BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

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COMMENTS TO AUTHORS

This article investigated the role of permeability score (PS) on CTP to predict HT in AIS patients. They concluded that pretreatment PS can predict the occurrence of HT on follow-up CT with reasonable accuracy. Overall it is a nicely written study, I recommend publication with minor revision:

1. Can the author provide some details on how PS is calculated with a reference? Is PS permeability surface area product?

Response- Thanks for your comments. Yes, the PS is Permeability surface area product. The PS was calculated using the vendor provided Neuro-VPCT software (Siemens Healthcare) based on the semiautomatic deconvolution algorithm "Auto Stroke".

The references are the following-

Hom J, Dankbaar JW, Soares BP, et al. Blood-brain barrier permeability assessed by perfusion CT predicts symptomatic hemorrhagic transformation and malignant edema in acute ischemic stroke. *Am J Neuroradiol* 2011; **32**: 41-48. [PMID: 20947643 DOI: 10.3174/ajnr.A2244]

Aviv RI, d'Esterre CD, Murphy BD, et al. Hemorrhagic transformation of ischemic stroke: Prediction with CT perfusion. *Radiology* 2009; **250**: 867-77. [PMID: 19244051 DOI: 10.1148/radiol.2503080257]

2. Of 84 total patients, 42 patients were followed by CT and 32 by MRI, why not include the 32 patients with follow up MRI which can detect HT? This can increase sample size and reduce selection bias.

Response- We agree with the reviewer's comments. However, the sensitivity of MRI to detect microscopic hemorrhagic transformation is significantly higher than that of plain-head CT. All the studies published on the implication of hemorrhagic transformation were based on plain-head CT. So, implication of diagnosis of microscopic hemorrhagic transformation detected on only MRI is uncertain at the present time. Considering this uncertainty around this issue, we decided to exclude patients who had only MRI (and no plain-head CT) on follow up.

3. The rationale for including 6 TIA patients is not clear, and one with cerebellar symptoms. The pathophysiology of TIA is variable and different from AIS. The authors used basal ganglia as ROI for TIA, this needs justification.

Response- We selected consecutive patients who came as stroke protocol and were imaged with the

institutional stroke protocol. These patients improved clinically only after imaging and hence diagnosed as TIA. Our inclusion criterion was patients with suspected stroke with CT perfusion done at the time of presentation. This was the reason these patients were included.

4. Can the authors provide some details on how to determine the location and size of ROIs. On Fig. 1, the lesion ROI and contralateral ROI are not symmetric relative to the midline.
Response- The PS was calculated for the side of the ischemia and/or infarction and for the contralateral unaffected side at the same level (Figure 1). The cerebral blood flow map was used to delineate the ischemic territory. Next, a region of interest (ROI) was drawn at the centre of this territory on the PS parametric map. Finally, a mirror ROI was created on the contralateral side at the same level. The region of interest (ROI) was placed manually by a single operator on both sides to include the area of ischemia and to avoid including any major blood vessel (artery or vein) or large CSF space. The mirror image was not used to enable the above mentioned features. We hope this answers the reviewer's question.

5. For comparison of ratio (rPS), t-test is not appropriate, either need (log) convert the ratio to normal distribution or use non-parametric statistics

Response- Thanks a lot for your suggestions. We agree with the reviewer and this was an oversight. We have log converted the ratio and used the t-test after that. This still shows the similar results. The results are edited accordingly.

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COMMENTS TO AUTHORS

In this study, the authors sought to use perfusion–derived permeability–surface area product maps to predict hemorrhagic transformation following thrombolytic treatment for acute ischemic stroke. The authors retrospectively analyzed their prospective database for patients with acute ischemic stroke (AIS) who had CT perfusion (CTP) done at arrival and follow-up CT. The permeability score (PS) was calculated for the side of the ischemia and/or infarction and for the contralateral unaffected side at the same level. The relative permeability score (rPS) was calculated as the ratio of the PS on the side of the AIS to the PS on the contralateral side. A paired t-test was performed on the rPS between patients with and without hemorrhagic transformation. For the group of patients who experienced intracranial bleed, a paired t-test was performed between those with only petechial hemorrhage and those with more severe parenchymal hematoma with subarachnoid hemorrhage. Of 84 patients with AIS and CTP at admission, only 42 patients had a follow-up CT. The rPS derived using the normal side as the internal control was significantly higher ($p = 0.002$) for the 15 cases of hemorrhagic transformation (1.71+ 1.64) compared to 27 cases that did not have any (1.07 + 1.30). Of the 15 cases of hemorrhagic transformation, there was no difference ($p = 0.35$) in the rPS between the eight cases of petechial and the seven cases of more severe hemorrhagic events. This is a reasonable study that is somewhat confirmatory. Prior studies have demonstrated that the extracted permeability surface area product (PS) shown to be an independent predictor of future hemorrhagic transformation (1,2). There are a few flaws/limitations to the present study.

The authors note that (CTP) is increasingly used in cases of suspected AIS to evaluate the tissue at risk. Since recent randomized clinical trials have not shown an independent predictive value for CTP in multivariate analysis in AIS patients, this modality is not used to as great a degree. At the authors' institution, are they still obtaining CTP on all AIS patients? It would appear not, as only half of the patients during this time period had CTP. What were the differences between patients that did and did not receive CTP?

Response- We agree that there is no evidence in the randomized control trials regarding use of CTP. However, we have found CTP to be very useful in the setting of acute stroke. So, it is being used routinely in our center for patients with symptoms of acute stroke. We recently published our experience on this:

Shankar JJS, Langlands G, Doucette S, Phillips SJ. Does CT Perfusion Imaging in Acute Ischemic Stroke Predict Final Infarct Volume— Inter-observer Study. Can J Neurol Sci. 2016 Jan;43(1):93-7.

One of the largest drawbacks is the small number of patients and the omission of a multivariate model. There are many factors that predict petechial and parenchymal hematoma following treatment of AIS. Large studies have been conducted to determine factors predictive of post-treatment hemorrhage that allow for multivariate analysis to determine predictive patient,

disease, and treatment characteristics. The present study does not include a multivariate analysis to demonstrate that the rPS is an independent predictor of hemorrhage. Due to the small number of patients this might not be robust.

Response- We agree with the reviewer with the small sample size and we have accepted this as an important limitation of the study. We also agree that due to the small number, multivariate analysis is not an appropriate approach.

It would be nice to have clinical follow up on patients. Is the rPS predictive of functional outcome (modified Rankin scale etc)? References 1. Hom J, Dankbaar JW, Soares BP, et al. Blood-brain barrier permeability assessed by perfusion CT predicts symptomatic hemorrhagic transformation and malignant edema in acute ischemic stroke. Am J Neuroradiol 2011; 32: 41-48. [PMID: 20947643 DOI: 10.3174/ajnr.A2244] 2. Aviv RI, d'Esterre CD, Murphy BD, et al. Hemorrhagic transformation of ischemic stroke: Prediction with CT perfusion. Radiology 2009; 250: 867-77. [PMID: 19244051 DOI: 10.1148/radiol.2503080257]

Response- We agree with the reviewer's comments. The present study is the first phase of the study to assess if permeability can predict hemorrhagic transformation on imaging. We are currently planning to do the second phase of the study where we will have to see if hemorrhagic transformation predicted by permeability imaging is associated with functional outcome. Thanks for the suggestion.