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Acute Damage to the Posterior Limb of the Internal Capsule

on Diffusion Tensor Tractography

as an Early Imaging Predictor of Motor Outcome after Stroke

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CERTIFICAT DEL DIRECTOR O CO-DIRECTOR DEL TREBALL DE RECERCA

Jo, Dr. Josep Lluís Martí Vilalta, en càrrec de Professor de Neurologia de la Universitat Autònoma de Barcelona i Director de la Unitat de Malalties Vasculars Cerebrals del Servei de Neurologia de l'Hospital de la Santa Creu i Sant Pau de Barcelona,

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que el treball titulat '*Acute Damage to the Posterior Limb of the Internal Capsule using Diffusion Tensor Tractography as an Early Imaging Predictor of Motor Outcome after Stroke´ ha e*stat realitzat sota la meva direcció pel llicenciat Josep Puig Alcántara, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna/Diagnòstic per la Imatge (curs 2009-2010), a la convocatòria de Setembre 2010.

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Acute Damage to the Posterior Limb of the Internal Capsule on Diffusion Tensor Tractography as an Early Imaging Predictor of Motor Outcome after Stroke

Abstract

Background and Purpose

Early prediction of motor outcome is of interest in stroke management. We aimed to determine whether lesion location at DTT is predictive of motor outcome after acute stroke and whether this information improves the predictive accuracy of the clinical scores.

Methods

We evaluated 60 consecutive patients within 12 hours of MCA stroke onset. We used DTT to evaluate CST involvement in the MC and PMC, CS, CR, and PLIC and in combinations of these regions at admission, at day 3, and at day 30. Severity of limb weakness was assessed using the m-NIHSS (5a, 5b, 6a, 6b). We calculated volumes of infarct and FA values in the CST of the pons.

Results

Acute damage to the PLIC was the best predictor associated with poor motor outcome, axonal damage, and clinical severity at admission (P<.001). There was no significant correlation between acute infarct volume and motor outcome at day 90 (P=.176, r=0.485). The sensitivity, specificity, and positive and negative predictive values of acute CST involvement at the level of the PLIC for

motor outcome at day 90 were 73.7%, 100%, 100%, and 89.1%, respectively. In the acute stage, DTT predicted motor outcome at day 90 better than the clinical scores (R^2=75.50, F=80.09, P<.001).

Conclusions

In the acute setting, DTT is promising for stroke mapping to predict motor outcome. Acute CST damage at the level of the PLIC is a significant predictor of unfavorable motor outcome.

Keywords

Diffusion tensor imaging, tractography, magnetic resonance imaging, stroke, outcome

Abbreviations

ANOVA=one-way analysis of variance; BI=Barthel Index; CR=corona radiate; CS=centrum semiovale; CST=corticospinal tracts; computed tomography=CT; DTI=diffusion tensor imaging; DTT=diffusion tensor tractography; DWI=diffusion-weighted imaging; EPI=echoplanar imaging; FA=fractional anisotropy; FLAIR=fluid-attenuated inversion recovery; GE=gradient-echo; IQR=interquartile range; ICC=intraclass correlation coefficient; MRI=magnetic resonance imaging; MC=motor cortex; MCA=middle cerebral artery; NIHSS=National Institute of Health Stroke Scale; m-NIHSS=motor subindex scores of the NIHSS; mRS= modified Rankin Scale; PLIC=posterior limb of the internal capsule; PMC=premotor cortex; PWI=perfusion-weighted imaging; r=Pearson product-moment correlation coefficient; r_{pb}=point-biserial correlation coefficient; rFA=FA ratio; ROC=receiver operating characteristic; ROI=region of interest; SENSE=sensitivity encoding; TR=repetition time; TE=echo time; WD=Wallerian degeneration.

Introduction

Accurate early prediction of motor functional outcome in the early stage of stroke is important for clinicians and researchers in management and rehabilitation.[1] Motor deficit after stroke is common and has a considerable influence on quality of life.[2] Several observational studies have demonstrated that the grade of initial motor deficit is the most important determinant of motor recovery.[1-5] Other valid predictors in regression models have included infarct site, volume of stroke, demographics, comorbidities, infarct side, and stroke subtype.[1-3,6]

The CST is the main pathway that mediates voluntary movements, and neurophysiological and structural imaging studies have evidenced that motor outcome is heavily dependent on the integrity of the motor fibers.[6-13] Thus, the involvement of motor-related cortical regions, CR, and internal capsule progressively decrease the probability of upper limb functional recovery.[6,14] Recently, these findings were complemented by DTI studies that have demonstrated the usefulness of DTT for predicting poor motor outcome when infarct involves the CST.[15-20] DTI enables in vivo visualization and quantification of microstructural damage to white matter tracts.[21] DTT uses data acquired through DTI to reconstruct a three-dimensional macroscopic orientation of the white matter fibers that enables the specific topographic relation between lesion location and CST fibers to be evaluated.[22] Decreases in FA, a DTI-derived structural measure, have been interpreted as WD and proposed as an index of axonal damage.[23] Decreased FA in the CST correlates with motor impairment one month after stroke.[24] On the other hand, although patients with large

infarcts tend to have a poor outcome, functional deficits due to moderate-size infarcts are more difficult to predict.[7,25,26] One of the major reasons functional outcome does not correlate strongly with infarct volume is that the specific site of the lesion is not taken into account.[4,9]

To our knowledge, no prospective controlled studies have assessed the ability of DTT to predict motor recovery immediately following acute MCA stroke. We aimed 1) to evaluate whether the specific site of a lesion in the CST (primary MC, PMC, CS, CR, PLIC, and combinations among them) at DTT predicts axonal damage to the motor pathway and motor outcome after acute stroke, and 2) to assess whether a model incorporating DTT information on the specific location of the stroke and clinical scores is more accurate in predicting motor outcome than clinical scores alone.

Subjects and Methods

Patients

The data reported were obtained from the same cohort of patients included in our previous study relating WD and motor outcome.[24] Patients included had a first-ever MCA infarction and were admitted to our stroke unit within 12 hours of symptom onset during a 19-month period. Patients with other lesions, cerebral hemorrhage, significant preexisting nonischemic neurological deficit, or a history of prior stroke that would hinder the interpretation of clinical and imaging data were excluded. Our institutional ethics committee approved the study, and written informed consent was obtained from all patients or from relatives.

Clinical Examination

A senior certified staff neurologist used the NIHSS to assess clinical deficit at admission, at day 3, at day 30, and at day 90 from stroke onset. The m-NIHSS subindex (5a, 5b, 6a, 6b) was used to categorize the severity of limb weakness as grade I (total m-NIHSS score of 0), grade II (m-NIHSS, 1-4), or grade III (m-NIHSS, 5-8). The mRS and BI were used to measure disability and dependence in activities of daily living at day 90. Poor overall outcome was defined as mRS>3 and/or BI<60.[27] All clinical assessments were performed without knowledge of the MRI findings. Patients were treated according to guidelines.[28]

MRI Protocol

All scans were performed with a whole-body 1.5-Tesla MR system (Gyroscan Intera, Philips Medical Systems, Best, the Netherlands) with a SENSE head coil. The routine protocol included axial trace DWI, FLAIR, T2*-weighted GE, PWI, time-of-flight angiography, and DTI sequences. DTI was performed using a single-shot EPI sequence with the SENSE parallel-imaging scheme (acceleration factor 2) after contrast agent administration. Diffusion-sensitized gradients were applied along 15 non-collinear directions with a b value of 1000 s/mm^2. In addition, diffusion-weighted b0 images were obtained. Other acquisition parameters were: TR/TE 6795/72ms, 23 x 23-cm field of view, and 112 x 112 matrix size. DTI voxel size was 2.05mm x 2.05mm x 3mm. Forty slices covering the entire brain were obtained parallel to the bicommissural line without interslice gaps. DTI acquisition took 3 minutes and 10 seconds.

Data Processing and DTI tractography

Diffusion-sensitized image sets were transferred to an offline workstation for analysis. We used DTIweb version 2.0 (http://trueta.udg.edu/DTI/index.html) to calculate tensor values for tractography.[29] Anisotropy maps were obtained using orientation-independent FA, and color FA maps were generated following the standard convention (red, left-right; green, anteroposterior; and blue, superior-inferior).

Tractography was based on a diffusion tensor deflection algorithm.[30] The threshold for stopping fiber propagation was FA<0.2 and angle<70º. The seeding method puts randomly inside each voxel with a FA>0.4. To reconstruct the CST, the ROIs were placed at the level of the cerebral peduncle and around the CR in the direction-coded color axial sections. Unrelated fibers, such as those going to the contralateral hemisphere, cerebellum, or thalamus, were removed using specific ROIs. All ROIs were placed by two of the authors (A.P.,G.B.); the CST depicted and the evaluation of the PMC were validated using landmarks from neuroanatomy atlases.[31]

Assessment of Damage to Specific CST regions

To decide which structures were affected by infarct, the tractograms of CSTs were superimposed on DW images, and the following specific regions were evaluated: MC, PMC, CS, CR, PLIC, and combinations of these regions (Fig.1). These regions were scored separately on each slice on 2 separate occasions 6 weeks apart by 1 rater (J.P.) and once by 2 raters (J.P.,S.R.); all raters were blinded to the clinical ratings. Discordant ratings were resolved by consensus.

Measurement of the FA values of CSTs

FA values for each ROI on axial slices of the affected and unaffected CST at the rostral pons were obtained by averaging all voxels of three contiguous slices. Second, the ipsilateral-to-contralateral CST FA ratios were calculated (rFA=FAaffected side/FAunaffected side). Two readers (J.P.,G.B.) blinded to the clinical scores quantified FA.[24]

Calculation of Infarct Volume

Infarct volumes were determined offline. Two readers (J.P.,G.B.) manually outlined the areas of abnormal hyperintensity on axial trace DW images. Surface areas of abnormal hyperintensity were summed and multiplied by slice thickness (6 mm) and interslice gap (1 mm) to calculate infarct volumes. The results of the two readers were averaged.[24]

Statistical Analysis

To determine whether acute-stage involvement of specific CST regions and combinations of CST regions were associated with stroke severity, clinical and motor outcome at day 30 and at day 90, axonal damage and/or acute-phase infarct volume, we used the chi-square test to compare categorical variables and Student's t test to compare quantitative variables. We used Cohen's Kappa coefficient to assess intraobserver and interobserver reliability. Intra- and inter-observer agreement were classified as slight (K=0.0–0.20), fair (K=0.21–0.40), moderate (K=0.41–0.60), substantial (K=0.61–0.80), or almost perfect (K=0.81–1.00) according to the scale proposed by Landis and Koch.[32]

Motor outcome was first analyzed using bivariate statistics. We calculated the correlation coefficients for lesion site and for clinical scores with motor deficit at day 3, day 30, and day 90. Each specific CST region was coded as 0 (unaffected) or 1 (affected by infarct). The predictive data set contained both dichotomous (involvement of specific CST region) and numerical and ratio variables (infarct volume, rFA, m-NIHSS) for which an r_{pb} or r was used, respectively. Coefficients with a p-value lower than 0.05 were considered significant.

Multiple regression analysis was used to predict motor outcome at day 90 after stroke using a combination of motor deficit, specific CST region involved, and imaging data. We also evaluated the additional predictive value conferred by adding the effect of region involved to that of the motor deficit. The dependent variable was the m-NIHSS score at day 90 after stroke, predicted from the following combinations of independent variables: 1) the specific CST region, m-NIHSS, and infarct volume in the first 12 hours after stroke; 2) the specific CST region, m-NIHSS, and infarct volume at day 3; and 3) the specific CST region, m-NIHSS, infarct volume, and rFA at day 30. To determine which combination of independent variables yielded the best predictive model, variables were deleted one by one from the model on the basis of the significance of their regression coefficients and the R-square selection method. The models with the highest R^2 and all predictor variables that were significant ($P<0.05$) were retained for each prediction. Only the model selected for the dataset obtained at day 3 fulfilled the assumption of normality. All statistical analyses were performed using Minitab version 15.1.0.0 (Minitab,State College, Pennsylvania).

Results

Subjects

Sixty-five consecutive patients with ischemic MCA stroke were scanned on admission, but data from 5 patients were incomplete at day 90 due to recurrence of stroke, death, and the presence of motion artifacts. Analyses were therefore based on 60 subjects (37 men, 23 women; aged 68±13 years). One patient missed the MRI study at admission but completed studies on day 3 and day 30. All patients underwent MRI and clinical assessment at day 30.

Clinical Characteristics and DTT analysis

Table 1 presents detailed clinical and MR data for all the patients. Median NIHSS score at admission was 11 (IQR 7-17), indicating that most patients had moderate to severe neurological deficits. All patients had started physiotherapy within 2 weeks after the stroke. At admission, 47 (78.3%) of 60 patients presented some motor deficits and 28 (59.6%) of these had moderate-severe motor deficit (m-NIHSS III). At day 3, a total of 28 patients (46.7%) presented some motor deficits and 13 (46.4%) of these were classified at m-NIHSS III. Improvements with respect to baseline scores were observed in 67.8% of patients at day 30 and in 85.7% at day 90, and 42.8%, and 39.2% of motor deficits were categorized as m-NIHSS III at day 30 and day 90, respectively. BI and mRS scores before the stroke were 100 and 0 in all patients, respectively.

The mean time for reconstructing and assessing the DTT to evaluate the damage to CST regions was 3 minutes and 30 seconds. At admission, the CST did not appear disrupted or displaced in any patient. Intrarater and interrater

agreement about the affected CST region was almost perfect (*K*=0.88 and *K*=0.84, respectively). No CST involvement by infarct on admission was observed in 14 (23.34%) patients; however, 5 of these had motor deficits (Table 1). On the other hand, CST involvement was observed on admission in 5 patients without motor deficits; the areas affected were the PMC (n=2), PMC and CR (n=1), CR (n=1), and PLIC (n=1). At day 30, involvement of at least one CST region was observed in all patients with motor deficit. Finally, PLIC involvement in the first 12 hours was associated with unfavorable overall outcome (mRS>3 and/or BI<60) (P<.001).

Motor outcome prediction and the involvement of the specific CST regions

Damage to the PLIC in the first 12 hours and at day 3 after stroke correlated with clinical severity, axonal damage expressed as decreased FA and rFA values and motor outcome at day 30 and day 90 (*P*<0.001) better than damage to any other CST region (Table 2). There was no significant correlation between acute infarct volume and motor outcome at day 90 (*P*=0.176, r=0.485) (Fig. 1 and Fig. 2).

CS and/or CR involvement at day 3 was associated with motor deficit at day 30 and day 90 (*P*<.004) and axonal damage (*P*<.003) (Table 2). It is noteworthy that, although other significant associations can be observed, combined PLIC and CS or CR involvement at day 3 was not significant for motor outcome at day 30 or at day 90 (*P*=0.157 and *P*=0.218 for the interaction between PLIC and CS at day 30 and at day 90, respectively; *P*=0.521 and *P*=0.457 for the interaction between PLIC and CR at day 30 and at day 90, respectively).

Therefore, the motor outcome at day 30 and at day 90 is secondary to PLIC damage.

Damage to the PLIC in the first 12 hours yielded the highest sensitivity, specificity, and predictive values for the prediction of motor outcome at day 90. Interestingly, PLIC damage by acute stroke clearly distinguishes subjects without motor deficit (m-NIHSS I) from those with motor deficit (NIHSS II and III) and even differentiates m-NIHSS II from m-NIHSS III at day 90 (Table 3).

Correlations analysis revealed significant coefficients only between PLIC involvement in the first 12 hours and motor outcome at day 90 (Table 4). Damage to the CR and/or CS, m-NIHSS, and acute-stage infarct volume were not related to motor outcome at 90 days. At day 3, PLIC damage and m-NHISS showed the most significant correlations with motor outcome at 90 days. At day 30, PLIC damage, m-NHISS, and axonal damage showed the most significant correlations with motor outcome at day 90. The only relation between infarct volume and motor outcome at day 90 was a modest correlation observed at day 3.

Table 5 summarizes the best predictive models achieved at each time point. The simplest model to predict m-NIHSS at day 90 based on the data available in the first 12 hours consisted only of PLIC damage; PLIC damage alone accounted for 75.5% of the variance in outcome. At day 3, regression analyses indicated that m-NIHSS accounted for 79% of the variance in motor outcome at day 90, and PLIC damage had a significant contribution of only 6.62%. Regression coefficients for these assessments were positive, indicating that an infarct affecting CST and m-NIHSS are predictive of greater motor deficit from day 3 to 90 days after stroke. The best model for predicting motor outcome at

day 90 based on the assessments at day 30 included only the m-NIHSS, which accounted for 90.10% of the variance in the measurement.

Association between the region of the CST affected in the first 3 days after stroke and FA indexes at day 30

Our previous study demonstrated that mean FA values along the affected CST were significantly lower than the normal contralateral side only at day 30 after stroke onset (*P*<.001), and these values were lower than the corresponding FA values obtained at admission and at day 3. Moreover, the decrease in mean FA values correlated positively with the motor deficit at 30 days after stroke[19]. Combined involvement of the PLIC and CS and/or CR at day 30 was not significantly associated to decreased FA indexes (*P*=0.445 for the interaction between PLIC and CS; P=0.830 for PLIC and CR). Hence, axonal damage reflected as decreased FA ratio values at day 30 was also secondary to PLIC damage. There was no association between infarct volume and WD (r=-0.221 *P*=0.090).

Discussion

We sought to determine whether acute stroke damage to specific CST regions evident at DTT can predict limb motor outcome on a categorical scale based on the m-NIHSS. We found that the involvement of the PLIC alone or in combination with other specific CST regions in the first 12 hours after stroke was strongly associated to severe motor deficits in the first 12 hours and poor motor functional outcome at day 90. Although damage to the CS and CR at day 3 was also associated with poor motor outcome at day 90, PLIC damage in the

first 12 hours after stroke was clearly the best predictor of motor deficits and of their severity.

Predictors of motor outcome proposed include location and extension of the stroke specifically within the CST, grade of initial motor deficit, and infarct volume. Our findings corroborate previous studies that found motor outcome is strongly dependent on the integrity of the CST and that the involvement of regions like the PLIC with more dense and organized corticofugal tract fibers is associated with poor long-term recovery after stroke.[6] Shelton et al.[14] found that the probability of recovery of upper limb movement at 2 months decreased progressively with the involvement of the MC, CR, or internal capsule. In turn, Schiemanck et al.[6] found that infarcts involving the internal capsule, alone or in combination with other areas, were associated with a significantly lower probability of hand motor deficit rather than infarcts in the MC, subcortex, or CR. We also found that axonal injury of the CST affected by the stroke (as determined by decreased FA values in the pons) in the acute stage was only associated with PLIC damage.

We found no correlation between infarct volume and motor outcome at day 90, and motor deficit was present only when critical motor regions were involved, suggesting that large lesions do not necessarily predict poor outcome. Although subcortical strokes are normally smaller than cortical strokes, they are more likely to involve both primary MC and PMC fibers, and patients with subcortical infarcts have worse motor outcome than those with cortical stroke.[14] These findings may indicate that the extent of damage specifically within the CST is a major determinant of motor deficit.

Previous structural imaging studies designed to predict motor recovery based on lesion location within the CST used conventional axial MRI slices and hand-drawn CST masks.[6,8] Using T2 changes to assess lesions may not accurately reflect specific neuronal damage, because lesions can be patchy and edema can contribute to T2 signal hyperintensity. Conventional T2-weighted MRI provides excellent contrast between white and gray matter, but provides no information about fiber direction.[33] In contrast, DTT clearly depicts the trajectory of the CST, making it possible to evaluate the topography and extent of tissue damage, particularly in acute stroke.[31] We found strong interrater agreement, indicating the reliability and validity of DTT as a lesion mapping technique for this purpose. Recently, some DTI studies have reported that motor outcome could be predicted using anatomic relationships between the stroke lesion and CST damage on DTT in patients with intracerebral hemorrhage, CR and lacunar infarcts.[15-20,34] Jang et al.[17] demonstrated that DTT performed at an early stage of pontine infarct (mean DTT scanning, 15 days; range, 5-30) is useful for predicting motor outcome. Similarly, another study reported that the degree of CST involvement on DTT within 3 days of stroke onset was strongly correlated with the severity of motor deficit and functional recovery at 3 months in patients with an acute lenticulostriate infarct.[19] To our knowledge, ours is the first prospective controlled study to examine consecutive patients with DTT within the first 12 hours after MCA stroke onset.

In the multiple regression analysis, the best model for predicting motor outcome at day 90 in the acute stage was PLIC damage by infarct on DWI alone (not in combination with the clinical parameters); therefore, PLIC damage could be considered an early imaging predictor of poor motor outcome. Several studies

have demonstrated that the grade of initial motor deficit is the most important determinant of motor recovery.[1-5] In this respect, at day 3 we found that the clinical assessment is the most useful predictor of motor outcome and that adding information about PLIC damage increases the accuracy of the prognosis. Our findings are in the line with those obtained by Feys et al.[4], who analyzed the site of the lesion on CT and MRI between 5 and 29 days after stroke (median,10) and obtained arm motor scores 13 to 37 days after stroke (median,22). These authors found that arm recovery at 2 months was best predicted by a combination of the motor performance (R^2=59.21) and purely subcortical lesion location (R^2=5.31) and that motor recovery at 12 months was best predicted by clinical tests alone (R^2=53.11) when clinical scores were measured at 2 months after stroke.

Clinical assessment in the acute setting has some limitations. First, it can be difficult to assess the grade of paresis clinically in uncooperative or severely cognitively impaired patients, and clinical findings are occasionally inconclusive and/or questionable with respect to motor outcome. Second, the ischemic penumbra evidenced by perfusion-diffusion mismatch (not evaluated in the current study) can produce symptoms that are clinically indistinguishable from those produced by the infarct core.[35] The ischemic penumbra represents severely hypoperfused tissue around an infarct core; the neurons in the penumbra are supposedly structurally intact but functionally inactive, so penumbral areas are potentially salvageable.[36] In our sample, the ischemic penumbra could explain why some patients without CST involvement by infarct presented motor deficits in the acute stage and why the initial motor deficit did not correlate with motor outcome. Hence, if perfusion is restored to penumbral

areas and disturbances disappear (e.g. at day 3) and the DWI abnormality does not involve the CST, the outcome will be good despite high m-NIHSS score on admission.

Our results show that DTT can be useful in the clinical scenario, making it possible to determine the damage to specific regions of motor pathways in acute stroke patients consistently, easily, and quickly. Including DTT in acute stroke protocols may generate valid prognostic information because motor outcome appears strongly influenced by CST damage, in particular at the level of the PLIC. In this scenario, DTT could improve the accuracy of prognosis and help improve management in individual stroke patients.

Several limitations to our study should be emphasized. First, we considered long-term clinical follow-up (90 days) because although motor recovery seems to occur predominantly in the first few months after stroke, some patients show considerable recovery in later phases.[1] However, while several longitudinal cohort studies and randomized controlled trials found that most of the overall improvement in motor functions occurred within the first month after stroke, some degree of motor recovery continued in some patients in later phases for up to 6 months, especially in subgroups with high motor severity score on admission (59.57% of patients with motor deficit in our cohort). Second, the aim of this study was to design a simple and easy method to evaluate different CST regions qualitatively (affected or not) in the acute stroke scenario; thus, we did not consider quantitative data like the proportion of damaged fibers, etc. that may have improved the accuracy of our predictions.[10,11] Nevertheless, our results indicate that DTT performed within hours of stroke onset is useful for determining which patients are likely to suffer long-term motor deficits.

Importantly, this approach eliminates the need for more advanced postprocessing techniques (which are more time consuming and require greater specialization), so it can be applied more widely and benefit more patients. Finally, DTI reflects the averaged water diffusion property within a voxel, which is considered an indirect indicator of the axons; therefore, this approach may oversimplify the model of the axonal structures.[31]

Conclusions

In summary, we conclude that DTT should be incorporated in MRI protocols for acute stroke because determining the damage to specific regions of motor pathways can help predict motor outcome. Our study lends support to the idea that motor outcome is highly dependent on lesion location and the extent to which acute stroke affects the CST. In particular, PLIC damage could be considered an early imaging predictor of poor motor outcome. These findings have implications for the use of lesion mapping techniques in the prognosis of motor outcome after stroke and for establishing more effective criteria for enrolling patients in experimental rehabilitation programs. Further research should focus on improving the accuracy of predictions of motor outcome after stroke based on early imaging predictors, with special attention to the prognostic value of DTI.

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APPENDIX

Figures and Legends

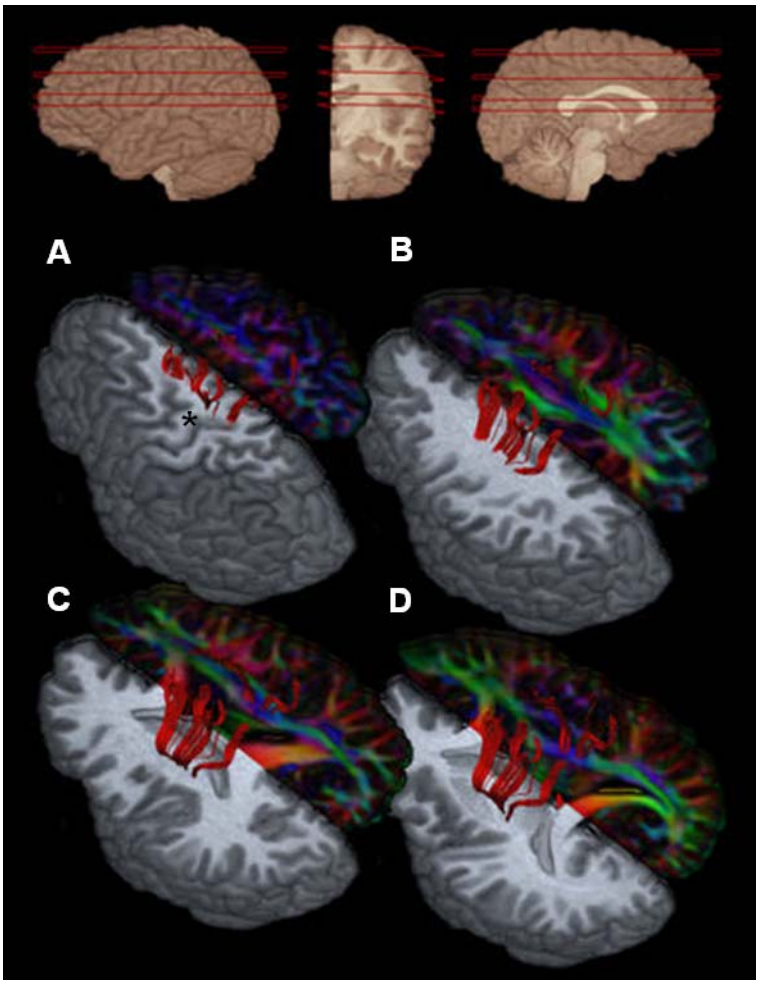

Figure 1. Specific regions evaluated to determine the integrity of the CST. Transaxial summed volumetric high-resolution T1-weighted images, FA color-maps, and tractograms show the origin of the CST from both the MC (asterisk at precentral gyrus) and PMC (*A*). The CST involves the CS (*B*) and CR (C) and finally converges at the level of the PLIC (D). The sectional levels are indicated as red horizontal lines (upper images).

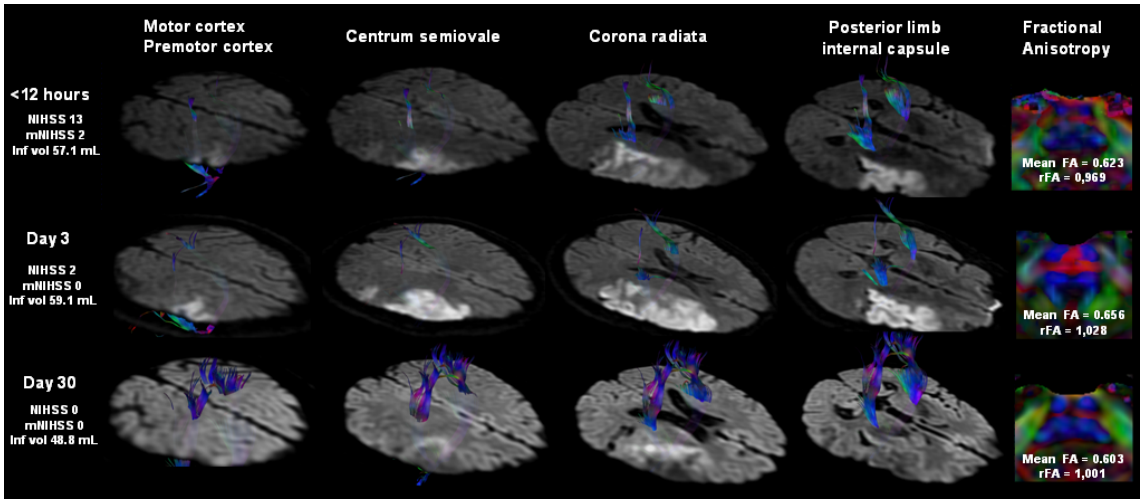

Figure 2. A 55-year-old man (patient 40) presented moderate right MCA territory infarction. DTT images show infarction near the right CST at the level of the CR and PLIC, although there is no direct involvement. At admission, ischemic penumbra (not shown) involved part of the CST at the level of the CR and could explain the motor deficit at this time. FA indices reveal CST axonal integrity at the anterior part of the pons.

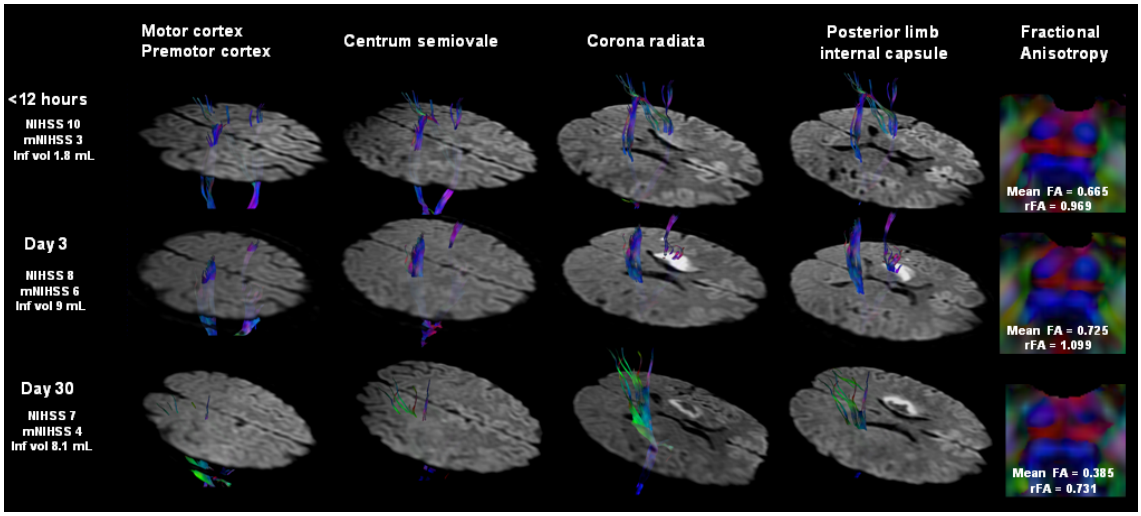

Figure 3. A 47-year-old man (patient 15) presented a mild right-sided hemiparesis lasting 45 minutes. Note the slight hyperintensity of the left CST involved by the infarct in the striatocapsular MCA territory due to the short time elapsed since the onset of symptoms. The reduced brightness and decreased FA value in the left descending CST at day 30 are regarded as WD.

Table 1. Patient MRI, clinical assessment, and disability data

Patient, Sex	Age (yr)	Infarct side	Time from onset to MRI(min)	Affected CST regions <12 h	Infarct volume < 12h (mL)	NIHSS /m-NIHSS<12h	m-NIHSS category(I-III)	Iv rTPA treatment	Affected CST regions day 3	Infarct volume day 3 (mL)	NIHSS /m-NIHSS day 3	m-NIHSS category(I-III)	Affected CST regions day 30	Infarct volume day 30 (mL)	rFA day 30	NIHSS /m-NIHSS day 30	m-NIHSS category(I-III)	NIHSS /m-NIHSS day 90	m-NIHSS category(I-III)	BI day 90	mRS day90
1,F	69	L	485	PMC	1.2	6/0	I	+	PMC	3.7	4/0	I	PMC	1.4	1.088	1/0	I	0/0	I	100	0
2,F	83	L	145	CR,PLIC	40.5	21/8	III	+	PMC,CR PLIC	46.2	9/1	II	SC,CR, PLIC	52.2	0.904	5/4	II	3/1	II	55	4
3,F	86	R	140	CR	2.1	12/7	III	-	CR	8.5	2/0	I	CR	8.4	1.027	1/0	I	0/0	I	65	4
4,M	43	R	115	CR	20.6	6/2	II	+	CR	22.5	1/0	I	-	9.8	1.018	1/0	I	1/0	I	100	1
5,M	73	L	145	-	6.7	5/0	I	-	-	9.4	4/0	I	-	6	0.922	1/0	I	1/0	I	100	2
6,F	68	L	150	PMC	54.2	9/0	I	+	PMC	56.7	4/0	I	PMC	55.3	0.932	1/0	I	0/0	I	100	1
7,M	83	L	135	ALL	24.5	20/7	III	+	ALL	82.3	21/8	III	ALL	75.2	0.493	20/8	III	15/7	III	10	5
8,M	65	R	210	MC,PMC	2.2	4/1	II	+	MC,PMC	3.1	3/1	II	PMC	2.5	1.000	2/0	I	0/0	I	100	0
9,F	67	L	540	CR	5.1	11/2	II	-	CR	18	9/2	II	CR	11.3	0.915	2/1	II	1/1	II	90	2
10,F	74	L	490	-	7.5	1/0	I	-	-	10.6	2/0	I	-	9.2	0.997	2/0	I	1/0	I	100	1
11,M	33	L	230	CR	7.9	19/8	III	+	-	7.3	2/0	I	-	3.2	1.253	1/0	I	0/0	I	100	0

12,M	61	L	420	CR	7.7	10/2	II	-	CR	10.4	2/0	I	CR	8.4	1.016	1/0	I	1/0	I	100	2
13,F	84	L	470	CR	4.5	10/1	II	-	CR	3.8	6/0	I	CR	4.1	0.978	2/0	I	1/0	I	100	1
14,M	72	L	360	-	15.5	2/0	I	-	-	14.5	0/0	I	-	11.5	1.003	0/0	I	0/0	I	100	0
15,M	47	L	45	PLIC	1.8	10/3	I	-	PLIC	9	8/6	III	PLIC	8.1	0.733	7/4	III	6/5	II	80	3
16,F	83	L	140	CR	11.7	11/3	II	-	CR	11	12/3	II	CR	4.7	0.983	5/0	I	1/0	I	90	3
17,F	85	R	150	CR	4.6	15/8	III	-	CR	15.1	7/3	II	CR	5.8	1.015	3/0	I	3/0	I	50	3
18,M	74	L	430	CR	5.2	4/0	I	-	CR	29.1	3/0	I	CR	20.3	0.966	3/0	I	4/0	I	100	2
19, F	48	L	140	CR	12.5	20/8	III	+	CR	76.7	8/0	I	CR	14.6	0.976	3/0	I	3/0	I	100	2
20,M	85	R	580	CR	12.2	15/8	III	-	CR,PLIC	26.5	7/4	II	CR PLIC	11.6	0.745	4/3	II	1/1	II	100	2
21,M	73	R	90	MC,PMC SC	68.9	15/6	III	+	MC,PMC SC,CR	132	13/6	III	MC,PMC,SC CR	116.5	0.688	10/4	II	9/2	II	15	4
22,M	70	L	380	-	2.1	11/0	I	-	-	13.1	6/0	I	-	8.8	0.990	8/0	I	7/0	I	90	3
23,M	76	L	150	CR	25.4	20/8	III	+	SC,CR	60.1	13/3	II	SC,CR	34.1	0.924	10/3	I	2/0	II	100	1
24,F	66	L	470	-	0.5	4/2	I	-	-	0.6	0/0	I	-	0.3	1.069	0/0	I	0/0	I	100	0
25,M	52	L	100	CR	9.3	12/3	II	+	CR	10.9	12/3	II	CR	4.5	0.928	5/0	I	0/0	I	100	1
26,F	56	L	240	-	32.2	7/0	I	+	-	41.7	3/0	I	-	16.1	1.214	1/0	I	0/0	I	100	2
27,M	74	R	390	-	14.2	11/6	III	+	-		2/0	I	-	3.7	0.990	1/0	I	1/0	I	100	2
28,M	73	L	320	-	7	19/8	III	+	-	6.3	1/0	I	-	3.4	0.987	0/0	I	0/0	I	100	0
29,M	78	L	300	-	5.4	4/1	II	-	-	10	6/0	I	-	2.9	0.997	1/0	I	3/0	I	100	2
30,M	81	R	350	MC,CR	35.4	9/4	II	-	MC,CR	37.4	1/0	I	CR	9.1	1.046	0/0	I	0/0	I	100	1
31,F	83	R	420	PMC,SC CR	42.3	10/2	II	-	PMC,SC,CR	48.9	2/0	I	PMC,SC,CR	26.1	1.086	0/0	I	0/0	I	100	2
32,M	84	L	210	MC,SC	4.3	9/2	II	-	MC,SC	22.9	7/1	II	MC,SC,CR	11.3	1.036	4/0	I	0/0	I	100	1
33,F	69	L	450	CR	1.9	16/4	II	+	CR	2.2	1/0	I	CR	1.8	0.995	0/0	I	0/0	I	100	1
34,F	21	R	235	CR	7	11/7	III	+	CR	10.2	4/2	II	CR	1.4	1.165	1/0	I	0/0	I	100	2

35,F	73	L	240	PLIC	4.8	19/8	III	+	PLIC	9.3	10/7	III	PLIC	3.9	0.676	11/7	III	11/7	III	30	4
36,F	42	R	310	-	4.7	12/8	III	-	-	8	0/0	I	-	0.7	0.990	0/0	I	0/0	I	100	0
37,M	80	R	390	MC,SC,CR	42.2	13/6	III	-	MC,PMC,SC,CR	65.9	5/2	II	MC,PMC,SC CR	58.8	0.659	9/4	II	9/4	II	25	4
38,M	58	R	530	MC,PMC,SC CR	53.9	7/1	II	-	MC,PMC,SC, CR	64.7	3/0	I	MC,PMC,SC CR	48	0.958	2/0	I	2/0	I	100	2
39,M	61	L	280	-	5.3	5/0	I	+	PMC	4.3	0/0	I	PMC	2.1	1.064	0/0	I	0/0	I	100	0
40,M	55	R	630	-	57.1	13/2	II	+	-	59.1	2/0	I	-	48.8	1.001	0/0	I	0/0	I	100	0
41,M	68	R	640	PMC,CR PLIC	92.9	18/8	III	-	PMC,SC, CR PLIC	164	16/8	III	PMC,SC,CR PLIC	120.6	0.854	13/8	III	11/7	III	10	4
42,F	67	L	435	PLIC	1.3	16/7	III	-	PLIC	77.9	20/8	III	PLIC	59.5	0.883	13/7	III	13/7	III	35	4
43,F	63	L	340	PMC,CR	4.8	6/0	I	-	CR	8.9	0/0	I	CR	2.8	0.724	0/0	I	0/0	I	100	0
44,F	45	R	425	PLIC	14.2	8/1	II	-	CR,PLIC	43	7/4	II	CR,PLIC	37.2	0.920	6/3	II	5/3	II	80	3
45,M	67	R	665	PLIC	22.8	17/8	III	+	CR,PLIC	38	15/8	III	CR,PLIC	32.3	0.659	11/7	III	11/7	III	35	4
46,F	80	R	240	PMC,PLIC	34	19/8	III	+	PMC,SC,CR PLIC	124	18/8	III	ALL	116.9	0.767	14/8	III	15/8	III	20	5
47,M	51	R	105	PLIC	20.8	17/7	III	+	SC,CR,PLIC	90.8	11/6	III	SC,CR,PLIC	50.3	0.595	8/5	III	8/5	III	65	3
48,M	57	L	669	MC	4.4	7/1	II	+	MC	7.7	2/0	I	MC	4	1.062	0/0	I	0/0	I	100	0
49,M	78	L	640	PMC,CR	2.7	21/8	III	-	PMC,CR	5.8	0/0	I	-	2.2	0.934	0/0	I	0/0	I	100	0
50,M	66	L	700	-	5	1/0	I	-	-	3.8	1/0	I	-	3.9	0.973	0/0	I	0/0	I	100	0
51,M	67	L	560	PLIC	66.3	21/8	III	+	PLIC	72.7	19/8	III	PLIC	65.3	0.639	16/8	III	10/6	III	30	5
52,M	67	R	432	MC SC CR	63.3	13/5	III	-	MC,SC,CR	84.5	9/4	II	MC,SC,CR	78.1	1.001	7/2	II	3/3	II	80	3
53,M	76	R	370	MC,PMC	28.8	18/3	II	+	MC,PMC	30.1	7/0	I	MC,PMC	26.7	1.032	7/0	I	4/0	I	90	3
54,M	79	L	390	-	3.9	6/0	I	+	-	6.5	0/0	I	-	1.1	1.132	0/0	I	0/0	I	100	0
55,M	71	R	150	MC,SC	9.1	4/1	II	-	MC,SC	10.4	0/0	I	MC,SC	8.9	1.067	0/0	I	0/0	I	100	0
56,F	73	R	720	CR PLIC	41	19/7	III	+	ALL	69.7	19/8	III	ALL	75.6	0.647	12/7	III	12/7	III	15	5
57,M	73	R	450	PLIC	14.4	17/6	III	+	PLIC	19.6	18/8	III	PLIC	11.1	0.747	10/7	III	7/7	III	50	4

58,M	80	L	210	MC,SC	5.4	7/5	III	+	MC,SC	5.4	6/4	II	MC,SC	5	0.778	3/1	I	1/0	II	90	3
59,F	75	L	100	MC,SC	13.3	14/8	III	+	MC,SC	15.2	5/4	II	SC	13.3	1.026	0/0	I	0/0	I	100	1
60,M	64	L	480	ALL	98.6	21/8	III	+	ALL	99.5	19/8	III	ALL	92	0.702	14/8	III	14/7	III	25	5
Mean	67.9		345.4		20.2					34.6				25.5	0.926					81.4	2.1
SD	13.7		182.8		23.3					36.8				31.9	0.161					30.3	1.6

Table 2. Associations between the specific CST regions affected in the acute stage and stroke severity, infarct volume, FA indexes at day 30, and motor outcome

	<12 hours							Day 3						
	Motor deficit day 30	Motor deficit day90	FA affected CST day30	FA ratio affected/ unaffected CST day30	Infarct Volume admission	Motor NIHSS admission	Total NIHSS admission	Motor deficit day30	Motor deficit day90	FA affected CST day30	FA ratio affected/ unaffected CST day30	Infarct Volume day3	Motor NIHSS day3	Total NIHSS day3
MC	0.639	0.873	0.686	0.575	**0.036**	0.959	0.969	0.392	0.558	0.334	0.327	0.082	0.383	0.481
PMC	0.949	0.710	0.659	0.224	**0.011**	0.826	0.251	0.218	0.107	0.485	0.132	0.011	0.360	0.193
CS	0.133	0.277	0.414	0.260	**0.039**	0.446	0.773	**0.001**	**0.014**	0.067	**0.019**	**0.001**	0.140	0.011
CR	0.914	0.941	0.155	0.974	0.069	0.054	**0.013**	**0.039**	**0.031**	0.763	**0.028**	**<.001**	0.125	0.054
PLIC	**<.001**	**<.001**	**<.001**	**<.001**	0.060	**0.001**	**0.001**	**<.001**	**<.001**	**<.001**	**<.001**	**0.004**	**<.001**	**<.001**
MC+PMC	0.339	0.231	0.684	0.209	**0.016**	0.659	0.192	0.161	0.095	0.128	0.058	**0.016**	0.245	0.153
CM+CS	0.069	0.172	0.219	0.155	**0.068**	0.302	0.699	0.058	0.127	0.183	0.131	**0.029**	0.090	0.190

CM+CR	0.191	0.123	0.628	0.277	**0.005**	0.493	0.305	**0.031**	**0.014**	0.227	0.063	**<.001**	0.145	0.161
PMC+CR	0.873	0.703	0.745	0.256	0.083	0.697	0.223	**0.001**	**<.001**	0.063	**0.005**	**0.010**	0.071	0.082
CM+PLIC	-	-	0.247	0.193	0.456	**0.032**	**<.001**	**0.015**	-	0.053	**0.037**	**0.014**	**-**	**<.001**
CS+CR	0.086	0.052	0.459	0.264	**0.017**	0.495	0.318	**<.001**	**<.001**	0.051	**0.006**	**<.001**	**0.003**	**0.003**
CS+PLIC	-	-	0.247	0.193	0.456	**0.032**	**<.001**	**<.001**	**<.001**	**0.024**	**<.001**	**0.003**	**<.001**	**<.001**
CR+PLIC	**0.028**	**0.015**	0.116	0.092	0.170	**<.001**	**<.001**	**<.001**	**<.001**	**0.004**	**<.001**	**0.005**	**<.001**	**<.001**
CS+CR+PLIC	**-**	**-**	0.247	0.193	0.456	**0.032**	**<.001**	**<.001**	**<.001**	**0.024**	**<.001**	**0.003**	**<.001**	**<.001**

Parameters with P value <.05 are highlighted in bold

Table 3. Sensitivity, specificity, and positive and negative predictive values for motor outcome according specific CST regions in acute stroke

	Motor outcome	m-NIHSS	Sensitivity	Specificity	PPV	NPV
PLIC<12 hours	day 30	I vs II/III	66.67	100.00	100.00	84.78
		II vs III	100.00	70.00	78.57	100.00
	day 90	**I vs II/III**	**73.68**	**100.00**	**100.00**	**89.13**
		II vs III	**100.00**	**71.43**	**85.71**	**100.00**
PLIC at day 3	day 30	I vs II/III	71.43	100.00	100.00	86.67
		II vs III	100.00	60.00	73.33	100.00
	day 90	I vs II/III	78.95	100.00	100.00	91.11
		II vs III	100.00	57.14	80.00	100.00
CS at day 3	day 30	I vs II/III	68.75	87.18	68.75	77.27
		II vs III	54.55	50.00	54.55	50.00
	day 90	I vs II/III	47.37	82.93	56.25	77.27
		II vs III	50.00	57.14	66.67	40.00

CR at day 3	day 30	I vs II/III	71.43	56.41	46.88	78.57
		II vs III	63.64	20.00	46.67	33.33
	day 90	I vs II/III	73.68	56.10	43.75	82.14
		II vs III	58.33	0.00	50.00	0.00

The highest overall values for all determinations are highlighted in bold

Table 4. Point-biserial and correlation coefficients between m-NIHSS at day 90 and the specific CST region involved, infarct volume, and motor score parameters in the first 12 hours, at day 3, and at day 30 after stroke

	m-NIHSS day 90		m-NIHSS day 90		m-NIHSS day 90
< 12 hours		Day 3		Day 30	
CR	$r_{pb=}$ -.243 $^{-}$	CR	$r_{pb=}$ -.052 $^{-}$	CR	$r_{pb=}$ -.139 $^{-}$
PLIC	$r_{pb=}$ .869 ***	PLIC	$r_{pb=}$ .817 ***	PLIC	$r_{pb=}$ .817 ***
SC	$r_{pb=}$ -.143 $^{-}$	SC	$r_{pb=}$ .112 $^{-}$	SC	$r_{pb=}$ .058 $^{-}$
m-NIHSS	$r_{=}$ .362 $^{-}$	m-NIHSS	$r_{=}$ .889 ***	m-NIHSS	$r_{=}$ .949 ***
Infarct volume	$r_{=}$ .363 $^{-}$	Infarct volume	$r_{=}$ .524 **	Infarct volume	$r_{=}$ .545 **
				rFA	$r_{=}$ -.720 ***

*** P<.001; ** P<.01; * P<.05; $^{-}$ NS

Table 5. Models selected from multiple regression analyses for predicting m-NIHSS 90 days after stroke from motor scores and specific CST regions

Predictors	B	t-value	Added R^2
Prediction of m-NIHSS at day 90 after stroke			
Measurements obtained <12 hours (R^2=75.50,F=80.09***)			
PLIC damage	5.36	8.95***	75.50
Constant	0.64		
Measurements obtained at 72 hours (R^2=85.62,F=74.39***)			
m-NIHSS	0.75	5.72***	79.00
PLIC damage	2.28	3.39**	6.62
Constant	-1.58		
Measurements obtained at day 30 (R^2=90.10,F=236.72***)			
m-NIHSS	0.96	15.39***	90.10
Constant	-0.40		

B = regression coefficient; *** P<.001; ** P<.01; * P <.05.