Increasing age is associated with worse outcome in patients with systemic diseases such as cancer, coronary heart disease, and neurological diseases such as SAH, TBI, and dementia.1,5,10,11,20,37,38,42,43,46 Traumatic brain injury is a major health and socioeconomic problem throughout the world and is the leading cause of death and disability in younger patients in more economically developed countries. It remains unclear how the association between patient age and outcome after closed TBI can be described best, however. In some studies researchers have treated outcome as a continuous function of age,5,29,41 whereas others have identified age threshold values between 30 and 60 years.3,10,30,33,35,38,43,44

In a study on early indicators in the management and prognosis of severe TBI, Chesnut, et al.,3 provided a detailed overview of published data on the association between patient age and outcome following TBI. These authors concluded that the probability of a poor outcome increased with patient age in a stepwise manner, suggesting an age threshold of 60 years. Note, however, that they recognized that this threshold might be an artifact of the age grouping used by various researchers in converting continuous data into categorical data.

Establishing the correlation between patient age and outcome more precisely is important in being able to predict outcome and understand how to adjust for age in epidemiological studies. Obtaining more knowledge about the shape of this association may also help to explain the relationship itself. Furthermore, identifying threshold values may be relevant to clinical research, for example, for purposes of stratification in randomized clinical trials or prognostic modeling.

Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients

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Object. Increasing age is associated with poorer outcome in patients with closed traumatic brain injury (TBI). It is uncertain whether critical age thresholds exist, however, and the strength of the association has yet to be investigated across large series. The authors studied the shape and strength of the relationship between age and outcome, that is, the 6-month mortality rate and unfavorable outcome based on the Glasgow Outcome Scale.

Methods. The shape of the association was examined in four prospective series with individual patient data (2664 cases). All patients had a closed TBI and were of adult age (96% < 65 years of age). The strength of the association was investigated in a metaanalysis of the aforementioned individual patient data (2664 cases) and aggregate data (2948 cases) from TBI studies published between 1980 and 2001 (total 5612 cases). Analyses were performed with univariable and multivariable logistic regression.

Proportions of mortality and unfavorable outcome increased with age: 21 and 39%, respectively, for patients younger than 35 years and 52 and 74%, respectively, for patients older than 55 years. The association between age and both mortality and unfavorable outcome was continuous and could be adequately described by a linear term and expressed even better statistically by a linear and a quadratic term. The use of age thresholds (best fitting threshold 39 years) in the analysis resulted in a considerable loss of information. The strength of the association, expressed as an odds ratio per 10 years of age, was 1.47 (95% confidence interval [CI] 1.34–1.63) for death and 1.49 (95% CI 1.43–1.56) for unfavorable outcome in univariable analyses, and 1.39 (95% CI 1.3–1.5) and 1.46 (95% CI 1.36–1.56), respectively, in multivariable analyses. Thus, the odds for a poor outcome increased by 40 to 50% per 10 years of age.

Conclusions. An older age is continuously associated with a worsening outcome after TBI; hence, it is disadvantageous to define the effect of age on outcome in a discrete manner when we aim to estimate prognosis or adjust for confounding variables.

Key Words • traumatic brain injury • metaanalysis • age • outcome • association

Abbreviations used in this paper: CI = confidence interval; CT = computerized tomography; EBIC = European Brain Injury Consortium; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; OR = odds ratio; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.
The primary aim of this study was to describe the relationship between age and outcome in patients with TBI, which fit the data well and was simple (that is, low-dimensional) and easily communicated and applied in clinical practice. We also examined whether a meaningful age threshold value could be determined. Furthermore, we quantified the extent of the effect of patient age on outcome in a metaanalysis.

**Clinical Material and Methods**

**Patient Population**

Two data sources were used in the present study: 1) individual patient data (2664 cases) from four different patient series; and 2) aggregate data (2948 cases) extracted from TBI outcome studies published between 1980 and 2001 (Table 1). Adults (patients ≥ 14 years of age) with severe closed TBI (GCS ≤ 8) were selected for analysis.

The shape of the association between patient age and outcome was studied in the individual patient data by using both continuous age transformations and age as a threshold value (for example, an age < 40 years compared with an age ≥ 40 years). The strength of the correlation was considered in a metaanalysis that included both aggregate data and individual patient data. Outcome measures at 6 months postinjury were death and the GOS score dichotomized into unfavorable outcome (death, vegetative state, and severe disability) and favorable outcome (moderate disability and good recovery).

**Data Collection**

Individual patient data included populations from three multicenter phase III randomized clinical trials and one prospective series of patients with closed TBI. Six-month outcome data were available from 2500 patients. In 164 patients outcome had not been assessed at 6 months postinjury, but could be assigned according to a specific algorithm that used GOS results obtained at other points in time.

We searched for relevant published studies by using the PubMed service to access the MEDLINE database of citations (period 1980–2001) with the key words "age," "outcome," "traumatic brain injury," and "metaanalysis." We included papers published in English that described patient populations and outcome at 6 months postinjury in patients with severe closed TBI (GCS ≤ 8). The shape of the association between patient age and outcome was studied in the individual patient data by using both continuous age transformations and age as a threshold value (for example, an age < 40 years compared with an age ≥ 40 years). The strength of the correlation was considered in a metaanalysis that included both aggregate data and individual patient data. Outcome measures at 6 months postinjury were death and the GOS score dichotomized into unfavorable outcome (death, vegetative state, and severe disability) and favorable outcome (moderate disability and good recovery).

**TABLE 1**

*Studies included in the analysis of the association between age and 6-month outcome in patients with severe TBI*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Period of Data Collection</th>
<th>Place of Data Collection</th>
<th>Patient Age Limits (yrs)</th>
<th>Age Coding (yrs)†</th>
<th>No. of Patients</th>
<th>Mortality Rate</th>
<th>Rate of Unfavorable Outcome‡</th>
<th>Specific Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>individual patient data (2664 cases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray, et al., 1999</td>
<td>1995</td>
<td>Europe</td>
<td>≥ 15</td>
<td>individual nos</td>
<td>471</td>
<td>40</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>aggregate data (2948 cases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*NA = not applicable; UA = unavailable.
† Indicates how age was classified in the original paper, either as individual numbers or age categories. Ellipses indicate that intermediate age ranges are included in the study mentioned.
‡ Severe disability, vegetative state, or death, according to the GOS. Outcome was determined at least 6 months postinjury.
come, "head injury," or "traumatic brain injury," and relation or "association." Additional papers were retrieved by tracking citations in the reference lists of the aforementioned reports. Studies published in the English language were selected if they included the following: 1) 35 or more adult patients with severe closed TBI; 2) frequency data on at least two age categories together with 6-month mortality data or 6-month unfavorable outcome data; and 3) patient data from Europe, Israel, North America, or Australia to ensure comparability with the data from the individual patient series. Of more than 100 studies initially considered, 11,14,15,16,19,23,35,36,42 met these criteria and constitute the aggregate data. Studies selected for the metaanalysis are listed in Table 1.

**Shape of the Association**

The shape of the association between patient age and outcome was studied using the following age transformations. 1) A smoothing spline14,34,36 is a very flexible way to describe an association, but cannot be expressed easily in a parametric formula. A penalty factor, which prevents wild oscillation of the spline, is based on the default nominal degree of freedom. Because the smoothing spline represents maximal goodness-of-fit but cannot be expressed in a formula easily, it was used as a reference for the performance of other age transformations. 2) We also considered a variety of continuous transformations: linear (age), linear plus quadratic (age plus age²), linear plus cubic (age plus age³), square root (age⁰·⁵), logarithmic (log[age]), exponential (exp [age]), and reciprocal (age⁻¹). We also analyzed a previously suggested piecewise transformation, that is, no effect of age until 50 years and a linear effect above this age.38 3) In addition, we determined age threshold values: all 60 threshold values between 15 and 76 years of age were evaluated, thus including thresholds discussed in previous studies.5,10,16,20,23,35,36,43,44 The 95% CIs were constructed with profile log-likelihood methods12 around the best fitting (optimal) threshold.

We included all transformations of age in logistic regression models, both univariable ones and those adjusted for potential confounders. The confounding variables considered were cause of injury, sex, geographical region, GCS score, hypoxia, hypotension, pupillary reactivity, raised ICP (defined as ≥ 20 mm Hg), traumatic SAH, and CT scanning–based classification.21 Interactions between the best fitting age transformation and the confounding variables were not statistically significant.

Values of missing confounders (4.6% of all values) were assigned to each patient, based on correlations with existing confounders.13,22 The fit of the models was expressed on the log-likelihood scale of the model chi-square function (deviance).6 The higher the model chi-square, the better the model fits the data. The fit of the different age transformations was compared with the smoothing spline and with age as a continuous linear term.

**Strength of the Association**

The strength of the association was analyzed with univariable (aggregate data and individual patient data) and multivariable (individual patient data) logistic regression, including age as a continuous linear term. Results were expressed as ORs for every 10 years of age. In the aggregate data, age was typically reported in categories with a range of values, for example, 10 to 20 years or 15 to 25 years. Consequently, the association with age as a continuous linear term could not be estimated directly. By using the overall age distribution (mean age and standard deviation) in the study under consideration, however, we could validly assign a mean age to each age category.39 If the overall age distribution was not reported, the age distribution from the combined data from the tirilazad trials24,26 was ascribed and matched to specific patient characteristics (for example, patients with epidural hematoma). All analyses were performed on available data sets sepa-
Age and outcome in patients with severe traumatic brain injury

rately as well as on pooled data sets. Because the association between patient age and death was statistically significantly different across the studies with aggregate data (test for heterogeneity, p = 0.0001), pooled effects were estimated using a random effects model, including study as a factor in the analyses. For all other associations, homogeneity in effects (p > 0.1) could be assumed and fixed effects methods were used.

Calculations were performed using commercially available software (SAS, version 6.12; SAS Institute, Inc., Cary, NC or S-plus, version 2000; Insightful, Inc., Seattle, WA).

Results

In the four individual patient series, the mean rate of death varied from 23 to 40% and the mean rate of unfavorable outcome varied from 43 to 60%, with the highest proportions in the unselected series of the EBIC (Table 1). Complete outcome data and the distribution of patients across age groups are listed in Table 2. Patient populations from the 11 studies gathered from the literature were diverse, some being relatively unselected and others highly selected (for example, patients with acute hematomas). Consequently, outcome varied considerably: 21 to 79% for mortality and 41 to 85% for unfavorable outcome.

The proportion of several confounding variables, such as low GCS score, traumatic SAH, and mass lesions, increased with age (Table 3). In contrast, no age-related effects were observed for unreactive pupils, hypotension, and hypoxia.

Shape of the Association Among Individual Patient Data

Poor patient outcome increased with age (Table 2 and Fig. 1); for example, the mortality rate increased from 21% at an age younger than 35 years to 72% at an age older than 65 years. For unfavorable outcome, these percentages were 39 and 85%, respectively. The smoothing splines look partly linear and partly quadratic (Fig. 1). Adding a slightly more or less liberal penalty factor did not clearly alter the shape of the curve. For ages older than 65 years, the splines were based on only 101 patients (4%), thus implying that the curve is uncertain above this age. Among survivors, the relative proportion of poor outcomes increased with age: severe disability and vegetative state occurred in just over 20% of the survivors at age 20 years and in approximately 50% of the survivors at age 60 years (Fig. 1 and Table 2).

Several continuous transformations of age resulted in a good fit: age as a linear variable reached 90 and 96% of the optimum (the smoothing spline is the reference) for rates of mortality and unfavorable outcome, respectively. The linear plus quadratic (age plus age²) and linear plus cubic (age plus age²) transformations resulted in even better fits (Table 4), which were statistically significant for mortality in both the univariable and multivariable analyses and for unfavorable outcome in the multivariable analysis. The absolute differences in estimated probabilities of poor patient outcome in a comparison of linear and linear plus quadratic, and linear and linear plus cubic age transformations were small, however (Fig. 1). The difference in the estimated mortality rate in a comparison of age linear and age linear plus quadratic transformations was a maximal 3.3% at age 47 years. Unfavorable outcome results were similar.

The fit of the linear, linear plus quadratic, and linear plus cubic age transformations was consistent in each individual study and remained constant after adjustment for confounding variables, indicating robustness of the findings. After adjustment, age linear resulted in 78% of the optimal goodness of fit for the mortality rate and 93% of the optimal fit for unfavorable outcome. Linear plus quadratic and linear plus cubic age transformations yielded 94 and 98% of the optimal goodness-of-fit for rates of mortality and unfavorable outcome, respectively. Other continuous transformations, such as age, log[age], and the piecewise transformation (a linear effect above the age of 50 years), performed worse.

Optimal age thresholds could be identified accurately, that is, 39 years for both death (95% CI 39–40 years) and unfavorable outcome (95% CI 39–39 years). These thresholds resulted in a maximal 73% (mortality) and 84% (unfavorable outcome) of the optimal fit (Table 3), however. The age threshold value at 39 years is graphically reflected in Fig. 2.

Strength of the Association

Among the individual patient data, the ORs were similar,
that is, 1.3 to 1.46 for mortality and 1.33 to 1.49 for unfavorable outcome per 10 years of age (Fig. 3). Metaanalyses of these data yielded a pooled OR of 1.37 (95% CI 1.3–1.46) for mortality and 1.43 (95% CI 1.35–1.51) for unfavorable outcome. Thus, the effect of a 10-year increase in age was a multiplication of the odds for mortality by 1.37 and for unfavorable outcome by 1.43. In the individual patient data, we adjusted the age–outcome association for potential confounding variables, as shown in Table 2. The pooled adjusted ORs of 1.36 (95% CI 1.31–1.41) for mortality and 1.46 (95% CI 1.36–1.56) for unfavorable outcome—were very similar to the pooled unadjusted ORs. Given that the 95% CIs did not include the value 1, age was independent of other risk factors in patients with severe TBI.

In the aggregate data, the ORs varied considerably: mortality, 0.87 to 2.92; and unfavorable outcome, 1.47 to 2.64 per 10-year increase in age (Fig. 3). The pooled ORs were 1.55 (95% CI 1.32–1.86) for mortality (10 studies, 2376 cases) and 1.61 (95% CI 1.49–1.73) for unfavorable outcome (six studies, 1982 cases) per 10 years of age.

When combining aggregate and individual patient data, total ORs were 1.47 (95% CI 1.34–1.63) for mortality and 1.49 (95% CI 1.43–1.56) for unfavorable outcome (Fig. 3 upper and lower).

Discussion

We compared various age transformations to identify simple and accurate descriptions of the associations between age and mortality and age and unfavorable outcome in patients with severe TBI. We found that these associations were continuous. Statistically, age linear plus quadratic transformations fit significantly better than age linear ones. This was primarily caused by the slightly better fit in younger patients, who constituted a large part of the study population. Nonetheless, the absolute difference in the estimated probability of poor outcome comparing age linear and age linear plus quadratic transformations was at most a few percent, which we consider clinically unimportant; therefore, both age linear and age linear plus quadratic transformations are adequate descriptions of the association between patient age and 6-month outcome following TBI. A linear relationship between age and outcome has also been reported in patients with aneurysmal SAH.18,21

The smoothing splines (Fig. 1) may also be interpreted as consisting of two linear parts. We found an optimal change point at 60 years for mortality and at 29 years for unfavorable outcome. These change points varied considerably across populations and contained broad CIs, however.

---

**Table 4**

<table>
<thead>
<tr>
<th>Models for Age Transformations</th>
<th>Performance vs Smoothing Spline</th>
<th>Performance vs Age Linear</th>
<th>Performance vs Smoothing Spline</th>
<th>Performance vs Age Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality Rate</td>
<td>Rate of Unfavorable Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>% of Optimum†</td>
<td>% of Optimum†</td>
<td>Gain‡</td>
<td>p Value§</td>
</tr>
<tr>
<td>age as a smoothing spline</td>
<td>134.4</td>
<td>100</td>
<td>13.7</td>
<td>0.003</td>
</tr>
<tr>
<td>continuous transformations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>120.7</td>
<td>90</td>
<td>reference</td>
<td>NA</td>
</tr>
<tr>
<td>age linear plus quadratic</td>
<td>128.9</td>
<td>96</td>
<td>8.2</td>
<td>0.004</td>
</tr>
<tr>
<td>age linear plus cubic</td>
<td>128.8</td>
<td>96</td>
<td>8.1</td>
<td>0.004</td>
</tr>
<tr>
<td>age thresholds based on the literature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 30 yrs**</td>
<td>69.5</td>
<td>52</td>
<td>−51.2</td>
<td>NA</td>
</tr>
<tr>
<td>at 35 &amp; at 55 yrs†</td>
<td>92.2</td>
<td>69</td>
<td>−28.5</td>
<td>&lt;0.001‡§</td>
</tr>
<tr>
<td>at 40 yrs‡</td>
<td>96.4</td>
<td>72</td>
<td>−24.3</td>
<td>NA</td>
</tr>
<tr>
<td>at 50 yrs</td>
<td></td>
<td></td>
<td>69.5</td>
<td>52</td>
</tr>
<tr>
<td>at 55 yrs***</td>
<td>66.1</td>
<td>49</td>
<td>−54.6</td>
<td>NA</td>
</tr>
<tr>
<td>at 60 yrs†</td>
<td>64.7</td>
<td>48</td>
<td>−56.0</td>
<td>NA</td>
</tr>
<tr>
<td>zero until 50 yrs.</td>
<td>96.3</td>
<td>72</td>
<td>−24.4</td>
<td>NA</td>
</tr>
<tr>
<td>best fitting age threshold‡</td>
<td></td>
<td></td>
<td>−22.7</td>
<td>NA</td>
</tr>
<tr>
<td>(39 years)</td>
<td>98.0</td>
<td>73</td>
<td></td>
<td>21.5</td>
</tr>
</tbody>
</table>

* Additional model chi square of the age variable to the fit of the model.
† The fit of the model using the smoothing spline was considered to be optimal (100%) and was used as a reference for this column.
‡ The gain of a model is defined as the additional model chi square for the model in question minus that for the model including age as a linear term. If the gain is positive, the transformation fits better than age linear; a negative number implies that it fits worse.
§ For a likelihood-ratio test, which tests the gain of the age transformation.
|| Zero degrees of freedom.
** Overgaard, et al., and Resnick, et al.
‡‡ Negative gain.
‡‡‡ Signorini, et al.
††† Chesnut, et al.
*** Gómez, et al.

Therefore, these piecewise linear transformations are less appropriate to describe the correlation between patient age and outcome. We also found a clear effect of age in those younger than 50 years, in contrast to a previous conclusion based on data in 372 patients.38 The use of age thresholds for describing the relationship between patient age and outcome resulted in a considerable loss of information and is therefore not recommended. Hence, our findings challenge the conclusions of authors who have published guidelines claiming that the association between patient age and outcome can be described in a stepwise manner.3 The reason why authors of previous studies have identified age thresholds with many different values3,10,30,33,35,38,43,44 is probably a consequence of the statistical methods used. Arbitrary categorization of age and relatively small numbers of patients in specific age categories means that few patients can change proportion of poor outcome considerably.

Furthermore, the value of the identified age threshold is determined by the distribution of age in the examined patient population. In the present study, with a close to linear association and a very large proportion of patients between 15 and 65 years of age, thresholds were situated approximately midway, at 39 years, which was partly induced by the age distribution of the examined patient population. When separately analyzing the nonselected population from the EBIC study, which contained a relatively greater number of older patients, threshold values included higher ages (that is, 59 years for mortality and 45 years for unfavorable outcome).

It may be hypothesized that increased mortality at an older age is in part caused by an increased number of (possibly extracerebral) medical complications, which would be expected to increase late mortality. The median time to death did not differ between patients younger than and older than 50 years of age, however (p = 0.75, tirilazad data). Moreover, in both age groups the primary cause of death was cerebral, and no clear difference was noted in the frequency of extracerebral (systemic) causes of death.

In accordance with data from several other studies,10,21,43 we observed that the proportion of survivors with poor outcomes (for example, severe disability or vegetative state) increased with age and that the proportion of patients with favorable outcomes declined. These results support the hypothesis that the adult brain has a decreased capacity for repair as it ages,2 because of a decreasing number of functioning neurons and a greater exposure to minor repetitive (often subclinical) insults to the brain as age increases. In adults, however, diminished cognitive or behavioral function may be influenced beneficially by regeneration or plasticity of the brain.24,31 Further investigation of the physi-
iological and pathophysiological features in the aging brain is required to identify new medical interventions that perhaps could prevent the poorer outcome associated with advanced age.

Several limitations of our analyses should be acknowledged. First, the individual patient data consisted mainly of selected populations from randomized clinical trials; therefore specific subgroups, such as patients with a GCS motor score of 1 or an age older than 65 years, were underrepresented. Whether our findings may be extrapolated to these or other subgroups of patients with closed TBI is uncertain. Nonetheless, applying results to specific patient categories may be valid, given that statistical interactions between patient age and important confounding variables were not significant. Second, the less detailed study parameters for example, the age categories in the aggregate data may have led to less reliable ORs. The ORs of the pooled individual data did not differ considerably from the ORs of the pooled aggregate data, however. The ORs were generally 1.4 to 1.5 per 10 years of age and univariable and adjusted ORs were similar, although we cannot exclude possible effects of other confounding factors that were not (consistently) present in the data set, such as extracranial injuries.

Our study has a number of implications. First, a better estimate for the odds on poor outcome is obtained, that is, a 40 to 50% increase per 10 years of age, which is independent of the presence of risk factors. Furthermore, the existence of threshold values was not supported. Finally, the association between patient age and outcome after severe TBI is a continuous function, which can be adequately described by an age linear term or even statistically better by an age linear plus quadratic term. We therefore advise applying one of these transformations in future studies on adults with severe TBI for purposes of prognostic modeling or adjusting for confounding variables.

Acknowledgments

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References


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