



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

C. T. Pollmann^{1,2} · M.R. Mellingsæter³ · B.E. Neerland⁴ · T. Straume-Næsheim^{1,5} · A. Årøen^{1,2,5} · L.O. Watne⁴

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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.

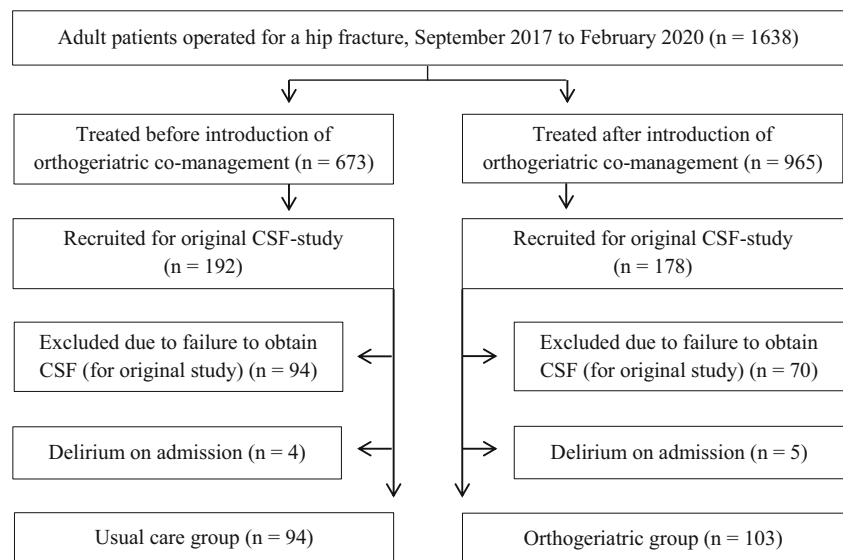
Data collection

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

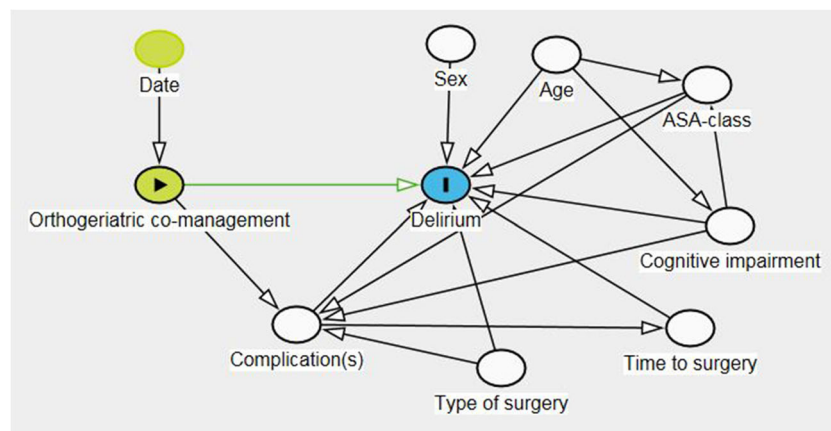


Fig. 2 Directed acyclic graph (DAG) depicting the causal model used as a basis for analysing the association between orthogeriatric co-management and the incidence of subsyndromal delirium/delirium. ● exposure ● outcome ● ancestor of exposure ○ adjusted variable — causal path — biasing path (none present)

risk ratio (RR) was derived from the odds ratio (OR) using a square root transformation ($RR \approx \sqrt{OR}$) [28]. The E-value ($E\text{-value} = 1/RR + \sqrt{1/RR \times (1/RR - 1)}$) 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).

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.

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 (<i>n</i> = 94)	Orthogeriatric co-management (<i>n</i> = 103)	Difference between groups (with 95% CI)	<i>p</i> -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, <i>n</i> (%)	60 (64)	61 (59)	− 5% (− 18 to 9)	0.51
ASA class, <i>n</i> (%)				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, <i>n</i> (%)	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, <i>n</i> (%)				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 (<i>n</i> = 94)	Orthogeriatric co-management (<i>n</i> = 103)	Difference between groups (with 95% CI)
No delirium, <i>n</i> (%)	38 (40)	61 (59)	19% (5 to 33)
Subsyndromal delirium, <i>n</i> (%)	12 (13)	6 (6)	− 7% (− 15 to 1)
Delirium, <i>n</i> (%)	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 (<i>n</i> = 82)	Orthogeriatric co-management (<i>n</i> = 97)	Difference between groups (with 95% CI)
No delirium, <i>n</i> (%)	38 (46)	61 (63)	17% (2 to 31)
Delirium preoperatively, <i>n</i> (%)	26 (32)	14 (14)	– 17% (– 30 to – 5)
Delirium postoperatively, <i>n</i> (%)	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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