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Reply to the Letter from Dale Ding, MD

Caroline MacCallum^a, Leonid Churilov^c, Peter Mitchell^b,
Richard Dowling^b, Bernard Yan^a

^aMelbourne Brain Centre at Royal Melbourne Hospital,

^bDepartment of Radiology at Royal Melbourne Hospital, The University of Melbourne, Melbourne, and ^cThe Florey Institute of Neuroscience and Mental Health, Melbourne, Vic., Australia

We are grateful to Dr. Dale Ding for his comments relating to our paper entitled ‘Low Alberta Stroke Program Early CT Score (ASPECTS) associated with malignant middle cerebral artery infarction’ [1]. As acknowledged by the author in his letter, our article concludes that ASPECTS ≤ 7 on initial brain CT in a patient with middle cerebral (MCA) infarction is associated with the development of malignant MCA infarction (MMI). Therefore, we recommend close monitoring of, and early consideration of decompressive hemicraniectomy for, acute stroke patients with ASPECTS ≤ 7 .

In the context of our paper, Dr. Ding referred to two recently published studies on MMI, and discussed the potential practical applications of those studies and our study in a clinical setting. Our response comprises a brief summary of the models contained in the two studies, followed by two areas of consideration. The first area of consideration is the generalisability of MRI in Kruetzelmann’s predictive model for the development of MMI, and the second area of consideration is whether these studies are predictive or associative.

The first article discussed is an original paper from 2014 by Shimoyama et al. [2]. The authors proposed a score (the DASH score) to assess the risk for development of MMI in large MCA infarctions. The paper refers to four variables that are independently associated with the development of MMI, according to their retrospective study. The variables are diffusion-weighted imaging (DWI) ASPECTS ≤ 3 ($p = 0.012$), anterior cerebral artery territory involvement ($p = 0.002$), MCA M1 segment susceptibility vessel sign ($p = 0.013$), and hyperglycaemia ($p = 0.002$). These variables were combined to develop the DASH score to assess risk for development of MMI, using multivariate logistic regression analysis. This is a useful study, which shows an association of the four factors with the development of MMI. However, as discussed further below, we would like to note that the paper shows an association model, rather than a predictive model, for the development of MMI.

Kruetzelmann et al. [3] has examined a predictive model for the development of MMI. The model incorporates two variables, which when combined, provides a sensitivity of 79% for predicting the

development of MMI. The first variable is an acute lesion volume of ≥ 78 ml on diffusion-weighted imaging lesion, which the same study group had already identified as a predictor of the development of MMI with a sensitivity of 59% [4]. The second variable uses the National Institutes of Health Stroke Scale (NIHSS), where a score of ≥ 22 after 24 h is associated with the development of MMI. As noted by Dr. Ding, this predictive model is different from our associative model because it utilises the use of clinical assessment in addition to radiographic findings. The other major difference is that the Kruetzelmann model uses DWI, whereas our model uses CT.

We agree that the use of DWI in the Kruetzelmann model has reasonable power, with good specificity, good positive predictive value, good negative predictive value, and good sensitivity (when combined with the clinical assessment at 24 h). However, we are concerned about the generalizability of MRI in the assessment of acute stroke patients. The implication is that the Kruetzelmann model may not be as easily applicable as an associative model based on the use of CT in the assessment of acute stroke patients. Two previous studies have shown that MRI is not feasible for 15 to 20% of acute stroke patients [5, 6]. Patient-specific issues include unstable medical conditions (such as confusion, low Glasgow coma scale, acute pulmonary oedema with hypoxia, vomiting), agitation, contraindications to MRI (examples include MRI-incompatible pacemaker and ferromagnetic material), and claustrophobia. Furthermore, MRI requirements to remain supine for up to 25 min are not practical or safe for medically unstable or agitated patients.

In addition, intravenous gadolinium is often used as a contrast medium for stroke protocol MRI. The use of gadolinium in patients with renal insufficiency may lead to the development of nephrogenic systemic fibrosis [7, 8]. This risk further reduces the number of acute stroke patients who are appropriate for MRI scanning. Overall, while we acknowledge the predictive power of DWI in determining which patients will develop MMI (particularly when used in combination with clinical assessment at 24 h), it is our view that in clinical practice, CT will remain practical for acute stroke patients.

The second area of consideration is looking at whether these studies are predictive or associative models for the development of MMI. As explained in the series of articles by Moons et al. relating to prognosis, in order to show that a model is predictive, it is necessary to test the model’s performance on a new series of patients [9–12]. The new patients are preferably external patients from another centre, but may be from the same centre and from another period of time. If this testing has not occurred, the model is associative rather than predictive, as is the case with our ASPECTS ≤ 7 model. The DASH score proposed by Shimoyama et al. assesses the risk for development of MMI in large MCA infarctions. This is an associative model, rather than a predictive model, as it has not been validated on a new set of individuals.

Kruetzelmann et al. claim that their two variable models, using acute MRI and clinical follow-up at 24 h, are predictive. However, the prediction performance of the model was not validated on an

independent data set, as is required to develop a predictive tool. Rather, the model's predictive ability was tested on the group of patients from which the model was developed. It is stated that Classification and Regression Trees (CART) analysis was used. It is possible that the CART model provided internal cross-validation,

but given that this was not stated in the paper, it is safer to assume that the authors did not use CART for cross-validation. Accordingly, the Krutzeltmann model is better described as associative rather than predictive. Overall, all three papers use associative models rather than predictive models.

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