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Multivariable Prognostic Analysis in Traumatic Brain Injury: Results from the IMPACT Study

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ABSTRACT

We studied the prognostic value of a wide range of conventional and novel prognostic factors on admission after traumatic brain injury (TBI) using both univariate and multivariable analysis. The outcome measure was Glasgow Outcome Scale at 6 months after injury. Individual patient data were available on a cohort of 8686 patients drawn from eight randomized controlled trials and three observational studies. The most powerful independent prognostic variables were age, Glasgow Coma Scale (GCS) motor score, pupil response, and computerized tomography (CT) characteristics, including the Marshall CT classification and traumatic subarachnoid hemorrhage. Prothrombin time was also identified as a powerful independent prognostic factor, but it was only available for a limited number of patients coming from three of the relevant studies. Other important prognostic factors included hypotension, hypoxia, the eye and verbal components of the GCS, glucose, platelets, and hemoglobin. These results on prognostic factors will underpin future work on the IMPACT project, which is focused on the development of novel approaches to the design and analysis of clinical trials in TBI. In addition, the results provide pointers to future research, including further analysis of the prognostic value of prothrombin time, and the evaluation of the clinical impact of intervening aggressively to correct abnormalities in hemoglobin, glucose, and coagulation.

Key words: GOS; multivariable analysis; multivariate analysis; prognosis; traumatic brain injury

INTRODUCTION

DETAILED ANALYSIS of prognostic factors in traumatic brain injury (TBI) forms an important part of the IMPACT project (Maas et al., 2007a). A series of papers based on the IMPACT database (Marmarou et al., 2007a) has reported details of the univariate associations between the Glasgow Outcome Scale (GOS) and demographic characteristics (Mushkudiani et al., 2007), cause of injury (Butcher et al., 2007a), secondary insults (McHugh et al., 2007a), Glasgow Coma Scale (GCS) and pupil response (Marmarou et al., 2007b), blood pressure

IMPACT: International Mission on Prognosis and Analysis of Clinical Trials in TBI.

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(Butcher et al., 2007b), computerized tomography (CT) scan features (Maas et al., 2007b), and laboratory parameters (van Beek et al., 2007). These papers have confirmed the prognostic effects of many known predictors (e.g., age, GCS, pupil response, and CT parameters), have disclosed the predictive value of hitherto insufficiently recognized parameters (e.g., race and laboratory parameters), and have identified potential candidates for therapeutic intervention (e.g., blood pressure and laboratory parameters). Notwithstanding the relevance of these univariate analyses, the ultimate value of predictors can only be established in multivariable analysis, adjusting for the influence of other variables. In the univariate manuscripts, we reported exploratory analyses of associations and performed a limited number of adjusted analyses. This paper reports the results of a more systematic multivariable analysis, where each variable is adjusted in turn for four sets of potentially confounding covariates. By bringing together all of the covariates from the series of earlier papers, this allows a direct comparison of the predictive power of each variable, as well as an assessment of the "added value" of each predictor over and above the predictive power of other groups of covariates. This will help to identify those variables that are most important in clinical trial design and prognosis.

METHODS

Our analyses were based on individual patient data from the three observational studies and eight randomized controlled trials (RCTs) in the IMPACT database (Marmarou et al., 2007a). The endpoint for the prognostic analyses was the 6-month GOS. In cases where the 6-month assessment was not available, we imputed the three month GOS. Thirty-five patients in the UK Four Centres study had partial information on GOS and were excluded to leave an analysis cohort of 8686 patients with full information on GOS. The partial information on GOS was sufficient to allow analysis of, for example, mortality, but not for the analysis over the full range of GOS, as is reported in the paper. This explains the slight differences between some of the sample sizes reported in the earlier papers in this series and the numbers reported in this paper. In addition, since the relatively small number of children in the database precluded accurate modeling of the association between age and GOS in children, the univariate analysis of age and all analyses adjusted for age were restricted to patients aged $\geq$14 years. This yielded a cohort of 8509 adults with full information on GOS. Multivariable logistic regression analysis was performed on the association between the prognostic factor of interest, with and without adjustment for other prognostic factors ("covariates") and outcome. All analyses were stratified by study.

For each prognostic factor of interest, the cases with that variable and GOS recorded were selected, and any missing covariates were replaced by imputed values (McHugh et al., 2007b). Such imputation is recommended as being more efficient than dropping cases with incomplete data (Little, 1992; Harrell, 2001). In addition, the imputation of missing values for covariates means that, for a given prognostic factor of interest, all adjusted analyses are performed on the same cohort of patients.

Proportional odds models were fitted separately for each study, and the resulting (adjusted) common odds ratios were pooled over the studies using a random effects model (McHugh et al., 2007b). The odds ratios were calculated so that for the categorical variables a value greater than one indicates an increased risk of a poor outcome relative to the reference category. For the continuous prognostic factors with a linear relation to outcome, the odds ratios were scaled so that they correspond to changing from the 25th percentile of that prognostic factor to the 75th percentile. For continuous prognostic factors with a U-shaped relation to outcome, a categorical transformation was performed and odds ratios calculated relative to the central category. This allows a direct comparison of the prognostic value of prognostic factors, which are recorded in different units or on different scales. An odds ratio of greater than one for a continuous prognostic factor indicates that the risk of a poor outcome increases as the variable increases.

Following the univariate analysis, a nested set of adjusted analyses was run. Model A used a core set of conventional TBI prognostic factors: age, GCS motor score, and pupil response to light. Model B added in the Marshall CT classification (Marshall et al., 1991) to Model A. Model C was taken from Hukkelhoven et al. (2005) and added hypoxia, hypotension, and traumatic subarachnoid hemorrhage (tSAH) to Model B. Finally, Model D added two laboratory variables—glucose and hemoglobin—to Model C. When presenting the odds ratios, values that were statistically significantly different from one at the 1% level (i.e., $p < 0.01$) were flagged. The 1% significance level was used in place of the more conventional threshold of 5% to make an allowance for the many tests that were being performed. It also allows for the fact that, with such large sample sizes as are available for this analysis, an effect that is of little clinical relevance can be statistically significant.

The predictive power of an individual prognostic factor was further assessed by using Nagelkerke's R^2 (Nagelkerke, 1991). Nagelkerke's R^2 is used in logistic regression and is an analogue of the conventional R^2 statistic, which is used in ordinary least squares (OLS) re-

gression. In the context of OLS, R^2 is precisely the percentage of the variability in the response variable which is explained by the covariates. It is simple to calculate under the assumption of a normally distributed continuous outcome variable. In logistic regression the situation is more complicated, but Nagelkerke's R^2 can still be interpreted as an approximation to the percentage of the variability in the GOS which is explained by the different prognostic factors. The calculation of Nagelkerke's R^2 uses the difference in the log-likelihood of a model with and without the prognostic factor of interest.

Nagelkerke's R^2 was used to measure the predictive value of individual prognostic factors by comparing proportional odds models with the prognostic factor of interest and study in the model, to a model with only study included. Nagelkerke's R^2 was also used to measure the predictive value of a prognostic factor after having adjusted for the effects of other covariates. This was done by comparing proportional odds models with the prognostic factor of interest, the covariates, and study included to a model with only the covariates and study included. Hence, all reported R^2 values are essentially partial R^2 values, reflecting the "added predictive value" of the prognostic factor of interest. Nagelkerke's R^2 is particularly useful in the context of these analyses in that it gives a measure which can be compared directly from variable to variable, irrespective of the sample size. This is in contrast to the *p*-value, where for a given strength of association, the *p*-value will become more extreme as the sample size increases. Moreover, with such large sample sizes as are available for most of our analyses, a very modest association, which would be of no clinical relevance in terms of prognosis, could still be statistically significant at even the 1% level.

Both *p*-values and R^2 are affected by the distribution of categorical prognostic factors. If a prognostic factor has a very skewed distribution, the *p*-value will be higher and the R^2 lower, relative to a more balanced prognostic factor with the same common odds ratio.

RESULTS

Table 1 gives the (adjusted) common odds ratios from all of the models. Odds ratios which are significantly different from one at the 1% level (i.e., $p < 0.01$) are highlighted in bold. Figure 1 shows the Nagelkerke partial R^2 values for each prognostic factor under the five different analyses. The open bars on the left of each cluster give the partial R^2 values, which are the measures of the strength of the univariate association of each variable with GOS. These range from the order of 15% for pupils to zero for gender. The hatched bars give the partial R^2 values on adjustment for increasing numbers of covariates. As more covariates are added the partial R^2 values tend to fall. For example, the partial R^2 for pupils is 7% on adjusting for Model A (in effect adjusting for age and GCS motor score, since pupils is already included within Model˘A), falling to under 4% on adjusting for Model D.

Demographic Variables and Cause of Injury

As expected, age comes out as a powerful prognostic factor. It is the single most powerful predictor in each of the four models, having the largest partial R^2 values of all the covariates considered. Cause of injury has the next highest univariate R^2 value, but the partial R^2 values after adjustment are all negligible. Indeed, we found that adjustment for age alone effectively abolishes any independent predictive power of cause of injury (Butcher et al., 2007a). Race and educational level both have modest predictive value which persists after adjustment for each of the models. The direction of these associations (Table 1) is that black patients tend to have poor outcomes relative to other racial groups and those with high educational attainment tend to have better outcomes than those with lower educational attainment. There is no suggestion of any association between gender and GOS, with or without adjustment for other covariates.

Secondary Insults/Blood Pressure

Hypotension and hypoxia have powerful univariate associations with GOS and modest but relevant associations remain after adjustment for the full Model D. Hypothermia has a more modest association, and the effect falls to a negligible level on adjustment for Model D. Systolic blood pressure and to a lesser extent mean arterial blood pressure have clear univariate associations with GOS. A modest effect of systolic blood pressure remains after adjustment for Models A or B, but the effect is reduced to a negligible level on adjustment for Model C (which includes hypotension). Mean arterial blood pressure has little effect after adjustment.

Clinical Predictors

As expected, both the GCS motor score and pupil response are powerful independent predictors of outcome, with effects which persist strongly after adjustment for all other covariates. The GCS eye and verbal scores are powerful univariate predictors with modest but relevant independent effects after adjustment for all of the other covariates.

Computed Tomography Scan Characteristics

The two most powerful CT characteristics are the Marshall CT classification and evidence of traumatic sub-

Table 1. Pooled Common Odds Ratios Derived from Proportional Odds Models Adjusting for a Range of Covariates

Variable	*Number of studies*	*Sample size*	*Adjusted sample size*[a]	*Reference category*	*Category*	*Common odds ratio from proportional odds model*				
						Univariate	*Model A*	*Model B*	*Model C*	*Model D*
Gender	11	8685	8508	Male	Female	1.01	0.94	0.94	0.94	0.88
Race	6	5320	5316	Caucasian	Black	**1.30**	1.44	1.45	1.48	1.50
					Asian	1.09	1.22	1.19	1.14	1.13
					Other	1.08	1.11	1.09	1.07	1.07
Education	3	2201	2198	0–8 years	9–12 years	0.78	0.87	0.86	0.87	0.84
					Over 12 years	0.70	0.74	0.72	0.70	0.69
Cause of Injury	11	8673	8496	Fall	Road traffic accident	**0.66**	1.08	1.15	1.16	1.14
					Assault	**0.66**	1.03	1.08	1.17	1.24
					Work-related	0.88	1.21	1.25	1.27	1.26
					Sports/recreation	**0.45**	0.74	0.76	0.80	0.81
					Other	0.91	1.06	1.11	1.15	1.15
Hypoxia	8	5626	5452	No	Suspected/definite	**2.08**	**1.65**	**1.65**	—	—
Hypotension	9	6595	6420	No	Suspected/definite	**2.67**	**2.06**	**2.06**	—	—
Hypothermia	5	4195	4178	No	Suspected/definite	**2.21**	1.63	**1.62**	1.40	1.36
CT class	7	5209	5192	Diffuse	No visible pathology	**0.45**	**0.47**	—	—	—
					Swelling/shift	**2.62**	**2.23**	—	—	—
					Mass lesion	**2.18**	**1.48**	—	—	—
Cisterns	6	3861	3857	Present	Compressed/absent	**2.45**	**1.83**	**1.68**	**1.64**	**1.63**
Shift	8	4698	4694	No	1–5 mm	**1.36**	**1.31**	1.09	1.10	1.08
					>5 mm	**2.20**	1.38	1.14	1.18	1.21
tSAH	10	7407	7393	No	Yes	**2.64**	**2.01**	**1.90**	—	—
EDH	9	7575	7409	No	Yes	**0.64**	**0.63**	**0.50**	**0.53**	**0.51**
SDH	9	7584	7418	No	Yes	**2.14**	**1.33**	1.17	1.17	1.19
Contusion	8	6656	6639	No	Yes	**1.34**	**1.40**	**1.34**	1.26	1.25
GCS eye score	11	8686	8509	Pain/sound/ spontaneous	None	**2.76**	**1.54**	**1.57**	**1.53**	**1.55**
					Missing/untestable	**1.96**	1.20	1.27	1.23	1.18
GCS verbal score	11	8686	8509	Sounds-orientated	None	**2.62**	**1.51**	**1.53**	**1.50**	**1.51**
					Missing/untestable	**2.60**	**1.42**	**1.44**	**1.33**	**1.33**
GCS motor score	11	8686	8509	Localizes/ obeys	None	**5.30**	—	—	—	—
					Extension	**7.48**	—	—	—	—
					Abnormal flexion	**3.58**	—	—	—	—
					Normal flexion	**1.74**	—	—	—	—
					Missing/untestable	**2.20**	—	—	—	—

Table 1. Pooled Common Odds Ratios Derived from Proportional Odds Models Adjusting for a Range of Covariates (Cont'd)

Variable	*Number of studies*	*Sample size*	*Adjusted sample size*[a]	*Reference category*	*Category*	*Common odds ratio from proportional odds model*				
						Univariate	*Model A*	*Model B*	*Model C*	*Model D*
Pupil response	9	7282	7126	Both reacting	One reacting	**2.71**	—	—	—	—
					Neither reacting	**7.31**	—	—	—	—
Systolic BP	9	6801	6797	120–150 mm Hg	<120 mm Hg	**1.53**	**1.28**	**1.27**	1.18	1.09
					>150 mm Hg	**1.42**	**1.30**	1.28	**1.33**	**1.33**
Mean arterial BP	9	6647	6643	85–110 mm Hg	<85 mm Hg	**1.30**	1.14	1.14	1.06	1.00
					>110 mm Hg	**1.45**	1.27	1.26	1.29	1.30
Sodium	7	5270	5266	137–142 mmol/L	<137 mmol/L	**1.40**	1.14	1.09	1.07	1.03
					>142 mmol/L	1.14	1.11	1.10	1.05	1.12
Age	11	8509	8509			**2.14**	—	—	—	—
pH	5	3398	3394			**0.80**	**0.84**	**0.83**	0.89	0.93
Hemoglobin	6	3875	3871			**0.69**	**0.76**	**0.76**	**0.76**	—
Glucose	6	4834	4830			**1.68**	**1.45**	**1.42**	**1.35**	—
Platelets	4	1629	1629			**0.70**	**0.79**	**0.80**	**0.81**	**0.80**
Prothrombin time	3	840	840			1.41	**1.63**	**1.60**	**1.55**	**1.46**

[a]The adjusted analyses (Models A–D) are restricted to patients aged ≥14 years.

Figures in bold correspond to $p < 0.01$.

Model A: Adjusted for age, GCS motor score, and pupils. Model B: Model A plus CT class. Model C: Model B plus hypoxia, hypotension, and tSAH. Model D: Model C plus Hb and glucose

The odds ratios for age through prothombin time are scaled to reflect the effect of an increase from the lower quartile of each variable to the upper quartile

CT, computerized tomography; tSAH, traumatic subarachnoid hemorrhage; EDH, epidural hematoma; SDH, subdural hematoma; GCS, Glasgow Coma Scale; BP, blood pressure.

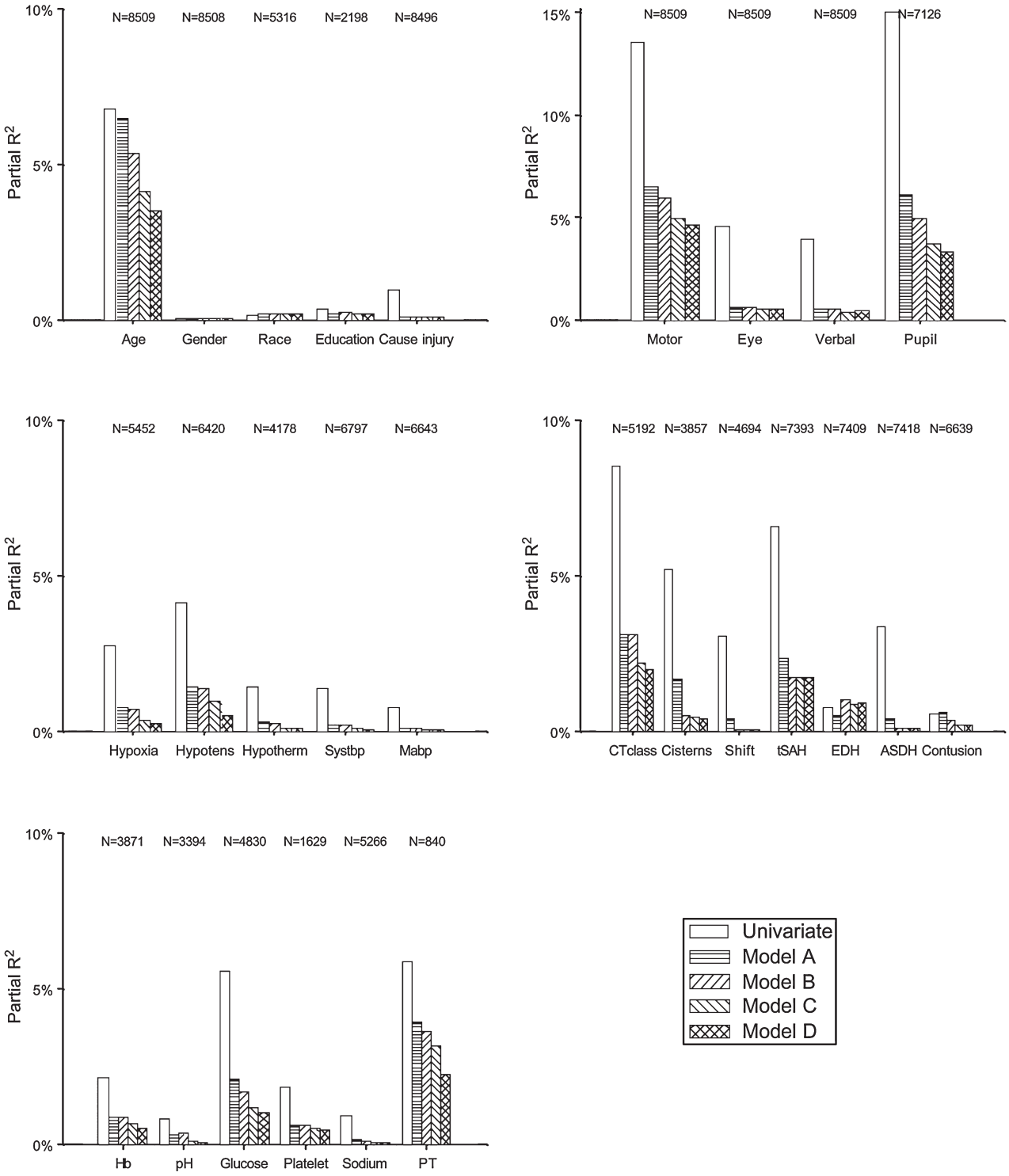

FIG. 1. Relative prognostic value of predictors expressed as Nagelkerke's partial R^2 values. The open bars give the partial R^2 values for univariate association of each variable with the Glasgow Outcome Scale (GOS); the hatched bars give the partial R^2 values on multivariable analysis adjusting for an increasing number of covariates.

arachnoid hemorrhage. Both have clear residual associations with GOS even after adjustment for all of the covariates in Model D. Presence of an epidural hematoma is the next most powerful independent predictor, and is associated with increased odds of a better outcome. Absent or compressed cisterns have a strong univariate association with GOS and a modest but relevant effect persists on adjusted analysis. Evidence of contusions has a modest association with outcome on univariate analysis, and this effect persists on multivariable adjustment. Both evidence of midline shift and presence of a subdural hematoma are strongly associated with adverse GOS on univariate analysis, but these effects are greatly attenuated on adjustment for the overall CT classification (i.e., going from Model A to Model B).

Laboratory Parameters

The results in Figure 1 show broadly that the findings reported in van Beek et al. (2007) persist after adjustment for all nine covariates in Model D. Prothrombin time has a striking effect comparable in terms of partial R^2 to pupil response or CT classification on adjusted analysis. Glucose is a strong independent predictor of outcome, as to a lesser extent are hemoglobin and platelets. The effects of sodium and pH are modest on univariate analysis and negligible on full adjustment (Model D).

DISCUSSION

There is a long history to the development of statistical models to predict outcome following head injury. This dates back essentially to the seminal papers by Teasdale and Jennett (1974), allowing quantification of impairment of consciousness, and Jennett and Bond (1975), standardizing the assessment of outcome following severe brain damage. Key papers on prediction include Jennett et al. (1976), Narayan et al. (1981), Titterington et al. (1981), Choi et al. (1991), Signorini et al. (1999), and Hukkelhoven et al. (2005). Many of the early papers on prediction pre-date the widespread availability of high-resolution CT scans, and others include data collected after admission. The IMPACT project focuses on the use of predictive models in the context of clinical trials, and so our analysis is restricted to data available at the time that a patient would be recruited into such a trial.

Our results confirm much of the received wisdom in the area of TBI prognosis: age is the single most powerful prognostic factor, followed by the GCS motor score, and pupil response to light. The Marshall CT classification, tSAH, and the secondary insults of hypotension and hypoxia all add further relevant independent predictive information. The GCS eye and verbal components then add yet further independent information, but each corresponds to a partial R^2 value of well below 1%. It is anticipated however that the added predictive value of the eye and verbal scores may well be greater in more moderately injured patients.

The most striking novel finding is the added value of several laboratory parameters over and above the conventional prognostic factors in TBI. Data on prothrombin time (PT) were only available in three of the 11 IMPACT studies, and the total sample size for the analysis of PT was only 840. Although modest in the context of IMPACT, this is still a large sample size in terms of the previously published literature on prognosis in TBI. Nevertheless, further research on the prognostic value of PT is required before one could recommend that PT be used in prognostic models of TBI. Given the routine availability these parameters, prognostic models in TBI should potentially include laboratory data, especially glucose, and possibly also hemoglobin and platelets.

It appears that the CT scan contains more useful prognostic information than is summarized in the Marshall CT classification and by recording the presence or absence of tSAH. Maas et al. (2005) have previously demonstrated that it may be preferable to combine individual CT characteristics into a CT prognosis model. The many interactions between CT characteristics however make this a complex issue, which requires more detailed further study.

Finally, we have identified modest but consistent independent effects of race and education. This possibly reflects aspects of the delivery of care or access to care, and merits further investigation.

The study has a number of limitations. First, the approach adopted for the regression modeling, even though it was based on the proportional odds model, was relatively unsophisticated. In particular, we assumed that all effects were additive, and did not include interaction terms in any of our models. We consider that this approach is appropriate for this paper which aims to give a broad overview of the IMPACT database, but we shall be reporting on more sophisticated approaches to the statistical analysis in future papers. Second, it may be argued that we included a large number of relatively old studies in our analysis, which may not necessarily reflect current practice in the management of TBI. We did not however identify any clear differences in the prognostic analysis between older and more recent datasets, but will address this further by the addition of more recent TBI trials and case series to the IMPACT database (Maas et al., 2007a). Third, we chose to restrict the adjusted analyses to adult patients (aged $\geq$ 14 years), as the low number of children in the database precluded confident regression modeling in children (Mushkudiani et al., 2007).

As a consequence the number of patients in the univariate analyses was in general slightly greater than for the adjusted analyses. This increased the precision of the estimation of the univariate odds ratios, at the cost of potentially introducing a very modest bias relative to the adjusted odds ratios. However, on comparison of the partial R^2 calculated for the age-selected cohort ($N = 8509$) versus the full unselected cohort ($N = 8686$), we only observed a marginal reduction of partial R^2 for the variable age, but no difference either in univariate or multivariate analyses for all other covariates.

In summary, we have quantified the prognostic strength of many conventional and novel prognostic factors in TBI. The most important prognostic factors identified include age, GCS motor score, pupil response, CT characteristics, hypotension, hypoxia, and glucose. The combination of the prognostic factors will provide a solid foundation for the estimation of the probabilities of each GOS category at 6 months for individual TBI patients. These estimated probabilities will underpin the core IMPACT activity of developing novel approaches to the design and analysis of clinical trials in TBI.

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