Am J Transl Res 2021;13(10):11513-11521
www.ajtr.org /ISSN:1943-8141/AJTR0133513

Original Article

Automated detection of 3D midline shift in spontaneous supratentorial intracerebral haemorrhage with non-contrast computed tomography using deep convolutional neural networks

Xiaona Xia[1], Xiaoqian Zhang[2], Zhaodi Huang[1], Qingguo Ren[1], Hui Li[1], Ye Li[1], Kongming Liang[3], Hao Wang[3], Kai Han[3], Xiangshui Meng[1]

[1]Shandong University, Cheeloo College of Medicine, Qilu Hospital (Qingdao), Department of Radiology, Qingdao, China; [2]Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; [3]Deepwise AI Lab, Beijing, China

Received March 25, 2021; Accepted June 28, 2021; Epub October 15, 2021; Published October 30, 2021

Abstract: Deep learning (DL)-based convolutional neural networks facilitate more accurate detection and rapid analysis of MLS. Our objective was to assess the feasibility of applying a DL-based convolutional neural network to non-contrast computed tomography (CT) for automated 2D/3D brain midline shift measurement and outcome prediction after spontaneous intracerebral haemorrhage. In this retrospective study, 140 consecutive patients were referred for CT assessment of sICH from January 2014 to April 2019. The level of consciousness of patients was evaluated using the Glasgow Coma Scale (GCS) score, and the Glasgow Outcome Scale (GOS) score was calculated to classify the outcome. The distance of midline shift (MLS-D) and volume of midline shift (MLS-V) were automatically measured via DL methods. Patients were divided into three groups based on GCS scores: mild degree (GCS score: 13-15), moderate degree (GCS score: 9-12), and severe degree (GCS score: 3-8). Spearman's correlation analysis revealed statistically significant ($P<0.01$) positive correlation between GCS and MLS-D ($r=0.709$) and MLS-V ($r=0.754$). The AUC of MLS-V was slightly larger than that of MLS-D (0.831 vs 0.799, $P=0.318$) in the midline shifting group. The AUC of MLS-V was significantly larger than that of MLS-D (0.854 vs 0.736, $P=0.03$) in patients with severe degree GCS scores. The DL-based measurements of both MLS-D and MLS-V enable the assessment of consciousness and the prediction of the outcome of sICH. Compared to MLS-D, MLS-V measurement can better indicate mass effect and predict outcomes, particularly in severe cases.

Keywords: Spontaneous intracranial haemorrhage, midline shift, Glasgow coma scores, Glasgow outcome scores, computed tomography

Introduction

Spontaneous intracranial haemorrhage (sICH) is a severe type of stroke that causes high morbidity and mortality with high treatment cost [1-3]. Patients with sICH often have greater neurological instability than patients with ischaemic stroke, as early deterioration is common in the first few hours after sICH ictus [4]. The midline shift is regarded as the marker of mass effect caused by unilateral, space-occupying lesions, and it is associated with increased intracranial pressure and elevated morbidity and mortality [5-9]. Earlier works reported the relation between the degree of midline shift in the brain and the diminution of consciousness and poor clinical outcomes [6, 10-14]. Therefore, accurate evaluation of MLS is very important in the assessment of consciousness, treatment, and prognosis of sICH.

The conventional measure of MLS-D is the length between the distal deformed midline of the brain and the ideal midline (connecting the most anterior and posterior visible points on the falx). However, MLS-D measurement lacks standardisation and shows considerable variation in early works. It is possible to measure MLS-D using the septum pellucidum (SP), pineal gland, or third ventricle as an anatomical landmark. Pullicino and his team [15] found crude risk factors for 14-day mortality correlated with an SP MLS of 9 mm or larger, or a pineal MLS of 4 mm or larger. Ross et al. [13] have reported that patients with septal shifts over 15 mm had a poor outcome at 3 months of injury. Zazulia and his team [16] indicated that SP shift was a more sensitive marker of mass effect after ICH than pineal shift, while Ropper [12] found that pineal gland shift was better correlated with the level of consciousness than SP shift. Yang et al. [17] investigated the different MLS locations (in the pineal gland, SP, and cerebral falx) for prediction and identified that maximal MLS tended to be the best neuroimaging predictor for unfavourable outcomes in patients with ICH.

Deep learning (DL) has been used to help doctors in clinical work, and many computer programs have been developed for automatic MLS measurements [18, 19]. In the present study, the largest deviation of the given midline structure from the ideal midline on the maximum offset slice was automatically measured as MLS-D. The DL-based automated estimation used in this study presented satisfactory accuracy. Compared to the gold standard, the shift distance and area errors were 1.14±0.91 mm and 0.88±0.79 cm^2, respectively, and the Pearson coefficients between the radiologist and the proposed method for total data were 0.943 and 0.911, respectively [20]. Moreover, the volume measurement of MLS was difficult to perform manually in the past, but it can be done quickly and accurately with the help of DL. The MLS-V measurement collects the entirety of middle shift voxel data, which reflects mass effect accurately. Additionally, it can avoid measurement bias caused by varying location in repeat tests, which may mislead neurosurgeons. We speculated that MLS-V might be a better predictive indicator for sICH.

The aim of this study is to assess the feasibility of DL-based automated 2D/3D brain midline shift measurement and outcome prediction after spontaneous intracerebral haemorrhage. The relationships between (1) MLS-D/MLS-V and alteration of the level of consciousness, and (2) MLS-D/MLS-V and clinical outcome of haemorrhage at 12 months follow-up, were analysed using DL-based methods.

Materials and methods

Data from our electronic database from patients with a primary diagnosis of supratentorial ICH, admitted to the acute-care stroke unit of Qilu Hospital of Shandong University (Qingdao) from January 2014 to April 2019, were retrospectively reviewed. This retrospective study was approved by the ethics committee (2013-24-224) and informed consent was not required. All CT scans were performed using Siemens (SOMATOM Definition FLASH, Siemens Healthcare) and Philips (Brilliance 64, Philips Medical Systems) scanners and post-processed by DL methods. Patients were eligible for our study if their non-enhanced CT scans were conducted within 24 hours after stroke ictus. Patients older than 18 years old without severe pre-existing co-morbidity (e.g., malignant disease, severe heart, lung, or endocrine disease) and without physical or mental disability were selected. Patients were excluded if the haemorrhage was due to an external cause such as trauma, anticoagulant therapy, tumour, aneurysm, or arteriovenous malformation and haemorrhagic transformation after acute ischaemic stroke. Moreover, patients with multiple or recurrent ICH were also excluded. CT findings of MLS-D and MLS-V were automatically detected by software named "*Dr. Wise Hemorrhagic Stroke Analyzer*".

Patients were grouped by the degree of midline shifting into no-shifting and midline-shifting groups. The baseline demographic and medical characteristics of patients are shown in **Table 1**. According to GCS scores, the severity of sICH was divided into mild degree (GCS: 13-15), moderate degree (GCS: 9-12), and severe degree (GCS: 3-8). The clinical outcome at 12 months follow-up was divided into good outcome, with a GOS score of 4-5, and poor outcome, with a GOS score of 1-3. Demographic characteristics, medical history, radiological data, and GCS/GOS scores were recorded in a standardised data collection form. The flowchart of the study process is shown in **Figure 1**. The automated midline delineation algorithm aligned an input brain CT image into the pre-established standard space, and the aligned image was processed by a segmentation network for the midline prediction [21]. Then, the optimal midline was selected based on the previous prediction using a pathfinding method

Table 1. Baseline characteristics of the patients (n=140)

	With MLS (n=94)	Without MLS (n=46)	p*
Age	55.5±14.7	58.9±12.0	0.18
Gender (M/F)	57/37	27/19	0.83
GCS	9.7±3.9	13.7±1.9	<0.01
Consciousness			
awake	16 (17.0%)	22 (47.8%)	<0.01
drowsy	32 (34.0%)	21 (45.7%)	
comatose	46 (48.9%)	3 (6.5%)	
Therapy (operative)	60 (63.8%)	3 (6.5%)	<0.01
GOS (favourable)	58 (61.7%)	39 (84.8%)	<0.01

Data are presented as n, n (%), or mean ± standard deviation. *The T, Wilcoxon and Pearson Chi-square tests were significant at P<0.05.

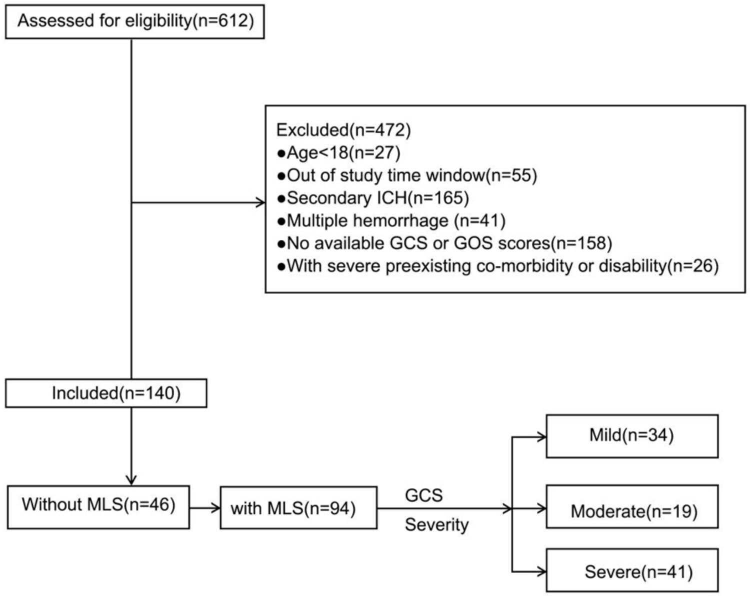

Figure 1. Consort diagram showing the inclusion and exclusion criteria of patients in this study.

(see **Figure 2**). The ideal midline was acquired by connecting the starting and ending points of the actual midline. The horizontal distances had been calculated between the actual midline and the ideal midline on all shifted slices and the largest one chosen as MLS-D. The MLS-V was calculated as the number of voxels between the actual and ideal midline multiplied by the physical size of a voxel. The voxel was defined as a discrete element of volume (x-spacing × y-spacing × z-spacing). The model had been validated using a dataset from three hospitals and one public dataset (CQ500) [21].

Data were analysed by SPSS software version 19.0 and MedCalc software version 19.4.1. All continuous variables were analysed using an unpaired t test for normally distributed data and the Wilcoxon test for skewed data. Categorical variables were compared using the Chi-square or Fisher exact tests. To explore the relation between MLS-D/MLS-V and GCS, Spearman's correlation coefficient was calculated. The area under the receiver operating characteristic curve (AUC) was calculated to compare the predictive power of MLS-D and MLS-V. The cut-off values of the ROC curve with optimal sensitivity and specificity for MLS-D and MLS-V were used for dichotomised analysis. Optimal cut-off points were determined using the Youden index method. A *P*-value of less than or equal to 0.05 (two-tailed) was considered as significant.

Results

In this study, 140 consecutive patients with supratentorial sICH admitted to the acute-care stroke unit of Qilu Hospital of Shandong University (Qingdao) from January 2014 to April 2019 were retrospectively analysed. The baseline characteristics of the patients are presented in **Table 1**.

There were 57 men out of 94 patients (mean age 55.5±14.7 years) in the midline-shifting group, compared with 27 men out of 46 patients (mean age 13.7±1.9 years) in the no-shifting group. The mean GCS score ± (SD) on admission was 9.7±3.9 in the midline-shifting group and 13.7±1.9 in the no-shifting group (P<0.01). Clinical outcomes revealed that 36 (38.3%) patients had poor or unfavourable outcomes in the midline-shifting group, and 7 (15.2%) had such outcomes in the no-shifting group, based on dichotomised GOS scores (P<0.01). At 12 months follow-up, one patient (2.2%) died in the no-shifting group, while 14 patients (14.9%) died in the middle-shifting group (P<0.05). In the no-shifting group, there

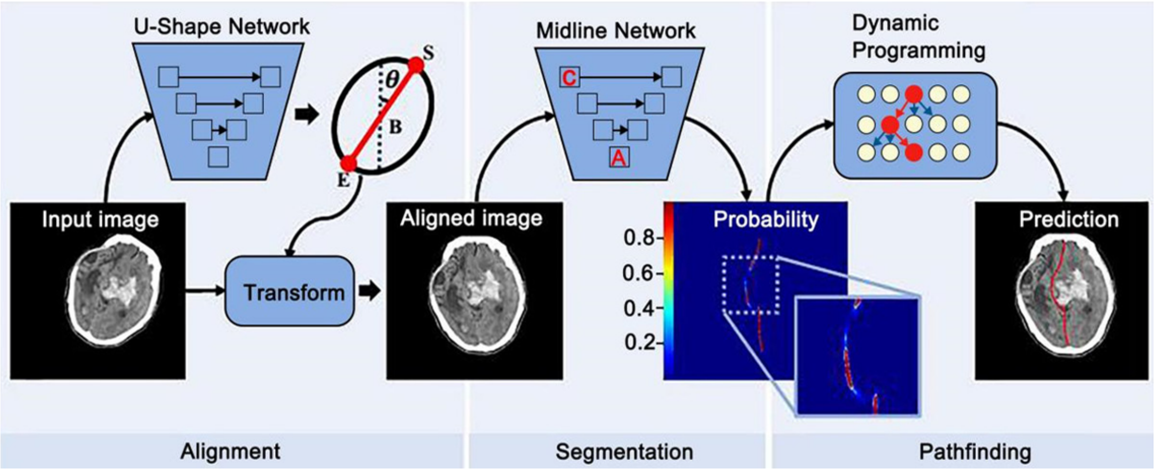

Figure 2. Proposed framework of automated midline detection and its application. The framework included three stages: image alignment, midline segmentation and pathfinding. From: (21).

Table 2. Midline shift and GCS score

	GCS severity			p*
	Mild	Moderate	Severe	
MLS-D (mm)	5.8±1.7	8.2±2.3	11.0±3.9	<0.01
MLS-V (ml)	13.0±3.9	21.9±6.8	29.0±12.0	<0.01

Data are presented as mean ± standard deviation. *The Kruskal Wallis tests were significant at P<0.05.

were 37 (80.4%), 8 (17.4%), and 1 (2.2%) patient(s) in the mild, moderate, and severe GCS degree groups, respectively, while in the middle-shifting group, there were 34 (36.2%), 19 (20.2%), 41 (43.6%) patients, respectively. A statistically significant difference was found between the no-shifting group and the middle-shifting group (P<0.01).

In the midline-shifting group, the medians of MLS-D in the mild, moderate, and severe groups were 5.8±1.7, 8.2±2.3, and 11.0±3.9 mm, respectively (P<0.01). The medians of MLS-V in the mild, moderate, and severe groups were 13.0±3.9 ml, 21.9±6.8 ml and 29.0±12.0 ml, respectively (P<0.01) (**Table 2**). Spearman correlation analysis showed that the correlation coefficients between GCS and MLS-D/MLS-V were 0.709 (P<0.01) and 0.754 (P<0.01), respectively. No statistically significant difference was found between MLS and MLS-V (P=0.513) (**Figure 3**). **Table 3** shows the AUC curve, sensitivity, specificity, and the cutoff values for MLS-D/MLS-V. The AUC of MLS-V was larger than that of MLS-D (0.831 vs 0.799, P=0.318), and the model of MLS-V predicting poor outcomes at 12 months follow-up had higher sensitivity but lower specificity than that of MLS-D (**Table 3** and **Figure 4**). This study identified MLS-D larger than 9.303 mm and MLS-V larger than 17.531 ml as two predictors of poor outcomes in patients at 12 months follow-up after sICH. In the mild GCS degree group, the AUC for MLS-V was 0.613 compared to 0.570 for MLS-D, and in the moderate GCS group, the AUC was 0.550 for MLS-V compared to 0.593 for MLS-D; for both investigated items, a statistically significant difference was not found (P=0.918, P=0.861).

In the severe GCS degree group, the AUC of MLS-V was larger than that of MLS-D (0.854 vs 0.736, P=0.030). The difference was statistically significant, and MLS-D larger than 11.859 mm and MLS-V larger than 27.353 ml appeared as the predictors of poor outcome at 12 months follow-up after sICH for patients with severe GCS (**Table 3** and **Figure 3**).

Discussion

The relationship between increasing midline brain shift caused by intracranial abnormalities and diminution of consciousness has been studied previously [13, 14]. These studies confirmed that the rate of coma patients in the middle-shifting group (48.9%) was significantly higher than that in the no-shifting group (6.5%) (P<0.05), which was in agreement with previous studies [13, 14]. To assess consciousness disorders, the Glasgow Coma Scale (GCS) was firstly proposed by Teasdale and Jennett in

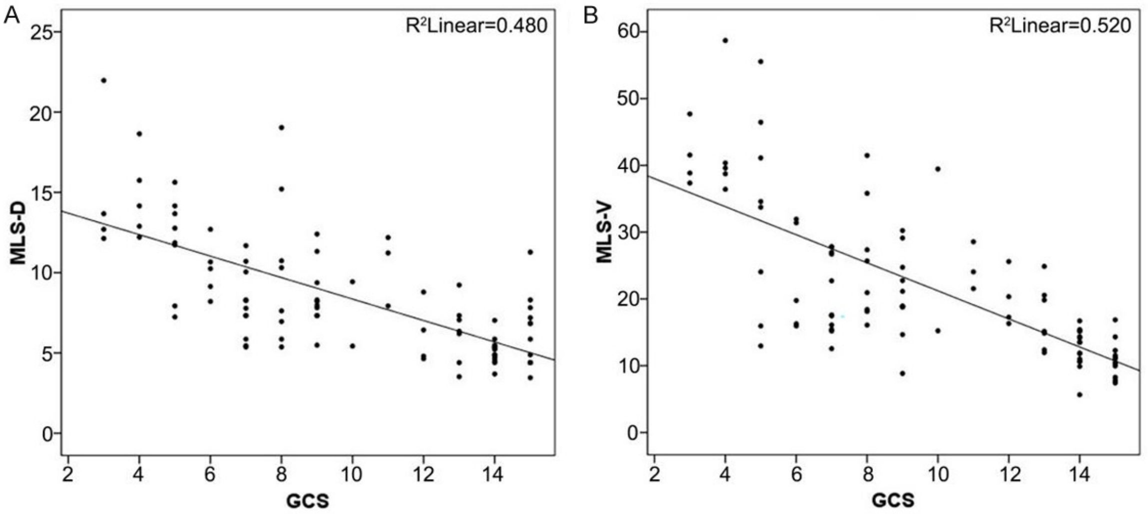

Figure 3. Scatterplots for Spearman correlation coefficients between the MLS and GCS. Both MLS-D (A, rs=0.709, P<0.01) and MLS-V (B, rs=0.754, P<0.01) showed moderate correlation with GCS.

Table 3. Poor outcome cutoff point

Poor outcome at 12 months					
	Cutoff point	AUC [95% CI]	Sensitivity (%)	Specificity (%)	p*
Midline shift group					
MLS-V (ml)	>17.464	0.831 [0.739-0.900]	86.1%	70.7%	0.318
MLS-D (mm)	>9.230	0.799 [0.704-0.875]	63.9%	84.5%	
Mild GCS subgroup					
MLS-V (ml)	>9.892	0.613 [0.431-0.774]	66.7%	90.3%	0.918
MLS-D (mm)	>6.188	0.570 [0.389-0.738]	66.7%	71.0%	
Moderate GCS subgroup					
MLS-V (ml)	>22.747	0.550 [0.309-0.775]	100.0%	50.0%	0.861
MLS-D (mm)	>6.426	0.593 [0.348-0.808]	100.0%	35.7%	
Severe GCS subgroup					
MLS-V (ml)	>27.353	0.854 [0.709-0.945]	71.4%	100.0%	0.030
MLS-D (mm)	>11.859	0.736 [0.575-0.861]	53.6%	92.3%	

*The tests were significant at P<0.05.

1974 and can objectively and reproducibly quantify the degree of neurological impairment and help perform early prediction of the clinical outcome [22, 23]. Chiewvit et al. [10] confirmed that the degree of midline shift was related to the severity of head injury (GCS=3-12), but the lower GCS (≤12) was not statistically significantly correlated with a large degree of midline shift (shift greater than 10 mm) in patients with brain injury (P=0.061). However, our study showed different results, i.e. the GCS decreased as the MLS-D increased. A similar relationship of increased MLS-V and decreased GCS was found as well. Few studies found the correlation coefficient between the MLS-D and GCS. In our study, there was a moderate correlation between the MLS-D and GCS (r=0.709, P<0.01). Many other factors such as hematoma volume, location, density, heterogeneity, and age may affect the GCS, and we speculated that it was one of the reasons for why the correlation between the MLS and GCS was moderate but appreciable.

In this study, patients who presented no midline shift had a higher GOS at 12 months follow-up than patients with midline shift (84.8% vs 61.7%, P<0.01), which was consistent with a

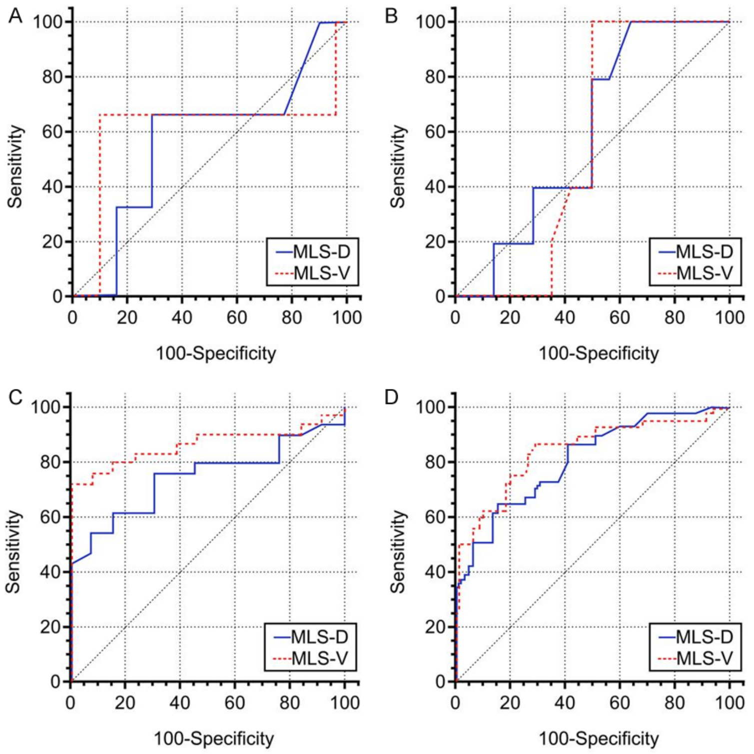

Figure 4. ROC Curve Analysis. A. Mild GCS group. MLS-D (cut off >6.188 mm) and MLS-V (cut off >9.892) AUC comparison in predicting poor outcome at 12 months (AUC: 0.570 vs 0.613, P=0.918). B. Moderate GCS group. MLS-D (cut off >6.426 mm) and MLS-V (cut off >22.747) AUC comparison in predicting poor outcome at 12 months (AUC: 0.593 vs 0.550, P=0.861). C. Severe GCS group. MLS-D (cut off >11.859 mm) and MLS-V (cut off >27.353) AUC comparison in predicting poor outcome at 12 months (AUC: 0.736 vs 0.854, P=0.918). D. Midline shift group. MLS-D (cut off >9.303 mm) and MLS-V (cut off >17.531) AUC comparison in predicting poor outcome at 12 months (AUC: 0.799 vs 0.831, P=0.318).

previous study [8]. Similarly, we observed that patients with midline shift had a higher rate of mortality than those with no midline shift (14.9% vs 2.2%, P<0.01). Furthermore, the univariate study showed that MLS-D was moderately associated with poor outcome (AUC: 0.799) with a cutoff value of 9.303. This was consistent with other studies, which also identified the midline shift as the predictor of functional outcome [11, 13, 24], and the same conclusion could also be obtained in paediatric patients with sICH [25]. A prospective cohort study [11] in Malaysia found the survival rate was only 45% at 6 months follow-up after sICH onset. Any patient with a midline shift exceeding 5 mm had almost 21 times higher chances of poor outcome. Another study found that lateral shift of cerebral midline structures less than 6 mm was one of the two most important predictors for 28-day survival in ICH [26]. Our study also showed a higher rate of favourable outcomes and a larger midline shift cut-off point than the previous studies. One recovery trajectory in a previous study revealed a possible continued outcome improvement if those patients were closely followed for longer than 6 months [8]. We speculated that the long-term follow-up might be attributable to the different outcomes of hematoma.

We found that the correlation coefficient of MLS-V and GCS was slightly higher than that of MLS-D and GCS (0.754 VS 0.709, P=0.513), but the difference was not significant. This result indicates that MLS-V is reliable in response to consciousness changes and has a tendency to improve accuracy contrast to MLS-D. We speculated that MLS-V might be a more accurate marker of consciousness changes. The ROC curve analysis revealed that the MLS-V had a slightly stronger predictive power of unfavourable outcome than MLS-D (AUC: 0.831 vs 0.799), although the results were not statistically significant. The optimal cut-off points for MLS-V and MLS-D were >17.531 ml and >9.303 mm, respectively. The MLS-V had a higher sensitivity and lower specificity than the MLS-D as a predictor of outcome at 12 months (86.1% vs 63.9%, 70.7% vs 84.5%). Therefore, the MLS-V may be preferable as a screening tool to identify patients with worse outcomes. However, if an invasive surgical intervention is planned, the MLS-D may be superior due to a lower number of false positives. The MLS-D merely provides the displacement information of the maximum shifted CT slice, ignoring the information of adjacent shifted slices, whereas the MLS-V can reflect more comprehensive deviation information at every middle shift plane. Previous studies [27-29] have unveiled that damage to any functional area adjacent to the midline structure may correlate with poor outcomes. At the upper level of the supratentorial brain, researchers [27] concluded that damage to cortical midline structures might bring about disturbed consciousness. At the middle level of the supratentorial brain, the author discovered that ICH affecting the thalamus was correlated with poor clinical outcomes [28]. At the lower level of the supratentorial brain, pineal shift may affect cerebral autoregulation, consequently reducing cerebral blood flow, interrupting the ascending reticular activation system, and leading to poor outcomes [29]. Therefore, MLS-V tends to be a better neuroimaging predictor than MLS-D for poor outcomes at 12-month follow-up.

Furthermore, we demonstrated that the AUC of MLS-V was larger than that of MLS-D in both mild and severe GCS groups (0.613 vs 0.570, P=0.918; 0.854 vs 0.736, P=0.030). In contrast, the AUC of MLS-V was smaller than MLS-D (0.550 vs 0.593, P=0.861) in the moderate group. Among them, the AUC comparison in the severe GCS group was statistically significant and the AUC was larger in the severe GCS group than in the other two groups. Moreover, both the MLS-D and MLS-V were more significant in the severe group than in the other two groups, and the difference between MLS-D and MLS-V was more dramatic. The results suggest that the MLS-V performs better in predicting poor outcome of sICH than MLS-D, particularly in critical cases with more notable MLS. Except for the moderate group, the results showed that the AUC of MLS-V was larger than that of MLS-D, despite without t statistical significance in the mild group. As there were only 19 patients in the moderate group, the results and conclusions may be biased because of the small sample size.

There were some limitations in our study. As a retrospective study, there were inherent methodological issues. The study was from only one hospital, and the therapeutic schedule for the patients might affect the outcome. The dataset was insufficiently large. Additionally, the outcome was assessed according to GOS, which provided relatively limited information about the disability and overall quality of life. Therefore, more complementary scales such as Functional Status Examination should be included to evaluate the outcome in the future [30]. Dhar et al. [31] developed an imaging algorithm based on deep learning that can accurately measure the bleeding volume and PHE volume. This is a fast and consistent automatic biomarker quantification that may accelerate the robust and accurate study of patients with massive cerebral hemorrhage, but the research failed to study the severity of the disease. While this paper aims to help analyse MLS and evaluate its severity more accurately and quickly based on DL convolutional neural network. The study performed the GCS score to evaluate the patient's level of consciousness, and calculated the GOS score to classify the prognosis. DL-based MLS-D and MLS-V measurements can assess awareness and predict the results of sICH. Compared with MLS-D, MLS-V measurement can better show the mass effect and predict the prognosis, especially in severe cases.

Conclusions

In summary, our study has demonstrated that the automatic measurement of MLS-D/MLS-V performs satisfactorily in evaluating consciousness and guiding clinical practice in patients with sICH. The DL-based method can provide fast, reproducible, and accurate data. The performance of MLS-V is slightly better in indicating mass effect, which provides further information than MLS-D, especially in severe cases. Further quantitative performance analysis is needed to confirm these findings.

Acknowledgements

This research was supported by Qingdao Science and Technology Demonstration and Guidance Project [grant numbers 20-3-4-37-nsh] and the Scientific Research Foundation of Qilu Hospital of Shandong University (Qingdao) (QDKY2020QN04).

Disclosure of conflict of interest

None.

Abbreviations

sICH, spontaneous intracranial haemorrhage; CT, computed tomography; ICP, increased intracranial pressure; MLS, midline shift; MLS-D, distance of midline shift; MLS-V, volume of midline shift; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; DL, deep learning; ROC, Receiver Operating Characteristic; AUC, Area under the Characteristic Curve.

Address correspondence to: Xiangshui Meng, Shandong University, Cheeloo College of Medicine, Qilu Hospital (Qingdao), Department of Radiology, Qingdao 266035, China. Tel: +86-18561811811; E-mail: xiangshuimeng@163.com

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