# Reports of Original Investigations

# Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression

*[Le délai opératoire est-il associé à une mortalité accrue chez les patients atteints d'une fracture de la hanche ? Synthèse systématique, méta-analyse et méta-régression]*

Toshiya Shiga MD PhD,* Zen'ichiro Wajima MD PhD,† Yoko Ohe MD PhD*

**Purpose:** Mortality associated with hip fracture is high in elderly patients. Surgical repair within 24 hr after admission is recommended by The Royal College of Physicians' guidelines; however, the effect of operative delay on mortality remains controversial. The objective of this study was to determine whether operative delay increases mortality in elderly patients with hip fracture.

**Methods:** Published English-language reports examining the effect of surgical delay on mortality in patients who underwent hip surgery were identified from electronic databases. The primary outcome was defined as all-cause mortality at 30 days and at one year. Effect sizes with corresponding 95% confidence intervals were calculated by using a DerSimonian-Laird random-effects model.

**Results:** Sixteen prospective or retrospective observational studies (257,367 patients) on surgical timing and mortality in hip fracture patients were selected. When a cut-off of 48 hr from the time of admission was used to define operative delay, the odds ratio for 30-day mortality was 1.41 (95% CI = 1.29–1.54, $P < 0.001$), and that for one-year mortality was 1.32 (95% CI = 1.21–1.43, $P < 0.001$).

**Conclusions:** In hip fracture patients, operative delay beyond 48 hr after admission may increase the odds of 30-day all-cause mortality by 41% and of one-year all-cause mortality by 32%. Potential residual confounding factors in observational studies may limit definitive conclusions. Although routine surgery within 48 hr after admission is hard to achieve in most facilities, anesthesiologists must be aware that an undue delay may be harmful to hip fracture patients, especially those at relatively low risk or those who are young.

CAN J ANESTH 2008 / 55: 3 / pp 146–154

***Objectif*** *: Le taux de mortalité associée à la fracture de la hanche est élevé chez les patients âgés. Les Directives du Collège royal des médecins recommandent une intervention chirurgicale de réparation de la hanche dans les 24 h suivant l'admission ; cependant, l'effet d'un délai opératoire sur le taux de mortalité demeure controversé. L'objectif de cette étude était de déterminer si un délai opératoire augmentait le taux de mortalité chez les patients âgés souffrant de fracture de la hanche.*

***Méthode*** *: Les bases de données électroniques nous ont permis d'identifier les comptes-rendus publiés en anglais étudiant l'effet d'un délai chirurgical sur le taux de mortalité des patients subissant une chirurgie de la hanche. Nous avons défini le critère principal comme la mortalité associée à toutes causes à 30 jours et à un an. Les effets de taille avec des intervalles de confiance à 95 % correspondants ont été calculés en utilisant le modèle de DerSimonian-Laird à effets aléatoires.*

***Résultats*** *: Seize études d'observation prospectives et rétrospectives (257,367 patients) traitant du délai de la chirurgie et du taux de mortalité chez des patients souffrant de fracture de la hanche*

From the Second Department of Anesthesiology,* Toho University School of Medicine, Tokyo; and the Department of Anesthesia,† Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan.

*Address correspondence to*: Dr. Toshiya Shiga, Second Department of Anesthesiology, Toho University School of Medicine, Ohashi 2-17-6, Meguro-ku, Tokyo 153-8515, Japan. Phone: +81-3-3468-1251; Fax: +81-3-3481-7336; E-mail: qzx02115@nifty.com

The work is attributed to the Second Department of Anesthesiology, Toho University School of Medicine. Support was solely from institutional and departmental sources. This study was presented in part at the annual meeting of the American Society of Anesthesiologists held in San Francisco, CA, USA on October 16, 2007.

*Accepted for publication August 9, 2007.*

*Revision accepted November 22, 2007.*

**This article is accompanied by an editorial. Please see Can J Anesth 2008; 55: 135–9.**

*ont été sélectionnées. Lorsqu'un seuil de 48 h depuis l'heure d'admission du patient était utilisée pour définir le délai opératoire, le rapport de cotes pour la mortalité à 30 jours était de 1,41 (95 % IC = 1,29–1,54, P < 0,001), et le rapport de cotes pour la mortalité à un an atteignait 1,32 (95 % IC = 1,21-1,43, P < 0,001).*

***Conclusions** : Chez les patients atteints d'une fracture de la hanche, un délai opératoire de plus de 48 h depuis l'heure d'admission pourrait faire augmenter les risques de mortalité, toutes causes confondues, à 30 jours de 41 %, et de mortalité à un an, toutes causes confondues, de 32 %. Dans les études d'observation, des facteurs confondants résiduels potentiels pourraient empêcher d'arriver à des conclusions définitives. Bien qu'il soit difficile d'effectuer les chirurgies de routine en moins de 48 h dans la plupart des établissements, les anesthésiologistes devraient avoir conscience qu'un délai excessif pourrait être néfaste pour les patients atteints d'une fracture de la hanche, particulièrement pour ceux à faible risque ou qui sont jeunes.*

HIP fracture is the leading fall-related injury to cause death among the elderly.[1] Hip fracture accounts for approximately 340,000 hospitalizations and upward of $2.9 billion (1996 United States dollars) in Medicare costs each year in the United States.[1] With the fast growth of elderly populations, the number of hip fractures is expected to exceed 500,000 in the United States[1] and 7 to 21 million worldwide by 2050.[2]

Mortality associated with hip fracture is reported to be 5–10% within 30 days (short-term) and 12–37% within one year (mid-term) after surgery.[1–4] The Royal College of Physicians' guidelines recommend that surgery be performed within 24 hr after admission[5] because early (*vs* late) surgical repair is believed to be associated with increased survival; decreased risk of infection, venous thromboembolism or decubitus ulceration; shorter hospital stay; and fewer costs. However, a recent literature review[6] yielded conflicting results on the association between mortality and timing of surgical repair. Randomized controlled trials would provide the best evidence of the effect of surgical timing on mortality. Nonetheless, there have been no such randomized controlled trials, and such trials are unlikely to be initiated in the future. Given that surgical repair is now the mainstay of treatment for hip fracture,[2,4] arbitrary delay of treatment can be considered unethical. Therefore, published observational studies remain the best evidence currently available.

Typically, the timing of surgery is decided on the basis of several factors including the patient's pre-existing medical condition, the orthopedist's preference, and availability of the operating room.[4] Anesthesiologists also play an important role in prioritizing patients on the surgical waiting list. The authors were therefore motivated to carry out a systematic review of published prospective and retrospective observational studies to determine whether operative delay increases the mortality of elderly patients with hip fracture.

## Methods

This systematic review was performed according to the reporting guidelines of the MOOSE Statement.[7] We searched the literature for all studies that tested the effect of surgical delay on mortality in patients who underwent hip surgery. Studies were identified from MEDLINE (1990 through March 2007), EMBASE (1990 through March 2007), CINAHL (1990 through March 2007), and the Cochrane Library (Issue 1, 2007). Only English language literature was included. The initial search terms were: "timing of surgery (or operation)," "surgical (or operative) delay," "hip fracture", "hip surgery," and various combinations of the aforementioned phrases. A manual search of references listed in reports and reviews was also performed.

The primary outcome was defined as all-cause mortality at 30 days and at one year. We first defined operative delay as "surgery more than 48 hr (> 48 hr) after admission." If this cut-off time was not incorporated into the studies, we used other cut-off times including 24 hr and 72 hr.

Our inclusion criteria were as follows: 1) the study must have been prospective or retrospective; 2) dichotomous outcome measures (from 2 × 2 contingency tables) or odds ratios with 95% confidence intervals (CIs) were available or could be derived from the published data; 3) the cut-off time for operative delay was 24 hr, 48 hr or 72 hr; 4) 30-day (short-term) or one-year (mid-term) mortality could be determined. If only in-hospital mortality was presented, we substituted it for short-term mortality. When dichotomous outcomes were not presented in the original paper in usable form, attempts were made to obtain additional data from the authors.

The methodological quality of the included studies was assessed by two independent investigators (T.S. and Z.W.) by using the checklist for assessment of the methodological quality of non-randomized studies developed by Downs and Black.[8] Briefly, the checklist, which consists of 27 items, evaluates the quality of reporting, external validity, internal validity (bias and confounding), and power. One to five points was given for each criterion that was met, for a maximum score of 32 and a minimum score of 0.

The extracted information included the following data: patient characteristics, country where the study was performed, type of fracture, whether or not recruitment involved consecutive patients, cut-off time that defined operative delay, time at which mortality was determined (e.g., 30 days or one year), and main reasons for the operative delay. Data were extracted by two independent investigators (T.S. and Z.W.). Disagreements or uncertainties were resolved by consensus. The effect sizes [for mean age, percentage of female patients, odds ratio, and number needed to treat or harm (NNT or NNH)] were calculated by means of the DerSimonian-Laird random-effects model.[9] The NNT or NNH is calculated by the inverse of the absolute risk differences. The NNT or NNH provides an estimate of the number of patients that must be subjected to operative delay to prevent or cause one additional death.[10] When a zero outcome occurred in a dichotomous measure, 0.5 was added to each cell of the respective contingency table. Homogeneity of effect size across trials was tested by the Cochran Q statistic.

We performed meta-regression analysis to explore the source of heterogeneity, if it existed. We tested possible factors hypothesized for heterogeneity as covariates using a mixed model (random-effect meta-regression model).[11] Tested factors included the cut-off time for age, percentage of female patients, the cut-off time for operative delay , and the observed risk of death in the control group (underlying risk). Each effect size was weighted by the inverse of each study's variances using the weighted least squares method. The univariate linear meta-regression model was as follows:[11]

$$T_i = ß_0 + ß_1 X_i + \mu_i + e_i,$$

where $T_i$ is an estimate of effect size in the $i$th study; $ß_0$ is the model intercept; $ß_1$ is the regression coefficient capturing the association between study characteristics and effect sizes; $X_i$ are coded characteristics of studies hypothesized to predict the study effect size; $\mu_i$ is the random effect of study $i$; and $e_i$ is the error estimated in the random-effects model.

To assess the potential for publication bias, a funnel plot was constructed in which log odds ratios were plotted against associated standard errors. In addition, rank correlation between standardized log-odds ratios and associated standard errors was determined by the Kendall correlation coefficient. Correlation between the sample size and odds ratio would be strong if small studies with null results were less likely than others to be published.[12] Significant correlation between the sample size and the odds ratio would not exist in the absence of a publication bias. Statistical significance for treatment effects was defined by $P < 0.05$; that for heterogeneity was defined by $P < 0.1$; and that for publication bias was defined by $P < 0.1$. Analyses were performed with Number Cruncher Statistical System 2004 (NCSS Statistical System, Kaysville, UT, USA) and Comprehensive Meta-Analysis version 2 (Biostat, Inc., Englewood, NJ, USA).

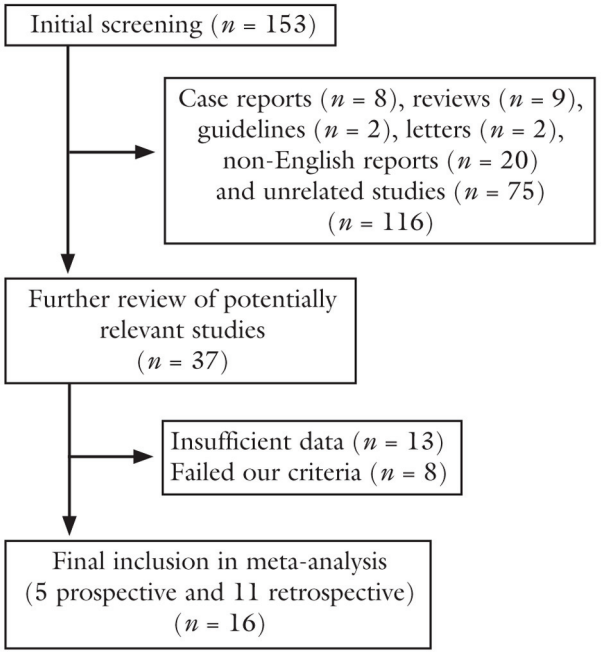


FIGURE 1 Meta-analysis flow chart.

## Results

After excluding 116 reports from the screening, we identified 37 studies for further review (Figure 1). Twenty-one of these were excluded, 13 with insufficient data and eight that did not meet our criteria. Thus, five prospective[13–17] and 11 retrospective studies[5,6,18–26] were included in our analysis. One report[17] was excluded from the analysis of 30-day mortality because of possible duplication with another study;[13] but it was included in the analysis of one-year mortality because the other study[13] was not included in this analysis. Details of the selected trials are shown in Table I. The pooled estimate of mean age was 80.8 yr (95% CI, 80.0–81.6 yr), and the overall percentage of female patients was 77.3% (95% CI, 75.7–78.9%). The median quality index was 14 (range: 11–17).

TABLE I Summary of prospective and retrospective observational studies meeting the inclusion criteria

| *Source* | *Year published* | *No. of patients* | *Country* | *Downs et al.*[8] *quality index* | *Mean or median age (range) (yr)* | *Female (%)* | *Type of fracture* | *Cut-off for delay* | *Endpoint mortality* | *Main reasons for delay* | *Adjusted odds ratio (95% CI) 30-day* | *1-yr* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Prospective studies* | | | | | | | | | | | | |
| Parker *et al.*[13] | 1992 | 765 | UK | 15 | 81 | 83% | Proximal femoral fracture | 48 hr | 30 days, 1 yr | Unavailability of OR or surgeon. | NA | NA |
| Zuckerman *et al.*[14] | 1995 | 367 | USA | 16 | ≥65 | 79% | Femoral neck fracture or intertrochanteric fracture | 72 hr | 1 yr | Patient's health status, surgeon's preference, and unavailability of OR | NA | NA |
| Elliott *et al.*[15] | 2003 | 1,780 | Ireland | 15 | 78 | 77% | Femoral neck fracture | 72 hr | 30 days | NS | NA | NA |
| Moran *et al.*[16] | 2005 | 2,660 | UK | 15 | 80 (17-103) | 76% | Femoral neck fracture | 48 hr | 30 days | Unavailability of OR or investigation of acute or chronic medical comorbidities | NA | NA |
| Siegmeth *et al.*[17] | 2005 | 3,628 | UK | 12 | 80 (60-103) | 81% | Intracapsular and extracapsular fracture | 48 hr | 1 yr | Unavailability of OR, surgeon, anaesthetist or surigical staff | NA | NA |
| *Retrospective studies* | | | | | | | | | | | | |
| Stoddart *et al.*[18] | 2001 | 138 | New Zealand | 11 | 83 | 75% | Isolated femoral neck fracture | 24 hr | 1 yr | NS | NA | NA |
| Grimes *et al.*[19] | 2002 | 9,598 | USA | 14 | 80.4 ±8.6 | 79.1% | Intertrochanteric, femoral neck, subtrochanteric | 24 hr | 30 days | Pending medical or cardiac clearance, other medical conditions or infection* | NA | NA |
| Gdalevich *et al.*[20] | 2004 | 651 | Israel | 14 | 78.8 | 75.6% | Intra-capsular and extra-capsular | 48 hr | 30 days, 1 yr | NS | 1.30 (0.55-3.11) | 1.39 (0.88-2.18) |
| McGuire *et al.*[21] | 2004 | 18,209 | USA | 14 | 82.6 | 79.1% | Pertrochanteric, subtrochanteric, and femoral neck | 48 hr | 30 day | NS | NS | NA |
| Franzo *et al.*[22] | 2005 | 6,629 | Italy | 13 | 82.2 | 81.3% | Hip fracture | 48 hr | In-hospital, 1 month, 1 yr | NS | 1.33 (1.08-1.64) | NA |
| Weller *et al.*[23] | 2005 | 57,315 | Canada | 13 | 80.4 | 74.9% | Hip fracture | 48 hr | 30 days, 1 yr | NS | 1.36 (1.23-1.52) | 1.26 (1.11-1.44) |
| Bergeron *et al.*[24] | 2006 | 977 | Canada | 13 | 79.5 | 73.5% | Fracture of proximal femur | 48 hr | In-hospital | NS | 1.16 (0.64-2.13) | NA |
| Bottle *et al.*[5] | 2006 | 129,522 | UK | 17 | 83.2 | 79.4% | Hip fracture | 48 hr | In-hospital | NS | 1.43 (1.37-1.49) | NA |
| Majumdar *et al.*[6] | 2006 | 3,981 | Canada | 13 | 82 (75-67) | 71% | Femoral neck, Inter- or subtrochanteric, or subcapital | 48 hr | In-hospital, 1 yr | NS | 1.30 (0.86-2.00) | NA |
| Sund *et al.*[25] | 2006 | 16,881 | Finland | 14 | 81.2 | 75.5% | Pertrochanteric, subtrochanteric, and femoral neck | 72 hr | 30 days, 1 yr | NS | NA | NA |
| Novack *et al.*[26] | 2007 | 4,633 | USA & Israel | 14 | 82 | 75% | Fracture at the neck of femur | 48 hr | 30 days, 1 yr | NS | NA | NA |

*Only top three are indicated due to space constraints. Y = yes; N = no; NS = not specified; NA = not available; CI = confidence interval; UK = United Kingdom; USA = United States of America; OR = operating room.

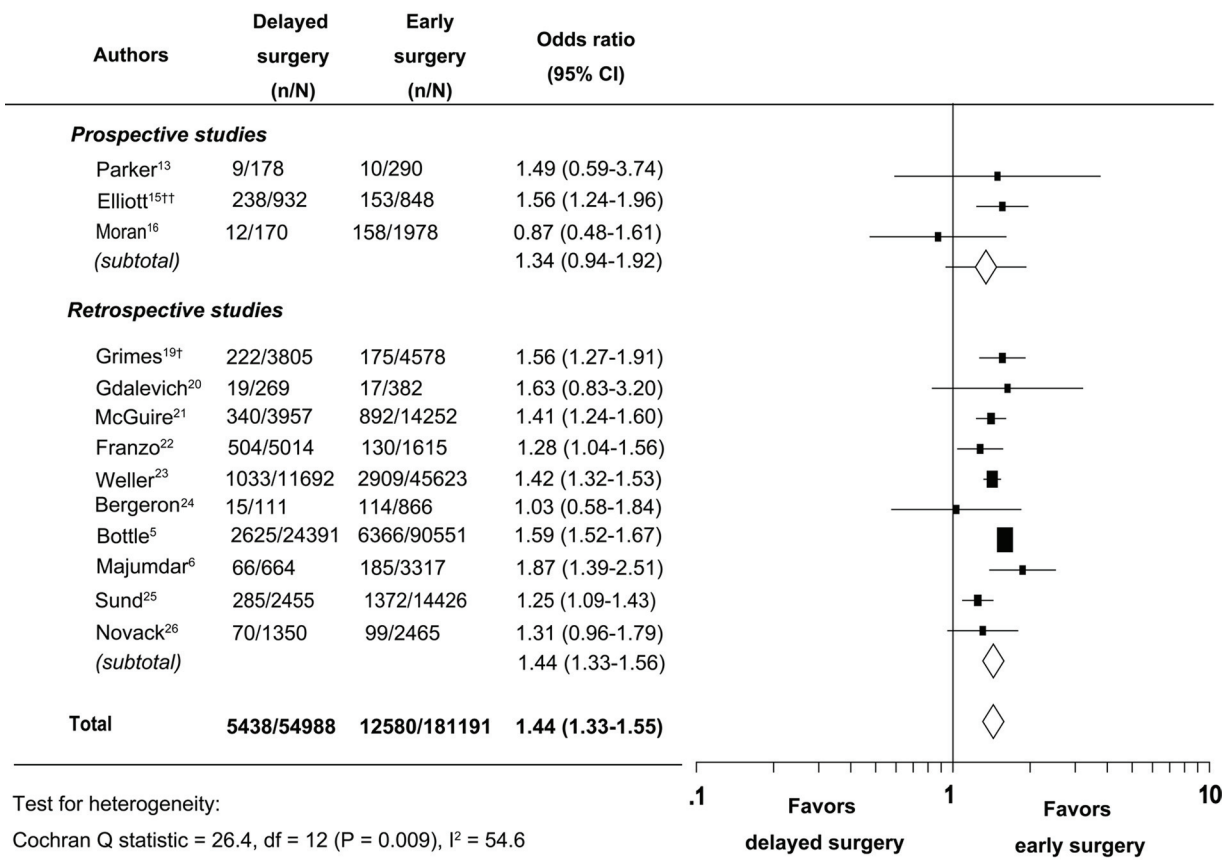


FIGURE 2 Forest plot of odds ratios for the influence of operative delay on 30-day mortality. Effect sizes were estimated according to study design (prospective *vs* retrospective) and overall. Diamonds indicate pooled odds ratios. Horizontal line for each trial denotes 95% confidence interval. Squares represent point estimates. The area of each square is proportional to the sample size. † Indicates that the study used a cut-off of 24 hr for delay, and †† indicates that the study used a cut-off of 72 hr for delay. All other studies used a cut-off of 48 hr to define operative delay. *n* = number of deaths, N = total number of patients in each group, CI = confidence interval.

Thirteen trials[5,6,13,15,16,19–26] (236,179 patients) evaluated 30-day mortality in association with early *vs* delayed surgery. Mortality occurred in 5,438 of 54,988 patients for whom surgery was delayed and in 12,580 of 181,191 patients for whom surgery was early. Delayed surgery increased mortality significantly (odds ratio = 1.44, 95% CI = 1.33–1.55, $P < 0.001$), with heterogeneity among trials (Cochran Q statistic = 26.4, $P$ for heterogeneity = 0.009) (Figure 2).

Nine trials[6,14,17,18,20,22,23,25,26] ($n$ = 93,391) evaluated one-year mortality with respect to early *vs* delayed surgery. Mortality occurred in 5,991 of 21,773 patients who underwent delayed surgery and in 16,547 of 71,618 patients who underwent early surgery. Delayed surgery increased mortality significantly (odds ratio = 1.33, 95% CI = 1.22–1.44, $P < 0.001$), with heterogeneity among trials (Cochran Q statistic = 17.8, $P$ for heterogeneity = 0.02) (Figure 3). The NNH was 20 (95% CI, 17–25) for 30-day mortality and 40 (95% CI, 31–56) for one-year mortality.

*Subgroup and sensitivity analysis*

Studies were grouped by design (prospective *vs* retrospective studies) and analyzed accordingly. The odds ratio for 30-day mortality in prospective studies[13,15,16] was 1.34 (95% CI, 0.94–1.92, Cochran Q statistic = 3.03, $P$ for heterogeneity = 0.22), and that in retrospective studies[5,6,19–26] was 1.44 (95% CI, 1.33–1.56, Cochran Q statistic = 23.3, $P$ for heterogeneity = 0.006). The odds ratio for one-year mortality in pro-

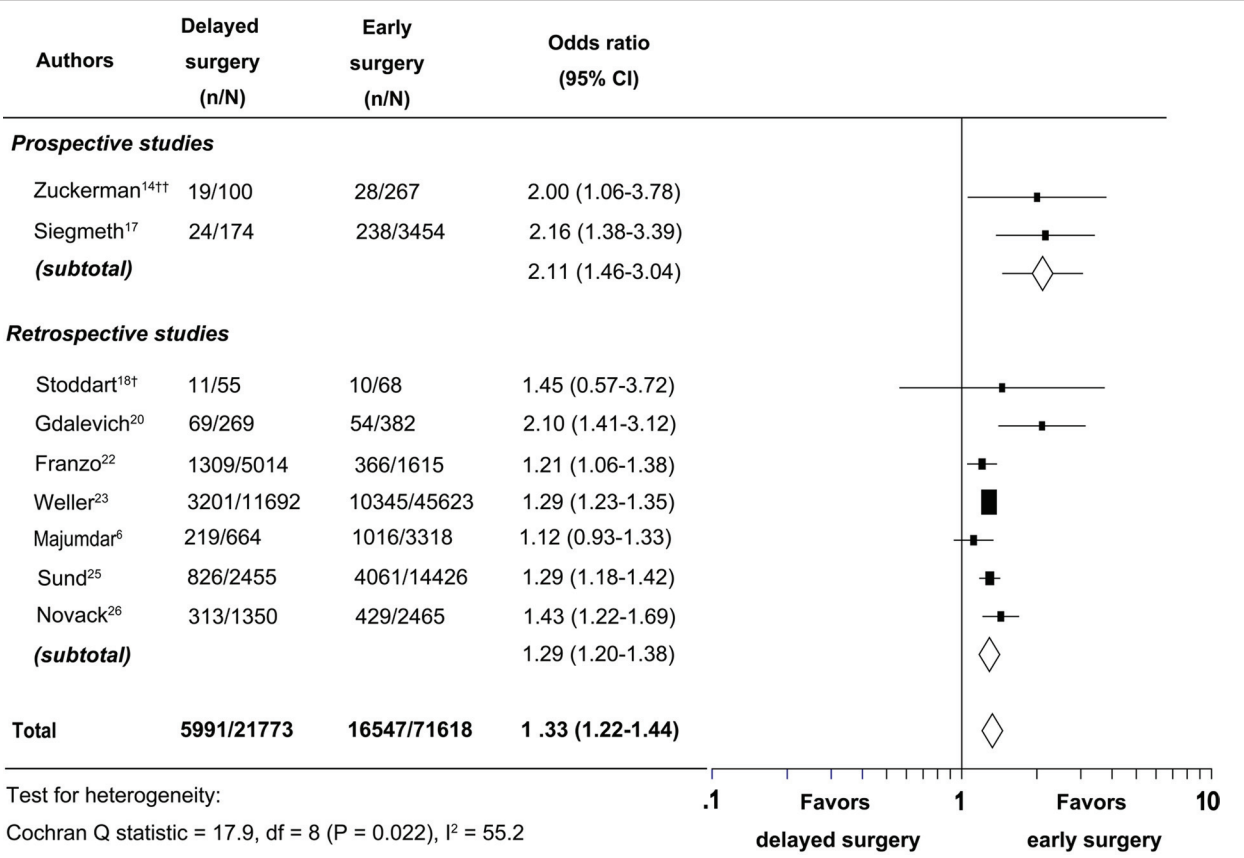


FIGURE 3 Forest plot of odds ratios for the impact of operative delay on one-year mortality. Effect sizes were estimated according to study design (prospective *vs* retrospective) and overall. Diamonds indicate the pooled odds ratios. Horizontal line for each trial denotes 95% confidence intervals. Squares represent point estimates. The area of each square is proportional to the sample size. † Indicates that the study used a cut-off of 24 hr for delay, and †† indicates that the study used a cut-off of 72 hr for delay. All other studies used a cut-off of 48 hr to define operative delay. *n* = number of deaths, N = total number of patients in each group, CI = confidence interval.

spective studies[14,17] was 2.11 (95% CI, 1.46–3.04, Cochran Q statistic = 0.037, *P* for heterogeneity = 0.85), and that in retrospective studies[6,18,20,22,23,25,26] was 1.33 (95% CI, 1.22–1.44, Cochran Q statistic = 10.9, *P* for heterogeneity = 0.09).

The effect size in one large study[5] was weighted 19% in a random-effects model for 30-day mortality analysis; therefore, we excluded this study and calculated the pooled odds ratio again to evaluate the effects of this one large study on overall outcome. After the study[5] was excluded, the odds ratio for 30-day mortality was 1.40 (95% CI, 1.31–1.49, Cochran Q statistic = 13.1, *P* for heterogeneity = 0.29), indicating little effect of the one large study on the overall odds ratio.

Given that studies varied in terms of the cut-off time for delay (e.g., 24, 48, 72 hr), studies with cut-off times of 24, 48 and 72 hr were combined in a separate analysis. The odds ratio for 30-day mortality in one study in which the cut-off was 24 hr[19] was 1.56 (95% CI, 1.27–1.91), and that for one-year mortality in one study[18] was 1.45 (95% CI, 0.57–3.72). The odds ratio for 30-day mortality in 11 studies that used a cut-off time of 48 hr[5,6,13,16,20–26] was 1.41 (95% CI, 1.29–1.54, Cochran Q statistic = 26.2, *P* for heterogeneity = 0.003), and that for one-year mortality in seven studies[6,17,20,22,23,25,26] was 1.32 (95% CI, 1.21–1.43, Cochran Q statistic = 16.0, *P* for heterogeneity = 0.013). The odds ratio for 30-day mortality in one study[15] that used a cut-off of 72 hr was 1.56 (95% CI,

TABLE II Meta-regression analysis

| | *Covariates* | *Regression coefficient* | *SE* | *95% CI for coefficient* | *P value* |
|---|---|---|---|---|---|
| 30-day mortality | Cut-off time | -0.0003 | 0.004 | -0.008-0.0079 | 0.95 |
| | Underlying risk | -0.005 | 0.011 | -0.044 | 0.66 |
| | Age | 0.01 | 0.03 | -0.04-0.06 | 0.66 |
| | % of female | -0.0005 | 0.01 | -0.03-0.03 | 0.96 |
| 1-year mortality | Cut-off time | 0.001 | 0.011 | -0.012-0.033 | 0.36 |
| | Underlying risk | -0.019 | 0.006 | -0.03--0.007 | 0.0019 |
| | Age | -0.1 | 0.05 | -0.20--0.006 | 0.037 |
| | % of female | 0.013 | 0.02 | -0.02-0.04 | 0.36 |

SE = standard error; CI = confidence interval.

1.24–1.96), and that for one-year mortality in one study[14] was 2.0 (95% CI, 1.06–3.78).

Six retrospective studies[5,6,19,22–24] computed an adjusted odds ratio for 30-day mortality; and two retrospective studies[20,23] computed an adjusted odds ratio for one-year mortality by means of a multivariate logistic regression model or multivariate Cox proportional hazards model. Therefore, we combined the adjusted odds ratios for 30-day and one-year mortality; and we compared these values with the unadjusted (crude) odds ratios. The adjusted odds ratio for 30-day mortality associated with operative delay was 1.42 (95% CI, 1.36–1.47, $P < 0.001$, $n = 189{,}869$, Cochran Q = 0.49, $P$ for heterogeneity = 0.91). The adjusted odds ratio for one-year mortality associated with operative delay was 1.27 (95% CI, 1.12–1.44, $P < 0.001$, $n = 57{,}966$, Cochran Q = 0.14, $P$ for heterogeneity = 0.70). Only slightly reduced odds ratios for 30-day and one-year mortality were found, but the differences in values were significant. Thus, the treatment effects did not appear to be influenced by the difference between unadjusted and adjusted odds ratios for 30-day and one-year mortality.

*Meta-regression analysis*

The results of meta-regression analysis against all covariates available are shown in Table II. No covariate could account for heterogeneity except underlying risk *vs* one-year mortality and age *vs* one-year mortality. A negative association was found between underlying risk or age and one-year mortality, indicating that effect size decreases with increasing underlying risk or increasing age in the control group. The Q statistic of the model for underlying risk *vs* one-year mortality was 9.68, whereas the residual Q statistic was 16.22. The Q statistic of the model for age *vs* one-year mortality was 4.36, whereas the residual Q statistic was 8.08. These values suggest that heterogeneity can be partially explained by these covariates, but residual heterogeneity remains.

*Reasons for the delay*

Five studies[13,14,16,17,19] examined the reasons for operative delay. Typical reasons included unavailability of an operating room; unavailability of the surgeon, anesthesiologist or nursing staff; and investigation into the patient's preoperative medical condition (Table I).

*Publication bias*

The funnel plot was symmetric, confirmed by a significant Kendall correlation coefficient of -0.03 for 30-day mortality ($P = 0.90$) and of 0.28 for one-year mortality ($P = 0.30$), indicating that publication bias was unlikely.

## Discussion

We found that operative delay of more than 24–72 hr from the time of admission may increase the odds of 30-day all-cause mortality by 44% (95% CI, 33–55%), and of one-year all-cause mortality by 33% (95% CI, 22–44%). When a cut-off of 48 hr from the time of admission is used to define operative delay, operative delay may increase the odds of 30-day mortality by 41% (95% CI, 29–54), and of one-year mortality by 32% (95% CI, 21–43%). The NNH for operative delay to cause one death was 40 (95% CI, 31–56) at 30 days and 20 (95% CI, 17–25) at one year. This means that 40 patients subjected to operative delay are required to cause one additional death within 30 days; and that 20 such patients are required to cause one additional death within one year. In other words, for every 1,000 patients who undergo delayed surgery instead of early surgery, there would be approximately 25 more deaths within 30 days after admission and approximately 49 more deaths within one year after admission.

Who will benefit the most from early surgery? Results of our meta-regression analysis indicate that patients with low baseline risk (in this case, underlying risk of death within one year) and young patients are at high risk of all-cause mortality. This may suggest that unnecessary delay of surgery is harmful, especially for patients at low risk or those who are young. In contrast, patients at high baseline risk and older patients will not benefit so much from early surgery in terms of one year outcome. We found a significant association between underlying risk or age and one-year mortality, but not between underlying risk or age and 30-day mortality. A plausible explanation is that the risk of death outweighs the benefit of early surgery. This actuality becomes more evident at one year, rather than at 30 days, because chronic comorbidities progress in older patients at high risk.

What are the main reasons for operative delay? According to the data we obtained, the reasons for operative delay can be classified as medical-related or system-related. Orosz *et al.*[27] classified the reasons for delay of surgery as follows: waiting for routine medical consultation or clearance, unavailability of an operating room or surgeon, waiting for family discussion, waiting for laboratory results, waiting for stabilization of a medical problem, admission too late in the day, and others. Delay related to stabilization of comorbidities may be inevitable in some patients. For instance, a patient with poorly controlled diabetes mellitus upon admission requires correction of the blood sugar level before surgery, which generally takes a certain amount of time. Failure to control diabetes mellitus before surgery may increase the risk of perioperative complications. However, delays related to scheduling problems can be prevented to some extent. Although shortening the time between admission and surgery is a complex issue in most facilities, anesthesiologists must keep in mind that an undue delay might compromise the surgical benefit.

Some may argue that operative delay itself is not responsible for mortality. Patients for whom surgery was delayed could have been sicker on admission than those for whom it was not. Such patients may have required more preoperative examinations to stabilize their medical condition, and such patients may have been more likely to die. Statistically, this implies that operative delay may be a confounding factor rather than an independent factor affecting survival. Controversy regarding this problem continues; however, most retrospective studies included in our analysis made an adjustment for preoperative risk factors. A significant influence of operative delay on mortality was found in our meta-analysis, even after adjustment was made for confounding preoperative factors. Therefore, we assume that the effect of confounding factors was minimized in our meta-analysis.

Our meta-analysis showed that the mean age, 80.8 yr; the percentage of female patients, 77.3%; and the 30-day and one-year baseline risk of elderly patients who underwent early surgery for hip fracture, 7% and 23%, respectively, lie within the limits reported in previous reviews.[2–4] Thus, the external validity of our meta-analysis is likely to be maintained. Furthermore, publication bias was not found in terms of crude odds ratios for 30-day and one-year mortality. Despite these strengths, certain aspects limited our findings. For instance, heterogeneity was found in terms of odds ratios for 30-day and one-year mortality. Although some heterogeneity was partially explained by underlying risk and age, residual heterogeneity exists. In addition, there are always problems specific to observational studies. The studies we selected have a poor or moderate quality score index, which means that poor methodological quality of observational studies may limit the conclusions. Some experts say[28] that meta-analysis of observational studies is prone to confounding or to selection bias. Potential residual confounding cannot be completely eliminated, even if adjustments are made for confounding factors by using multivariate statistical models. We reiterate that randomized controlled trials would be ideal but are not really feasible.

In conclusion, operative delay of more than 48 hr is associated with increased short-term and mid-term mortality in elderly patients with hip fracture. Early surgery is associated with an increased benefit in patients at low risk or those who are young. Potential residual confounding factors in observational studies may limit definitive conclusions. Although routine surgery within 48 hr after admission is hard to achieve in most facilities, anesthesiologists must be aware that undue delay may be harmful to hip fracture patients, especially those at low risk or those who are young.

**Acknowledgments**

We sincerely thank Alex Bottle, MD. (Department of Primary Care and Social Medicine, Imperial College, London, UK) for providing additional information, and Reijo Sund, MD. (National Research and Development Centre for Welfare and Health [STAKES] Outcomes and Equity Research, Helsinki, Finland) for providing additional data and giving us helpful suggestions.

## References


1 Hip Fractures Among Older Adults. Atlanta: Centers for Disease Control and Prevention. National Center for Injury Prevention and Control. Available from URL; http://www.cdc.gov/ncipc/factsheets/adulthip-fx.htm (cited 2007 May 12).

2 *Parker M, Johansen A.* Hip fracture. BMJ 2006; 333: 27–30.

3 *Morrison RS, Chassin MR, Siu AL.* The medical consultant's role in caring for patients with hip fracture. Ann Intern Med 1998; 128: 1010–20.

4 *Lyons AR.* Clinical outcomes and treatment of hip fractures. Am J Med 1997; 103: 51S–63S.

5 *Bottle A, Aylin P.* Mortality associated with delay in operation after hip fracture: observational study. BMJ 2006; 332: 947–51.

6 *Majumdar SR, Beaupre LA, Johnston DW, Dick DA, Cinats JG, Jiang HX.* Lack of association between mortality and timing of surgical fixation in elderly patients with hip fracture: results of a retrospective population-based cohort study. Med Care 2006; 44: 552–9.

7 *Stroup DF, Berlin JA, Morton SC, et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–12.

8 *Downs SH, Black N.* The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52: 377–84.

9 *DerSimonian R, Laird N.* Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88.

10 *Cook RJ, Sackett DL.* The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995; 310: 452–4.

11 *Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.* Methods for Meta-Analysis in Medical Research, 1st ed. West Sussex: John Wiley & Sons, Ltd; 2000.

12 *Begg CB, Mazumdar M.* Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–101.

13 *Parker MJ, Pryor GA.* The timing of surgery for proximal femoral fractures. J Bone Joint Surg Br 1992; 74: 203–5.

14 *Zuckerman JD, Skovron ML, Koval KJ, Aharonoff G, Frankel VH.* Postoperative complications and mortality associated with operative delay in older patients who have a fracture of the hip. J Bone Joint Surg Am 1995; 77: 1551–6.

15 *Elliott J, Beringer T, Kee F, Marsh D, Willis C, Stevenson M.* Predicting survival after treatment for fracture of the proximal femur and the effect of delays to surgery. J Clin Epidemiol 2003; 56: 788–95.

16 *Moran CG, Wenn RT, Sikand M, Taylor AM.* Early mortality after hip fracture: is delay before surgery important? J Bone Joint Surg Am 2005; 87: 483–9.

17 *Siegmeth AW, Gurusamy K, Parker MJ.* Delay to surgery prolongs hospital stay in patients with fractures of the proximal femur. J Bone Joint Surg Br 2005; 87: 1123–6.

18 *Stoddart J, Horne G, Devane P.* Influence of preoperative medical status and delay to surgery on death following a hip fracture. ANZ J Surg 2002; 72: 405–7.

19 *Grimes JP, Gregory PM, Noveck H, Butler MS, Carson JL.* The effects of time-to-surgery on mortality and morbidity in patients following hip fracture. Am J Med 2002; 112: 702–9.

20 *Gdalevich M, Cohen D, Yosef D, Tauber C.* Morbidity and mortality after hip fracture: the impact of operative delay. Arch Orthop Trauma Surg 2004; 124: 334–40.

21 *McGuire KJ, Bernstein J, Polsky D, Silber JH.* The 2004 Marshall Urist award: delays until surgery after hip fracture increases mortality. Clin Orthop Relat Res 2004; 428: 294–301.

22 *Franzo A, Francescutti C, Simon G.* Risk factors correlated with post-operative mortality for hip fracture surgery in the elderly: a population-based approach. Eur J Epidemiol 2005; 20: 985–91.

23 *Weller I, Wai EK, Jaglal S, Kreder HJ.* The effect of hospital type and surgical delay on mortality after surgery for hip fracture. J Bone Joint Surg Br 2005; 87: 361–6.

24 *Bergeron E, Lavoie A, Moore L, et al.* Is the delay to surgery for isolated hip fracture predictive of outcome in efficient systems? J Trauma 2006; 60: 753–7.

25 *Sund R, Liski A.* Quality effects of operative delay on mortality in hip fracture treatment. Qual Saf Health Care 2005; 14: 371–7.

26 *Novack V, Jotkowitz A, Etzion O, Porath A.* Does delay in surgery after hip fracture lead to worse outcomes? A multicenter survey. Int J Qual Health Care 2007; 19: 170–6.

27 *Orosz GM, Hannan EL, Magaziner J, et al.* Hip fracture in the older patient: reasons for delay in hospitalization and timing of surgical repair. J Am Geriatr Soc 2002; 50: 1336–40.

28 *Egger M, Smith GD, Shneider M.* Systematic reviews of observational studies. *In*: Egger M, Smith GD, Altman DG (Eds). Systematic Reviews in Health Care: Meta-analysis in Context, 2nd ed. London: BMJ Books; 2001: 211–27.