BMJ Open High risk of adverse events in hospitalised hip fracture patients of 65 years and older: results of a retrospective record review study

Hanneke Merten,^{1,2} Paul C Johannesma,³ Sanne Lubberding,¹ Marieke Zegers,¹ Maaike Langelaan,¹ Gerrolt N Jukema,⁴ Martin J Heetveld,⁵ Cordula Wagner^{1,2}

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For numbered affiliations see end of article.

Correspondence to Hanneke Merten; h.merten@vumc.nl

ABSTRACT

Objectives: Hip fracture patients of 65 years and older are a complex patient group who often suffer from complications and difficult rehabilitation with disappointing results. It is unknown to what extent suboptimal hospital care contributes to these poor outcomes. This study reports on the scale, preventability, causes and prevention strategies of adverse events in patients, aged 65 years and older, admitted to the hospital with a primary diagnosis of hip fracture.

Design, setting and outcome measures:

A retrospective record review study was conducted of 616 hip fracture patients (\geq 65 years) admitted to surgical or orthopaedic departments in four Dutch hospitals in 2007. Experienced physician reviewers determined the presence and preventability of adverse events, causes and prevention strategies using a structured review form. The main outcome measures were frequency of adverse events and preventable adverse events in hospitalised hip fracture patients of 65 years and older, and strategies to prevent them in the future.

Results: 114 (19%) of the 616 patients in the study experienced one or more adverse events; 49 of these were preventable. The majority of the adverse events (70%) was related to the surgical procedure and many resulted in an intervention or additional treatment (67%). Human causes contributed to 53% of the adverse events, followed by patient-related factors (39%). Training and close monitoring of quality of care and the health professional's performance were the most often selected strategies to prevent these adverse events in the future.

Conclusions: The high percentage of preventable adverse events found in this study shows that care for older hospitalised hip fracture patients should be improved. More training and quality assurance is required to provide safer care and to reduce the number of preventable adverse events in this vulnerable patient group.

INTRODUCTION

Owing to the ageing population in Western countries, the number of patients with a hip

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unclear, however, to what extent errors in healthcare management may be a contributing factor to these negative outcomes and whether these can be prevented.

In several countries, retrospective medical record review studies have been conducted to gain insight into the incidence, preventability and causes of adverse events (AEs) in hospitals.⁷ An AE is defined as an unintended injury that results in temporary or permanent disability, death or prolonged hospital stay, and is caused by healthcare management rather than by the patient's underlying disease process.8 For Western countries in general, a mean overall incidence of inhospital AEs was estimated at 9.2%. Moreover, nearly half of these AEs were classified as preventable.⁷ In the Netherlands, Zegers et al,⁹ showed that one or more AEs were found in 5.7% of all Dutch hospital admissions and a preventable AE was found in 2.3% of all hospital admissions. These incidence rates describe the situation for the general hospital population. To our knowledge, no specific results on AE rates and their preventability are available for hip fracture patients; thus, it is still unknown to what extent suboptimal hospital care contributes to poor outcomes in this patient group. Therefore, the aim of our study was to report on the scale, preventability, causes and prevention strategies of AEs in patients, aged 65 and older, admitted to the hospital with a primary diagnosis of hip fracture.

METHODS

A structured retrospective medical record review study was conducted. Four hospitals participated in this study; 1 university, 2 tertiary teaching and 1 general hospital. The methods and instruments used in this study were based on the Harvard Medical Practice Study.⁸ The method has been modified in subsequent studies.¹⁰⁻¹⁵ In our study, instead of a 2-stage review process with nurses screening the records in the first stage, we only used experienced physician reviewers and let them screen all the records. We considered all our patients at high risk of suffering from an AE, making the first screening stage redundant. From each hospital, all admissions in 2007 of patients, aged 65 and older, admitted to the hospital with a primary diagnosis of hip fracture were selected using the hospital administration data with a maximum of 200 patients per hospital. One hospital had more than 200 patients, so a random sample was selected. Pathological fractures, polytraumas and patients with fractures who did not undergo surgery were excluded from this selection due to differences in the required medical treatment.

Nine physician reviewers received a 2-day training in record review and a specific half-day training for this study in which the review form was explained and discussed; they were also provided with several cases for practice. The reviewers were retired surgeons (less than 7 years of retirement) with at least 15 years of clinical experience in surgery and actively involved with the

treatment of hip fractures during their career. The review period was between June 2008 and July 2009. Nine per cent (55 records) of the records were independently reviewed by a second physician reviewer to determine an inter-rater reliability rate. For the review process, the reviewers used the medical, nursing and outpatient records and the images made during and after hospital stay. The time-frame of the review period was from the moment of admission until 6 months after discharge of the patient. These 6 months after discharge made it possible to also record AEs that are a result of the hospital admission, but were detected in the follow-ing outpatient visits. The reviewers used a standardised procedure and review form. They first had to register 2 general patient characteristics and comorbidities. They made an inventory of all known comorbidities and categorised the level of comorbidity based on their expert judgement as: none, insignificant, moderate or significant comorbidity. Next, they had to determine the presence of complications and AEs, followed by the degree of preventability and prevention strategies.

In addition to AEs, the following concepts were used in the study. A complication is an unintended and unwanted outcome during or following medical treatment that requires the healthcare professional to adjust the treatment or when irreparable damage has occurred.¹⁶ It is broader than an AE because it can also be the result of a calculated risk. A preventable adverse event is an AE resulting from an error in management due to failure to follow accepted practice at an individual or system level. Accepted practice was defined as 'the current level of expected performance for the average practitioner or system that manages the condition in question'.¹⁷ Preventability was measured on a 6-point scale; an AE was considered preventable with a score of 4 and higher. For a more detailed description of the outcome measures, see box 1.

When an AE was present, the reviewers had to determine one or more underlying causal factors and for preventable AEs, also the possible prevention strategies. The causal factors and prevention strategies were based on the PRISMA classification system and the Canadian Adverse Events Study.¹⁰ ¹⁸ ¹⁹ The reviewers selected the causal factors and potential prevention strategies based on information in the patient record and their perception of the situation. They had the option to choose from five main causal categories: technical, organisational, human, patient-related and other causes. Technical causes involve problems with physical items **8** such as equipment, software and materials. Organisational causes indicate problems with protocols and procedures, transfer of knowledge, management priorities and safety culture. Human causes can be described as the unsafe acts committed by the people who are in direct contact with the patient or the system. Actions they perform or decisions they make may result in errors that can have an immediate impact on safety. This, however, does not automatically mean that the AE

Definitions and outcome measures¹⁷ Box 1

Adverse Event determination

AE determination was based on the presence of three criteria:

- an unintended (physical and/or mental) injury, which
- resulted in temporary or permanent disability, death or prolongation of hospital stay and was
- caused by healthcare management rather than the patient's disease

Causation

To determine whether the injury was caused by healthcare management or the disease process a six-point scale was used:

- (Virtually) no evidence for management causation
- Slight to modest evidence of management causation 2
- 3. Management causation not likely (less than 50/50, but 'close call')
- Management causation more likely (more than 50/50, but 4. (close call)
- Moderate to strong evidence of management causation 5.
- (Virtually) certain evidence of management causation

Causation scores of 4-6 were classified as AEs.

Timing of AEs

The index hospital admission was the sampled admission for the hip fracture. AEs were included if they occurred during the index admission and were detected during or within 6 months after the index admission.

Preventability

The degree of preventability of AEs was measured on a six-point scale, grouped into three categories:

No preventability

- 1. (Virtually) no evidence for preventability
- Low preventability
- Slight to modest evidence of preventability
- Preventability not quite likely (less than 50/50, but 'close call') High preventability
- 4. Preventability more than likely (more than 50/50, but 'close call')
- 5. Strong evidence of preventability
- 6. (Virtually) certain evidence of preventability

AEs with preventability scores of 4-6 were defined as preventable AEs

was preventable in retrospect. Patient-related causes are related to patient characteristics or conditions that are beyond the control of staff and which influence the treatment. Finally, other causes are failures that cannot be classified in another category.^{20–22} Next, for each preventable AE, 1 or more of the following 10 prevention strategies could be selected by the reviewers: Technology/Equipment, Procedures, Information and Communication, Training, Motivation, Upscaling, Evaluation, Quality Assurance/Peer review, Financial Investment and Personnel. The prevention strategies are described in more detail in the results section.

All statistical analyses were performed using SPSS V.18.0. Patient characteristics, complications, AEs, preventable AEs, causes and prevention strategies were analysed using descriptive statistics and frequency tables. Difference in median length of hospital stay between hospitals was tested with a median test for independent

samples. Differences in AEs between groups were tested with χ^2 tests. For the inter-rater agreement between physicians, the percentage of agreement and a κ -statistic was calculated for the determination of complications and AEs. The classification system of Landis and Koch²³ was used for the interpretation of the κ -statistic. The study and methods have been granted ethical approval by the medical ethical review board of the VU University Medical Center, Amsterdam, the Netherlands,

RESULTS

Protected In total, the records of 616 patients, aged 65 and older, ŝ admitted to the hospital with a primary diagnosis of hip 8 fracture were reviewed; table 1 describes the patient characteristics and complications during hospitalisation. Three-quarters of the patients were females and most patients were admitted to the surgical department. During admission, 35 (5.7%) patients died. Of the other patients, almost half were discharged to a nursing home after the hospital admission. For 43% of all patients, 1 or more complications were registered in the patient record; delirium (11%) was the most common complication. The reliability of the assessment on the occurrence of a complication was substantial (κ =0.70), the percentage of agreement was 85%. The mean age of the admitted hip fracture patients varied between the hospitals from 82.7 to 84.5 years. The overall median length of đ hospital stay was 11 days, with a range between 2 and e 147 days. The median hospital stay differed significantly between hospitals ($X_3^2=9.41$, p=0.024); posthoc analysis showed a significant difference between hospital 2 and 3 in the median length of stay (9 vs 12 days, $X_1^2=9.41$, mining p=0.003). Patients with a short length of stay were mostly transferred to a psychogeriatric facility within a nursing home for more specialised care.

≥ Table 2 describes the occurrence of AEs and preventtraining able AEs in the study sample. In total, 124 AEs were found in 114 patient records. This means that in 19% of these hip fracture patients one or more AEs were detected. In total, 49 of these AEs (40%) were judged to be preventable. There were no significant differences for gender or age category (65-75, 76-85, >85 years) in the occurrence of AEs and preventable AEs. The agreement between reviewers for the determination of the presence of an AE was 85% with a κ -value of 0.52, which can be classified as moderate. For the preventable AEs, no $\kappa\text{-statistic}$ could be calculated since only 4 preventable $\textbf{\texttt{G}}$ AEs were included for a second review. For two AEs, both reviewers agreed that it was potentially preventable. For 1 AE, the first reviewer judged the preventability as more than likely (score 4), while the second reviewer judged the preventability as not quite likely (score 3). The fourth AE was not judged as an AE by the second reviewer.

The analyses for the different fracture types showed a relatively high AE rate with femoral neck fractures (21%) and subtrochanteric (24%) hip fractures, compared to the other fracture types, but these differences

Patient characteristics and complications during Table 1 hospitalisation

Population characteristics	Frequency (valid %)
Distribution of records	
Hospital 1	200 (33)
Hospital 2	132 (21)
Hospital 3	162 (26)
Hospital 4	122 (20)
Gender: female	469 (76)
Admission department	, , , , , , , , , , , , , , , , , , ,
Surgery	489 (81)
Orthopaedics	86 (14)
Trauma surgery	27 (4)
Other	5 (1)
Discharge status	- ()
Alive	580 (94)
Deceased	35 (6)
Discharge to	(-)
Nursing home	271 (48)
Transfer department within the	73 (13)
hospital	
Home with care	66 (12)
Home for the elderly	60 (11)
Home without care	44 (8)
Rehabilitation centre	25 (4)
Other	27 (4)
Number of complications during the inde	
0	352 (57)
1	148 (24)
2	81 (13)
>3	35 (6)
Type of complication during the index ad	
Delirium	70 (11)
Ischaemia/heart failure	37 (6)
Urinary tract infection	30 (5)
Pneumonia	30 (5)
Wound infection	28 (5)
Bleeding/haematoma	20 (3)
Other, unspecified complications	52 (8)
Age of patients	Mean age (SD)
Age of patients	(in years)
Hospital 1	84.0 (7.9)
Hospital 2	83.0 (7.0)
Hospital 3	84.5 (7.4)
Hospital 4	82.7 (7.6)
-	
Length of hospital stay*	Median number
Hospital 1	of days (range)
Hospital 1	11 (2–67)
Hospital 2	9 (2-84)‡
Hospital 3	
Hospital 4	12 (3–147)‡ 11 (2–107)

The median length of stay was used to eliminate the influence of outliers.

‡Significant difference (X₁²=9.41, p=0.003) between median length of stay hospital 2 and 3.

were not significant. Preventable AEs occurred relatively often in subtrochanteric hip fractures (17%), but this difference was also not significant. When distributed over the different operation procedures, no significant

uses rela

differences were detected for the occurrence of AEs and preventable AEs, although preventable AEs occurred most frequently when a long gammanail was placed (15%). AEs occurred significantly more often in patients with a significant level of comorbidity (25%) compared to the other groups (X_3^2 =11.97, p=0.007). AEs were preventable in 9% of the patients with significant comorbidity; this was not significantly different from the other comorbidity categories.

After establishing that an AE was present, these were classified by clinical procedure and the consequences otect were determined. Table 3 reports these outcomes for all 124 identified AEs and 49 preventable AEs. The majority of the AEs (70%) and preventable AEs (71%) were related to the surgical procedure itself. AEs and preventable AEs resulted most often in additional treatment or intervention, prolonged hospital stay or readmission to the hospital. For 6 of the 35 deceased patients, a preventable AE contributed substantially to their death; these are the potentially preventable deaths.

Next, the reviewers assessed what were the underlying causal factors for the occurrence of the AE. For 14 of the 124 AEs, the reviewers did not select a causal factor. Consequently, these AEs were removed from the causal factor analyses. In total, 180 causes were selected for the remaining 110 AEs. The total number of selected causal factors in the 49 preventable AEs is 84. Figure 1 shows how often the five causal factors were selected and the percentð age of AEs for which this factor was a cause. No ĸ-statistic e could be calculated for the inter-reliability of this judgement since there were not enough AEs in relation to the number of causal categories. For two AEs there was complete agreement between the reviewers in the selected causal categories. For 2 AEs, the second reviewer did not fill out any causes, for 2 other AEs, the first reviewer identified patient-related causes and the second reviewer selected the causal category 'not to be determined/other'.

Figure 1 shows that human causes predominantly contributed to the occurrence of AEs (53% of AEs); for example, when an antibiotics allergy of a patient was missed by the nurse on the ward although this had been documented in the emergency room. The second main cause was the patient-related factor, such as severe preexisting diseases like heart failure; this contributed to 39% of the AEs. Human and organisational factors had a relatively high proportion of AEs that were prevent-able. Out of all AEs that had at least one human cause, 62% was considered preventable; for organisational 39% of the AEs. Human and organisational factors had factors this was 83%.

Finally, the physician reviewers had to indicate which prevention strategies they considered useful to prevent the AE in the future. For the 49 preventable AEs, they selected 110 prevention strategies. These are described in table 4.

Improvement of training programmes for required skills (51%) and continuous peer review/monitoring of quality (51%) were both selected for the prevention of half of the preventable AEs. An example of a

Table 2 Frequencies of AEs and preventable AEs by gender, age category, fracture type, operation procedure and	evel of
comorbidity	

	Records reviewed: frequency (n (%))	Of which contained one or more AEs: frequency (valid row %)	Of which contained one or more preventable AEs: frequency (valid row %)
Total study sample	616 (100)	114 (19)	49 (8)
Gender			
Male	147 (24)	31 (21)	16 (11)
Female	469 (76)	83 (18)	33 (7)
Age category (years)			
65–75	95 (15)	20 (21)	9 (9)
76–85	254 (41)	51 (20)	21 (8)
>85	267 (43)	43 (16)	19 (7)
Fracture type			
Femoral neck	309 (50)	65 (21)	24 (8)
Pertrochanteric	242 (39)	35 (14)	16 (7)
Subtrochanteric	46 (7)	11 (24)	8 (17)
Lateral	17 (3)	2 (12)	0 (0)
Operation procedure			
Femoral head replacement	239 (39)	52 (22)	20 (8)
Gammanail	194 (31)	27 (14)	14 (7)
Sliding hip screw	112 (18)	21 (19)	9 (8)
Long gammanail	39 (6)	10 (26)	6 (15)
Cannulated hip screws	25 (4)	3 (12)	0 (0)
Total hip replacement	6 (1)	1 (17)	0 (0)
Judged level of comorbidity			
None	35 (6)	4 (11)	1 (3)
Insignificant	101 (16)	12 (12)	7 (7)
Moderate	228 (37)	35 (15)	18 (8)
Significant	215 (35)	54 (25)*	19 (9)

preventable AE in which more training was recommended is when the performed surgery was too drastic (femoral head replacement) even though cannulated screws were also sufficient. Online supplementary appendix 1 describes more examples of adverse events, their causal factors and prevention strategies.

DISCUSSION

The results show that almost one-fifth of the hip fracture patients in our study experienced an AE related to their hospital admission and almost 40% of these AEs were potentially preventable. Not surprisingly, AEs occurred more often in patients with significant comorbidity. These patients have severe other medical problems which complicates care. Therefore, it is often not possible to prevent these AEs and this was confirmed by the results: there were no significant differences in the rate of preventable AEs between the comorbidity levels. This, however, does not suggest that this finding is of no clinical relevance since this could also be the result of a lack of power to detect significant differences for the preventable AEs. The high percentage of AEs in patients with significant comorbidity may be a good starting point for future development in the care for this patient group; AEs that are currently not preventable, may

become preventable in the future by advances in technology, education and care. The causes of AEs were, in more than half of the cases, related to human error. AEs with human and organisational causal factors were often preventable. The improvement of training for the skills needed for the treatment of this patient group in general and emphasis on quality assurance are two strategies that could be useful to prevent AEs in the future.

Our results show that the percentage of AEs and preventable AEs is two-and-a-half times higher for older hip fracture patients than the incidence rates in the general Dutch hospital population of 65 years and older.²⁴ One explanation for this difference could be that older hip fracture patients are a difficult patient group to manage clinically, which makes this group more at risk of suffering from AEs. This could be supported by other studies showing high numbers of adverse outcomes in hip fracture patients. For example, Sathiyakumar *et al*²⁵ found an AE rate of 25.2% in their database study in which they classified complications in hip fracture patients as major or minor AEs. Another factor for the high percentages found in our study may be that we used only physician reviewers in our review process; perhaps more AEs were found because the physician reviewers were required to look at all patient records instead of only receiving the triggered records from nurse reviewers.

	AEs: N (%) (N=124)	Preventable AEs: N (%) (N=49)
	(N=124)	AES. N (/0) (N=49)
Classification by clinical procedure*		
Surgical procedure (operative procedures)	87 (70)	35 (71)
Medical procedures (procedure not in operating room)	13 (10)	4 (8)
Diagnostic process (eg, missed, delayed or inappropriate diagnostic process)	9 (7)	4 (8)
Medication (eg, side effects, allergic reactions, anaphylaxis)	7 (6)	4 (8)
Other clinical management (including nursing and allied healthcare)	5 (4)	1 (2)
Other (eg, fall)	1 (1)	_
Discharge procedure (eg, inappropriate discharge)	_	-
Missing	2 (2)	1 (2)
Consequences [‡]		
Intervention/treatment	83 (67)	35 (71)
Prolonged hospital stay	43 (35)	20 (41)
Readmission to hospital	36 (29)	16 (33)
Health limitation at discharge	28 (23)	15 (31)
Death	20 (16)	6 (12)
Extra outpatient care	12 (10)	8 (16)
Other	16 (13)	11 (22)

Percentages do not add up to exactly 100 due to rounding up.

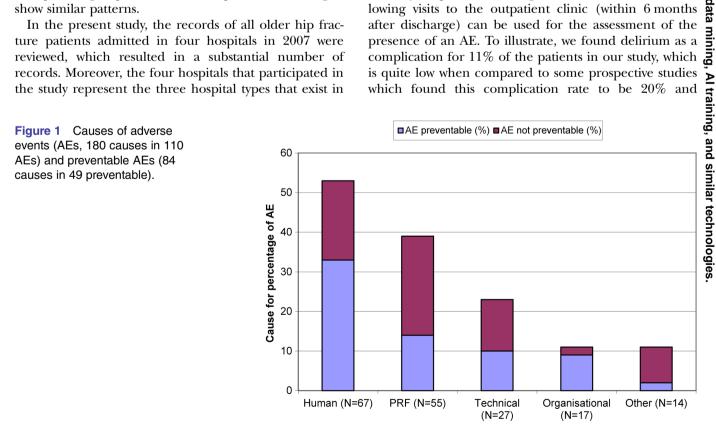
‡Multiple consequences could be selected for each AE.

In accordance with previous studies, we also found that human error was mainly involved in the causation of the AE and that these are often preventable.¹⁵²⁶ Our findings that AEs with organisational causes are mostly preventable are also similar to previous findings.²⁶ So even though previous studies used a representative sample of all hospital admissions and we selected a specific patient group, the causes and prevention strategies show similar patterns.

In the present study, the records of all older hip fracture patients admitted in four hospitals in 2007 were reviewed, which resulted in a substantial number of records. Moreover, the four hospitals that participated in the study represent the three hospital types that exist in

the Netherlands, namely university, tertiary teaching and general hospitals. Therefore, it seems plausible that the results of this study are of general value to improve the care for older hip fracture patients.

Record review studies have some well-known limitations. First, reviewers have to rely on the information that is available in the record. Only information that is registered by hospital staff during the admission or in the following visits to the outpatient clinic (within 6 months after discharge) can be used for the assessment of the presence of an AE. To illustrate, we found delirium as a complication for 11% of the patients in our study, which is quite low when compared to some prospective studies which found this complication rate to be 20% and



and

selected in following frequency (%)	Table 4 Strategies to prevent AEs				
Quality assurance/ peer reviewContinuously monitoring of data on quality based in prespecified standards and assessment of a health professional's performance by one or more individuals in the same field25 (51)ProceduresCompleting or improving formal and informal procedures19 (39)EvaluationEvaluating the current behaviour regarding safety18 (37)Information and 	Prevention strategy	Description	3		
peer reviewstandards and assessment of a health professional's performance by one or more individuals in the same fieldProceduresCompleting or improving formal and informal procedures19 (39)EvaluationEvaluating the current behaviour regarding safety18 (37)Information andCompleting or improving available sources of information and11 (22)communicationcommunication structures8 (16)MotivationIncreasing the level of voluntary obedience to generally accepted8 (16)rules by applying principles of positive behaviour modification4 (8)Up-scalingHandling the problem at a higher organisational level, for example,–	-		. ,		
EvaluationEvaluating the current behaviour regarding safety18 (37)Information and communicationCompleting or improving available sources of information and communication structures11 (22)MotivationIncreasing the level of voluntary obedience to generally accepted rules by applying principles of positive behaviour modification8 (16)Technology/equipmentRedesigning of hardware, software or interface parts of the man- machine system4 (8)Up-scalingHandling the problem at a higher organisational level, for example,–	-	standards and assessment of a health professional's performance by	25 (51)		
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Machine systemUp-scalingHandling the problem at a higher organisational level, for example,	Motivation	· · · · · · · · · · · · · · · · · · ·	8 (16)		
	Technology/equipment		4 (8)		
	Up-scaling		-		
Financial investment Financial investments in required areas, for example, increasing the – availability of facilities and equipment	Financial investment		-		
Personnel Increasing the number of personnel –	Personnel	Increasing the number of personnel	-		

more.^{27 28} Second, the inter-rater agreement between reviewers was moderate in this study and this was also an issue in other retrospective review studies.⁸ ⁹ Third, not all relevant information regarding the AE is registered in the patient record; therefore, gathering information on all contributing factors can become more difficult. Human and patient-related factors that contribute to the causation of an AE are more regularly reported in the patient record and therefore, these are the most visible factors for reviewers.²⁶ Organisational and technical factors are more difficult to find in a patient record as they often indicate more general problems and are, therefore, often reported in other incident-reporting systems within a hospital.²⁶ It is recommended for future studies to also include additional sources of information, such as complications discussed during trauma meetings and incident reports, when performing an indepth analysis of (preventable) AEs in older hip fracture patients. This would also provide more insight into more concrete possibilities for prevention of AEs. In the current study, the prevention strategies were the same as in previous retrospective record review studies.⁹ However, it can be argued that these are too generic and it is unknown to what extent they would in fact prevent the AEs. Prospective study designs are more useful for this purpose and are therefore recommended to uncover more detailed information on causes of AEs, and to subsequently select or design prevention strategies tailored to the causes found.

The results of this study show that improvements in patient safety for older hip fracture patients are necessary. We recommend that healthcare professionals should be trained more extensively in how to provide optimal care for this patient group. For example, simulation training could be used to improve skills and for the implementation of new techniques.²⁹ Training should not only focus on medical-technical aspects of care but also on identifying patients who may be at risk for complications or AEs. When specific risks are identified and dealt with in individual patients with, for example, a comprehensive geriatric assessment, outcomes may improve.³⁰ In addition, peer review of a professional's performance with structured standards can provide useful opportunities to learn from each other.³¹ Regular patient record review, morbidity and mortality meetings, ⊳ and incident reporting can be usable tools for this goal.^{32–36} More research is needed to investigate the effects of these tools on quality and safety of care, specifically for older hip fracture patients. One important factor to take into account are the specific circumstances and conditions within hospitals. In the current study, all Dutch hospital types were represented to provide a general overview for one patient group. Owing to the limited number of hospitals and preventable AEs in the current study, it was not justified to look at differences between hospital types. This, however, is important when designing interventions for improvement because the setting and context within an university hospital can be very different from those in a general hospital.

To conclude, this study shows that hip fracture patients of 65 years and older suffer from preventable AEs relatively often. More training of healthcare professionals to deal with the specific needs of older hip fracture patients and a focus on quality assurance is needed to reduce the number of preventable AEs in this vulnerable patient group.

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Author affiliations

 $^1 \ensuremath{\text{NIVEL}}$, Netherlands Institute for Health Services Research, Utrecht, the Netherlands

²Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands

³Department of Trauma Surgery, VU University Medical Center, Amsterdam, the Netherlands

⁴Department of Surgery, Division of Trauma Surgery, University Hospital Zurich, Zurich, Switzerland

⁵Department of Surgery, Kennemer Gasthuis, Haarlem, the Netherlands

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Contributors CW obtained the funding and supervised all stages of the study. CW, HM and SL designed the study. The acquisition of data was performed by HM, SL and MZ. HM, ML, MZ and CW performed the statistical analysis, the interpretation of the data and drafting of the manuscript. PCJ, GNJ and MJH were involved in the critical revision of the manuscript for important intellectual content. All authors commented on, revised sequential drafts and approved the final version of the manuscript.

Competing interests None.

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Data sharing statement No additional data are available.

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