Metaanalysis of risk factors for mortality in patients with hip fracture

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ABSTRACT

INTRODUCTION: The aim of this metaanalysis is to assess the association of three different clinical score systems with the mortality in hip fracture patients.

METHODS: A literature search was conducted on November 13, 2011 using PubMed and Embase. The search yielded 315 publications which were reviewed on the basis of the inclusion criteria.

RESULTS: Thirteen studies were included for further processing. The following clinical score systems were found to be of prognostic value for mortality in hip fracture patients: a high American Society of Anesthesiologists (ASA) score of three or above (odds ratio (OR): 3.07; 95% confidence interval (CI): 2.78-3.38; $p < 0.00001$, 15,625 study participants included), a Charlson Comorbidity Index (CCI) score of one or more (OR: 2.05; 95% CI: 1.79-2.34; $p < 0.00001$, 13,570 study participants included) and dementia (assessed with Mini Mental State Examination or obtained from journal extraction) (OR: 2.73; 95% CI: 1.64-4.57; $p = 0.0001$; 1,782 study participants included).

CONCLUSION: The present metaanalysis showed that the ASA score, the CCI score and assessment of preexisting dementia are useful in predicting the mortality of hip fracture patients.

Hip fracture constitutes a worldwide public health problem among the elderly [1]. The most common cause of hip fractures is low-energy trauma combined with osteoporosis, and is most frequently seen in elderly women.

Several studies have demonstrated an increased risk of mortality in hip fracture patients [2-6]. The highest risk of mortality is seen in the immediate post fracture period [7], but increased mortality is still seen 12 month post fracture [2, 8]. Over the first 12 months, the crude mortality ranges from 27.6% to 40.5 % in men and from 15.8% to 23.3% in women [9]. The mortality rate depends on a variety of factors including age, gender, co-morbidity and pre-fracture functional state [10].

Numerous studies have explored the impact of different factors on the outcome following a hip fracture, such as admission blood tests, co-morbidities, clinical score systems etc. [3, 10-23].

If we are able to identify high risk patients, treatment can be optimized and outcome might be improved. If such identification can be performed by the use of simple clinical score systems, it will be an easily accessible tool for adjusting and specializing treatment. It would furthermore be an inexpensive and quickly performed assessment, which would be highly useful for clinicians.

In this metaanalysis we chose to focus exclusively on simple bedside tests and their ability to predict mortality in hip fracture patients. Thus, we chose score systems containing parameters directly observable in the patient or parameters derived from questionnaires. Score systems containing paraclinical data such as blood tests or requiring the use of highly technological equipment in general were thus excluded.

Three clinical score systems, the American Society of Anesthesiologist score (ASA), Charlson Comorbidity Index (CCI) and dementia score (MMSE: Mini Mental State Examination) (**Table 1**) met the inclusion criteria, and the aim of this metaanalysis was to assess the association of these score systems with mortality in hip fracture patients.

METHODS

The PRISMA guidelines for metaanalyses were followed [24].

Search strategy

A search for articles in the Medline Database using PubMed was conducted on November 13, 2011. The string, used for this search, consisted of three concepts, as shown below:

I. ("hip fracture" OR "hip fractures" OR ("femoral neck" AND fractur*) OR (*trochant* AND fractur*) OR ("collum femoris" AND fractur*) OR (intertrochant* AND fractur*) OR "proximal femoral fracture*")
II. (mortality OR death OR fatal* OR survival)
III. (ASA OR "ASA score" OR "American Society of Anesthesiologists").

The first concept was designed to retrieve articles relating to hip fractures and the second to retrieve those relating to mortality or survival.

The last concept was constructed to search for the three score systems individually, thus resulting in three different search strings, one for each score. ASA is shown as an example:

METAANALYSIS

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TABLE 1

Clinical score systems, overview.

ASA score	
5-category classification system used to assess the physical status of patients	1. A normal, healthy patient 2. A patient with mild systemic disease 3. A patient with severe systemic disease 4. A patient with severe systemic disease that is a constant threat to life 5. A moribund patient who is not expected to survive without the operation
CCI score	
Assesses a variety of co-morbidities Each condition, depending on the associated risk of dying, is assigned with a score of 1, 2, 3 or 6	1 each: myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease 2 each: hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukaemia, lymphoma 3 each: moderate or severe liver disease 6 each: malignant tumour, metastasis, AIDS
Dementia, MMSE score	
30-point questionnaire: ≥ 25 normal cognition 21-24 mild impairment 10-20 moderate impairment ≤ 9 severe impairment	Orientation to time (up to 5 points) Orientation to place (up to 5 points) Registration (up to 3 points) Attention and calculation (up to 5 points) Recall (up to 3 points) Language (up to 2 points) Repetition (1 point) Complex commands (up to 6 points)

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; MMSE = Mini Mental State Examination.

"hip fracture" OR "hip fractures" OR ("femoral neck" AND fracture*) OR (*trochant* AND fracture*) OR ("collum femoris" AND fracture*) OR (intertrochant* AND fracture*) OR "proximal femoral fracture*") AND (mortality OR death OR fatal* OR survival) AND (ASA OR "ASA score" OR "American Society of Anesthesiologists")

Third concept strings for CCI and dementia: CCI: (Charlson OR "Charlson co-morbidity" OR "co-morbidity score"). Dementia: (dementia).

Articles were chosen through an iterative process; headlines and abstracts were screened and articles found relevant were reviewed in full text version. The reference lists of the selected articles were screened, and the service "related citations" in PubMed was applied, to find additional publications and additional words for the search strings. The selection process was repeated three times. The search yielded a total of 315 publications.

The publications were further sorted based on the inclusion criteria (English language; full-text editions electronically available at the Royal Library of Denmark; study population larger than 100 subjects; trial population of mixed gender; trial duration less than or equal to two years).

Figure 1 shows the search which resulted in the inclusion of thirteen studies [3, 10, 12-22]. Essential characteristics, including clinical score system, number of studies included, number of study participants and average days of follow-up, are listed in **Table 2** (n = 14, some of the included studies evaluated more than one clinical score system).

DATA ANALYSIS

Odds ratios (OR) with matching 95% confidence intervals (CI) were calculated for the individual studies as described by Bland and Altman [25], using a contingency 2 χ^2 table. p-values were calculated using χ^2-tests. $p < 0.05$ was considered significant.

The calculations were conducted with Microsoft Office Excel 2007.

Review Manager (RevMan), developed by the Cochrane Collaboration, was used to carry out the systematic review [26]. The standard errors and ORs were plotted in a funnel plot to create a visual aid for the detection of any systematic heterogeneity or publication bias, also known as Egger's test [27].

The I^2 statistic was used to evaluate the degree of dissimilarity between the individual studies. I^2 describes the percentage of inconsistency between studies that is due to heterogeneity rather than sampling error [28]. $I^2 > 50\%$ was used as a threshold, indicating high heterogeneity.

Studies were analyzed using the fixed effect model when $I^2 < 50\%$ and the random effect model when $I^2 \geq 50\%$.

RESULTS

Table 2 shows the characteristics of the studies in the analyses, including first author, clinical score system, important demographics, length of follow-up, design of studies, ORs and p-values.

FIGURE 1

Flow chart.

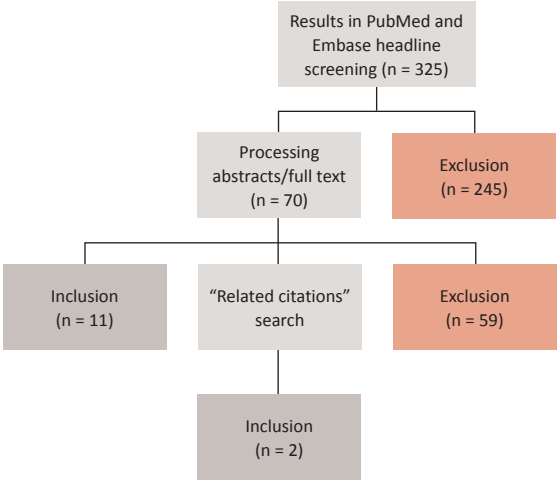


TABLE 2

Characteristics of studies included in the analyses.

Score	Reference	Year	Patients, n	Male, %	Average age, years	Length of follow-up, days	Study design	OR (95% CI)	p-value
ASA	[3]	2006	2,617	23.4	79.9/73.0	365	Pro	2.70 (2.10-3.47)	< 0.0001
	[18]	2003	1,780	23.3	–[a]	365	Pro	3.07 (2.32-4.07)	< 0.0001
	[19]	2010	567	22.4	85.1	365	Retro	2.63 (1.74-3.97)	< 0.0001
	[10]	2010	2,423	21.5	81.1	180	Pro	2.85 (2.17-3.75)	< 0.0001
	[22]	2009	6,018	26.2	83.2	30	Retro	3.13 (2.78-3.95)	< 0.0001
	[20]	2009	1,921	25.3	84	730	Pro	3.19 (2.57-3.94)	< 0.0001
	[21]	2011	299	24.1	84.7	90	Pro	4.94 (2.33-10.50)	< 0.0001
CCI	[16]	2005	6,629	19.7	> 65	365	Retro	2.26 (1.86-2.74)	< 0.0001
	[17]	2011	485	26.6	75-89	30	Retro	1.82 (0.74-4.44)	0.2
	[22]	2009	6,456	26.2	83.2	30	Retro	1.93 (1.61-2.32)	< 0.0001
Dementia	[12]	2005	965	23.8	81.4	In-hospital	Retro	1.64 (1.11-2.43)	0.01
	[13]	2010	374	24.9	83.8	730	Pro	4.71 (2.26-9.85)	< 0.0001
	[14]	2009	180	25.6	> 70	365	Pro	2.50 (1.11-5.64)	0.02
	[15]	2010	263	21.7	84	365	Pro	3.51 (1.91-6.44)	< 0.0001

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; CI = confidence interval; OR = odds ratio; Pro = prospective; Retro = retrospective.
a) Data not given.

In the funnel plots, the data were distributed equally around the vertical axis, implying no presence of publication bias (not shown).

In both the ASA and CCI analyses, statistical dissimilarities were absent, evidenced by $I^2 = 0\%$. This indicates full homogeneity, and a fixed effect analysis was therefore chosen.

The dementia analysis showed high statistical heterogeneity with an I^2 of 64%. This suggests that the studies might not have a common effect size. Differences in outcome are more likely to result from variance than from pure chance. Thus the random effect model was used. With this model, each study is weighted equally. It will further incorporate greater variability, resulting in wider confidence intervals [29].

Besides statistical heterogeneity, the studies are to some extent different with regard to design and the type of personnel carrying out the tests.

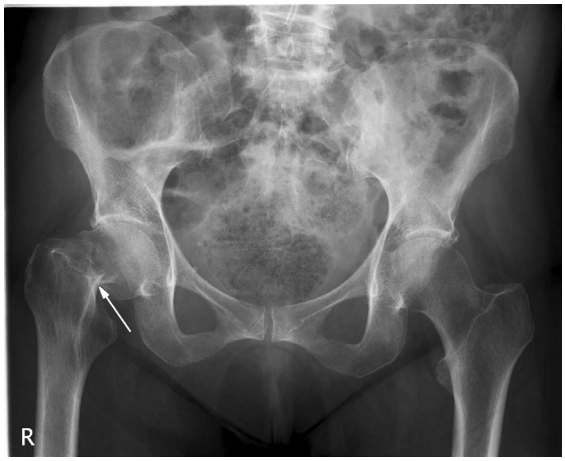
Metaanalyses

Seven studies were included in the analysis of the association of a high ASA score with mortality (**Figure 2**). 56.4% of the patients had a high ASA score of three or above. The results showed no statistical heterogeneity, $I^2 = 0$, and the 95% confidence intervals (95% CI) overlapped implying that the effects are similar [29]. All seven studies had ORs above one and, with related p-values all below 0.0001, they were statistically significant. The ORs ranged from 2.63 (95% CI 1.74-3.97) in the study by Holvik et al to 4.94 (95% CI 2.33-10.50) in the study by Talsnes et al, resulting in a total OR of 3.07 with a narrow 95% CI (2.78-3.38), ($p < 0.0001$). Thus patients who scored three or more have an approx. three times increased risk of dying compared with those who scored 1-2.

Three studies were included in the analysis dealing with the Charlson Comorbidity Index. 38.6% of the patients scored one or more on the CCI (Figure 2). The results showed no statistical heterogeneity, $I^2 = 0$. All studies had an OR above one, but only the studies by Franzo et al and Nielsen et al showed statistical significance with a p value below 0.0001.

The study by Kirkland et al, in contrast, had a p value of 0.2, which is above the established 0.05 threshold. However, the pooled OR of 2.05 with a narrow 95% CI (1.79-2.34) showed statistical significance ($p < 0.00001$) for a 2.05 times increased risk of dying if co-morbidity is present.

Four studies were included in the analysis of the association of dementia with mortality (Figure 2). 41.2% of



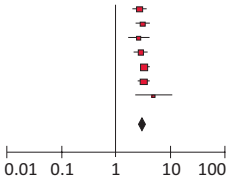
Hip fracture (arrow).

FIGURE 2

Forest plots.

ASA

	Alive, n		Dead, n (%)			Odds Ratio
Reference	events	total	events	total	weight	M-H, fixed, 95% CI
[3]	690	2,082	83	535	(17,5)	2.70 [2.10, 3.47]
[18]	551	1,389	69	391	(12.9)	3.07 [2.32, 4.07]
[19]	234	434	41	133	(5,7)	2.63 [1.74, 3.97]
[10]	663	1,972	68	451	(14.6)	2.85 [2.17, 3,75]
[22]	3,372	5,399	207	619	(27.6)	3.31 [2.78, 3.95]
[21]	113	240	9	59	(1.5)	4.94 [2.33, 10.50]
Total (95% CI)		12,734		2,891	(100.0)	3.07 [2.78, 3.38]
Total event	6,185		626			

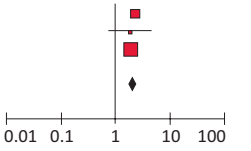


Heterogeneity: $\chi^2 = 4.19$, df= 6 (p = 0.65); $I^2 = 0\%$

Test for overall effect: Z = 22.28 (p < 0.00001)

CCI

	Alive, n		Dead, n (%)			Odds Ratio
Reference	events	total	events	total	weight	M-H, fixed, 95% CI
[16]	5,226	5,995	476	634	(36.6)	2.26 [1.86-2.74]
[17]	108	445	6	40	(2.8)	1.82 [0,74-4.44]
[22]	2,340	5,796	171	660	(60.7)	1.94 [1.61-2.32]
Total (95% CI)		12,236		1,334	(100.0)	2.05 [1.79-2.34]
Total events	7,674		653			

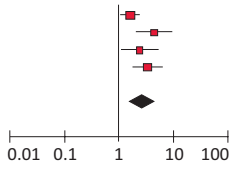


Heterogeneity: $\chi^2 = 1.37$, df = 2 (p = 0.50); $I^2 = 0\%$

Test for overall effect: Z = 10.51 (p = 0.00001)

Dementia

	Alive, n		Dead, n (%)			Odds Ratio
Reference	events	total	events	total	weight	M-H, random, 95% CI
[12]	552	850	61	115	(32.5)	1.64 [1.11-2.43]
[13]	128	306	9	68	(21.9)	4.71 [2.26-9.85]
[14]	110	151	15	29	(20.0)	2.50 [1.11-5.64]
[15]	148	206	24	57	(25.7)	3.51 [1.91-6.44]
Total (95% CI)		1,513		269	(100.0)	3.51 [1.64-4.57]
Total events	938		109			



Heterogeneity: $Tau^2 = 0.17$; $\chi^2 = 8,41$, df = 3 (p = 0.04); $I^2 = 64\%$

Test for overall effect: Z = 3.84 (P = 0.00001)

ASA = American Society of Anesthesiologists; CI = confidence interval; CCI = Charlson Comorbidity Index; df = degrees of freedom; M-H = Mantel-Haenszel.

the patients had dementia on admission. The results showed a high statistical heterogeneity, I2=64%, which is why the random effect model was used. All four studies had ORs above one and showed statistical significance with p values < 0.05. The ORs ranged from 1.64 (95% CI 1.11-2.43) in the study by Bergeron et al to 4.71 (95% CI 2.26-9.85) in the study by Hershkovitz et al, resulting in a statistically significant (p = 0.0001) pooled OR of 2.73 (95% CI 1.64-4.57).

DISCUSSION

This metaanalysis has found all three clinical score systems to be of prognostic value for mortality in hip fracture patients.

The ASA analysis demonstrated an excess mortality three times greater in patients with an ASA score of 3-5 compared with those who score 1-2. The statistically significant (p < 0.0001) OR was 3.07 with a narrow 95% CI (2.78-3.38).

The CCI analysis showed an excess mortality in patients who score 1+ compared with patients who have no co-morbidities present. The statistically significant (p < 0.0001) OR of this study is 2.05 with a narrow 95% CI (1.79-2.34).

The patients with premorbid dementia demonstrated an almost three times greater mortality compared with non-demented patients, with the statistically significant (p = 0.0001) OR of 2.73 (95% CI 1.64-4.57).

However, the analyses of the CCI and dementia do not comprise many studies. It would, of course, be pref-

erable to re-analyze the two score systems and their relation with mortality in hip fracture patients when more studies are available. Furthermore, different methods were used for the assessment of dementia, MMSE or journal extraction. It would be useful for future studies if the same diagnostic methods were used and were well documented in the papers as well.

With the help of these three bed-side clinical score systems, the clinicians can perform a rapid and inexpensive assessment of their patients and and increased risk of dying without needing paraclinical tests to optimize care and treatment.

In this metaanalysis we were interested in investigating the sole effect of the clinical score systems on the assessment of mortality. Nevertheless, the clinical score systems can easily be combined with other types of risk assessment methods, thereby potentially improving the assessment. Some studies have alone focused on the effect of paraclinical tests, others have combined paraclinical tests with clinical score systems. Markers, such as haemoglobin, albumin, total leukocyte count, creatinine and parathyroid hormone in admission blood tests, can be used as significant outcome predictors in hip fracture patients [11, 23].

Other scoring systems with a proven predictive value do exist, but they require additional investigations such as blood samples, X-rays etc.

The Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system is comprised of a preoperative risk score, a surgical stress score, and a comprehensive risk score based on the preoperative risk score and surgical stress score [30]. It seems useful for predicting postoperative risk, estimating costs and for comparison of outcome in patients following surgery of hip fractures [30, 31].

The Nottingham Hip Fracture Score (NHFS) is a scoring system validated for the prediction of 30-day mortality after hip fracture surgery [32]. It is made up of seven independent predictors of mortality that have been incorporated into a risk score: age (66–85 and ≥ 86 years); sex (male); number of co-morbidities (≥ 2), admission mini-mental test score (≤ 6 out of 10), admission haemoglobin concentration (≤ 10 g × dl^{-1}), living in an institution; and the presence of malignancy [33]. The NHFS uses data that are easily and routinely collected from all patients presenting with hip fractures. The NHFS can be calculated on admission to hospital [33].

The physiologic and operative severity score for the enumeration of mortality and morbidity (POSSUM) system predicts mortality and morbidity in surgical patients using physiologic and operative factors [34]. This system has also been presented in a modified version for orthopedic use that has been validated for patients with femoral neck fractures [35]. The POSSUM requires surgical and anaesthetic data [34] and in some studies the orthopedic POSSUM scoring system has been shown to over-predict mortality in patients with hip fractures [36, 37]. However, it has been pointed out that this may be due to the method of analysis used in these studies [35].

FACTS

Hip fracture is a major social problem.

Hip fracture is associated with high morbidity and mortality.

Clinical score systems may predict mortality in hip fracture patients.

Identification of high-risk patients will allow for more intensive treatment of these.

These scoring systems, however, remain complex and it can be difficult to single out the effect of each of the individual components comprised by the systems. This metaanalysis therefore focused on individual clinical scoring systems allowing for differentiation of care, e.g. in assigning the patients to specialized orthogeriatric units.

The functional outcome in hip fracture patients can further be optimized by combining the orthopaedic surgeon's and the geriatrician's expertise this has yielded a significant reduction of the overall length of hospital stay while still maintaining a high quality of care [38, 39].

Furthermore, ongoing adjustments in treatment may be conducted on the basis of the simple clinical score systems.

Moreover, the rate of postoperative complications and mortality may be reduced by using an optimized hip fracture treatment, i.e. a fast-track programme, where improvements such as a more efficient pain treatment and reduction of time to surgery are applied [40].

Factors such as functionality (New Mobility Score, Cumulated Ambulation Score), type of fracture, type of surgery, time to surgery and the geriatric follow-up are other possible predictors of mortality in hip fracture patients [41, 42].

A future study of interest is one that looks at all factors: paraclinical parameters, bedside clinical scoring systems, co-morbidities, logistical parameters such as waiting times for surgery and medication consumption and the correlation with mortality in hip fracture patients in a large patient material.

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