014 the reporting rate from our institution was 66% for reoperations after osteosynthesis and 81.6% for reoperations after hemiarthroplasty [24].

Surgical site infection

The Department of Microbiology and Infection Control, AHUS, surveys surgical site infections after hemiarthroplasty and total arthroplasty of the hip under the Norwegian Surveillance System for Antibiotic Use and Hospital-Acquired Infections (NOIS) [25] with 30-day and one-year follow-up. Sliding hip screws are not monitored by NOIS, but the Department of Microbiology and Infection Control, AHUS, surveys surgical site infection also in these patients with a 30-day follow-up using the same criteria. The completeness of the 30-day follow-up ranged from 97.7 to 99.6% per calendar year. The completeness of the 1-year follow-up ranged from 98.7 to 99.5% for hemiarthroplasties and from 87.6 to 91.9% for total hip arthroplasties.

Internal fixations of femoral neck fractures and intramedullary nails are not systematically surveyed for surgical site infection.

Time to event was calculated from the time of the index operation.

Composite 30-day outcome

A patient was considered to have had this (negative) outcome if any of the following had occurred: death within 30-days from arrival at the hospital, reoperation or infection within 30-days from the index operation.

Readmission

Readmission was defined as any cause, non-elective readmission within 30 days after discharge from the index admission. These data were extracted from the electronic hospital records.

Admission time, time to surgery and length of hospital stay

Admission time (time from arrival at the hospital to arrival at the orthopaedic ward), time to surgery (time from arrival at the hospital to skin incision) and length of hospital stay were extracted from the electronic hospital records.

Statistical analysis

A sample size calculation based on a reduction of the 30-day mortality rate after hip fracture from 10.7% (AHUS in 2011 [26]) to 6.8% (hospital with lowest mortality rate in Norway in 2011 [26]), 85% power and a level of significance of 0.05 yielded a total sample size of approximately 1800 patients [27].

Fisher's exact test was used for unadjusted comparisons of proportions, while the Chi square test was used for unadjusted comparisons of ordinal and nominal distributions. Student's T test was used for unadjusted comparisons of continuous variables. However, comparisons of admission times, time to surgery and length of hospital stay were made with non-parametric Mann-Whitney U tests, rather than t-tests, due to the skewed distributions of these variables.

Logistic regression was used to analyze the effects of different predictors on the binary outcomes of mortality at 30 days, 90 days and 1 year follow-up, reoperation and surgical site infections at 30 days and 1 year follow-up, as well as 30-day readmission and the composite 30-day outcome. The main predictor of interest in these models was the conventional treatment/fast track care indicator. Other variables were included as confounders if they showed statistical significance at the 0.05 level, except for patient age and gender, which were always included. All municipalities and Oslo districts belonging to AHUS' catchment area were included in the analysis with a distinct identifier while patients from outside our hospital's catchment area were coded as one group. This variable was considered as a random effect in the models, but turned out not to have a significant effect. Reducing time to surgery is one of the intended effects of fast track care. Therefore, the logistic regression model analyzing the effect of fast track care on mortality was run with and without including time to surgery as an independent predictor. This did not relevantly change the result for the effect of fast track care on mortality.

Survival analysis by Cox regression was considered for the binary outcomes, since these were all associated with event times. However, there were problems with the assumptions of proportional hazards, measured by Schoenfeld residuals ph-test. Concerning mortality there was no loss to follow-up, so the logistic regression models' inability to handle right-censoring was not an issue. Also, the standard quality indicators of hip surgery are defined as the number of adverse outcomes after 30 days, 90 days and 1 year, which is in line with logistic regression. Logistic regression was therefore chosen.

A post hoc power analysis was performed using standard normal distribution approximation.

Subgroup analyses

Patients were divided into two subgroups according to their comorbidity (ASA score). Frailer patients were defined by an ASA score ≥ 3.

Results

Baseline characteristics for the conventional treatment group and the fast track group are shown in Table 1.

Data on surgical treatment for the conventional treatment group and the fast track group are shown in Table 2.

Mortality

30-day, 90-day and 1-year mortality did not differ significantly between the conventional treatment group and the fast track group (Table 3). This was consistent in both unadjusted and adjusted analyses. In the adjusted analyses, age, male gender, cognitive impairment and increasing ASA score were independent predictors of increased mortality (Table 4) while fast track care, time to surgery, surgeon's experience, type of fracture, type of operation, type of anaesthesia, operating time and municipality were not.

Fast track hip fracture care had no significant effect on 30-day, 90-day or 1-year mortality in subgroup analyses of healthier (ASA score ≤ 2) and frailer (ASA score ≥ 3) patients.

30-day mortality was 10.7% in 2011 [26], before the start of the study. It decreased to 8.6% in 2012 and 6.7% in 2013 before the introduction of fast track care and remained stable in 2014 (6.5%) and 2015 (6.8%) (Fig. 2).

A post hoc power analysis, given the sample size and the observed 30-day mortality rate of 7.9% in the conventional treatment group, showed that the study had 80% power to detect a decrease of the 30-day mortality rate to 5.0% in the fast track group with a level of significance of 0.05.

Secondary outcome measures

Secondary outcome measures for the conventional treatment group and the fast track group are presented in Table 5.

Table 1 Baseline characteristics

	Conventional treatment group (n^a = 1090)	Fast track group (n^a = 1140)	p-value[b]
Age[c] (years)	79.7 (0.3)	79.6 (0.3)	0.69
Gender[d]			0.5
Women	740 (67.9)	789 (69.2)	
ASA[d]			0.002
ASA 1	36 (3.4)	27 (2.4)	
ASA 2	292 (27.3)	358 (32.1)	
ASA 3	609 (56.9)	641 (57.5)	
ASA 4	130 (12.1)	85 (7.6)	
ASA 5	3 (0.3)	4 (0.4)	
Missing	20 (1.8)	25 (2.2)	
Cognitive impairment[d]			0.041
No	679 (65.9)	737 (70.2)	
Uncertain	102 (9.9)	107 (10.2)	
Yes	249 (24.2)	206 (19.6)	
Missing	60 (5.5)	90 (7.9)	
Type of fracture[d]			0.69
Femoral neck, undisplaced	171 (15.7)	181 (15.9)	
Femoral neck, displaced	445 (40.9)	439 (38.6)	
Basocervical	31 (2.9)	25 (2.2)	
Trochanteric, 2 fragments	166 (15.3)	176 (15.5)	
Trochanteric, > 2 fragments	169 (15.5)	180 (15.8)	
Intertrochanteric	21 (1.9)	27 (2.4)	
Subtrochanteric	37 (3.4)	42 (3.7)	
Other	47 (4.3)	66 (5.8)	
Missing	3 (0.3)	4 (0.4)	

[a]Number of patients in group
[b]Test for equal distribution in both groups (Student's T-test for age, Chi square test for all other parameters)
[c]Mean (standard error)
[d]n (%)

Table 2 Surgical treatment

	Conventional treatment group (n^a = 1090)	Fast track group (n^a = 1140)	p-value[b]
Type of operation[c]			0.25
Hemiarthroplasty	450 (41.3)	434 (38.1)	
Screw osteosynthesis	169 (15.5)	193 (16.9)	
Sliding hip screw	403 (37.0)	422 (37.0)	
Intramedullary nail	29 (2.7)	34 (3.0)	
Total hip replacement	38 (3.5)	57 (5.0)	
Resectionarthroplasty	1 (0.1)	0 (0)	
Missing	0 (0)	0 (0)	
Type of anesthesia[c]			0.002
Spinal	916 (88.6)	912 (85.5)	
General	74 (7.2)	122 (11.4)	
Other	44 (4.3)	33 (3.1)	
Missing	56 (5.1)	73 (6.4)	
Surgeon's experience[c]			0.75
≤ 3 years	141 (14.3)	157 (14.9)	
> 3 years	842 (85.7)	900 (85.1)	
Missing	107 (9.8)	83 (7.3)	
Operating time[d] (min.)	60 (1)	63 (1)	0.003

[a]Number of patients in group
[b]Test for equal distribution in both groups (Student's T-test for operating time, Chi square test for all other parameters)
[c]n (%)
[d]Mean (standard error)

Table 3 Mortality

	Conventional treatment group (n^a = 1090)	Fast track group (n^a = 1140)	Between group difference
	% (95% CI [b])	% (95% CI [b])	% (95% CI [b])
30-day mortality	7.9 (6.4 to 9.7)	6.5 (5.1 to 8.1)	−1.4 (−3.7 to 0.9)
90-day mortality	13.5 (11.5 to 15.7)	12.5 (10.6 to 14.5)	−1.0 (−3.9 to 1.8)
1-year mortality	22.8 (20.4 to 25.5)	22.8 (20.4 to 25.4)	0 (− 3.6 to 3.5)

[a]Number of patients in group
[b]95% confidence interval

The 30-day reoperation rate was lower in the fast track group (0.6%) than in the conventional treatment group (1.7%) ($p = 0.017$). After adjusting for age and gender, fast track hip fracture care remained an independent predictor of a lower 30-day reoperation rate (OR = 0.35, (95% CI: 0.15–0.84), $p = 0.019$, 0% missing).

The composite 30-day outcome (reoperation, surgical site infection and/or death) was less frequent in the fast track group (8.1%) compared to the conventional treatment group (10.7%) in an unadjusted analysis ($p = 0.035$). However, after adjusting for age, gender, cognitive impairment and ASA score, the odds-ratio for fast track care was no longer statistically significant (OR = 0.85 (95% CI: 0.63–1.16), $p = 0.31$, 8.0% missing).

Reoperation within 1 year, surgical site infection and 30-day readmission did not differ significantly between the conventional treatment group and the fast track group.

Admission time, time to surgery and length of hospital stay

The median time from arrival at the hospital to arrival at the orthopaedic ward (admission time) and from arrival at the hospital to the start of surgery was significantly shorter in the fast track group compared to the conventional treatment group while the median length of hospital stay did not differ significantly (Table 6).

Discussion

Although the introduction of fast track hip fracture care significantly reduced admission time, time to surgery and the risk of reoperation within 30 days, we observed no significant change in 30-day, 90-day or 1 year mortality. The composite 30-day outcome (reoperation, surgical site infection and/or death) was significantly less frequent in the fast track group in univariate analysis. However, in multivariate analysis this difference was no longer significant. There was a numerical trend towards fewer reoperations within 1 year, fewer surgical site infections and fewer 30-day readmissions in the fast track group, but this was not statistically significant. The length of hospital stay did not differ significantly between the conventional treatment group and the fast track group.

Our study was observational, investigating the effect of introducing fast track care as a quality improvement measure. This entailed that the patients did not follow a rigorous study protocol. We do not know exactly how many patients were admitted via the fast track admission pathway, but the data on admission time would suggest that this was the case for only about half of the patients. Thus, the relatively high percentage of patients who were not “fast tracked” to the orthopaedic ward may have contributed to not finding a statistically significant effect of fast track care on mortality. However, the importance of admission time for postoperative outcome is still controversial with shorter admission time being associated with higher in-hospital mortality in one study [28] and with fewer postoperative complications in another [13]. The effect of preoperative waiting time on postoperative outcome is not unequivocal either [29]. However, an increasing body of evidence suggests that a longer time to surgery correlates with increased mortality

Table 4 Independent predictors of mortality

	30-day mortality		90-day mortality		1-year mortality	
	Odds ratio (95% CI[a])	*p*-value	Odds ratio (95% CI[a])	*p*-value	Odds ratio (95% CI[a])	*p*-value
Age (years)	1.05 (1.03–1.07)	< 0.0001	1.05 (1.03–1.07)	< 0.0001	1.04 (1.03–1.05)	< 0.0001
Male gender	2.08 (1.45–2.98)	< 0.0001	1.91 (1.43–2.56)	< 0.0001	1.73 (1.40–2.19)	< 0.0001
Cognitive impairment uncertain	1.75 (1.03–2.96)	0.037	1.66 (1.09–2.54)	0.018	1.45 (1.02–2.06)	0.037
Cognitive impairment	2.86 (1.95–4.19)	< 0.0001	3.03 (2.24–4.09)	< 0.0001	2.56 (1.99–3.29)	< 0.0001
ASA[b]-score	3.44 (2.54–4.65)	< 0.0001	3.34 (2.61–4.26)	< 0.0001	3.09 (2.53–3.77)	< 0.0001

Logistic regression; 8.0% missing
[a]95% confidence interval
[b]American Society of Anaesthesiologists

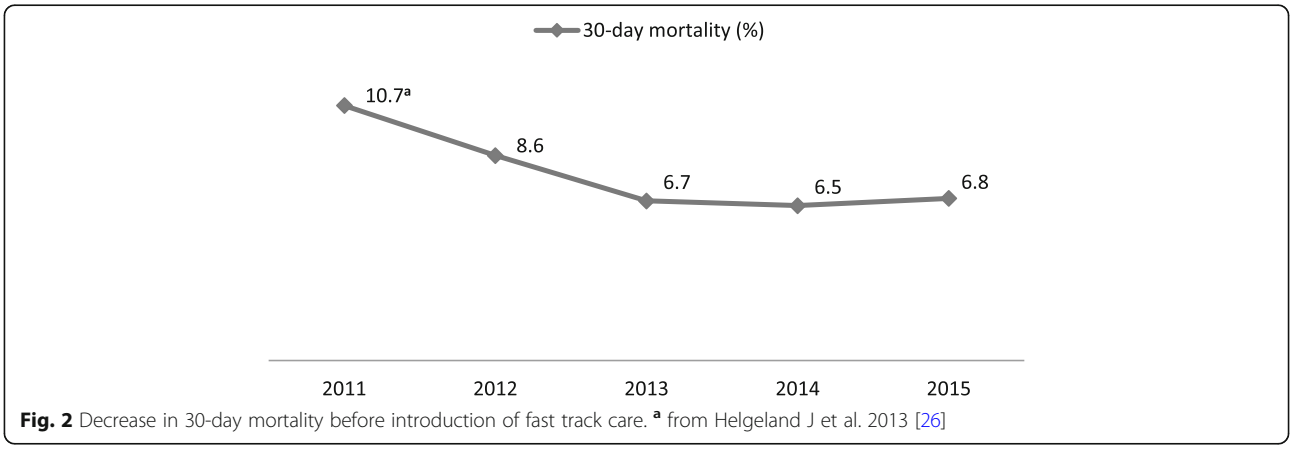

Fig. 2 Decrease in 30-day mortality before introduction of fast track care. [a] from Helgeland J et al. 2013 [26]

[4, 30], risk of infection [31] and other complications [32]. Thus, the rather modest reduction in time to surgery of just over two hours in the fast track group compared to the conventional treatment group might have contributed to not finding a statistically significant effect of fast track care on mortality. However, time to surgery was not an independent predictor of mortality in our cohort.

Our sample size calculation was based on our institution's 30-day mortality rate in 2011. However, 30-day mortality decreased considerably in 2012 and 2013, before fast track care was introduced, and subsequently levelled off. Thus, our sample size calculation was based on a higher mortality rate in the conventional treatment group than we did observe, which would have made it difficult to detect a possible effect of fast track care on mortality. What caused this improvement is unclear. The preparations to introduce fast track care started in 2012 and one could speculate that the increased focus on hip fracture patients may have had a positive effect already before fast track care was taken into practice. Another possible scenario is that the introduction of fast track care had a negative effect and interrupted a positive time trend of decreasing mortality. However, this seems less likely since the 30-day mortality levelled off at a value that lies in the lower range of reported rates [1–4].

One also has to consider the possibility that the continuous improvement of in-hospital hip fracture care has resulted in mortality rates for this frail group of patients which become increasingly difficult to reduce. This notion seems to be supported by the fact that also other recent approaches to improve hip fracture care, such as geriatric co-management, had mixed results with some studies reporting a statistically significant effect on mortality [33, 34] while other studies did not [35, 36]. A recent Cochrane review was not quite conclusive concerning mortality, but stated that comprehensive geriatric assessment probably reduces mortality in older people with hip fracture (risk ratio 0.85, 95% CI 0.68 to 1.05; 5 trials, 1316 participants, inconsistency (I^2) = 0%; moderate-certainty evidence) [37]. While in-hospital care is undoubtedly a cornerstone of hip fracture treatment, improvements in rehabilitation in the primary health care sector might also be warranted [19].

Table 5 Secondary outcome measures

	Conventional treatment group (n^a = 1090) % (95% CI [b])	Fast track group (n^a = 1140) % (95% CI [b])	Between group difference % (95% CI [b])
Any cause reoperation 30 days	1.7 (1.1 to 2.7)[¥]	0.6 (0.2 to 1.3)[¥]	−1.1 (− 2.2 to − 0.03)
Any cause reoperation 1 year	5.8 (4.5 to 7.3)	4.3 (3.2 to 5.6)	− 1.5 (− 3.4 to 0.5)
Surgical site infection 30 days[c]	2.5 (1.6 to 3.7)	1.8 (1.0 to 2.8)	−0.7 (− 2.2 to 0.7)
Surgical site infection 1 year[c, d]	3.0 (2.0 to 4.4)	2.0 (1.2 to 3.1)	−1.0 (− 2.7 to 0.5)
Composite 30-day outcome	10.7 (9.0 to 12.7)[#]	8.1 (6.6 to 9.8)[#]	−2.6 (−5.3 to −0.06)
30-day readmission	12.8 (10.9 to 15.0)	11.7 (9.9 to 13.7)	−1.1 (−4.0 to 1.6)

[a]Number of patients in group
[b]95% confidence interval
[c]Data available for hemiarthroplasty, total hip arthroplasty and sliding hip screws
[d]Sliding hip screws only followed up for infection for 30 days
[¥]Statistically significant difference in unadjusted (Fisher's exact test, $p = 0.017$) and adjusted analysis (binary logistic regression) (odds ratio = 0.35 (95% CI: 0.15–0.84), $p = 0.019$, 0% missing)
[#]Statistically significant difference in unadjusted analysis (Fisher's exact test, $p = 0.006$)

Table 6 Admission time, time to surgery and length of hospital stay

	Conventional treatment group ($n^a = 1090$)		Fast track group ($n^a = 1140$)	
	n[b]	Median (IQ-range[c])	n[b]	Median (IQ-range[c])
Admission time (hours)	1053	3.9 (2.9–5.2)*	1061	1.1 (0.6–3.2)*
Time to surgery (hours)	1054	25.7 (18.9–39.7)[#]	1072	23.6 (18.0–32.6)[#]
Length of stay (days)	1054	5.3 (4.0–7.0)	1072	5.2 (4.0–7.3)

[a]Number of patients in group
[b]Number of patients with available data
[c]Interquartile range
*Statistically significant difference (Mann Whitney U test, $p < 0.0001$)
[#]Statistically significant difference (Mann Whitney U test, $p < 0.0001$)

Our findings are in agreement with several other studies of fast track care systems for hip fracture patients that found no effect on mortality [14–17, 19]. While Eriksson et al. [14], Larsson et al. [16] and Hansson et al. [19] focused on bypassing the A&E department to reduce time to surgery, Haugan et al. [17] reported on a more comprehensive fast track system, comparable to the one described in our study. Using a retrospective study design they compared a cohort of 788 hip fracture patients treated before to 1032 patients treated after the introduction of fast track care and found no difference in 30-day, 90-day or 1 year mortality. In contrast, Pedersen et al. [18], who retrospectively investigated a similar fast track system, found a significantly lower 1-year mortality rate in their fast track group (12 versus 23%) when looking at the subgroup of community dwelling patients. This reduction in mortality is quite pronounced and the reason for this apparent discrepancy with our and the above mentioned findings is unclear. The study by Pedersen et al. [18] was based on a retrospective chart review. However, the intervention group was defined by time period and mortality data was obtained from the Civil Registration Office leaving little room for error. Another conceivable explanation for a potentially spurious positive finding by Pedersen et al. may be their relatively small sample size. Their cohort comprised 553 patients of which 376 were community dwellers compared to a total of 1820 patients in the report by Haugan et al. [17] and 2230 patients in this paper. Information on prefracture living arrangements was not available in our study. However, we performed a subgroup analysis of healthier patients, who can be expected to live in the community, and found no statistically significant effect of fast track care on mortality.

The presented study has several strengths. This study is, to our knowledge, the largest to date investigating fast track care for hip fracture patients. There was no loss to follow-up concerning the main outcome measure of mortality. The wide inclusion criteria imply that the study population was representative and that the results thus can be generalized.

Furthermore, this study is based on high quality data. The NHFR records its data prospectively. In addition, the data from the NHFR were cross referenced with data from the electronic hospital records thereby further increasing the data quality.

The study also has limitations. Data from the electronic hospital records were acquired retrospectively. It is not possible to discriminate the effects of the different components of the described fast track care system. Data on admission time suggests that only about half of all patients in the fast track group were admitted via the fast track admission pathway. However, the expedient admission is only one of several components of a fast track hip fracture care system. There were small, but due to the large number of patients, statistically significant differences between the groups in several of the baseline characteristics. However, in the multivariate logistic regression analyses these differences were adjusted for. During the study period, 11% of all primary hip fracture operations at our institution were not reported to the NHFR. However, with a reporting rate of 87.9% before and 90.8% after the introduction of fast track hip fracture care we consider it reasonable to assume that the reporting practice remained largely unchanged throughout the study. The reporting rate of reoperations to the NHFR is inferior to the reporting rate of primary operations [24]. Nevertheless, there is no reason to believe that the reporting rate of reoperations changed during the study period. Thus, the crude number of reoperations is probably higher than reported in this study, but the risk differences between the groups of patients studied should not be influenced by under-reporting of reoperations in only one of the groups. While surgical site infections after hemiarthroplasty and total arthroplasty of the hip were followed up after 30 days and one year, sliding hip screws were only followed up after 30 days and internal fixations of femoral neck fractures and intramedullary nails were not followed up for this complication. However, this procedure specific difference in follow-up for surgical site infection applies equally to both the conventional treatment group and the fast track group.

Since this study is based on register data it is not possible to determine to what extent an individual

patient received treatment according to the department's fast track hip fracture care guidelines. However, while the inclusion in a clinical trial will in itself influence any outcome measure [38] this is not the case for this register based study. The presented data thus reflect the effect on mortality and the secondary outcome measures one can expect by introducing a fast track hip fracture care system similar to the one described as a quality improvement measure.

We observed no increase in complications or readmissions after the introduction of fast track care which seems to indicate that "fast tracking" hip fracture patients to the orthopaedic ward after triage by trained health care personnel is safe. Even though fast track care did not significantly change mortality in this study, there was a numerical trend to improvement for all outcome measures and fast track care for hip fracture patients is still in place at our institution. Efforts to further improve hip fracture care should probably focus on even shorter preoperative waiting times [4] in combination with a fast track care system, geriatric co-management [37] and intensified rehabilitation after hospital discharge [19].

Conclusions

Fast track hip fracture care is safe. However, we observed no statistically significant change in 30-day, 90-day or 1-year mortality after the introduction of fast track hip fracture care.

Abbreviations

95% CI: 95% confidence interval; A&E: Accident and emergency; AHUS: Akershus university hospital; ASA: American Society of Anaesthesiologists; IQ-range: Interquartile range; NHFR: Norwegian Hip Fracture Register; OR: Odds ratio; RECORD: REporting of studies Conducted using Observational Routinely-collected health Data Statement

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Availability of data and materials

Due to regulations from the Norwegian Data Inspectorate and according to Norwegian personal protection laws publication of the complete dataset is not legal or appropriate.

Authors' contributions

CP contributed to study conception and design, data collection and analysis and drafted the manuscript. JHR contributed to study conception and design, data analysis and critical revision of the manuscript. JEG contributed to data collection and analysis and critical revision of the manuscript. FD performed the more advanced statistical analyses and contributed to the critical revision of the manuscript. OL extracted the data from the electronic hospital records and linked these data with the data from the NHFR. AÅ contributed to study conception and critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was evaluated by the Regional Ethics Committee South East and was deemed to not require approval (reference number 2015/409). Data was collected and handled in accordance with requirements from the local data protection officer. The study was exempt from consent to participate. The Norwegian Data Inspectorate has approved the registration of data in the NHFR.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Department of Orthopaedic Surgery, Akershus University Hospital, Lørenskog, Norway. [2]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway. [3]Norwegian Hip Fracture Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway. [4]Department of Clinical Medicine (K1), University of Bergen, Bergen, Norway. [5]Health Services Research Unit, Akershus University Hospital, Lørenskog, Norway. [6]Department of Data and Analytics, Akershus University Hospital, Lørenskog, Norway. [7]Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway.

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II

Surgical site infection after hip fracture – mortality and risk factors: an observational cohort study of 1,709 patients

Christian T POLLMANN [1,2], Fredrik A DAHL [2,3], Jan Harald M RØTTERUD [1], Jan-Erik GJERTSEN [4,5], and Asbjørn ÅRØEN [1,2,6]

1 Department of Orthopedic Surgery, Akershus University Hospital, Lørenskog; [2] Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo; [3] Health Services Research Unit, Akershus University Hospital, Lørenskog; [4] Norwegian Hip Fracture Register, Department of Orthopedic Surgery, Haukeland University Hospital, Bergen; [5] Department of Clinical Medicine (K1), University of Bergen, Bergen; [6] Department of Sports Medicine; Norwegian School of Sport Sciences, Oslo, Norway
Correspondence: christian.pollmann@ahus.no
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Background and purpose — Surgical site infection (SSI) is a devastating complication of hip fracture surgery. We studied the contribution of early deep SSI to mortality after hip fracture surgery and the risk factors for deep SSI with emphasis on the duration of surgery.

Patients and methods — 1,709 patients (884 hemiarthroplasties, 825 sliding hip screws), operated from 2012 to 2015 at a single center were included. Data were obtained from the Norwegian Hip Fracture Register, the electronic hospital records, the Norwegian Surveillance System for Antibiotic Use and Hospital-Acquired Infections, and the Central Population Register.

Results — The rate of early (≤ 30 days) deep SSI was 2.2% (38/1,709). Additionally, for hemiarthroplasties 7 delayed (> 30 days, ≤ 1 year) deep SSIs were reported. In patients with early deep SSI 90-day mortality tripled (42% vs. 14%, $p < 0.001$) and 1-year mortality doubled (55% vs. 24%, $p < 0.001$). In multivariable analysis, early deep SSI was an independent risk factor for mortality (RR 2.4 for 90-day mortality, 1.8 for 1-year mortality, $p < 0.001$). In univariable analysis, significant risk factors for early and delayed deep SSI were cognitive impairment, an intraoperative complication, and increasing duration of surgery. However, in the multivariable analysis, duration of surgery was no longer a significant risk factor.

Interpretation — Early deep SSI is an independent risk factor for 90-day and 1-year mortality after hip fracture surgery. After controlling for observed confounding, the association between duration of surgery and early and delayed deep SSI was not statistically significant.

Hip fractures, in usually frail, elderly patients, have high mortality rates of around 9% within 30 days (Sheikh et al. 2017) and up to 30% within 1 year (Lund et al. 2014). If a deep surgical site infection (SSI) ensues, a 1-year mortality rate of 50% (Edwards et al. 2008) has been reported. However, it is not clear to what extent this increased mortality rate is due to the infection and the treatment thereof and to what extent it is due to a more pronounced frailty which predisposed these patients to SSI (Belmont et al. 2014).

Considering the serious consequences of SSI for hip fracture patients it is important to optimize modifiable risk factors. However, reported risk factors differ, ranging from operative delay to the lead surgeon's experience, duration of surgery, choice of implant, and patient factors such as obesity (Harrison et al. 2012, Cordero et al. 2016, de Jong et al. 2017, Zajonz et al. 2019).

Duration of surgery is a risk factor commonly focused upon. However, the question remains as to whether longer duration of surgery increases the risk of SSI by prolonging exposure to possible bacterial contamination (Stocks et al. 2010) or if prolonged duration of surgery represents a surrogate parameter for a difficult procedure or a complication as the main cause for an increased risk of SSI.

In this observational cohort study, we investigated the contribution of early deep SSI to mortality after hip fracture surgery and risk factors for early and delayed deep SSI in hip fracture patients with particular emphasis on the role of duration of surgery.

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Patients and methods

Patients

All patients 18 years of age or older who were operated with a hemiarthroplasty or a sliding hip screw for a non-pathologic fracture of the proximal femur at a single institution (Akershus university hospital [AUH]) from January 2012 through December 2015 and who were reported to the Norwegian Hip Fracture Register (NHFR) (Gjertsen et al. 2008) were included in this study (Figure 1). In patients who sustained 2 hip fractures during the study period (n = 92), only the 1st fracture was included in the analyses.

Other data from the present cohort of hip fracture patients have previously been used in an observational study on the effect of fast-track hip fracture care on mortality (Pollmann et al. 2019).

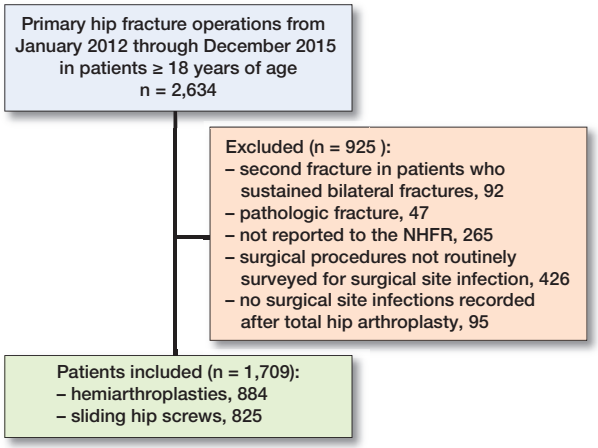

Figure 1. Flowchart of patient inclusion. NHFR: Norwegian Hip Fracture Register.

Data collection

In Norway, hip fracture operations are prospectively reported to the NHFR (Gjertsen et al. 2008) by the surgeon on a 1-page questionnaire, which includes information on the time elapsed from fracture to surgery, cognitive impairment ("no", "uncertain," "yes"), ASA score, type of fracture, type of operation, type of anesthesia, pathological fractures, intraoperative complications ("no"/"yes" with supplemental free text), duration of surgery (time from incision to skin closure), and the surgeon's experience (at least 1 surgeon present with > 3 years of experience in hip fracture surgery; "yes"/"no"). Using the unique 11-digit Norwegian personal identification number data from the NHFR and the electronic hospital records were linked deterministically.

Surgical site infection

SSIs after hemiarthroplasty and total arthroplasty of the hip are surveyed under the Norwegian Surveillance System for Antibiotic Use and Hospital-Acquired Infections (NOIS) with 30-day and 1-year follow-up. A questionnaire is sent to each patient or, in the case of cognitive impairment or institutionalization, to the primary health care provider. If the patient reports an SSI or a suspicion of SSI this has to be confirmed by a physician on the same questionnaire. In equivocal cases the electronic hospital records are scrutinized and/or the primary health care provider is contacted. Until 2014, cases of SSI were defined according to the American Centers for Disease Control and Prevention (Horan et al. 2008) while from 2014 onwards case definitions from the European Centre for Disease Prevention and Control have been applied (Dalli 2012). Concerning SSIs, both definitions are practically identical. Sliding hip screws are not monitored by NOIS, but the Department of Microbiology and Infection Control at AUH also surveys SSIs with 30-day follow-up in these patients using the same method and criteria. The completeness of follow-up was 99%. In this study, SSI within 30 days of the index operation is termed early SSI, while an SSI diagnosed between 30 days and 1 year from the index operation is termed delayed SSI.

Mortality

Mortality data from the Central Population Register are routinely imported into the electronic hospital records. There was no loss to follow-up regarding mortality. Mortality rates were calculated from the time of arrival at the hospital. Survival was censored at 1 year.

Antibiotic prophylaxis

Fixation with antibiotic-loaded bone cement (0.5 g gentamicin per 40 g cement) was used in all hemiarthroplasties. All patients received perioperative systemic antibiotic prophylaxis.

Statistics

Fisher's exact test was used for unadjusted comparisons of proportions.

Due to the relatively high mortality rates we chose risk ratios as the statistical effect measure (Davies et al. 1998) for the multivariable model analyzing the effect of early deep SSI on mortality. Since log-binomial regression did not converge, Poisson regression with robust variance was chosen as the statistical model (Barros and Hirakata 2003). Risk ratios (RR) are presented with 95% confidence intervals (CI). We considered survival analysis by Cox regression. However, the Schoenfeld residuals ph-test showed that the proportional hazards assumption was not met, which is also illustrated by the Kaplan–Meier survival curve (Figure 2). Age squared was not a significant risk factor for mortality indicating that the effect of age on mortality was linear in our cohort. Age was therefore included as a continuous variable in the regression models. The type of intraoperative complication, specified as free text, ranged widely from myocardial infarction to technical prob-

Table 1. Patient characteristics. Values are n (%) unless otherwise specified

Factor	Entire cohort (n = 1,709)	Survivors at 90 days (n = 1,459)	Deceased at 90 days (n = 250)	No SSI (n = 1,664)	SSI (n = 45)
Age, mean (SD)	82 (9.5)	81 (9.7)	85 (7.5)	82 (9.5)	81 (8.6)
Female sex	1,166 (68)	1,019 (70)	147 (59)	1,138 (68)	28 (62)
ASA					
1	27 (1.6)	27 (1.9)	–	27 (1.6)	–
2	451 (26)	429 (29)	22 (8.8)	444 (27)	7 (16)
3	1,021 (60)	865 (59)	156 (62)	988 (59)	33 (73)
4	171 (10)	104 (7.1)	67 (27)	166 (10)	5 (11)
5	3 (0.2)	1 (0.1)	2 (0.8)	3 (0.2)	–
Not reported	36 (2.1)	33 (2.3)	3 (1.2)	36 (2.2)	–
Cognitive impairment					
No	1113 (65)	1009 (69)	104 (42)	1091 (66)	22 (49)
Uncertain	178 (10)	143 (9.8)	35 (14)	169 (10)	9 (20)
Yes	374 (22)	267 (18)	107 (43)	362 (22)	12 (27)
Not reported	44 (2.6)	40 (2.7)	4 (1.6)	42 (2.5)	2 (4.4)
Type of fracture					
Femoral neck					
undisplaced	68 (4.0)	62 (4.2)	6 (2.4)	64 (3.8)	4 (8.9)
displaced	806 (47)	683 (47)	123 (49)	782 (47)	24 (53)
Basocervical	54 (3.2)	45 (3.1)	9 (3.6)	54 (3.2)	-
Trochanteric					
2 fragments	341 (20)	301 (21)	40 (16)	334 (20)	7 (16)
> 2 fragments	345 (20)	282 (19)	63 (25)	337 (20)	8 (18)
Intertrochanteric	39 (2.3)	34 (2.3)	5 (2.0)	38 (2.3)	1 (2.2)
Subtrochanteric	33 (1.9)	32 (2.2)	1 (0.4)	32 (1.9)	1 (2.2)
Other	19 (1.1)	16 (1.1)	3 (1.2)	19 (1.1)	–
Not reported	4 (0.2)	4 (0.3)	–	4 (0.2)	–

Percentages are column percentages;
SSI: early (sliding hip screws) and early and delayed (hemiarthroplasties) deep surgical site infection.

lems to nausea and vomiting, to name a few. Therefore, we made no attempt at further classification and intraoperative complication was treated as a binary variable. Both the ASA score (≤ 2/≥ 3) and time from fracture to surgery (≤ 24 hours/> 24 hours) were dichotomized and included as binary variables.

Since there were relatively few cases of SSI, the analysis of risk factors for SSI was based on both early (sliding hip screws and hemiarthroplasties) and delayed (hemiarthroplasties only) SSIs to achieve a more robust statistical analysis. Logistic regression was used to analyze the risk factors for early and delayed deep SSI.

In all multivariable models, the variables to be adjusted for were chosen from directed acyclic graphs (DAG), which were constructed using DAGitty (Textor et al. 2017).

We performed a sensitivity analysis for the effect of early deep SSI on mortality by calculating the E-value. "The E-value is the minimum strength of association on the risk ratio scale that an unobserved confounder would need to have with both the exposure and the outcome, above and beyond the measured covariates, to fully explain away a specific exposure–outcome association" (VanderWeele and Ding 2017).

A p-value < 0.05 was considered as statistically significant. Data were analyzed with the SPSS statistical package version 25.0.0.1 (IBM Corp, Armonk, NY, USA).

Ethics, registration, funding, and potential conflicts of interest

The Regional Ethics Committee South East deemed this study not to require approval (reference number 2015/409). Data were collected and handled in accordance with the requirements of the local data protection officer. The study was exempt from consent to participate. The Norwegian Data Inspectorate has approved the registration of data in the NHFR.

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The authors declare no conflicts of interest.

Results

Patient characteristics are presented in Table 1; baseline data on the primary surgical treatment are given in Table 2 (see Supplementary data).

Surgical site infection

The rate of early SSI for all included procedures (hemiarthroplasties and sliding hip screws) during the study period was 2.2% (38/1,709) with a variation of between 0.5% and 3.1% per calendar year. For hemiarthroplasties the rate of early SSI was 2.4% (21/884) while it was 2.1% (17/825) for sliding hip screws. The cumulative 1-year SSI rate (early and delayed) for hemiarthroplasties was 3.2% (28/884). All SSIs were classified as deep and all but 1 patient with an infected hemiarthroplasty, who declined surgical treatment, were reoperated due to the SSI.

Early deep surgical site infection and mortality

30-day mortality did not differ statistically significantly between patients with or without early deep SSI (Table 3). However, 90-day mortality tripled and 1-year mortality more than doubled in patients with early deep SSI (Table 3). A Kaplan–Meier cumulative survival curve illustrates that the increased mortality in patients with early deep SSI becomes apparent from approximately 6 weeks postoperatively (Figure 2).

The analysis of the causal association between early deep SSI and mortality was based on a DAG (Figure 3a, see Supplementary data) and confounders to be adjusted for were chosen from this DAG (Figure 3b, see Supplementary data). In this model, obesity, diabetes mellitus, and smoking represent unobserved confounders. In a multivariable analysis adjusted for age, sex, cognitive impairment, ASA score, the occurrence of an intraoperative complication, and time from fracture to surgery, early deep SSI was an independent risk factor for both 90-day and 1-year mortality (Table 4).

Table 3. Mortality (% and 95% CI) with and without early deep surgical site infection

Mortality	No SSI (n = 1,671)	Early deep SSI (n = 38)	Between-group difference	p-value [a]
30-day	8.3 (7.1–9.8)	5.3 (0.9–19)	–3.0 (–12 to 5.5)	0.8
90-day	14 (12–156)	42 (27–59)	28 (11 to 45)	< 0.001
1-year	24 (22–26)	55 (39–71)	31 (14 to 49)	< 0.001

SSI: surgical site infection.
[a] Fisher's exact test.

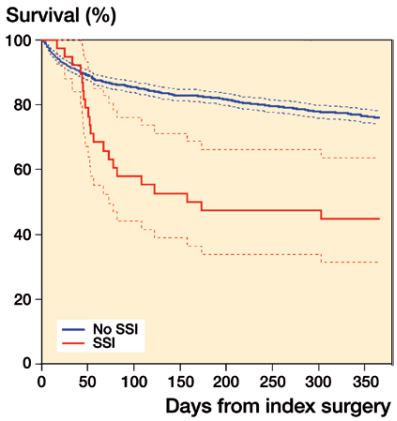

Figure 2. Kaplan–Meier patient survival curves with 95% confidence intervals for patients with and without early deep surgical site infection. SSI: early deep surgical site infection.

Table 4. Multivariable Poisson regression with robust variance of independent risk factors for 90-day and 1-year mortality

Factor	90-day mortality Risk ratio (CI)	p-value	1-year mortality Risk ratio (CI)	p-value
Age	1.04 (1.02–1.06)	< 0.001	1.03 (1.02–1.04)	< 0.001
Male sex	1.7 (1.4–2.2)	< 0.001	1.5 (1.3–1.8)	< 0.001
Cognitive impairment				
uncertain	1.5 (1.1–2.2)	0.02	1.3 (1.0–1.7)	0.05
yes	2.2 (1.7–2.8)	< 0.001	1.8 (1.5–2.2)	< 0.001
ASA score ≥ 3	3.0 (1.9–4.8)	< 0.001	2.5 (1.9–3.5)	< 0.001
Intraoperative complication	1.1 (0.7–1.6)	0.7	1.2 (1.0–1.6)	0.1
Time from fracture to surgery > 24 h	1.2 (0.9–1.5)	0.2	1.0 (0.8–1.2)	0.9
Early deep SSI	2.4 (1.6–3.5)	< 0.001	1.8 (1.3–2.5)	< 0.001

SSI: surgical site infection; 9.8% missing.

Omitting the variables intraoperative complication and time from fracture to surgery reduces missing cases from 9.8% to 3.9% while the parameter estimates for the remaining variables remain practically unchanged.

For the association between early deep SSI and mortality the E-values for the point estimate of the RR and for the lower bound of its CI were 4.2 and 2.6 for 90-day and 3.0 and 1.9 for 1-year mortality. Hence, an unobserved confounder that is associated with both early deep SSI and 90-day mortality by an RR of 4.2 each could explain away the observed RR of 2.4. An unobserved confounder that is associated with both early deep SSI and 90-day mortality by an RR of 2.6 each could move the lower bound of the CI to 1 (VanderWeele and Ding 2017).

Risk factors for early and delayed deep surgical site infection

In a univariable analysis, cognitive impairment, the occurrence of an intraoperative complication, and longer duration of surgery were statistically significantly associated with an increased risk of early and delayed deep SSI (Table 5, see Supplementary data). An ASA score ≥ 3 bordered on being a statistically significant risk factor for early and delayed deep SSI (Table 5, see Supplementary data).

Duration of surgery and early and delayed deep surgical site infection

The analysis of the causal association between duration of surgery and early and delayed deep SSI was based on a DAG (Figure 4a, see Supplementary data). Figure 4b shows which variables have to be adjusted for to control for observed confounding. Obesity represents an unobserved confounder.

In a multivariable analysis adjusted for the occurrence of an intraoperative complication and for surgeon's experience the association between duration of surgery and early and delayed deep SSI is no longer statistically significant (Table 6, see Supplementary data).

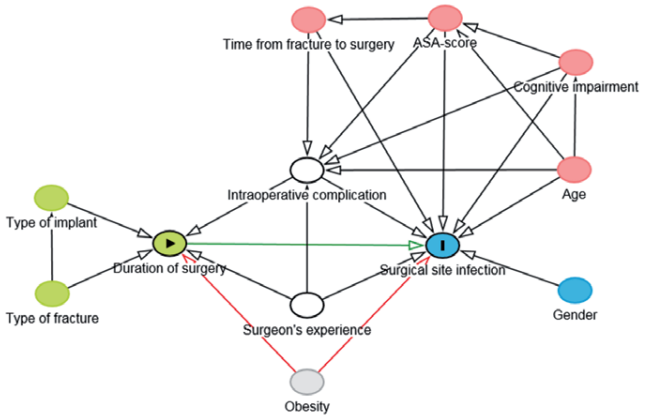

Figure 4b. Directed acyclic graph depicting the adjustment for observed confounding of the association between duration of surgery and early and delayed deep surgical site infection. exposure; outcome; ancestor of exposure; ancestor of outcome; ancestor of exposure *and* outcome (confounder); adjusted variable; unobserved; causal path; biasing path.

Discussion

Early deep surgical site infection and mortality

In our cohort, 90-day mortality tripled and 1-year mortality more than doubled in patients with early deep SSI compared with patients without SSI.

In multivariable analysis, early deep SSI was an independent and important risk factor for both 90-day and 1-year mortality. Adjusting for age, cognitive impairment, and ASA score controls for a large part of frailty and the fact that SSI remained an independent risk factor for mortality indicates that SSI in itself increases the mortality rate.

The 30-day mortality rate did not differ statistically significantly between patients with early deep SSI and without SSI in our cohort and was in fact slightly lower in patients with early deep SSI. Edwards et al. (2008) observed a similar phenomenon. As the authors pointed out, this observation might have been caused by survival bias. The increase in 1-year mortality in our cohort was similar to the one reported by Merrer et al. (2007) (50% vs. 20%) and by Edwards et al. (2008) (50% vs. 30%).

The rate of deep SSI in our cohort was in the mid-range of earlier reported rates (Harrison et al. 2012, Sprowson et al. 2016, de Jong et al. 2017). Interestingly, we observed only deep SSIs as opposed to most other studies that report both deep and superficial SSIs (Merrer et al. 2007, Edwards et al. 2008, de Jong et al. 2017). What caused this discrepancy is unclear. Superficial SSIs may have been underreported in our cohort. Another possible explanation might be a difference in treatment strategy. It can be difficult to ascertain that an SSI is purely superficial and we might have a more aggressive approach revising SSIs that others might classify as superficial. Since a diagnosis of deep SSI made by the surgeon is one of the possible criteria that define a deep SSI (Horan et al. 2008, Dalli 2012), an aggressive revision policy could partly explain why no superficial SSIs were reported.

Risk factors for early and delayed deep surgical site infection

In the univariable analysis cognitive impairment, the occurrence of an intraoperative complication and an increasing duration of surgery were statistically significantly associated with an increased risk of early and delayed deep SSI, while the association with an ASA score ≥ 3 bordered on statistical significance.

For clinical practice it is most relevant to identify modifiable risk factors for SSI. Pre-existing cognitive impairment can be considered non-modifiable, while delirium, which has a high incidence amongst hip fracture patients (Watne et al. 2014), and therefore probably accounts for some of the reported cognitive impairment in our cohort, may be preventable in some patients. A high ASA score might be modifiable if it is due to an acute condition or an acute deterioration of an existing ailment. However, most often the ASA score will not be modifiable. Some intraoperative complications may be preventable with adequate preoperative planning and experienced staff; however, it is in the nature of complications that not all of them can be prevented or even foreseen. An association between a longer duration of surgery and SSI has been shown before in several other studies (Harrison et al. 2012, Daley et al. 2015, Cheng et al. 2017, de Jong et al. 2017). On this basis, some authors have advocated measures to reduce duration of surgery (Cheng et al. 2017), such as expeditious surgical technique (Daley et al. 2015). However, the question remains how much of this association is due to the prolonged exposure to possible microbial contamination (Stocks et al. 2010) and how much is due to a longer duration of surgery being an indicator of a more complex surgical procedure, an inexperienced surgeon, or an intraoperative complication. To try to approach this question, we used a DAG with duration of surgery as the exposure and SSI as the outcome. From this DAG we determined that controlling for the occurrence of an intraoperative complication and for surgeon's experience would control for all the observed confounders in our cohort. In the corresponding logistic regression model duration of surgery was no longer an independent risk factor for SSI. The fact that controlling for the occurrence of an intraoperative complication and for surgeon's experience eliminated the statistical significance of the duration of surgery cannot readily be interpreted as duration of surgery not having a direct influence on the risk of SSI. However, this finding highlights the uncertainty that the prolonged exposure to possible bacterial contamination is the main reason for an association between duration of surgery and SSI. De Jong et al. (2017) reported an increased risk of SSI after hemiarthroplasty of the hip for both short (< 45 minutes) and long (> 90 minutes) durations of surgery. This might support the notion that careless tissue handling (short durations of surgery) and intraoperative complications (long durations of surgery) might play an important role in the development of SSI.

Our study has several strengths. With 1,709 patients the studied cohort is quite large. By using data from the NHFR, NOIS, the electronic hospital records, and the Central Population Register the cohort was well characterized. The loss to follow-up for SSI was small and no patients were lost to follow-up concerning mortality.

The study also has limitations. It is a single-center study. However, approximately 8% of all hip fracture operations in Norway are performed at our institution making this a relevant sample of Norwegian hip fracture patients. The number of cases of SSI was small (38 early SSIs, 7 delayed SSIs), limiting the number of covariates that could be included in and the statistical power of the multivariable regression model analyzing the risk factors for SSI. Information on delayed SSIs was only available for patients operated with a hemiarthroplasty.

Data on patients' comorbidities was restricted to the ASA score and cognitive impairment, while no information was available on some known risk factors for SSI, such as diabetes mellitus (Tsang and Gaston 2013), obesity (Zajonz et al. 2019), or smoking (Durand et al. 2013). Obesity, in par-

ticular, represents an unobserved confounder in the association between duration of surgery and SSI. However, for the association between early deep SSI and mortality the E-values indicate that the evidence for causality is rather robust (VanderWeele and Ding 2017).

The variable "intraoperative complication" comprises a wide range of different events, which makes a detailed analysis impossible.

While a DAG can help to decide which variables to include in an analysis, it will always represent a simplification of reality.

In conclusion, our results indicate that an early deep SSI has a clinically significant impact on mortality in hip fracture patients and, hence, that the prevention of SSI should be seen as an essential aspect of hip fracture treatment. While we found no easily modifiable risk factors for early and delayed deep SSI in our cohort, we highly recommend adherence to the existing guidelines for the prevention of SSI (Ban et al. 2017). Additional measures, such as the use of high-dose dual-impregnated antibiotic-loaded bone cement in hemiarthroplasties (Sprowson et al. 2016) might be considered. We question the common wisdom that a longer duration of surgery in itself is closely associated with an increased risk of SSI and suggest that the underlying reason for a longer duration of surgery might be at least equally as important.

Supplementary data

Tables 2, 5, and 6 and Figures 3 and 4a are available as supplementary data in the online version of this article, http://dx.doi.org/10.1080/17453674.2020.1717841

CP conceived the study and drafted the manuscript. CP and FD performed the statistical analyses. All authors interpreted the results, contributed to the discussion, and reviewed the manuscript.

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IV

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ORIGINAL ARTICLE

Orthogeriatric co-management reduces incidence of delirium in hip fracture patients

C. T. Pollmann[1,2] · M.R. Mellingsæter[3] · B.E. Neerland[4] · T. Straume-Næsheim[1,5] · A. Årøen[1,2,5] · L.O. Watne[4]

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Abstract

Summary Hip fracture patients often display an acute confusional state (delirium) which is associated with worse outcomes. In this observational study, we found that co-management of hip fracture patients by a multidisciplinary team including a geriatrician and an orthopaedic surgeon could reduce the incidence of delirium.

Introduction Delirium after hip fracture is common and is associated with negative outcomes. We investigated if orthogeriatric co-management reduced the incidence of delirium in hip fracture patients.

Methods In this single-centre, prospective observational study, we compared the incidence of delirium and subsyndromal delirium (SSD) before (usual care group, n = 94) and after (orthogeriatric group, n = 103) the introduction of orthogeriatric co-management as an integrated care model. The outcome measure 'no delirium/SSD/delirium' was treated as an ordinal variable and analysed using the chi-squared test and multivariable ordinal logistic regression.

Results The groups had similar baseline characteristics except for a higher proportion of patients with pre-existing cognitive impairment in the usual care group (51% vs. 37%, p = 0.045). Fewer patients in the orthogeriatric group developed SSD or delirium (no delirium: 59% vs. 40%/SSD: 6% vs. 13%/delirium: 35% vs. 47%; p = 0.021). The number needed to treat (NNT) to avoid one case of SSD or delirium was 5.3 (95% CI: 3.1 to 19.7). In a multivariable analysis adjusted for age, sex, ASA class, pre-existing cognitive impairment, time to surgery, type of surgery, and medical or surgical complications, the odds ratio for the development of SSD/delirium was lower in the orthogeriatric group (OR = 0.46, 95% CI: 0.23–0.89, p = 0.023).

Conclusion Orthogeriatric co-management as an integrated care model reduced the incidence of SSD/delirium in hip fracture patients.

Keywords Delirium · Hip fracture · Orthogeriatric co-management · Subsyndromal delirium

Introduction

Hip fracture patients are typically old and frail and up to 50% have dementia [1]. Acute trauma, surgery, advanced age, frailty, and dementia are important risk factors for the development of delirium [2, 3], and consequently, the incidence of delirium among hip fracture patients is high with reported rates of up to 50% [1, 2]. Both delirium and subsyndromal delirium (SSD), a condition which falls between no delirium and delirium [4], are associated with negative outcomes [3, 5, 6]. For delirium, this includes an increased risk of dementia [5] and further decline of pre-existing cognitive impairment [7]. Therefore, delirium prevention is important in the management of hip fracture patients.

In recent years, different models of orthogeriatric co-management have been advocated to address the medical complexity of hip fracture patients [8–10] and orthogeriatric

✉ C. T. Pollmann
Christian.Pollmann@ahus.no

1 Department of Orthopedic Surgery, Akershus University Hospital, Lørenskog, Norway

2 Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway

3 Department of Geriatric Medicine, Akershus University Hospital, Lørenskog, Norway

4 Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway

5 Oslo Sports Trauma Research Center (OSTRC), Norwegian School of Sports Sciences, Oslo, Norway

co-management has become the standard of care in the UK [11]. However, the reported effects of orthogeriatric co-management on the incidence of delirium in hip fracture patients are ambiguous with some studies showing a positive effect [12–14] while others were inconclusive [15, 16] or showed no effect [1, 17]. The aim of this single-centre, observational cohort study was to investigate if the introduction of an integrated care model [8] of orthogeriatric co-management reduced the incidence of delirium and SSD in hip fracture patients.

Patients and methods

Patients

The patients in this study were originally recruited for a study with the aim to investigate pathophysiologic mechanisms in delirium by analysing cerebrospinal fluid (CSF) sampled from hip fracture patients operated in spinal anaesthesia. Incidentally, approximately half of the cohort was included before (usual care group) and half of the cohort was included after the introduction of orthogeriatric co-management (orthogeriatric group) at our hospital in October 2018.

All adult patients operated for a hip fracture (neck of femur, trochanteric or subtrochanteric) at Akershus University Hospital (AUH) during the study period (September 2017 to February 2020) were eligible for the study. Participation required written informed consent by the patient or, in case of cognitive impairment, by the family. Failure to obtain cerebrospinal fluid was the only exclusion criterion for the original, cerebrospinal fluid project. Delirium already on hospital admission, which would not have been amenable to orthogeriatric co-management, was the only exclusion criterion for the present study. A flow chart of patient inclusion is shown in Fig. 1.

Orthogeriatric co-management

Orthogeriatric co-management was introduced at AUH as an integrated care model [8]. The patients are admitted to the orthopaedic ward and the geriatrician is part of a multidisciplinary team with orthopaedic surgeons, physiotherapists, nurses and occupational therapists. The geriatrician goes rounds together with the orthopaedic surgeon every weekday, treats medical conditions and relevant comorbidities, contributes to discharge planning and is responsible for the medication review and list at discharge. The geriatrician sees the patients mainly after surgery, but some are seen preoperatively. The orthogeriatric multidisciplinary team focuses on early detection of pain, constipation, nutritional problems and dehydration, and encourages early mobilization. In addition, involvement of relatives is highlighted. A summary of the geriatrician's assessments accompanies the patient's discharge note to the primary health care service. Outside of regular daytime working hours and during weekends, an orthopaedic surgeon is responsible for the patients, with the option to consult a geriatrician on call.

Data collection

Delirium was assessed according to the DSM-5 criteria [18], based on a standardized procedure described previously [19]. All assessments were done by study nurses trained in delirium assessment by the study physician (LOW). In short, level of arousal was assessed with the Richmond Agitation Sedation Scale (RASS) [20] and the Observational Scale for Level of Arousal (OSLA) [21], attention with Months of the Year backwards (MOYB), Days of the Week backwards (DOWB), the vigilance A-task SAVEHAART, and counting from 20 to 1 [22] (DSM-5 criterion A, disturbance in attention and awareness). Acute change in the patient's mental status and fluctuations of any disturbance (DSM-5 criterion B) were ascertained through informant history from nursing staff and carers as well as derived from clinical notes. Assessment of additional disturbance in cognition (DSM-5 criterion C) was performed by asking the patient a list of pre-defined questions in addition to information obtained from nursing staff and clinical notes. Recall test of three words (different each day) was performed at each assessment. The 4'A's test (4AT) [23] was used as a delirium screening tool by the study nurses. The results from each of the four 4AT variables (awareness, cognition, attention, acute change or fluctuation), as well as the total 4AT score, were also used as a source of information in the delirium assessment process. Evaluation of DSM-5 criterion D (A and C not better explained by other neurocognitive disorder) was based on information from history/chart/clinical assessment. DSM-5 criterion E (direct physiological consequence of another medical condition) was fulfilled in all patients since they were acutely admitted with a hip fracture. Two experienced delirium researchers (LOW and BEN) independently used all available information on each patient to decide if the DSM-5 criteria for delirium were fulfilled. The interrater agreement for the diagnosis of delirium was excellent (kappa 0.97), and disagreements were resolved through discussion.

SSD was defined (in patients not fulfilling all DSM-5 criteria for delirium) as evidence of change in mental status, in addition to any one of these: (a) altered arousal, (b) attentional deficits, (c) other cognitive change, (d) delusions or hallucinations.

Delirium was assessed daily in all participants preoperatively and until the 5th postoperative day (all) or until discharge (patients with delirium). Participants were regularly assessed on weekdays only, but staff members who had worked on weekends were interviewed on Mondays, and the case notes were read to reveal potential episodes of delirium.

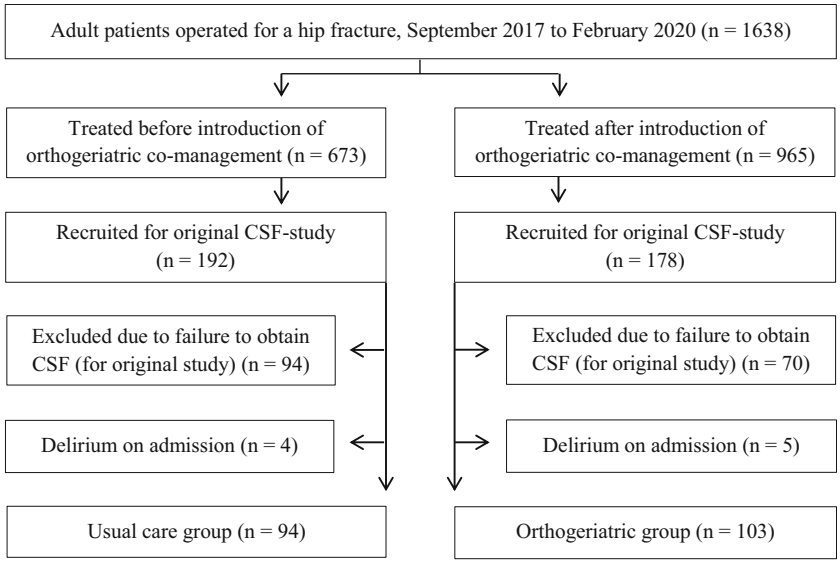

Fig. 1 Flow chart of patient inclusion. CSF, cerebrospinal fluid

Pre-fracture cognitive status was assessed by Informant Questionnaire on Cognitive decline in the Elderly (IQCODE) with a score ≥ 3.44 indicating cognitive impairment [24]. If the IQCODE was missing ($n = 6$), pre-fracture cognitive status was determined from the electronic hospital records based on previous mention of cognitive impairment, living arrangements and other clues to pre-admission cognitive functioning. Five of these patients were in the orthogeriatric group. Of these, two patients had a previous diagnosis of dementia and three were judged to not have signs of cognitive impairment. The concerned patient in the usual care group was also judged to not have signs of cognitive impairment.

The evaluation if delirium already was present on admission was based on the admission notes in the electronic patient records.

Time to surgery was calculated from hospital admission to skin incision.

The type of surgery performed was classified into screw osteosynthesis for femoral neck fracture, osteosynthesis for trochanteric/subtrochanteric fractures (sliding hip screw or intramedullary nail), hemiarthroplasty or total hip arthroplasty.

Other medical complications than delirium and surgical complications were recorded prospectively by the study nurses.

Statistics

The diagnosis of delirium requires a certain number of symptoms to be present [18], thus making delirium a binary outcome (yes/no). However, clinically, delirium may be considered a more continuous spectrum of symptoms with some patients presenting with SSD, which has been shown to be associated with outcomes intermediate between the outcomes of patients with and without delirium [6]. To account for this fact, we chose to treat delirium as an ordered categorical variable ('no delirium/SSD/delirium').

Medical and/or surgical complications and pre-existing cognitive impairment were treated as binary variables.

We used the chi-squared test for unadjusted comparisons of proportions, the independent samples *t*-test for unadjusted comparisons of means and the Mann-Whitney *U* test for unadjusted comparisons of the distribution of continuous variables.

95% confidence intervals (CI) for the difference in proportions were derived using the normal approximation. 95% CIs for the difference in medians are presented as the Hodges-Lehman median difference.

We performed a proportional odds model multivariable ordinal logistic regression analysis with 'no delirium/SSD/delirium' as the dependent variable and orthogeriatric co-management, age, sex, ASA class, pre-existing cognitive impairment, time to surgery, type of surgery and the occurrence of any type of complication as explanatory variables. The variables we adjusted for were chosen based on prior clinical knowledge [25]. To visualize the postulated causal associations between the exposure (orthogeriatric co-management), other covariates and the outcome (SSD/delirium), and identify possible problems with adjusting for the chosen variables (such as a collider), we created a directed acyclic graph (DAG) using DAGitty [26] (Fig. 2).

As an impact measure, we calculated the NNT to prevent one case of SSD or delirium (i.e., we dichotomized the outcome to 'no delirium' vs. 'SSD or delirium'). The 95% CI for the NNT was derived using the Wald method.

In a subgroup analysis, we compared the outcome 'no delirium/SSD/delirium' between the study groups separately for patients with or without pre-existing cognitive impairment. In the context of the subgroup analysis, we also dichotomized the outcome to 'no delirium' vs. 'SSD or delirium'.

As a sensitivity analysis for the causal association between orthogeriatric co-management and the incidence of SSD/delirium, we calculated the E-value [27]. For this purpose, an approximated

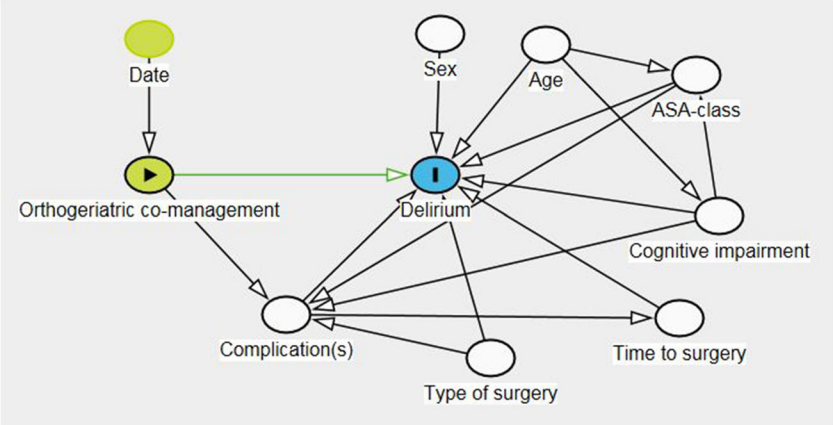

Fig. 2 Directed acyclic graph (DAG) depicting the causal model used as a basis for analysing the association between orthogeriatric co-management and the incidence of subsyndromal delirium/delirium. exposure outcome ancestor of exposure adjusted variable causal path biasing path (none present). Complication(s): any medical and/or surgical complication during hospital admission; time to surgery: time from hospital admission to skin incision; cognitive impairment: pre-existing cognitive impairment.

risk ratio (RR) was derived from the odds ratio (OR) using a square root transformation (RR ≈ sqrt[OR]) [28]. The E-value (E-value = 1/RR + sqrt[1/RR × (1/RR − 1)] is 'the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, above and beyond the measured covariates, to fully explain away a specific exposure-outcome association' [27].

Data were analysed with the SPSS statistical package version 26.0.0.1. A p-value < 0.05 was considered as statistically significant.

Results

The usual care group (n = 94) and the orthogeriatric group (n = 103) were similar with respect to age, sex distribution, the distribution of ASA classes, time from hospital admission to surgery, type of surgery performed and the proportion of patients who experienced any type of complication (Table 1). The proportion of patients with pre-existing cognitive impairment was higher in the usual care group (Table 1).

The median length of hospital stay was 6 days in both groups (usual care group: median 5.9, interquartile range (IQR): 4.6–7.8; orthogeriatric group: median 6.0, IQR: 4.8–8.1; p = 0.48) and a third of the patients in both groups were discharged directly to their own private home.

The patients included in the study were comparable to the patients excluded from the study with respect to age, sex distribution, proportion of patients with ASA class ≥ 3 and distribution of fracture types (Online Resource 1).

Incidence of subsyndromal delirium/delirium

The incidence of SSD/delirium was lower in the orthogeriatric group (Table 2). The NNT to avoid one case of SSD or delirium was 5.3 (95% CI: 3.1 to 19.7).

While the preoperative incidence of delirium was lower in the orthogeriatric group, the postoperative incidence of delirium was similar in both groups (Table 3) (time to event was not available for SSD).

In a multivariable ordinal logistic regression analysis adjusted for age, sex, ASA class, pre-existing cognitive impairment, time to surgery, type of surgery and the occurrence of any type of complication, the odds ratio for the development of SSD/delirium was lower in the orthogeriatric group (OR = 0.46, 95% CI: 0.23–0.89, p = 0.023). The complete regression model is presented in Online Resource 2.

Subgroup analysis of patients with and without pre-existing cognitive impairment

A subgroup analysis showed a tendency towards a more pronounced effect of orthogeriatric co-management on the incidence of SSD in patients without pre-existing cognitive impairment and on the incidence of delirium in patients with pre-existing cognitive impairment (Online Resource 3). With a dichotomized outcome ('no delirium' vs. 'SSD or delirium'), the difference between the study groups was significant for patients with pre-existing cognitive impairment ('no delirium': 7 of 48 usual care group vs. 13 of 38 orthogeriatric group; p = 0.032), but not for patients without pre-existing cognitive impairment ('no delirium': 31 of 46 usual care group vs. 48 of 65 orthogeriatric group; p = 0.46).

Sensitivity analysis

Using a square root transformation of the adjusted odds ratio, the estimated adjusted risk ratio for developing SSD/delirium in the orthogeriatric group was 0.68. The E-values on the risk ratio scale for the causal association between orthogeriatric co-management and a reduced incidence of SSD/delirium were 2.3 for the point estimate and 1.3 for the upper limit of its 95% CI. In other words,

Table 1 Comparison of patient characteristics by study group

	Usual care (n = 94)	Orthogeriatric co-management (n = 103)	Difference between groups (with 95% CI)	p-value[c]
Age, years, mean (SD)	79.1 (10.4)	77.5 (9.7)	− 1.6 (− 4.4 to 1.2)	0.27
Female sex, n (%)	60 (64)	61 (59)	− 5% (− 18 to 9)	0.51
ASA class, n (%)				0.97
ASA 1	6 (6)	8 (8)	2% (− 6 to 9)	
ASA 2	45 (48)	47 (46)	− 2% (− 16 to 12)	
ASA 3	40 (43)	44 (43)	0% (− 14 to 14)	
ASA 4	3 (3)	4 (4)	1% (− 5 to 6)	
Pre-existing cognitive impairment, n (%)	48 (51)	38 (37)	− 14% (− 28 to − 0.4)	0.045
Time to surgery[a] in hours, median (IQR)	29 (21–45)	31 (25–45)	1 (− 3 to 5)[d]	0.43
Type of surgery, n (%)				0.85
Screw osteosynthesis	13 (14)	14 (14)	0% (− 9 to 10)	
Sliding hip screw/nail	33 (35)	42 (41)	6% (− 8 to 19)	
Hemiarthroplasty	42 (45)	42 (41)	− 4% (− 18 to 10)	
Total hip arthroplasty	6 (6)	5 (5)	− 1% (− 8 to 5)	
Complication[b]	31 (33)	41 (40)	7% (− 7 to 20)	0.32

CI, confidence interval; *ASA*, American Society of Anesthesiologists; *IQR*, interquartile range

[a] Time from hospital admission to skin incision

[b] Any type of medical (other than delirium) or surgical complication during hospital admission

[c] Independent samples t-test, chi-squared test or Mann-Whitney U test, as appropriate

[d] Hodges-Lehman median difference

an unmeasured confounder that is associated with the development of SSD/delirium by a RR of 2.3 and unevenly distributed between the groups by a RR of 2.3 could explain away the observed RR of 0.68. An unmeasured confounder that is associated with the development of SSD/delirium by a RR of 1.3 and unevenly distributed between the groups by a RR of 1.3 could move the upper bound of the 95% CI to 1.

Discussion

In this observational cohort study of hip fracture patients, the incidence of SSD/delirium was significantly reduced after the introduction of orthogeriatric co-management. The NNT was 5.3 to avoid one case of SSD or delirium. We believe this is clinically relevant since delirium is a common [1] and serious [3, 7] complication in hip fracture patients.

Orthogeriatric co-management represents a multidisciplinary intervention package with tailored care for the individual patient, striving to optimize mobilization, nutrition and bowel function as well as the management of comorbidities, complications, pain and fluid imbalances. The current study cannot evaluate which components contribute the most to the prevention of delirium. However, other authors have proposed improved prevention, detection and treatment of medical complications and optimized management of pain, fluid balance and medication choice as possible explanations [9].

Orthogeriatric co-management was effective in preventing preoperative but not postoperative delirium. At first sight, this might seem curious since the geriatrician did not see all patients preoperatively. However, this underlines that the effect of orthogeriatric co-management is due to a multidisciplinary and multifaceted intervention rather than the impact of one single component. Why orthogeriatric co-management was effective in preventing preoperative but not postoperative

Table 2 Incidence of subsyndromal delirium and delirium by study group

	Usual care (n = 94)	Orthogeriatric co-management (n = 103)	Difference between groups (with 95% CI)
No delirium, n (%)	38 (40)	61 (59)	19% (5 to 33)
Subsyndromal delirium, n (%)	12 (13)	6 (6)	− 7% (− 15 to 1)
Delirium, n (%)	44 (47)	36 (35)	− 12% (− 26 to 2)

p = 0.021 (chi-squared test); *CI*, confidence interval

Table 3 Pre- and postoperative incidence of delirium by study group

	Usual care (n = 82)	Orthogeriatric co-management (n = 97)	Difference between groups (with 95% CI)
No delirium, n (%)	38 (46)	61 (63)	17% (2 to 31)
Delirium preoperatively, n (%)	26 (32)	14 (14)	− 17% (− 30 to − 5)
Delirium postoperatively, n (%)	18 (22)	22 (23)	1% (− 12 to 13)

p = 0.017 (chi-squared test); *CI*, confidence interval

delirium is unclear. One could speculate that in only somewhat vulnerable patients the intervention was able to prevent delirium entirely, while in especially vulnerable patients, the intervention was only able to prevent delirium after the first insult, the fracture, but not after the second insult, the operation.

The tendency towards a more pronounced effect of orthogeriatric co-management on the incidence of SSD in patients without pre-existing cognitive impairment and on the incidence of delirium in patients with pre-existing cognitive impairment in the subgroup analysis is not straightforward to interpret and may be a spurious finding due to the small sample size in the subgroups. However, with a dichotomized outcome ('no delirium' vs. 'SSD or delirium'), the effect of orthogeriatric co-management was significant in patients with but not in patients without pre-existing cognitive impairment. This might indicate that the most fragile patients stand to gain the most from this treatment concept.

A fast track pathway for hip fracture patients, which has been described elsewhere [29], was established at our hospital before the start of this study. It is noteworthy that orthogeriatric co-management conveyed a measurable effect on the incidence of SSD/delirium when added to an already improved patient pathway.

Our results are comparable with other published findings. Marcantonio et al. conducted a randomized controlled trial investigating the influence of daily geriatric consultations on the incidence of delirium in hip fracture patients [12]. They randomized a total of 126 patients and found a reduced incidence of delirium from 50 to 32% (p = 0.04) in the orthogeriatric group (RR = 0.64; NNT = 5.6). Lundström et al. randomized 199 hip fracture patients to be treated either in a geriatric unit specializing in geriatric orthopaedic patients or in the orthopaedic department [13]. The authors found a reduced incidence of delirium from 75 to 55% (p = 0.003) in the geriatric unit. In a retrospective study with a total of 313 hip fracture patients treated at two different hospitals, one of which had orthogeriatric co-management, Friedman et al. reported a lower odds ratio of 0.27 (p < 0.001) for delirium in the orthogeriatric cohort after adjusting for baseline differences between the groups [14].

On the other hand, other investigators have reported inconclusive or negative results. Vidán et al. conducted a randomized controlled trial with a total of 319 hip fracture patients comparing daily, multidisciplinary geriatric intervention to usual care [15]. The authors found a reduced incidence of delirium from 44 to 34% in the intervention group. However, this reduction was not statistically significant (p = 0.07). Deschodt et al. reported on a non-randomized, parallel group trial with a total of 171 hip fracture patients comparing the effect of a geriatric consultation team to usual care [16]. While they reported a reduced incidence of delirium from 53 to 37% in the intervention group (p = 0.04), the odds ratio of 0.56 in a multivariable analysis was not statistically significant (p = 0.07). Watne et al. found no difference in the incidence of delirium in a randomized controlled trial with a total of 329 hip fracture patients comparing treatment in a geriatric ward to treatment in an orthopaedic ward (49% vs. 53%, p = 0.51) [1]. Flikweert et al. reported on a cohort study with a historical control group comprising a total of 401 hip fracture patients comparing a multidisciplinary care pathway including daily geriatric consultation with usual care [17]. The authors found no difference in the incidence of delirium between the groups (16% geriatric consultation group vs. 14% usual care, p = 0.48).

Two recent systematic reviews reported similar results for the effect of comprehensive geriatric assessment (CGA) on the incidence of delirium in hip fracture patients (RR = 0.81, 95% CI: 0.69–0.94) [30] and in surgical patients (RR = 0.75, 95% CI: 0.60–0.94) [9]. However, while the authors of the former concluded that CGA reduces the incidence of delirium [30], the authors of the latter came to the conclusion that 'CGA may make little or no difference for delirium' [9].

Overall, there is some evidence that multidisciplinary geriatric intervention can reduce the incidence of delirium in hip fracture patients and our study further supports this conclusion. In addition, orthogeriatric co-management is associated with other positive effects, such as improved mobility in the months after discharge [1, 31], lower probability of discharge to an increased level of care [9] and, probably, reduced mortality [9].

The main strength of this study was the thorough, daily evaluation of delirium. The limited exclusion criteria should convey high external validity to our results. Also, data were collected prospectively.

The study also has limitations. Since this is an observational study, the risk of bias due to unmeasured confounding is inherently more pronounced compared to a well-conducted randomized trial. Also, the E-value for the upper limit of the 95% CI for the causal association between orthogeriatric co-management and the incidence of SSD/delirium indicates that

a relatively weak unmeasured confounder could have rendered the effect of orthogeriatric co-management statistically non-significant [27]. However, since the multivariable regression analysis was adjusted for numerous known risk factors for the development of delirium, we would argue that the risk of important unmeasured confounding was limited.

Pre-existing cognitive impairment, which is an important risk factor for the development of delirium [2], was more common in the usual care group. However, in the multivariable regression analysis, which was adjusted for pre-existing cognitive impairment, the effect of orthogeriatric co-management remained statistically significant.

We do not have quantitative data on differences in management between the study groups such as frequency of medication adjustments, the frequency of detection of dehydration or the amount of opioids used. Therefore, we can only deduce that multidisciplinary orthogeriatric co-management as an integrated care model had a positive effect on delirium incidence without being able to identify the individual, effective components of this management concept.

Only a limited proportion of eligible hip fracture patients were included in this study, which might raise concerns about the representativeness of our sample. This was due to the logistics involved in procuring cerebral spinal fluid for the study these patients were originally recruited for. However, included and excluded patients were comparable with respect to basic patient characteristics.

The evaluation if a patient already had delirium on admission was based on the admission notes rather than on the rigorous testing employed during the remainder of the hospital stay. Thus, we cannot exclude that some cases of SSD or even delirium on admission may have gone undetected. However, there is no reason to believe that the quality of the admission notes differed between the study groups.

The IQCODE was missing for six patients. However, a diagnosis of dementia in the hospital records makes pre-existing cognitive impairment very certain. In the patients who were judged to not have pre-existing cognitive impairment from the hospital records (3 in the orthogeriatric group; 1 in the usual care group), we may have missed less obvious signs of cognitive decline and some bias from this cannot be excluded. However, if any bias arose from this, it is more likely to have biased the multivariable analysis towards a smaller effect of orthogeriatric co-management since this concerned more patients in the orthogeriatric group.

Time to event data is missing for SSD. For delirium, our data only allow to determine if it occurred pre- or postoperatively.

The variable ‘complication(s)’ was treated as a binary variable and did thus not take the severity of a complication into account. However, almost any medical or surgical complication has the potential to cause delirium. Also, attempting to classify the severity of different complications would have involved a certain extent of subjectivity.

In conclusion, in this single-centre, observational cohort study, the introduction of orthogeriatric co-management as an integrated care model reduced the incidence of SSD/delirium in hip fracture patients. With a NNT of 5.3 (95% CI: 3.1 to 19.7), this effect was clinically relevant. However, the observational nature of the study conveys some uncertainty to this finding.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-05974-8.

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Author contribution CTP and LOW conceived the study. CTP performed the statistical analyses and drafted the manuscript. All authors interpreted the data and reviewed the manuscript.

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Data availability The data are available upon reasonable request to the corresponding author. However, availability is dependent on approval from the Regional Ethics Committee and the data protection officer at AUH.

Code availability Not applicable.

Declarations

Ethics approval The Regional Ethics Committee REC Central approved this study (reference number 2016/1368; 26 January 2017). The study was conducted according to the standards defined by the Helsinki Declaration. Data was collected and handled in accordance with requirements from the local data protection officer.

Consent to participate Study participation required written informed consent by the patient or, in case of cognitive impairment, by the family.

Consent for publication Not applicable.

Conflicts of interest None.

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