Preoperative Risk Assessment for Delirium After Noncardiac Surgery: A Systematic Review

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Delirium is a common postoperative complication in older adults associated with adverse events including functional decline, longer lengths of stay, and risk of institutionalization. The purpose of this article is to systematically review preoperative risk factors associated with delirium following noncardiac surgery.

A medical literature search was conducted using several bibliographic databases (PubMed, CINAHL, Cochrane, PsychInfo), supplemented by a manual search of the references of retrieved articles. Studies were retained for review after meeting strict inclusion criteria that included only operative patients with incident postoperative delirium diagnosed prospectively using criteria derived from the *Diagnostic and Statistical Manual of Mental Disorders Third* or *Fourth Edition*. Quantitative analyses included significance testing, homogeneity testing, and effect-size pooling.

Twenty-five articles were included for review. The incidence of delirium ranged from 5.1% to 52.2%, with greater rates after hip fracture and aortic surgeries. This review found two scales, a clinical prediction rule, and a delirium risk classification system that were validated in other operative settings.

Individual risk factor analysis suggested that cognitive impairment, older age, functional impairment, sensory impairment, depression, preoperative psychotropic drug use, psychopathological symptoms, institutional residence, and greater comorbidity were associated with postoperative delirium. Of the risk factors examined, evidence was most robust for an association between delirium and cognitive impairment or psychotropic drug use, with moderate effect sizes for both. Missing data and measurement differences did not allow for inferences to be made about other risk factors.

Effect-size pooling supports the concept that delirium is a heterogeneous disorder with multiple risk factors. More research is needed to better identify patients at risk for postoperative delirium and to develop preventive strategies.
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Key words: postoperative delirium; effect-size pooling; preoperative risk factors; noncardiac surgery

Delirium is an acute confusional state characterized by fluctuating symptoms including inattention, disturbances of consciousness, or disorganized thinking.[1,2] Other important hallmarks of this syndrome include disorientation, memory impairment, perceptual disturbances, altered psychomotor activity, and disturbed sleep–wake cycles.[2] Delirium occurs commonly as a perioperative complication in older adults, with reported incidences varying from 0 to 73.5%.[3] Perioperative delirium is associated with greater cost,[4,5] longer lengths of stay,[5] complications,[5–7] poor recovery,[5,6] institutionalization,[6,7] and mortality.[6,7] Given the high incidence and morbidity associated with perioperative delirium, preoperative delirium risk assessment is important to guide informed decision-making and possible preventative options.

Numerous clinical reviews of postoperative delirium and its risk factors exist, but there are few systematic reviews. Previously published systematic reviews often involved both nonsurgical and surgical patients[8] or included patients undergoing cardiac surgery.[3,9] Cardiac surgeries involving cardiac bypass have typically been distinguished from other surgeries in other areas of preoperative risk assessment.[10] The purpose of this article is to systematically review commonly assessed preoperative risk factors for incident delirium in noncardiac surgery so as to guide preoperative risk assessment for delirium in this setting.

METHODS

A PubMed search of English or French studies (1960 to January 2006), using the Medical Subject Headings (MeSH) "delirium" or "confusion" and combining with the MeSH headings "postoperative complications" or "risk factors" or "risk assessment" was conducted using exploded headings. The Cochrane databases (MeSH heading "delirium"), CINAHL, and PsychInfo databases were also searched. Manual searches of references from study arti-

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cles and reviews and individual author searches of prominent researchers in the field were also conducted to obtain additional articles.

Both authors selected articles. Studies were included if they provided original data on preoperative risk factors; included only adult patients ($\geq$18) who underwent noncardiac surgery; had a minimum of 10 cases of delirium; included a concurrent, nonhistorical, control group of nondelirious patients; and provided data on incident delirium. (If delirium was not stated as being incident, articles involving elective surgeries were still included, because it was assumed that acutely delirious patients would not undergo elective surgery.)

In addition, original risk-factor or therapeutic intervention studies had to actively survey for delirium prospectively with patient interviews or observations using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), *Third* or *Fourth Edition*,[1] or DSM-derived criteria (the Confusion Assessment Method[2]). This was not required of validation studies if the original scale being validated used prospective surveillance and DSM-derived criteria to diagnose delirium. Therapeutic delirium-prevention trials were eligible if the intervention had no statistically significant effect on delirium incidence as reported in the original study and if data on baseline characteristics were provided.

Studies were excluded if they exclusively studied intra- or postoperative risk factors, included data on prevalent (present on admission) delirium, did not use the DSM or DSM-derived criteria to assess delirium, used retrospective methods to diagnose delirium, or included patients undergoing cardiac bypass (e.g., for pulmonary thromboendarterectomy).

For each of the selected studies, information was collected on the type of study (validation or risk factor), number and incidence of delirium cases, type(s) of surgical procedures, method for diagnosing delirium, whether prevalent or incident delirium was included, sample size, specific data on any preoperative risk factors, and the method used to assess risk factors. Because delirium is a symptom complex, with potentially multiple predisposing risk factors and causes, all preoperative risk factors were potentially eligible for inclusion, although not all were necessarily included in study analyses.

Analysis

For studies that assessed individual risk factors, analysis was considered if the risk factor was assessed in at least two studies. Before proceeding with any quantitative analysis, the percentage of data known to be missing (if original data was not provided in the article) was calculated. Quantitative analyses were not performed if missing data exceeded 25%. The method of risk factor measurement across different studies was also examined before any analysis to determine whether similar risk states were being evaluated.

When performed, quantitative analyses included significance testing (whether across all studies there was a significant association between the risk factor and delirium), homogeneity testing (whether the strengths of association were similar across studies) and pooling (performed if the *P*-value with the test of homogeneity exceeded .05). For strictly categorical risk factors (e.g., sex), the Mantel-Haenszel method[11] was used.

For risk factors that could be measured categorically or continuously (e.g., aged $\geq$70 or mean age), different inferential statistics (e.g., the chi-square test or *t* test statistic) were transformed to common metrics, namely the Z statistic (significance level) and the effect size (or the product-moment correlation, *r*), as previously described.[12–14] The Z statistics from individual studies were used to conduct significance and homogeneity testing across studies.[12] Pooling of effect sizes, *r* (weighted by sample size and unweighted), were calculated.[12] Squared effect sizes (r^2) represent the proportion of variance of a dependent variable accounted for by an independent variable. By convention, *r* of 0.1, 0.3, and 0.5 generally represent small, medium, and large associations, respectively.[15]

Sources of Heterogeneity

Each study is unique and can therefore introduce significant heterogeneity, or differences, observed in results across studies. This can limit inferences that can be made in a systematic review. General causes of heterogeneity include random error and unknown and known factors (e.g., different study methodologies and populations).

Attempts to limit some of the possibly predictable (or known) sources of heterogeneity were addressed in this review a priori. For instance, included studies were mainly of similar design, namely prospective observational studies involving a nondelirious control group. However, the quality of the included observational studies is difficult to judge, given that there are no universally accepted methods for grading observational studies. Other possible methodological differences included the study populations and methods of measuring risk factors and outcomes. In this review, the outcome (delirium) was measured similarly across studies using DSM-derived criteria, hence controlling the introduction of potential heterogeneity.

All the studies involved adult surgical populations with incident delirium, although surgical type may still introduce considerable heterogeneity. It was assumed that different surgical types would have different associated inherent risks of delirium. This is similar to other postoperative complications in which the risk of complication also depends on the inherent risk of the surgical procedure.[10] Studies including different surgical types may therefore yield different point estimates of delirium risk associated with a risk factor when surgical procedures are unequally distributed between people with or without a risk factor from point estimates of studies enrolling only a single type of procedure. For example, some of the included studies involved both hip fracture and elective orthopedic procedures. Based on the results of previous research,[16] it was postulated that emergent hip fracture repair would be associated with a higher inherent risk of developing delirium than would purely elective arthroplasty. Risk factors that predispose individuals to having falls or osteoporosis,[17] which are themselves risk factors for sustaining a fracture (e.g., advanced age, cognitive impairment, visual impairment, permanent residence in an institution, and female sex[18]), could be associated with a greater risk of delirium in studies that enrolled

both hip fracture and elective orthopedic procedures than in studies that enrolled only arthroplasty or only hip fracture surgeries. This may introduce significant heterogeneity across studies. Studies were therefore grouped according to the types of procedures they contained (mixed or single surgical types), and analysis was sometimes restricted to studies involving only single surgical types. Examples of the latter include studies exclusively examining elective arthroplasty, hip fracture procedures, or limb peripheral vascular disease surgery, whereas mixed studies included all hip surgeries, vascular surgery (e.g., encompassing aortic, peripheral vascular, and carotid surgery), and all major procedures (Table 1).

The method by which studies measured a risk factor was also considered to be a potential source of heterogeneity. For risk factors such as comorbidities, alcohol intake, and depression, the use of different methods of measurement could potentially cause some heterogeneity in study results. This was taken into consideration when deciding whether and how to pool results.

RESULTS

A total of 2,737 abstracts and titles were reviewed for potential eligibility, from which 139 original English or French articles were retrieved. One hundred fourteen papers were excluded for not meeting one or more eligibility requirements (Figure 1). Twenty-five studies met the inclusion criteria, of which 21 were isolated risk factor studies, three were validation studies only, and one was both a validation and risk factor study. The incidence of delirium across studies ranged from 5.1% to 52.2%, with higher incidences in hip fracture (range 16.0–43.9%) and aortic surgeries (range 46.0–52.2%). One study on bilateral simultaneous knee replacements[19] also showed a high incidence of delirium (41%).

Table 1. Summary of Included Studies

Study Author	Surgery Type	Sample Size	Delirium Assessment Method	Overall Incidence of Delirium (%)
	Single			
Berggren et al.	Emergent hip fracture	57	DSM III	43.9
Edlund et al.	Emergent hip fracture	71	DSM IV	18.8
Fisher et al.	Elective orthopedic	80	CAM	17.5
Morrison et al.	Emergent hip fracture	541	CAM	16.0
Rogers et al.	Elective orthopedic	43	DSM III	28.0
Sasajima et al.	Elective peripheral vascular bypass	110	CAM	29.1
Schuurmans et al.	Emergent hip fracture	92	DSM IV*	19.6
Williams-Russo et al.	Bilateral elective knee replacement	51	DSM III	41.0
Zakriya et al.	Emergent hip fracture	168	CAM	28.0
Yoshimura et al.	Elective liver resection	100	CAM	17.0
Benoit et al.	Elective abdominal aortic aneurysm	102	DSM IV	33.0
Contin et al.	Elective orthopedic	236	DSM III	22.0
Kudoh et al.	Elective orthopedic	328	CAM	26.0
Freter et al.	Elective arthroplasty	132	CAM	13.6
	Mixed			
Andersson et al.	Emergent or elective hip	457	DSM IV	11.2 (20.2 in hip fracture, 3.6 in elective hip)
Bohner et al.	Elective vascular	153	DSM IV	39.2 (48.8 in aortic, 28.8 in nonaortic)
Dai et al.	Elective orthopedic or urological	701	DSM IV	5.1 (6.8 in orthopedic, 1.7 in urological)
Duppils et al.	Elective and emergent hip	225	DSM IV	20.0 (24.3 in hip fracture, 11.7 in elective hip)
Galankis et al.	Emergent or elective hip	105	CAM	23.8 (40.5 in hip fracture, 14.7 in elective hip)
Litaker et al.	Major elective	500	DSM IV	11.4
Marcantonio et al.	Major elective	876	CAM	9.0 (46.0 in aortic)
Schneider et al.	Elective vascular	47	DSM IV	36.2 (52.2 in aortic, 20.8 in nonaortic)

*Using Delirium Observation Scale.[33]

DSM III = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*; DSM IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; CAM = Confusion Assessment Method (see Inouye et al.[2]).

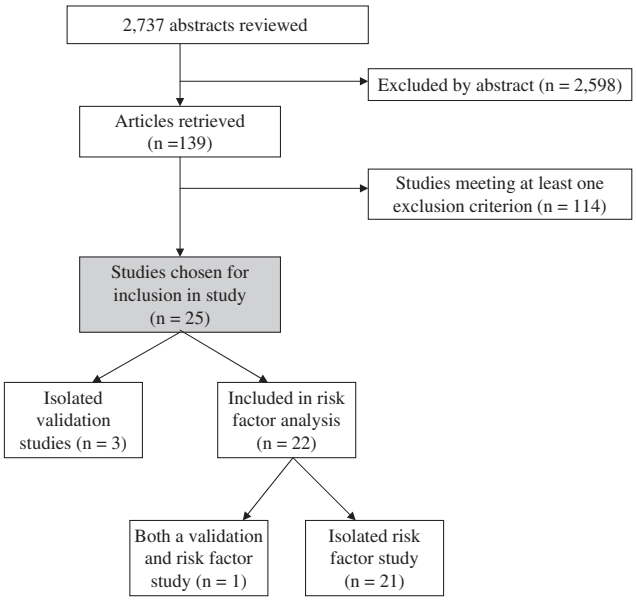

Figure 1. Selection of studies for review.

Validation Studies

Four of the studies reviewed[5,20–22] were studies that validated a previously published scale. Three of these[5,20,21] validated the Clinical Prediction Rule, a tool that assigns points for cognitive impairment, functional dependence, older age, specific laboratory abnormalities, self-reported excess alcohol use, and aortic procedures. A person's predicted risk for delirium increases with the number of points. The Clinical Prediction Rule was originally tested in an elective surgical setting.[7] The original paper described the development of the scale and its validation in a separate validation cohort. The other validation study[22] was an intervention study that also validated a delirium risk classification system previously developed for use in an acute medical setting[23] that assigns points for cognitive impairment, dehydration, severity of illness, and visual impairment. More points are associated with greater delirium risk.

Risk Factor Studies

Twenty-two studies reviewed individual risk factors[4,7,16,19,21,24–40] (Table 1), including the Clinical Prediction Rule[7] and another study that was a validation study and evaluated individual risk factors.[21] In 11 studies,[19,24,28–30,34,36–40] incident delirium was assumed because the procedures were elective. One study[26] on incident and prevalent delirium was included, because separate data on incident delirium were occasionally provided.

The following risk factors were assessed in at least two studies (Table 2): age, sex, cognitive impairment, depression, the presence of psychological symptoms, preoperative psychotropic drug use, alcohol use, a history of prior delirium, American Society of Anesthesiologists (ASA) status, smoking history, body mass index (BMI), comorbidity, institutional residence, functional impairment, hearing or visual impairment. Specific laboratory abnormalities (e.g., albumin, electrolyte, or glucose abnormalities) and medical conditions (e.g., cerebrovascular disease or chronic pulmonary disease) were also examined as possible risk factors. See Tables 3–5 for a summary of risk factor analyses and pooling results for nonheterogeneous risk factors, respectively.

Individual Risk Factors

Age

Older age was assessed as a risk factor in 21 (95.4%) of the studies reviewed.[4,7,16,19,21,24–39] Data were not available from three studies[4,29,38] that showed no association between increasing age and delirium, resulting in the omission of 2.8% of possible data from the analysis (data missing for 137 patients from a possible total of 4,847, or 2.8%).

Across the 18 studies with available data, there was significant heterogeneity (homogeneity rejected, $P<.001$). It was suspected that this might be due to differences in surgical types across age groups. Older people, for instance, may be more likely to undergo emergent procedures such as hip fracture repair[41] and be more prone to osteoporosis.[18] When the analysis was restricted to the 13 studies involving single surgical types, there was still significant heterogeneity ($P<.03$). Overall, there was an association suggested between older age and delirium ($P<.001$), although two negative studies were excluded in this analysis; effect sizes ranged from small ($r=0.03$)[33] to large (0.59) correlations.[27]

Sex

Sex was examined as a risk factor in 19 (86.3%) of the studies reviewed,[7,16,19,21,24–27,29–39] but there was a large amount of missing data (34.6%) from four negative studies.[7,21,31,38] It was postulated a priori that there may be some heterogeneity secondary to the differential distribution of surgical types by sex. (For instance, women may be more likely to have hip fracture surgery, whereas men may be more likely to have aortic or urological surgery.) When examining only single surgical-type studies,[19,24,26,29–33,36–39] data were missing from two negative studies,[31,38] resulting in the omission of 16.5% of data from the analysis. In the remaining 10 single surgical-type studies, there was still significant heterogeneity observed ($P<.03$). Across these studies, there was insufficient evidence to support an association between male sex and delirium ($P<.06$).

Cognitive Impairment

Cognitive impairment or dementia was variably assessed in 13 (59.1%) studies.[7,21,25–30,32–35,37] One study[26] was excluded, because data for both incident and prevalent delirium were provided. One positive study[16] was not included in the analysis, because original data were not available (11.4% of data missing overall). One study[29] provided two measures of cognition but provided raw data for only one measure, which was used in the analysis.

There was significant heterogeneity across all 12 studies ($P<.001$). When the analysis was restricted to studies involving single surgical types,[29,30,32,33,37] less heterogeneity was observed ($.05<P<.10$), and cognitive impairment was associated with delirium ($P<.001$). Pooled effect sizes were 0.27 (weighted) and 0.29 (unweighted), consistent with medium-sized associations between delirium and cognitive impairment.

Table 2. Univariate Risk Factors Assessed by Study

Study by Surgical Type	Risk Factors Evaluated																
	Age	Sex	Cognitive Impairment	Depression	Psychological Function	Psychotropic Drug Use	Alcohol Use	Prior Postoperative delirium	American Society of Anesthesiologist Classification	History of Smoking	Body Mass Index	Medical Comorbidities	Specific Medical Conditions	Lab Abnormalities	Nursing Home Residence	Functional Impairment	Visual Impairment	Hearing Impairment
	Statistically Associated with Delirium?																	
Single																		
Berggren et al.	no			yes		yes							no				no	no
Edlund et al.	no	yes		no				no										
Fisher et al.	no	yes	yes	no			no	no				no	no			no	no	no
Morrison et al.	yes	no	yes									yes	yes	yes	no	yes		
Rogers et al.	no	no		no														
Sasajima et al.	yes	no	yes					no			no		yes	yes				
Schuurmans et al.	yes	yes	yes			no						yes	no		yes	yes	no	no
Williams-Russo et al.	yes	yes		no*	no*		yes					no	no					
Zakriya et al.	no	no					no		yes	no			yes	yes				
Yoshimura et al.	yes	no					no			no	no		no	yes			no	no
Freter et al.	no	no	yes			yes†	yes†	yes†								no	no‡	no‡
Benoit et al.	no	no		no		yes	no											
Contin et al.	yes	no							no									
Kudoh et al.						yes												
Mixed																		
Andersson et al.	yes	no	yes									yes			yes	yes	yes	yes
Bohner et al.	yes	no	yes	yes	yes	no	no	no	no	no				no§			no	yes
Dai et al.	yes	no	yes											yes		yes	no	no
Duppils et al.	yes	no	yes			yes							yes		yes		no	yes
Galanakis et al.	yes	no	yes	yes		yes						yes			yes		yes	yes
Litaker et al.	yes	no	yes	no		yes	no	yes				yes		yes		yes		
Marcantonio et al.	yes	no	yes	no‖			yes		no			no	no	yes		yes		
Schneider et al.	no		yes	yes	yes				no				yes	no				

* Study combines depression and psychiatric disease into one category.

Note: "Yes" indicates that the risk factor was assessed and was found to be associated with delirium; "no" indicates that the risk factor was assessed and found not to be associated with delirium; a missing value indicates that the risk factor was not evaluated in the study.

† See appendix in Freter.[37]

‡ Study combines auditory and visual impairments into one category.

§ Authors also examined C-reactive proteins and antithrombin-3 (statistically associated with postoperative delirium), but no other studies assessed this as a risk factor.

‖ Unclear definition of depression (see Marcantonio[7]).

Lab = laboratory.

Table 3. Summary of Risk Factor Analysis for Postoperative Delirium by Risk Factor

Risk Factor	Quantitiative Analysis Possible?	Missing Data Exceeding 25% Across All Studies? (% Missing Data)	Significant Heterogeneity Across All Studies?	Types of Studies Included in Quantitative Analysis	Significant Heterogeneity Across Restricted Studies Used for Analysis?	Significant Association in Quantitative Analysis?	Pooling Possible?
Age	Yes	No (2.8)	Yes	Single surgical type	Yes	Yes	No
Sex	Yes	Yes (34.6)	n/a	Single surgical type	Yes	No	No
Cognitive impairment	Yes	No (11.4)	Yes	Single surgical type	No	Yes	Yes
Depression	Yes	Yes (70% missing overall; when restricted to studies using a depression scale: 0)	n/a	Studies using depression scale	Yes	Yes	No
Psychopathologic symptoms	Yes	No (0)	No	All	n/a	Yes	Yes
Psychotropic drug use	Yes	No (9)	No	All	n/a	Yes	Yes
Alcohol use	No, because of variable definitions	Yes (34)	n/a	n/a	n/a	n/a	No
Prior postoperative delirium	No	Yes (52)	n/a	n/a	n/a	n/a	No
American Society of Anesthesiologists classification	No	Yes (59)	n/a	n/a	n/a	n/a	No
History of smoking	No	Yes (60)	n/a	n/a	n/a	n/a	No
Body mass index	No	Yes (48)	n/a	n/a	n/a	n/a	No
Medical comorbidity	Yes	Yes (46)	n/a	Studies using counts of medical conditions	No	Yes	Yes
Specific medical conditions	No	Yes (30–90)*	n/a	n/a	n/a	n/a	No
Laboratory abnormalities	Yes (only with abnormal BUN)	Yes with most (17–40); not for BUN	n/a for most; no for BUN	Restricted to BUN	No (BUN abnormal)	No (BUN abnormal)	Yes (abnormal BUN)
Institutional residence	Yes		Yes	Single surgical type	No	Yes	Yes
Functional impairment	Yes	No (2.4)	n/a	Specific functional status scales	No	Yes	Yes
Visual impairment	Yes	No (10)	Yes	n/a	n/a	Yes	No
Hearing impairment	Yes	No (10)	Yes	n/a	n/a	Yes	No

* For specific medical conditions, 30–90% of the data were unavailable, depending on the identified disease (e.g., for chronic obstructive pulmonary disease/respiratory disease, 30% unavailable; for diabetes mellitus, 77% unavailable; for neurological disease, 57% unavailable; for hypertension, 92% unavailable; and for heart disease, 58% unavailable).

BUN = blood urea nitrogen; n/a = not applicable.

Table 4. Pooling Results for Nonheterogeneous Risk Factors

	Pooled Risk Factors						
Pooling Results	Cognitive Impairment	Psychopathologic Symptoms?	Psychotropic Drug Use	Number of Medical Comorbidities	Blood Urea Nitrogen Abnormal	Nursing Home Residence	Functional Impairment- Barthel Index or SAS
Overall pooled estimate (*r* or OR)	$r = 0.29$ or 0.27 (w)*	BPRS $r = 0.37$ or 0.34* ASGS $r = 0.46$ or 0.42 w* GAS $r = 0.44$ or 0.37 w*	$r = 0.26$ or 0.20 (w)*	$r = 0.19$ or 0.15*	OR = 1.45	OR = 1.8	SAS OR = 1.9 Barthel $r = 0.35$ or 0.45*
P-value of pooled estimate or 95% confidence interval	$P < .001$	$P < .001$ (all scales)		$P < .001$	95% CI = 0.8–2.5	95% CI = 1.1–3.1	SAS 95% CI = 1.2, 2.9 Barthel: $P < .001$
Total sample size of all studies included in pooled analyses	955	200	1,541	549	811	633	SAS total n = 1,376 Barthel total n = 793

* Weighted point estimate.
r = correlation coefficient; SAS = Specific Activity Scale; OR = odds ratio; CI = confidence interval; BPRS = Brief Psychiatric Rating Scale; ASGS = General Severity Score; GAS = Global Assessment Scale.

Depression

Depression was assessed in 11 (50%) of studies and was variably measured using standardized depression scales[24,25,28,34,36] by noting a positive history of depression or other psychiatric illness[4,7,21,26,29] or a combination of these.[19] Because depression may be undetected unless specifically screened for,[42] analysis was restricted to studies that used a depression scale or a formal psychiatric interview to screen for depression. Across studies that used a depression scale,[19,24,25,28,34,36] there was significant heterogeneity ($P < .01$), although, overall, an association with delirium was suggested ($P < .001$). Effect sizes ranged from -0.23[24] to 0.56.[28]

Psychopathological Symptoms

Only two (9.1%) studies[28,34] assessed psychopathological symptoms with the use of specific scales, namely the Brief Psychiatric Rating Scale, the General Severity Score, and the Global Assessment Scale. Across these studies, psychopathological symptoms were associated with delirium ($P < .001$ for all three scales). Heterogeneity was not evident, and pooled effect sizes were medium-sized to large, with weighted *r*-values of 0.33, for Brief Psychiatric Rating Scale score, 0.42 for General Severity Score, and 0.37 for Global Assessment Scale score. (Unweighted effect sizes were 0.37, 0.46, and 0.44, respectively.)

Psychotropic Drug Use

Nine (40.9%) of the studies[4,21,25,33–37,40] examined the relationship between preoperative psychotropic drug use and delirium, although data were unavailable from one negative study,[34] resulting in the omission of 9% of possible data. Studies assessing perioperative drug use[19,27,39] or involving both incident and prevalent delirium[26] were excluded.

Some studies only examined one class of psychotropic use (e.g., benzodiazepine or narcotic use), whereas others included various drug classes (e.g., combining data on lithium and anxiolytic, hypnotic, and other drug classes into one category[33]). If data on more than one kind of psychotropic drug use were provided from a study (e.g., separate data for benzodiazepine or narcotic use), the definition with the largest number of users was chosen for the analysis. Because separate data on the different classes of psychotropic drug use were not always available, the analysis sometimes included different drug classes in the broader category of psychotropic drug use. One study combined alcohol and benzodiazepine use in the larger category of substance abuse.[37]

Despite differences in how psychotropic drugs were defined across the eight studies with available data, there was insufficient evidence to suggest heterogeneity ($P > .10$), and the pooled weighted and unweighted effect sizes were 0.19 and 0.26, respectively, consistent with a small to medium correlation with postoperative delirium. Results were not significantly different when incorporating results from the study[37] that included alcohol use in its definition (insufficient evidence for heterogeneity, $P > .10$, weighted and unweighted effect sizes of 0.20 and 0.26, respectively). However, these effects sizes may be overestimated, given that data from a negative study were not available.

Table 5. Results from Individual Studies Used to Pool Results for Nonheterogenous Risk Factors

	Point Estimates						
Study Name	Cognitive Impairment	Psychopathologic Symptoms?	Psychotropic Drug Use	Number of Medical Comorbidities	Blood Urea Nitrogen Abnormal	Nursing Home Residence	Functional Impairment: Barthel Index or SAS
Andersson et al.				$r = 0.13$			
Benoit et al.			$r = 0.33$				
Bergrren et al.			$r = 0.57$				
Bohner et al.		BPRS scale $r = 0.30$ ASGS scale $r = 0.38$ GAS scale $r = 0.32$					
Dai et al.					OR = 1.9 (95% CI = 0.9–3.7)		Barthel $r = 0.44$
Duppils et al.			$r = 0.18$				
Fisher et al.	$r = 0.37$						
Freter et al.	$r = 0.34$		$r = 0.26$				
Galanakis et al.			$r = 0.28$				
Kudoh et al.			$r = 0.15$				
Litaker et al.			$r = 0.12$				(SAS) OR = 1.7 (95% CI = 0.9–2.9)
Marcantonio et al.							(SAS) OR = 2.3 (95% CI = 1.2–4.6)
Morrison et al.	$r = 0.24$					OR = 1.8 (95% CI = 0.9–3.3)	
Sasajima et al.	$r = 0.26$				OR = 0.9 (95% CI = 0.3–2.3)		
Schneider et al.		BPRS scale $r = 0.44$ ASGS scale $r = 0.53$ GAS scale $r = 0.54$					
Schuurmans et al.	$r = 0.21$		$r = 0.15$	$r = 0.25$		OR = 2.0 (95% CI = 0.7–5.8)	$r = 0.23$

r = correlation coefficient; SAS = Specific Activity Scale; OR = odds ratio; CI = confidence interval; BPRS = Brief Psychiatric Rating Scale; ASGS = General Severity Score; GAS = Global Assessment Scale.

Alcohol Use

Alcohol use was assessed in nine (40.9%) of the studies.[6,19,21,29,31,36–38] To assess alcohol use, two studies posed the question "Do you have a present problem drinking too much alcohol?" and both found an association with delirium.[7,21] Some studies used the CAGE questionnaire,[21,29] whereas others quantified alcohol use[7,19,31,34,36–38] but used different cutoff points to define levels of alcohol use. Because original data were sometimes not available and alcohol use was defined differently in studies, quantitative analyses were not performed.

Prior Postoperative Delirium

A prior history of delirium was examined as a potential risk factor in six (27.3%) of the studies reviewed.[21,26,29,30,34,37] Raw data were only available from one positive study[21] or combined with other measures of preoperative cognitive impairment,[37] thus precluding quantitative analyses (percentage of missing data 52%).

ASA Classification

ASA status was assessed in five (22.7%) studies.[7,28,31,34,39] Quantitative analyses were not conducted on this risk factor, because there was too much missing data (percentage of missing data 60%).

Smoking

The effects of smoking were assessed in three (13.6%) studies.[31,34,38] Quantitative analyses were not conducted on this risk factor, because there was too much missing data (60% missing). None of the studies that assessed smoking as a risk factor found it to be statistically associated with delirium, although one study[36] found greater number of pack-years of smoking to be associated with higher rates of delirium.

Body Mass Index

BMI was assessed as a risk factor in two (9.1%) studies.[30,38] Quantitative analyses were not conducted on this risk factor because there was too much missing data (48%). None of the studies that assessed BMI as a risk factor found it to be statistically associated with delirium.

Medical Comorbidity

Eight (36.4%) studies[7,16,19,21,25,29,32,33] examined the relationship between medical comorbidity and delirium. Comorbidity was measured variably using the Charlson index,[7,19,21,25] counts of medical conditions,[16,29,33] and a modified RAND index.[32] Forty-six percent of the data were unavailable; studies that used the Charlson Comorbidity Index were more likely to have missing data.

In the three (13.6%) studies that examined counts of medical conditions[16,29,33] data were unavailable from one,[29] resulting in the omission of 12.7% of data from the analysis. Across the other two studies, there was insufficient evidence for heterogeneity ($P<.27$), and an association was suggested between increasing numbers of medical conditions and delirium ($P<.001$). Pooled effect sizes were 0.15 (weighted) and 0.19 (unweighted), consistent with small correlations, although these may be overestimates, given the omission of a negative study.

Specific Medical Conditions

Individual medical conditions were assessed as delirium risk factors in 11 (50%) of the studies reviewed.[4,7,19,28–33,35,38] Studies often used a "known history" of a medical condition or different definitions to assess for the presence of a medical condition. Given that differing disease definitions were used across studies and that many diseases can be asymptomatic (e.g., diabetes mellitus or hypertension), comparisons could not be made across studies, and quantitative analyses were not performed.

Laboratory Abnormalities

Quantitative analyses on laboratory abnormalities were not conducted because of the variability in definitions of abnormalities (e.g., for hematocrit) across studies or because missing data exceeded 40% (for isolated electrolyte abnormalities, creatinine, albumin, white blood cell count, liver enzymes, albumin, and total serum protein). In one study,[7] sodium, potassium, or glucose abnormalities were a risk factor for delirium, but because of too few cases of isolated electrolyte disturbances, data on specific electrolyte abnormalities were not reported. Of three studies[27,30,31] examining blood urea nitrogen (BUN) abnormalities, data were missing from one study,[31] resulting in the omission of 17.2% of possible data from the analysis. Overall, there was insufficient evidence to suggest that abnormal BUN is associated with delirium (probability of there being no association <0.10). An elevated BUN/creatinine ratio is one of the characteristics associated with delirium in the risk classification scale developed previously.[23]

Institutional Residence

Residence in an institution was assessed as a risk factor in five (22.7%) of the studies, all of which involved elective or emergent hip surgery.[16,25,32,33,35] There was significant heterogeneity ($P<.03$) across the five studies. Because nursing home residents may be more likely then community-dwelling older people to sustain a fall and possibly a hip fracture,[17] it was postulated a priori that, in studies with both hip fracture and elective orthopedic procedures, there might be a greater incidence of delirium in institutionalized patients than in single surgery–type studies. The analysis was therefore repeated using the two studies[32,33] that involved patients undergoing only emergent hip fracture surgery. Pooling ($P<.41$ in homogeneity test) of these two studies revealed a weighted odds ratio of 1.82 (95% confidence interval (CI) = 1.06–3.12) and effect sizes of 0.08 (weighted) and 0.11 (unweighted), consistent with a small correlation with postoperative delirium.

Functional Status

Functional impairment was assessed in eight (36.4%) of the studies,[7,16,21,27,29,32,33,37] but raw data were not available from one[29] negative study (2.4% missing). Across the seven studies, an association was suggested between functional dependence and delirium ($P<.001$), but there was significant heterogeneity evident ($P<.01$). Functional status, as measured using the Barthel index in two studies[27,33] was associated with delirium ($P<.001$) and pooling of the two studies ($P<.35$, in the test of homogeneity) revealed unweighted and weighted effect sizes of 0.35 and 0.45, respectively, indicating medium to large correlations with

delirium. In the two studies that used the Specific Activity Scale,[7,21] pooling ($P<.22$ on the test for homogeneity) yielded a weighted odds ratio of 1.88 (95% CI = 1.25–2.95), with effect sizes of 0.08 (both weighted and unweighted), consistent with small correlations between the specific activity scale and delirium.

Visual and Hearing Impairment

Visual or hearing impairment was assessed in 10 (45.5%) of the studies,[4,16,25,27,29,33–35,37,38] but data were unavailable from two negative studies,[29,38] resulting in the omission of 10% of possible data. One study assessed visual and hearing impairment jointly.[37] Unlike the situation with specific medical diagnoses, the authors felt that significant visual or hearing impairment would likely be symptomatic and that the historical presence of these conditions seemed adequate for the analysis. For visual and hearing impairment, there was significant heterogeneity across all eight studies with available data (for both, $.001<P<.01$, using the Mantel-Haenszel method).

Because sensory impairment is a risk factor for falls[17] and could therefore possibly lead to a greater risk of hip fracture, it was postulated a priori that surgical type may be a source of heterogeneity when comparing single surgery–type studies with mixed-type studies, but because of a large amount of missing data from two[29,38] negative single-surgery studies (39%), quantitative analyses were not performed.

Across all studies with available data, an association between delirium and visual or sensory impairment was suggested ($P<.01$), although two negative studies were omitted from the analysis. Odds ratios across studies varied from 1.0[33] to 8.6[16] for visual impairment and from 0.5[33] to 7.0[35] for hearing impairment.

DISCUSSION

The incidence of delirium in the studies reviewed in this study varied from 5.1% to 52.2%, with certain procedures (including hip fracture and aortic surgery) having higher associated delirium risk. This is similar to the situation for cardiac and pulmonary postoperative complications (in which operative risk is also greater in aortic and emergency procedures)[10] and is consistent with findings from other studies.[16] This review identified two scales that were further validated in other studies.[7,23] Although further testing is needed to confirm the psychometric properties of these tools, the findings from this review provide further validation of their prognostic abilities.

Twenty-two studies meeting the inclusion criteria assessed individual preoperative risk factors. Cognitive impairment, which is also a component of the Marcantonio prediction rule and Inouye's risk classification system, was consistently associated with delirium and had moderate effect sizes in pooled analyses. Increased age and functional dependence are also factors described by Marcantonio's prediction rule, which were also found to be associated with delirium across studies, although considerable heterogeneity did not allow for pooling. Alcohol abuse and electrolyte disturbances are other risk factors described by Marcantonio's prediction rule, but inferences could not be made across other studies because of differences in methods of measurement and missing data. Visual impairment is included in the Inouye scale, and an association between sensory impairment and delirium was also suggested, although there was considerable heterogeneity across studies.

This review also found other risk factors not contained within the two validated scales that were found to be associated with delirium, including depression (assessed through a formal psychiatric interview or depression scale, although significant heterogeneity was evident), preoperative psychotropic drug use, and the presence of psychopathological symptoms (the latter in the vascular surgical setting). Greater numbers of medical conditions were associated with delirium, but conclusions could not be drawn about any particular disease state (excluding dementia or depression). Institutional residence was associated with delirium in the orthopedic surgery setting.

Heterogeneity was least evident for seven risk factors, namely cognitive impairment, presence of psychopathological symptoms, psychotropic drug use, number of comorbid medical conditions, abnormal BUN, nursing home residence, and functional impairment (Table 4). This review also suggests that cognitive impairment and psychotropic drug use are the risk factors most robustly associated with delirium, given their moderate range of effect sizes, less evidence of heterogeneity, and patient enrollment, even when analyses were restricted to try to minimize heterogeneity (5 studies involving 955 participants for cognitive impairment and 8 studies involving 1,541 participants for psychotropic drug use).

Previous systematic reviews of delirium risk factors have noted heterogeneity between studies.[9] Attempts were made to control for some possible causes of heterogeneity by including only studies that diagnosed delirium using prospective and active surveillance methods according to DSM or DSM-derived criteria. Prevalent delirium and delirium occurring in nonsurgical settings were also excluded. Prior studies suggest that individuals with preoperative (prevalent) delirium may have different risk factors and a worse prognosis than individuals who exclusively experience delirium postoperatively.[43] Delirium occurring in the nonoperative setting may also have a different natural history, predisposing factors, and response to preventative measures.[44]

Other potentially predictable causes for heterogeneity were also accounted for a priori. Despite these attempts, there was still significant heterogeneity seen, and it was often not possible to perform pooled quantitative analyses. Even when pooling was performed, effect sizes were in the mild to moderate range, suggesting that risk factors alone account for a small amount of the variability in delirium incidence. Unknown (and as of yet unpredictable) sources of heterogeneity, such as other unknown contributing factors, may have contributed to the overall mild to moderate effect sizes found in this review.

This review supports that delirium is a heterogeneous and multifactorial disorder with potentially multiple risk factors.[8] Other studies[45] have discussed the importance of predisposing and precipitating factors for delirium, with susceptible persons developing delirium more easily even when confronted with minimal noxious stimuli. This review only examined the stressor of the surgical setting, although apart from the surgery itself, precipitating factors in

the operative setting that have been associated with delirium have included perioperative blood loss,[46] pain,[47] meperidine use,[32] sleep deprivation,[48] serum anticholinergic activity,[49] melatonin abnormalities,[50] operative delay,[6] and poor postoperative mobility.[51] Differences in some of these perioperative factors may have contributed to some of the heterogeneity seen across the studies.

The fact that most of the studies included for review were observational in nature limited this study. Randomized, controlled trials of negative outcomes are only ethically acceptable when the intervention involves the removal of putative risk factors. Original data from negative studies that found no significant association between the risk factor and delirium were also not always available for analysis, limiting the strength of potential inferences by biasing some of the conclusions against the null hypothesis. Attempts were made to fully disclose biases that were potentially associated with missing data. Although a systematic search strategy including manual searches of references from other review articles and studies was performed, publication bias and the possibility of missing negative studies remain. Most tests of homogeneity are limited in their power to detect heterogeneity, and the ability to truly pool results may be questioned. For this reason, pooled effect sizes and effect size ranges were considered within broad categories of association (e.g., mild or moderate) to provide a rough estimate of their association with postoperative delirium. Limitations related to the heterogeneity of delirium have already been discussed extensively and are important to consider in light of study findings.

CONCLUSION

In this review, effect sizes were used to compare and systematically analyze different studies of delirium risk factors in the noncardiac surgical setting. Identifying patients at risk for delirium can be accomplished through the use of two previously developed delirium scales. The presence of other risk factors, such as psychotropic drug use, depression, the presence of multiple comorbid illnesses, and institutional residence can also identify patients who have a greater risk of developing postoperative delirium. These individuals should be targeted in future delirium prevention or treatment trials.

Nevertheless, this study also highlights the fact that there remain considerable clinical uncertainties about delirium, as the mainly mild to modest effect sizes and observed heterogeneity in the strengths of association across many of the included studies demonstrated. Several other, possibly unknown, important factors likely contribute to a person's risk for developing delirium. Future research is needed to elucidate some of the possible causes of this heterogeneity and should incorporate some of the intra- and postoperative risk factors that may also affect the occurrence of postoperative delirium.

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REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Association, 1994.
2. Inouye SK, van Dyck CH, Alessi CA et al. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–948.
3. Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium. A review of 80 primary data-collection studies. Arch Intern Med 1995;155:461–465.
4. Berggren D, Gustafson Y, Eriksson B et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. Anesth Analg 1987;66:497–504.
5. Weed HG, Lutman CV, Young DC et al. Preoperative identification of patients at risk for delirium after major head and neck cancer surgery. Laryngoscope 1995;105:1066–1068.
6. Edlund A, Lundstrom M, Lundstrom G et al. Clinical profile of delirium in patients treated for femoral neck fractures. Dement Geriatr Cogn Disord 1999; 10:325–329.
7. Marcantonio EJ, Goldman L, Mangione CM et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994;271:134–139.
8. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 1999;10:393–400.
9. Smith LW, Dimsdale JE. Postcardiotomy delirium: Conclusions after 25 years. Am J Psychiatry 1989;146:452–458.
10. Goldman L, Caldera DL, Nassbaum SR et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845–850.
11. Pagano M, Gauvreau K. Principles of Biostatistics, 2nd Ed. Pacific Grove, CA: Duxbury Press, 2000.
12. Mullen B. Advanced BASIC Meta-Analysis. Hillsdale, NJ: Lawrence Erlbaum Associates, 1989.
13. Mullen ML, Mullen B, Carey M. The association between beta-agonist use and death from asthma. A meta-analytic integration of case-control studies. JAMA 1993;270:1842–1845.
14. Bhogal SK. Pharmacological vs. Non-pharmacological Cinical Trials: Methodological Differences Influencing Treatment Effect. MA Thesis. University of Western Ontario, 2004.
15. Cohen J. Statistical Power Analysis for the Behavioral Sciences, Revised Edition. New York: Academic Press Inc., 1977.
16. Andersson EM, Gustafson L, Hallberg IR. Acute confusional state in elderly orthopaedic patients: Factors of importance in detection in nursing care. Int J Geriatr Psychiatry 2001;16:7–17.
17. Rao SS. Prevention of falls in older patients. Am Fam Physician 2005;72:81–88.
18. Rungby J, Hermann A, Mosekilde L. Epidemiology of osteoporosis: Implications for drug therapy. Drugs Aging 1995;6:470–478.
19. Williams-Russo P, Urquhart BL, Sharrock NE et al. Post-operative delirium: Predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 1992;40:759–767.
20. Aguero-Torres H. Clinical prediction guide. A risk assessment system based on preoperative factors was fairly specific in predicting postoperative delirium risk in patients having major elective surgery. Evid Based Ment Health 2002;5:27.
21. Litaker D, Locala J, Franco K et al. Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 2001;23:84–89.
22. Kalisvaart KJ, de Jonghe JF, Bogaards MJ et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: A randomized placebo-controlled study. J Am Geriatr Soc 2005;53:1658–1666.

23. Inouye SK, Viscoli CM, Horwitz RI et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119:474–481.
24. Rogers MP, Liang MH, Daltroy LH et al. Delirium after elective orthopaedic surgery: Risk factors and natural history. Int J Psychiatry Med 1989;19:109–121.
25. Galanakis P, Bickel H, Gradinger R et al. Acute confusional sate in the elderly following hip surgery: Incidence, risk factors and complications. Int J Geriatr Psychiatry 2001;16:349–355.
26. Edlund A, Lundstrom M, Brannstrom B et al. Delirium before and after operation for femoral neck fracture. J Am Geriatr Soc 2001;49:1335–1340.
27. Dai YT, Lou MF, Yip PK et al. Risk factors and incidence of postoperative delirium in elderly Chinese patients. Gerontology 2000;46:28–35.
28. Schneider F, Bohner H, Habel U et al. Risk factors for postoperative delirium in vascular surgery. Gen Hosp Psych 2002;24:28–34.
29. Fisher BW, Flowerdew G. A simple model for predicting postoperative delirium in older patients undergoing elective orthopedic surgery. J Am Geriatr Soc 1995;43:175–178.
30. Sasajima Y, Sasajima T, Uchida H et al. Postoperative delirium in patients with chronic lower limb ischaemia: What are the specific markers? Eur J Vasc Endovasc Surg 2000;20:132–137.
31. Zakriya KJ, Christmas C, Wenz JF Sr. et al. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. Anesth Analg 2002;94:1628–1632.
32. Morrison RS, Magaziner J, Gilbert M et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 2003;58A:M76–M81.
33. Schuurmans MJ, Duursma SA, Shortridge-Baggett LM et al. Elderly patients with a hip fracture: The risk for delirium. Appl Nurs Res 2003;16:75–84.
34. Bohner H, Hummel TC, Habel U et al. Predicting delirium after vascular surgery: A model based on pre-and intraoperative data. Ann Surg 2003; 238:149–156.
35. Duppils GS, Wikblad K. Acute confusional states in patients undergoing hip surgery. Gerontololgy 2000;46:36–43.
36. Benoit AG, Campbell BI, Tanner JR et al. Risk factors and prevalence of perioperative cognitive dysfunction in abdominal aneurysm patients. J Vasc Surg 2005;42:884–890.
37. Freter SH, Dunbar MJ, MacLeod H et al. Predicting post-operative delirium in elderly orthopaedic patients. The Delirium Elderly At-Risk (DEAR) Instrument. Age Ageing 2005;34:169–171.
38. Yoshimura Y, Kubo S, Shirata K et al. Risk factors for postoperative delirium after liver resection for hepatocellular carcinoma. World J Surg 2004;28:982–986.
39. Contin AM, Perez-Jara J, Alonso-Contin A et al. Postoperative delirium after elective orthopedic surgery. Int J Geriatr Psychiatry 2005;20:595–597.
40. Kudoh A, Takase H, Takahira Y et al. Postoperative confusion increases in elderly long-term benzodiazepine users. Anesth Analg 2004;99:1674–1678.
41. Bowman AM. The relationship of anxiety to development of postoperative delirium. J Gerontol Nurs 1992;18:24–30.
42. Allen N, Ames D, Ashby D et al. A brief sensitive screening instrument for depression in late life. Age Ageing 1994;23:213–218.
43. Stromberg L, Lindgren U, Nordin C et al. The appearance and disappearance of cognitive impairment in elderly patients during treatment for hip fracture. Scand J Caring Sci 1997;11:167–175.
44. Brauer C, Morrison RS, Silberzweig SB et al. The cause of delirium in patients with hip fracture. Arch Intern Med 2000;160:1856–1860.
45. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852–857.
46. Marcantonio ER, Goldman L, Orav EJ et al. The association of intraoperative factors with the development of postoperative delirium. Am J Med 1998; 105:380–384.
47. Duggleby W, Lander J. Cognitive status and postoperative pain: Older adults. J Pain Symptom Manage 2000;19:240–248.
48. Bowman AM. Sleep satisfaction, perceived pain and acute confusion in elderly clients undergoing orthopaedic procedures. J Adv Nurs 1997;26:550–564.
49. Tune L, Carr S, Cooper T et al. Association of anticholinergic activity of prescribed medications with postoperative delirium. J Neuropsychiatry Clin Neurosci 1993;5:208–210.
50. Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. Anesth Analg 2002;94:338–339.
51. Kamel HK, Iqbal MA, Mogallapu R et al. Time to ambulation after hip fracture surgery: Relation to hospitalization outcome. J Gerontol A Biol Sci Med Sci 2003;58A:M1042–M1045.