The overfitting could have been corrected by multiplying each regression coefficient in the model with a shrinkage factor. This factor can be estimated by a heuristic formula,[3] by cross validation, or by a bootstrap resampling procedure. This can be done with the Design library,[4] which was already used by the authors. The shrinkage factor is close to unity when there is no overfitting. When the selection of predictors is unstable or predictors have small effects, a lower shrinkage factor might be found— for example, 0.8.

We regret that the model is presented as giving "reasonable accurate predictions of long term survival", especially because the external validation showed a significant lack of calibration. Correction with a shrinkage factor would have resulted in a recalibration of the probability of survival in the nomogram presented in the paper (fig 3)[1] and in the formula used in a subsequent paper.[5]

We hope that modern modelling techniques will increasingly be applied in clinical prediction problems such as traumatic brain injury, such that prognostic models are developed that reliably support the physician in clinical decision making.

CHANTAL W P M HUKKELHOVEN
MARINUS J C EIJKEMANS
EWOUT W STEYERBERG
Centre for Clinical Decision Sciences, Department of Public Health, Erasmus University Rotterdam, The Netherlands

Correspondence to: Chantal W P M Hukkelhoven, Center for Clinical Decision Sciences, Ee2073, Department of Public Health, Erasmus University Rotterdam, The Netherlands
email hukkelhoven@ mgz.fgg.eur.nl

1 Signorini DF, Andrews FJD, Jones PA, *et al*. Predicting survival using simple clinical variables: a case study in traumatic brain injury. *J Neurol Neurosurg Psychiatry* 1999;**66**:20–5.
2 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**:361–87.
3 Van Houwelingen JC, le Cessie S. Predictive value of statistical models. *Stat Med* 1990;**8**: 1303–25.
4 Harrel FE Jr. Design: S-plus functions for biostatistical epidemiologic modelling, testing, estimation, validation, graphics, prediction, and typesetting by storing enhanced model design attributes in the fit. http://hesweb1.med.virginia.edu/biostat/s/.
5 Signorini DF, Andrews PJD, Jones PA, *et al*. Adding insult to injury: the prognostic value of early secondary insults for survival after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 1999;**66**:26–31.

Signorini et al reply:

Hukkelhoven *et al* give a thorough and constructive criticism of the statistical procedures used to construct the model presented in the paper. Their main points of concern regard the effective number of degrees of freedom (df), possible corrections to the apparent overfitting, and the usefulness of the model for individual predictions in specific patients.

It is true that the 6 df present in the final model do not reflect the total uncertainty present in the model, and that some preprocessing of individual predictors was performed to derive appropriate functional forms. The rule of thumb regarding the number of predictor variables which can be assessed in a multivariate model is a guideline, and it should always be remembered that the reason behind it is to prevent false positive findings and hence spurious associations between predictors and outcomes. It is directly analogous to the 5% significance level for hypothesis testing, and we worry that in its increasing prevalence in the literature it is becoming similarly dogmatic. We do not think that we have indulged in any data-dredging to construct these models, and are confident that the false association rate is small. To fully incorporate the overall uncertainty into the final model would perhaps involve methods discussed by Draper,[1] with a corresponding increase in the complexity of the modelling process.

The use of shrinkage estimators to prevent overfitting is of course a valuable tool, yet as Hukkelhoven *et al* point out, there are several options for their calculation and little guidance as to which should be used in a particular circumstance. They are available within the design library used to build our model, but the model building process as described in the original paper is achievable using any standard statistical software package. The purpose of the paper was to demonstrate what we think of as a sensible approach, and to go beyond what is possible in standard software would be to dilute that message.

Finally, the model perhaps should not be described as providing "accurate" predictions of long term survival, as the out of sample calibration was not good. From a discrimination point of view, however, the out of sample performance was adequate, and this serves to illustrate that the uses to which a model will be put should play a part in the model building process. Whether calibration (individual predictions) or discrimination (case mix adjustment) is more important can result in different models from the same training set.

One of the most important points of the paper was to stress that there is a lot more to proper statistical model building than clicking the correct menu option in a statistical package. We would hope that this correspondence has emphasised the need for a certain level of statistical knowledge and experience in the analysis of any research data. We agree wholeheartedly with the views expressed in the correspondents' final paragraph.

D F SIGNORINI
P J D ANDREWS
P A JONES
J M WARDLAW
University Department of Clinical Neurosciences, Bramwell-Dott Building, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

1 Draper D. Assessment and propagation of model uncertainty. *Journal of the Royal Statistical Society, Series B* 1995;**57**:45–97.

Distinctions between critical illness polyneuropathy and axonal Guillain-Barré syndrome

In this letter we comment on the publication of Yuki and Hirata who postulate a possible relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome.[1] The authors mentioned a nosological relation, which at that time still had to be demonstrated by the presence of antiganglioside antibodies in the serum of patients with critical illness polyneuropathy. Critical illness polyneuropathy is a neuromuscular disorder that has been recognised in critically ill patients.[2] The clinical picture consists of difficulty in weaning from the artificial respirator, tetraparesis, and muscle wasting of the limbs. The tendon reflexes are mostly decreased or absent. The neurophysiological examination shows an axonal polyneuropathy and sometimes myopathic altered motor unit potentials. The morphological features in the nerve point to a primarily distal axonal degeneration of motor and sensory fibres. Muscle biopsy shows scattered atrophic fibres in acute denervation and grouped atrophy in chronic denervation. Also, necrotic muscle fibres can be found suggesting the contribution of a myopathy or a primary myopathy.[3] On clinical and electrodiagnostic grounds neuromuscular complications in the critically ill patients may be due to a polyneuropathy or myopathy. Because it is not always possible to differentiate between an axonal motor neuropathy and myopathy, we prefer to use the descriptive term critical illness polyneuropathy and myopathy (CIPNM).

To test the hypothesis of Yuki and Hirata we studied the serum of eight patients obtained during the acute phase of CIPNM and from two controls, which were patients that were also on the artificial respirator and critically ill. In all 10 patients sepsis or systemic inflammatory response syndrome occurred. The serum samples were tested for IgG and IgM reactivity against gangliosides GM1 and GD1a. In none of these samples could any reactivity be detected. Therefore, it is unlikely that in these Dutch patients with CIPNM, axonal damage is mediated through anti-GM1 or anti-GD1a antibodies as was suggested by the authors.

To distinguish CIPNM from the acute motor axonal variant of Guillain-Barré syndrome the following characteristics may be useful:

- Guillain-Barré syndrome is the primary neurological reason of admission on the intensive care unit; CIPNM on the other hand develops during a patient's stay on the intensive care unit for another reason
- Infectious symptoms such as fever and diarrhoea have usually subsided before the clinical features of Guillain-Barré syndrome appear
- The characteristic alterations in the CSF of patients with Guillain-Barré syndrome, with a raised protein and normal to slightly increased cell count
- The possibility of detecting IgG antibodies against GM1, GM1b, GD1a, and Ga1Nac-GD1a as immunological markers in the serum of patients with axonal Guillain-Barré syndrome.

Electrodiagnostic changes in Guillain-Barré syndrome occur in both sensory and motor nerves in about 80% of the patients in the western world. In CIPNM there is a predominantly motor dysfunction in both the clinical and electrodiagnostic evaluations.

During the progression of Guillain-Barré syndrome the demyelinating features of the nerve conduction study may change into a secondary axonal pattern. In axonal Guillain-Barré syndrome slow nerve conduction velocity remains in some patients and the initial needle EMG study lacks spontaneous activity.[4] In CIPNM phrenic nerve conduction studies usually show no significantly prolonged latencies.[5]

Severe autonomic disturbances are more common in patients with Guillain-Barré syndrome after the polyneuropathy has developed than in patients with CIPNM.[5]

M A C J DE LETTER
LH VISSER
Department of Neurology, St Elisabeth Hospital Tilburg, The Netherlands.

M A C J DE LETTER
W ANG
F G A VAN DER MECHÉ
Department of Neurology, University Hospital Rotterdam and Erasmus University Rotterdam, the Netherlands

W ANG
H F J SAVELKOUL
Department of Immunology

Correspondence to: M A C J de Letter, Department of Neurology, St Elisabeth Hospital Tilburg, PO box 90151, 5000 LC Tilburg, The Netherlands email megens-deletter@wxs.nl

1 Yuki N and Hirata K. Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 1999;**67**:128–9.
2 Bolton CF. Neuromuscular abnormalities in critically ill patients. *Intensive Care Med* 1993; **19**:309–10.
3 Latronico N, Fenzi F, Recupero D, *et al*. Critical illness myopathy and neuropathy. *Lancet* 1996; **347**:1579–82.
4 Chen R. Electrophysiological studies in the critical care unit: Investigating polyneuropathies. *Can J Neurol Sci* 1998;**25**:32–35.
5 Bolton CF, Laverty DA, Brown JD, *et al*. Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 1986;**49**:563–73.

Yuki replies:

Critical illness polyneuropathy, a complication of sepsis and multiple organ failure, may be a common cause of the difficulty of weaning patients in critical care units from the ventilator.[1] Its aetiology has yet to be determined and needs to be clarified to treat such patients more effectively. Critical illness polyneuropathy and Guillain-Barré syndrome are both monophasic illnesses of acute onset, characterised by limb weakness and areflexia. Whereas classic pathological studies of Guillain-Barré syndrome show demyelination and inflammatory infiltrates in peripheral nerves, electrophysiological and pathological studies of critical illness polyneuropathy show the presence of primary axonal degeneration of the peripheral nerves but no evidence of inflammation. The two types of polyneuropathies, therefore, have been considered separate entities, but recent pathological studies have established that there is a primary axonal form of Guillain-Barré syndrome. We mentioned that axonal Guillain-Barré syndrome should be the diagnosis for some patients with critical illness polyneuropathy, and that investigation of the presence of serum IgG antibodies against GM1, GM1b, GD1a, or GalNAc-GD1a (possible immunological markers for axonal Guillain-Barré syndrome) in patients with critical illness polyneuropathy should help test this hypothesis.[2]

I deeply appreciate de Letter *et al* for testing our hypothesis. Some patients with Guillain-Barré syndrome who do carry either anti-GM1 or anti-GD1a IgG antibodies, however, have anti-GM1b, anti-GalNAc-GD1a antibodies, or both.[3 4] I am willing to investigate anti-GM1b and anti-GalNAc-GD1a IgG antibodies in their patients with critical illness polyneuropathy. Further examinations using many more serum samples as well as the additional markers are necessary to reject our hypothesis. If some patients with critical illness polyneuropathy do have those autoantibodies, they would benefit from intravenous immunoglobulin therapy,[5] which is also useful for treating the sepsis associated with critical illness polyneuropathy.

NOBUHIRO YUKI
Department of Neurology, Dokkyo University School of Medicine, Japan

Correspondence to: Dr. Nobuhiro Yuki, Department of Neurology, Dokkyo University School of Medicine, Kitakobayashi 880, Mibu, Shimotsuga, Tochigi 321–0293, Japan.

1 Zochodne DW, Bolton CF, Wells GA, *et al*. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain* 1987;**110**:819–42.
2 Yuki N, Hirata K. Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 1999;**67**:128–9.
3 Kusunoki S, Iwamori M, Chiba A, Hitoshi S, Arita M, Kanazawa I. GM1b is a new member of antigen for serum antibody in Guillain-Barré syndrome. *Neurology* 1996;**47**:237–42.
4 Kusunoki S, Chiba A, Kon K, *et al*. *N*-acetylgalactosaminyl GD1a is a target molecule for serum antibody in Guillain-Barré syndrome. *Ann Neurol* 1994;**35**:570–6.
5 van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med* 1992;**326**:1123–9.

New hope for patients with pure lower motor neuron syndromes

Readers of the editorial by Wokke and van den Berg[1] may be left with the impression that the immunoglobulins could provide hope for the future for patients with pure lower motor neuron syndromes but no conduction block. Their evaluation of the results obtained by Ellis *et al*[2] in four of the total series of 10 patients may tend towards overoptimism, however.

We agree with their second conclusion regarding the criteria for referring this subgroup of patients with lower motor neuron disease to a highly specialised centre for further analysis. However, we would recommend referral for all patients with motor neuron disease, especially in cases in the initial stages or in atypical forms, in which the diagnosis may be difficult if strict criteria are applied, given the complexity and multidisciplinary management of this condition and the difficulty of the decision regarding when and to whom pharmacological and life sustaining therapy should be applied.

Great care must be taken to avoid misdiagnosis in the selection of candidates for therapy, as the high cost of long term treatment does not justify indiscriminate immunoglobulin use. A critical reading of work of Ellis *et al* shows that only three responding patients of the 10 treated presented an objective improvement in the pinch and grip myometries and no statistically significant modification in the MRC scale or significant objective improvement in the paired *t* test was found.

Finally, of the 10 patients with lower motor neuron syndrome included in the assay, there were four cases of amyotrophic lateral sclerosis (ALS), one of spinal muscular atrophy (SMA), one doubtful case of multifocal motor neuropathy (MMN), and four probable cases of MMN at follow up. These last five presented no conduction blocks and only one had anti-GM1 antiganglioside antibodies.

If we accept and if we can demonstrate the usefulness of immunoglobulins in lower motor neuron forms, two questions arise. Firstly, can we accept the existence of MNN without conduction block? Katz *et al* tried to answer this question by proposing that conduction block was only one of many electrodiagnostic features in a segmental demyelination. They advocated the inclusion of other features, such as conduction velocity, temporal dispersion, delayed F wave responses, and prolonged distal latencies

Ellis *et al* admit that their study was not designed as an electrophysiological study, and that the exhaustive nerve conduction studies described by Lang *et al* and Katz *et al* were not performed.[3 4] Secondly, if we accept that we are dealing with patients lower motor neuron disease, we would have to re-examine the hypothesis that has been considered to be flawed regarding the role played by immune mechanisms in motor neuron diseases.[5]

Another point about which we have our reservations is that it cannot be affirmed that the non-introduction of this treatment leaves the patients at the mercy of the disease's natural course. The problem lies in the difficulty in diagnosing these patients, especially those who present neither conduction blocks nor anti-GM1 antiganglioside antibodies. As we have previously stated, the final diagnosis in 50% was ALS or SMA. Given these results, it seems more reasonable to persist with differential diagnosis by magnetic resonance neurography and repetition of neurophysiological examinations, including magnetic transcortical stimulation.

Patients with motor neuron disease and their relatives, who have been anxiously waiting for a breakthrough in treatment, have been disappointed time and again in recent years by promises regarding therapies that have been both expensive and of little use. It can only be hoped that the immunoglobulins will improve this situation, and that our scepticism is mistaken.

JOSEP GAMEZ
CARLOS CERVERA
AGUSTIN CODINA
Servicio de Neurologia, Hospital Gral, Universitari Vall d'Hebron, Passeig Vall d'Hebron 119–135, 08035 Barcelona, Spain

Correspondence to: Dr Josep Gamez email 12784jgc@ comb.es

1 Wokke JHJ, van den Berg LH. New hope for patients with pure lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 1999;**67**:6.
2 Ellis CM, Leary S, Payan J, *et al*. Use of human intravenous immunoglobulin in lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 1999;**67**:15–19.
3 Lange DL, Trojaborg W, McDonald TD, *et al*. Persistent and transient "conduction block" in motor neuron disease. *Muscle Nerve* 1993;**16**: 896–903.
4 Katz JS, Wolfe GI, Bryan WW, *et al*. Electrophysiologic findings in multifocal motor neuropathy. *Neurology* 1997;**48**:700–7.
5 Rowland LP. Amyotrophic lateral sclerosis: theories and therapies. *Ann Neurol* 1994;**35**: 129–30

BOOK REVIEWS

Intra-Operative Diagnosis of CNS Tumours. Edited by TIM H MOSS, JAMES A R NICOLL, JAMES W IRONSIDE. (Pp193 £99.00). London: Arnold, 1997. ISBN 0-340-67737-6.

This is a handsome and liberally illustrated guide to smear and frozen section diagnosis in neuropathology. This aspect of practice remains a central part of a clinical neuropathologist's role and this book can be recommended to trainees and practitioners for its wealth of illustration and practically oriented text. It is particularly useful to see a wide range of appearances for each tumour illustrated—for example, 20 figures illustrating metastatic tumours, 13 illustrating pituitary adenomas, and 38 illustrating various grades of astrocytic tumours. This enables the less readily diagnosed examples to be considered as well as more typical varieties. Typical varieties tend to be the only ones illustrated in a less specialised text. There are