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The Impact of Incident Postoperative Delirium on Survival of Elderly Patients After Surgery for Hip Fracture Repair

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Abstract

Background—The impact of delirium on survival of elderly patients remains undetermined with conflicting results from clinical studies and meta-analysis. In this study we assessed the relationship between long-term mortality and incident postoperative delirium in elderly patients undergoing hip fracture repair.

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Methods—Patients 65 years old who were not delirious before undergoing hip fracture repair were included in a database maintained prospectively from March 1999 until July 2009. All participating patients underwent delirium assessment on the 2nd postoperative day using the confusion assessment method. Survival of the participants was determined as of October 2012.

Results—In 459 patients the mean (SD) period of evaluation from surgery until death or study closure was 4.1 (3.5) years with patients followed for as long as 13.6 years. Preoperative cognitive impairment was present in 120 patients (26.1%) and delirium on the 2nd postoperative day was observed in 151 (32.9%) of these. Although univariate analysis demonstrated a strong association between incident postoperative delirium and survival, this relationship did not persist in a multivariate model. Survival was a function of age at the time of surgery ($p < 0.001$), illness severity as determined by the ASA physical status score ($p < 0.001$), and duration of admission to the intensive care unit after surgery ($p < 0.001$). Incorporation of incident postoperative delirium did not meaningfully ($p = 0.22$) enhance the final survival model. In such a model, the hazard ratio [CI95] for incident postoperative delirium was 1.25 [0.92, 1.48].

Conclusions—Incident postoperative delirium was not significantly associated with decreased survival in elderly patients undergoing hip fracture repair.

Introduction

Incident delirium is frequently observed in elderly patients after various types of surgery.^{1–4} In hospitalized elderly patients delirium has been associated with increased hospitalization, dementia, institutionalization, morbidity, and mortality after discharge.^{1;3–6} However, the role of delirium as an independent risk factor for decreased survival is variable.^{5;7–22} Therefore, when elderly patients experience incident delirium in the perioperative setting, it remains uncertain as to whether this portends a decrease in their survival.

A substantial portion of what is known about the relationship between delirium in hospitalized elderly patients and their survival comes from studies of patients presenting for hip fracture repair.^{9–16;22;23} Additional information about patients who undergo hip fracture repair is available from patients admitted for rehabilitation, though a number of these studies include both medical and other orthopedic patients.^{7;8;17;18} Regardless, only a few of the available studies^{9;14} extend beyond 2 years of follow-up. In addition to delirium, these and other studies have collectively examined the role of age, gender, cognitive impairment, depression, various measures of illness severity, and time from presentation until hip fracture repair^{24;25} on patient survival. Delirium is frequently observed to be a univariate risk factor for decreased survival in patients with hip fractures, but may be less important when data are adjusted for other risk factors.^{9;10;12;13;16;22} Nonetheless, consistent with what is observed for severe medical illnesses,^{19;20} hip fracture patients with prolonged delirium can experience increased mortality.^{14;15} Cognitive impairment and depression are other factors that alone or in combination with delirium have also been associated with increased mortality.^{7;8;12;13;16–18;21}

Thus, despite considerable investigative effort spanning several decades, the prognostic significance of incident postoperative delirium with respect to the long-term survival of elderly patients remains an important open question that concerns about delirium and

mortality⁵ have made more acute. The availability of data collected prospectively from patients presenting to a specialized hip fracture service (HFS) for more than a decade offers the opportunity to further elucidate this relationship. The current study seeks to determine the extent to which incident postoperative delirium is an independent risk factor for decreased long-term survival of elderly patients undergoing hip fracture repair.

Methods

The HFS at Johns Hopkins Bayview Medical Center in Baltimore, Maryland is an interdisciplinary model of care whose function has been described previously.^{26;27} Patients presenting to the emergency room with suspected hip fractures are initially evaluated by an orthopedic surgeon who confirms the diagnosis and refers the patient to a geriatrician. Geriatricians, anesthesiologists, and orthopedic surgeons then jointly render a decision regarding a patient's fitness for surgery. Hip fracture repair commences as soon as possible after a patient is deemed ready for surgery, with the goal of repair within 24 hours of presentation.

A database is maintained with IRB approval on patients presenting to the HFS who are 65 years old, are scheduled to undergo hip fracture repair, can communicate in English, and have given written preoperative consent to the collection and use of their medical information. For those whose capacity to provide consent may have been limited by existing cognitive impairment, consent was obtained from their legally authorized representative. Since the initial purpose of data collection was to evaluate the relationship between surgery and incident postoperative delirium, those with preoperative delirium diagnosed via the confusion assessment method (CAM)²⁸ were excluded from further study, with delirium status reassessed on the day of surgery in the case of delays after the initial assessment.

Hip fracture repair was performed under either general or spinal anesthesia where the choice was guided by patient preference if contraindications to spinal anesthesia were not identified. At the completion of surgery, a joint decision by the attending anesthesiologist and surgeon determined whether patients were transferred to the postanesthesia care unit or the intensive care unit (ICU) before eventual transfer to the hospital ward. Analgesic therapy followed a protocol for which incident postoperative delirium was previously demonstrated to be unassociated with pain or opioid administration.²⁷ Postoperatively, an interdisciplinary team continued to participate in each patient's care until discharge.

After receipt of IRB approval, all subjects in the HFS database were subsequently evaluated for survival from the operative day. For those patients with multiple presentations for hip fracture repair, survival from the initial procedure was determined, and the cognitive state associated with that presentation was used in the analysis. Survival was determined using hospital reports, the Social Security Death Index, the National Death Index, and obituaries.

Measures

In addition to the preoperative delirium assessment described above, delirium was assessed midmorning of the 2nd postoperative day via the CAM²⁸ by either the attending geriatrician or a trained research nurse. If a patient was unable to respond to questions because of

external constraints such as tracheal intubation with sedation, the CAM was administered after extubation of the trachea.

The criteria for cognitive impairment were a preoperative mini-mental status examination (MMSE) score²⁹ of less than 24 in the absence of delirium, documented history of dementia based on the primary care provider record, or determination of dementia status by the attending geriatrician during the preoperative evaluation. Regardless of the means of assessing cognitive impairment, patients with a positive result were classified as having cognitive impairment. A diagnosis of depression was recorded based on a history of depression obtained at the time of admission.

Each patient's illness severity was ranked using the ASA physical status score routinely assigned preoperatively by the attending anesthesiologist. This integer score ranges from 1–5 where 1=a normal healthy patient; 2=mild systemic disease; 3=systemic disease which limits physical activity; 4=systemic disease that is a constant threat to life; and 5= moribund patient. Additionally, the number of postoperative days in the surgical ICU, the number of units of erythrocytes transfused, and the number of days from admission to completion of surgical repair of the hip were obtained.

Statistical Analysis

Unless otherwise indicated, data are reported as the number of events and their percentage for frequency data, median and interquartile range for ordered categorical data, and as mean and standard deviation for continuous data. Group comparisons were analyzed by Fisher's exact test for frequency data, the Wilcoxon rank-sum test for ordered categorical data, and analysis of variance for continuous data. The Poisson distribution was used to determine the confidence intervals related to the actual number of subjects presenting during given periods of the week assuming the null hypothesis of uniform daily enrollment.

Kaplan-Meier survival estimates were initially used to evaluate relevant categorical variables with significance determined by the log-rank test. Cox regression³⁰ was then used to perform univariate analysis on relevant categorical and continuous covariates. These were then combined in a multivariate model and covariates eliminated 1 at a time based on their significance level. The relevance to the model of the eliminated covariates was later assessed by both the likelihood ratio test and the impact of their elimination on the size of the coefficients of the remaining covariates. P values reported for this process are those from the likelihood ratio test comparing the final survival model against one that differs only by the inclusion of the eliminated covariate. The linearity of the hazard function with respect to the covariates was then determined and, where necessary, nonlinear terms were introduced. Interactions between the covariates were then assessed. The resulting model was then tested for goodness-of-fit using the test devised by Groennessby and Borgan,³⁰ and tests of the proportional hazards assumption were performed by interacting analysis time with the covariates and by regression on the scaled Schoenfeld residuals. Results from Cox regression were confirmed using a parametric survival model based on the generalized gamma distribution.

All significance values reported are from two-tailed tests. Differences were considered significant for $p \leq 0.05$. Statistical analysis was facilitated by the use of Stata 12.0 (StataCorp, College Station, TX).

Results

Between March 5, 1999 and July 8, 2009, during periods when qualified research personnel were on staff to perform patient assessment, 750 patients presented to the Johns Hopkins Bayview Medical Center for surgical hip fracture repair. Of these, 120 patients were < 65 years old, 30 refused to participate in further data collection, and 141 were delirious before surgery and were not further studied. The survival of the remaining 459 patients was determined until October 8, 2012. Preoperative cognitive impairment was present in 120 patients (26.1%) and delirium on the 2nd postoperative day was observed in 151 (32.9%) of these. The mean (SD) period of evaluation from surgery until death or study closure was 4.1 (3.5) years with patients followed for as long as 13.6 years. Eighty-three percent of subjects underwent surgical repair of their fracture within 2 days of presentation. For those enrolled, the actual number [95% confidence interval assuming uniform daily enrollment] presenting to the emergency room on the weekend was 110 [109,154], with the largest number 87 [50,82] presenting on Friday, the fewest 49 [50, 82] presenting on Sunday, and with 97 surgical procedures performed on Friday. Delirium assessment on the second postoperative day was achieved for all subjects who were enrolled. The demographic, perioperative, and postoperative features of this population are summarized in Table 1. These data are notable for older age in those with cognitive impairment and postoperative delirium, larger proportion of men experiencing postoperative delirium, greater illness severity as reflected by the ASA physical status score in those with cognitive impairment or postoperative delirium, and increased incidence of admission to the ICU or erythrocyte transfusion in those experiencing postoperative delirium.

Kaplan-Meier survival estimates appear to show a meaningful impact of cognitive state on survival for both cognitive impairment and incident postoperative delirium (Fig. 1A–B). However, given that age, gender, illness severity, ICU admission and erythrocyte transfusion are also associated with cognitive function (Table 1), and illness severity and ICU admission are also associated with survival (Fig. 1C–D), a Cox regression model was developed to determine the contribution of incident postoperative delirium to survival after surgery for hip fracture repair.

Univariate analysis of survival is shown in Table 2 for the variables of Table 1. Those variables for which $p \leq 0.2$ were then used to generate the multivariate model of Table 3. The nonsignificant variables were eliminated 1 at a time in order of increasing significance (cognitive impairment, male gender, units of erythrocytes transfused, and incident postoperative delirium), and the model solved for the remaining variables, with the least significant of the remaining variables eliminated next. The resulting 3-variable model included age, ASA score, and length of stay in the ICU, and was further refined by considering the contribution of nonlinearities. The variable most likely to benefit from introduction of a nonlinear term is length of stay in the ICU since less than 25% of the study population was admitted there (Table 1). Introduction of the square of the length of stay in

the ICU (Table 4) leads to improvements in the model ($p = 0.02$). When the best nonlinear functions of age (a linear, square and cubic term) were introduced, there was some improvement in the model ($p=0.06$) but, because the improvement was not significant, the more parsimonious model with only a linear age term (Table 4) was retained. The model did not benefit from the introduction of a nonlinear ASA score. Interactions among the variables of Table 4 were highly nonsignificant (not shown). Variables deleted earlier in the process were incorporated into the final model 1 at a time with the resulting model tested against the final model. Importantly, the quality of the model was not improved with the inclusion individually of cognitive impairment ($p = 0.99$), depression ($p = 0.96$), or incident postoperative delirium ($p = 0.22$). In such a model, the hazard ratio [CI95] for incident postoperative delirium was 1.25 [0.92, 1.48].

Although the goodness-of-fit for the Cox regression model presented in Table 4 (footnote) was satisfactory, both interaction of analysis time with the covariates and regression on the Schoenfeld residuals of the final model indicated that the proportional hazards assumption over the entire study period was reasonable only for age. Therefore, a parametric survival model was generated based on the generalized gamma distribution. These results are also presented in Table 4 and are consistent with the model generated using Cox regression, where the addition of postoperative delirium to the parametric model did not improve it significantly ($p = 0.19$).

Discussion

Survival was determined for a cohort of elderly patients undergoing hip fracture repair without prevalent delirium who were prospectively enrolled over the course of a decade and followed for 3 additional years. This study revealed that incident postoperative delirium that could be observed on the second postoperative day was not a significant risk factor for decreased survival. When considered alone, cognitive impairment and incident postoperative delirium each appear to be associated with decreased survival (Fig. 1A–B, Table 2). However, incorporating age, illness severity, and ICU admission into the survival model demonstrates that for this cohort cognitive impairment and incident postoperative delirium are not significant harbingers of increased mortality.

These results both support and conflict with results from prior shorter-term follow-up studies and meta-analysis seeking to determine the implications of cognitive dysfunction in older hospitalized patients. In contrast to the current study, a number of studies of elderly patients undergoing hip fracture repair or which include such patients as part of a population undergoing rehabilitation note that cognitive impairment alone or in combination with delirium predicts decreased survival.^{7;8;12;16;21} Many of these studies may have benefitted from graded assessments of all participants with the MMSE rather than the current study's discrete determination of cognitive impairment using a variety of data that could include the MMSE. Although postoperative delirium is frequently a univariate predictor of decreased survival, as in the current study, a number of shorter-term studies incorporating additional variables such as age and illness severity conclude that postoperative delirium is not associated with decreased survival.^{9;10;12;13;16} Nonetheless, studies of patients with severe illness^{19;20} and meta-analysis of mixed medical and surgical populations⁵ implicate delirium

as a risk factor for decreased survival, suggesting, as discussed below, that results of the current study may not apply beyond the study population.

The fact that strong univariate associations between cognitive impairment, postoperative delirium, and survival were not borne out in multivariate models implies the existence of common underlying risk factors. In the current study, patients with cognitive impairment were on average 3.3 years older than those without and experienced a median survival 2.4 years less. Similarly, patients in whom incident delirium was observed were on average 2.4 years older than those in whom it was not observed and experienced a median survival 2.3 years less. These observations are consistent with the increased prevalence of cognitive impairment with increasing age³¹ and that cognitive impairment is a major risk factor for delirium.^{3;6;23} Illness severity as indicated by the ASA physical status score was also greater in both cognitively impaired patients and those who would experience incident delirium. Medical comorbidities have often been linked with cognitive impairment and delirium in hospitalized patients.^{6;32} In the current study, cognitively impaired patients were no more likely to be admitted to the ICU than those with intact cognition. However, incident delirium was observed more often in patients admitted to the ICU. Patients are generally admitted to the ICU out of concern for established comorbidities or because of events transpiring during surgery, both of which can negatively affect survival, and ICU admission is not uncommon after hip fracture repair.³³ ICU admission is a known risk factor for incident delirium in general³⁴ and, specifically, after hip fracture repair.³³ Thus, risk factors for decreased survival of the study population are also established risk factors for cognitive impairment and incident delirium.

An established history of depression at the time of hospital admission was not associated with decreased long-term survival of the study population. In contrast, depression near the time of surgery^{13;16} or after admission to a rehabilitation hospital^{8;17;18} has been associated with decreased survival after hip fracture repair. It may be more relevant when considering survival of more than 6 months,^{13;16} and may be particularly concerning when it occurs simultaneously with dementia.¹⁷ The current study did not formally evaluate depression and relied on the history at admission. This precluded use of any type of graded depression score¹³ or depression symptomatology in the analysis, may have limited diagnostic accuracy, and did not consider incident depression during the rehabilitation period. Since the prevalence of depression in the current study is 14.7% which is essentially identical to the prevalence of 12.7% reported in another hip fracture study,¹⁶ it is unlikely that many cases of depression at the time of admission were missed in the current investigation.

Time from presentation with a hip fracture until its surgical repair has been a marker of decreased survival in other studies^{24;25} but was not significant in univariate and multivariate models in the current study. However, it did demonstrate a trend toward significance and improved goodness-of-fit when incorporated in the final model of Table 4 (see footnote to table). At the study institution, a delay from the time of presentation until surgical repair occurs primarily to permit additional medical optimization when this is necessary. Therefore, prolonged delay until surgery may signal illness severity not otherwise accounted for. However, this trend was not incorporated into the final model because it did little to elucidate the relationships between incident postoperative delirium and survival.

The extent to which this study's results can be generalized to other populations may further illuminate the basis for similarities and differences between its conclusions and those of other studies. This study evaluated survival only in patients who actually underwent surgical repair of their hip fracture and were without prevalent delirium. As such, regardless of cognitive state, it filtered out the historical 1%³³ of those considered too medically fragile to tolerate surgery who, therefore, should have been at risk for decreased survival after their injury. More important may be the emphasis of the current study on incident delirium since prevalent delirium in the absence of cognitive impairment is a risk factor for increased mortality after hip fracture.¹⁵ Furthermore, since delirium risk and its duration increase with dementia severity,³⁵⁻³⁷ eliminating those with prevalent delirium may also eliminate those with the most severe cognitive impairment from further consideration. Additionally, the focus on those undergoing hip fracture repair rather than medical admissions^{19;20} or other types of surgery may have selected a cohort with a more reversible process, rather than those whose reason for hospital admission may be more strongly associated with prolonged delirium and decreased survival.

Although reliable in the perioperative setting when used by trained personnel,^{28;38} delirium assessment with the CAM on just the second postoperative day would have missed episodes of delirium that did not include this day and precluded use of delirium duration or subtype in the analysis of survival. Delirium assessment after the first postoperative day helps preclude the inference from residual anesthetic effects.³⁹ Moreover, in elderly patients undergoing hip fracture repair, postoperative delirium usually presents approximately 24 hours after surgery and generally resolves within 48 hours of presentation,⁴⁰ though it certainly can present after the second postoperative day in older patients undergoing major elective surgery.⁴¹ However, incident delirium apparent on the second postoperative day is more likely to reflect the contributions of surgery and anesthesia than delirium presenting later in the hospital course. Inclusion of postoperative delirium duration might refine survival estimates, since mortality increases with delirium duration in elderly hospitalized medical patients,^{19;20;42} and patients undergoing hip fracture repair with delirium of more than 4 weeks duration die more frequently.¹⁴ However, another study noted no difference in 1-year mortality for patients whose delirium during the presenting admission had cleared when examined 2 months later compared to those for whom it did not.¹¹ Delirium subtype may also have prognostic significance, because those with hypoactive delirium in a population of older patients with planned admission to an intensive care setting after elective surgery experienced a higher 6-month mortality.⁴³ Importantly, delirium assessments were consistently obtained on the second postoperative day for all subjects enrolled in the study.

An additional limitation of this study is that it did not fully capture the entire population during the study period, because delirium assessment required the presence of trained evaluators who were not continuously available for the entire study period of a little more than a decade. Unfortunately, hospital databases do not permit the total number of patients presenting for hip fracture repair during the study period to be determined with precision. However, the historical estimate³³ of about 128 cases/year over a 3.6-year period coincident with the current study's final years of enrollment indicate that the 750 patients considered here represent at least 57% of the entire population. Since the primary reason preventing enrollment was due to periods when trained research personnel were not on staff, missing

data were likely not informative with respect to time of day or day of week. This is supported by the observation that for the patients enrolled, the number presenting on the weekend was not proportionately different from those presenting during the remaining days of the week. Moreover, delirium assessments on the second postoperative day were performed for the 97 subjects who underwent surgery on Friday.

In conclusion, in this prospective evaluation of survival after hip fracture repair spanning more than a decade, incident postoperative delirium detected on the second postoperative day was not significantly associated with decreased survival when age, illness severity, and the duration of ICU admission were considered. These results may not be generalizable to those who present for hip fracture repair with prevalent delirium or when the onset of delirium occurs later in the hospital course.

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Figure 1.

Kaplan-Meier survival estimates after hip fracture repair comparing those with and without preoperative cognitive impairment (A), with and without incident postoperative delirium (B), stratified by comorbidities as indicated by the ASA physical status score (C), and comparing those admitted to the intensive care unit (ICU) and those who were not (D). Differences between curves were assessed with the log-rank test with p values indicated on each graph.

Table 1

Summary of patient variables.

Variable	Overall (n=459)	No Cognitive Impairment (n=339)	Cognitive Impairment (n=120)	p ^a	No Delirium On POD 2 (n=308)	Delirium On POD 2 (n=151)	p ^a
Preoperative Demographic Variables							
Age (years) ^b	81.3 (7.1)	80.4 (7.2)	83.7 (5.9)	<0.001*	80.5 (7.0)	82.9 (6.8)	<0.001*
Gender (M/F)	123/336	92/247	31/89	0.81	71/237	52/99	0.01*
Cognitive Impairment (n)	120 (26.1%)	n/a	n/a	n/a	48 (15.6%)	72 (47.7%)	<0.001*
Depression History (n)	67 (14.6%)	42 (12.4%)	25 (20.8%)	0.03*	42 (13.6%)	25 (16.6%)	0.40
ASA (2/3/4)	74/324/61 (16.1/70.6/13.3%)	67/236/36 (19.8/69.6/10.6%)	7/88/25 (5.8/73.3/20.8%)	<0.001*	65/212/31 (21.1/68.8/10.1%)	9/112/30 (6.0/74.2/19.9%)	<0.001*
Perioperative Variables							
Time until Surgery (d)	1 [1, 2]	1 [1, 2]	1 [1, 2]	0.07	1 [1, 2]	1 [1, 2]	0.016*
Spinal Anesthesia (n)	181 (39.4%)	133 (39.2%)	48 (40.0%)	0.91	127 (41.2%)	54 (35.8%)	0.27
Transfused (n)	262 (57.1%)	189 (55.8%)	73 (60.8%)	0.39	164 (53.2%)	98 (64.9%)	0.021*
Erythrocytes Transfused (units) ^c	1 [0, 2]	1 [0, 2]	1 [0, 2]	0.58	1 [0, 2]	1 [0, 2]	0.001*
Admitted to ICU (n)	111 (24.2%)	79 (23.3%)	32 (26.7%)	0.46	55 (17.9%)	56 (37.1%)	<0.001*
Length of Stay in ICU (d) ^c	0 [0, 0]	0 [0, 0]	0 [0, 1]	0.07	0 [0, 0]	0 [0, 2]	<0.001*
Delirium on POD 2 (n)	151 (32.9%)	79 (23.3%)	72 (60.0%)	<0.001*	n/a	n/a	n/a
Long-term Outcomes							
Death (n)	340 (74.1%)	245 (72.3%)	95 (79.2%)	0.15	213 (69.2%)	127 (84.1%)	0.001*
Median Survival (years)	3.75 [3.13, 4.54]	4.56 [3.75, 5.14]	2.21 [1.30, 2.92]	0.002*	4.82 [3.86, 5.80]	2.51 [1.80, 3.12]	<0.001*

ASA = American Society of Anesthesiologists physical status score; ICU = intensive care unit; n/a=not applicable; POD 2 = postoperative day 2

Significant differences are indicated by an asterisk.

^aP values determined using Fisher's exact test for frequency data, Wilcoxon rank-sum test for ordered categorical data, and analysis of variance for continuous data. Frequency data is given as n (%), ordered categorical data as median [interquartile range], and continuous data is given as mean (standard deviation). Median survival [95% confidence interval] is given with differences between groups assessed with the log-rank test as with the Kaplan-Meier survival estimates of Fig. 1.

^b Age is given in fractions of year from date of birth until surgical procedure. Thus, on average age will be approximately one half year greater than age at last birthday. For the current data, age at surgery is 0.48 years greater than age at last birthday.

^cThe length of stay in the ICU and number of erythrocytes transfused are given for the entire study population, not just those admitted to the ICU or receiving erythrocyte transfusion. For those actually admitted to the ICU, the median [lower quartile, upper quartile] length of stay was 3 [1, 5] days. For those admitted to the ICU without cognitive impairment it was 3 [1, 5] days, and 3 [2, 6.5] days for those with cognitive impairment (p = 0.44). For those admitted to the ICU and did not manifest delirium on the second postoperative day, it was 2 [1, 4] days, and for those who did it was 3 [2, 5.5] days (p = 0.07). For those receiving transfusion the overall median [lower quartile, upper quartile] number of units of erythrocytes transfused was 2 [1, 3]. For those receiving transfusion this was 2[1,3] units for those who were not cognitively impaired and 2 [1, 2] for those who were (p = 0.47). For those transfused, this was 2 [1, 2] units in those who did not manifest delirium on the second postoperative day, and 2 [1, 3] units in those who did (p = 0.004).

Table 2

Univariate analysis of survival using Cox regression.

Variable	Hazard Ratio	95% Confidence Interval	P
Age (Years)	1.04	1.02, 1.06	<0.001*
Male	1.25	0.98, 1.58	0.07
Cognitive Impairment	1.44	1.14, 1.83	0.002*
Depression History	1.10	0.81, 1.48	0.55
ASA Score ^a	2.01	1.65, 2.45	<0.001*
Time until Surgery (d)	1.00	0.96, 1.04	0.87
Spinal Anesthesia	1.07	0.86, 1.34	0.55
Transfused	1.33	1.07, 1.66	0.009*
Erythrocytes Transfused (units)	1.09	1.03, 1.15	0.001*
Admitted to ICU	1.62	1.28, 2.07	<0.001*
Length of Stay in ICU (days)	1.10	1.07, 1.12	<0.001*
Delirium on POD 2	1.65	1.32, 2.06	<0.001*

ASA = American Society of Anesthesiologists physical status score; ICU = intensive care unit; POD 2 = postoperative day 2

Significant differences are indicated by an asterisk.

^a ASA scores were treated as a continuous variable in what follows as no precision or clarity appeared to be lost when compared to alternative analyses which treated it categorically. Here, the hazard ratio [95% CI] and p value for ASA 3 vs. ASA 2 are 2.10 [1.51, 2.93], $p < 0.001^*$ and those for ASA 4 vs. 2 are 4.07 [2.71, 6.12], $p < 0.001^*$.

Table 3

Initial multivariate model using Cox regression ($\chi^2 = 83.7$, $p < 0.001$).^b

Variable ^a	Hazard Ratio	95% Confidence Interval	P
Age (Years)	1.03	1.01, 1.05	<0.001*
Male	1.12	0.87, 1.45	0.38
Cognitive Impairment	0.98	0.75, 1.27	0.87
ASA Score	1.63	1.31, 2.02	<0.001*
Erythrocytes Transfused (units)	0.97	0.91, 1.04	0.38
Length of Stay in ICU (days)	1.08	1.04, 1.12	<0.001*
Delirium	1.20	0.93, 1.54	0.16

ASA = American Society of Anesthesiologists physical status score; ICU = intensive care unit.

Significant differences are indicated by an asterisk.

^a Since they were more informative, the duration of ICU stay and number of units of erythrocytes transfused were used rather than the corresponding categorical variables indicating ICU admission or erythrocyte transfusion.

^b Likelihood ratio tests were performed comparing the current model with one where the eliminated variables from Table 2 were incorporated one at a time in the model of the current table without achieving significance (depression, $p = 0.95$; time until surgery, $p = 0.18$; use of regional anesthesia, $p = 0.40$).

Table 4

Multivariate model after introduction of nonlinear term (length of stay in ICU squared) to the model ($\chi^2 = 85.0$, $p < 0.001$).^{a, b} and corresponding parametric survival model assuming the generalized gamma distribution. ($\chi^2 = 79.0$, $p < 0.001$).^{c, d}

Variable	Cox Regression Model			Parametric Model		
	Hazard Ratio	95% Confidence Interval	P	Coefficient	95% Confidence Interval	P
Age (Years)	1.03	1.02, 1.05	<0.001*	-0.0380	-0.0592, -0.0169	<0.001*
ASA Score	1.62	1.31, 1.99	<0.001*	-0.653	-0.954, -0.352	<0.001*
Length of Stay in ICU (days)	1.15	1.09, 1.23	<0.001*	-0.210	-0.303, -0.114	<0.001*
(Length of Stay in ICU) ²	0.9978	0.9958, 0.9998	0.028*	0.00334	0.00019, 0.00648	0.038*

ASA = American Society of Anesthesiologists physical status score; ICU = intensive care unit.

Significant differences are indicated by an asterisk.

^aThe likelihood ratio test comparing the Cox regression model to one without the nonlinear term demonstrated significant improvement ($p = 0.02$). The test for goodness-of-fit for the Cox regression model of Table 4 revealed, for the eight quantiles of risk evaluated, only one significant deviation ($p = 0.10$) with the remainder highly nonsignificant ($p = 0.31$). If time until surgery is included in the model of Table 4, then in the test for goodness-of-fit, all quantiles are highly insignificant ($p = 0.35$). If Time Until Surgery is incorporated ($\chi^2 = 88.3$, $p < 0.001$), age, ASA and length of stay in ICU remained highly significant ($p < 0.001$), the square of length of stay in ICU remained significant ($p = 0.01$), and time until surgery was a trend ($p = 0.11$). The addition of dementia, depression, or incident postoperative delirium to such a model did not significantly improve the quality of the model with Time Until Surgery as revealed by likelihood ratio tests (cognitive impairment, $p = 0.88$; depression, $p > 0.99$; delirium, $p = 0.20$).

^bLikelihood ratio tests comparing the Cox regression model of Table 4 with one where the eliminated variables from Table 2 were incorporated one at a time in the nonlinear model did not achieve significance (male gender, $p = 0.42$; cognitive impairment, $p = 0.99$; postoperative delirium, $p = 0.22$; depression, $p = 0.96$; time until surgery, $p = 0.07$; use of regional anesthesia, $p = 0.27$; number of units of erythrocytes transfused, $p = 0.88$).

^cThe use of the generalized gamma distribution rather than less general distributions such as the lognormal or Weibull, which are both special cases of the generalized gamma distribution, is justified respectively by a value of κ [95% CI] of 0.746 [0.378, 1.115] different from zero and a value of σ [95% CI] of 1.35 [1.16, 1.58] different from 1.

^dLikelihood ratio tests comparing the parametric survival model of Table 4 with one where the eliminated variables from Table 2 were incorporated one at a time in the nonlinear parametric model of the current table without affecting conclusions (male gender, $p = 0.53$; cognitive impairment, $p = 0.47$; incident postoperative delirium, $p = 0.19$; depression, $p = 0.99$; time until surgery, $p = 0.04$; use of regional anesthesia, $p = 0.50$; number of units of erythrocytes transfused, $p = 0.88$). When time until surgery is explicitly incorporated in the model $p = 0.07$ for its coefficient, and the likelihood ratio test with the further addition of incident postoperative delirium reveals that the model is not significantly improved ($p = 0.16$).