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Original article

CLINICAL PREDICTOR OF VOLUME HYPOPERFUSION IN PATIENTS TREATED WITH EXTENDED WINDOW MECHANICAL THROMBECTOMY: AN EXTERNAL VALIDATION STUDY

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Abstract

Introduction: Treatment of ischemic stroke has expanded beyond the 6-hour window, but identification of eligible patients requires advanced imaging, which is often unavailable.

This study aimed to validate a prediction model using the NIHSS score (a measure of stroke severity) to estimate hypoperfusion volume and determine eligibility for DEFUSE 3 treatment criteria.

Materials and methods: Data from ischemic stroke patients with less than 24 hours' evolution were analyzed. A previously developed prediction rule based on the NIHSS score was used to estimate the volume of hypoperfused tissue with Tmax>6s, a marker for eligibility for the DEFUSE 3 treatment criteria. This estimated volume was compared with actual perfusion volumes obtained by magnetic resonance imaging or computed tomography with AI segmentation. Sensitivity, specificity and predictive values for determining DEFUSE 3 eligibility were calculated.

Results: Sixty-one patients were included (age: 71.9 ± 14.8 years, female: 60%, NIHSS: 16.5 ± 7.4 points). The prediction rule showed high accuracy in determining DEFUSE 3 eligibility with a sensitivity of 0.96, specificity of 0.93, positive predictive value of 0.98 and negative predictive value of 0.87.

Discussion: Estimating hypoperfusion volume directly from the NIHSS score using a simple prediction rule provides a reliable and readily available method for identifying patients potentially eligible for DEFUSE 3 treatment. Rapid and reliable estimation of hypoperfusion volume could improve access to advanced stroke care in settings with limited imaging resources.

Key words: ischemic stroke, perfusion imaging, thrombectomy

Resumen

Volumen de hipoperfusión estimado clínicamente en pacientes tratados con trombectomía mecánica en ventana extendida. Un estudio de validación externa

Introducción: El tratamiento del accidente cerebrovascular isquémico se ha ampliado más allá de la ventana de 6 horas, pero la identificación de pacientes elegibles requiere imágenes avanzadas, que a menudo no están disponibles. Este estudio tuvo como objetivo validar un modelo de predicción utilizando la escala NIHSS (una medida de la gravedad del accidente cerebrovascular) para estimar el volumen de hipoperfusión y determinar la elegibilidad para los criterios de tratamiento DEFUSE 3.

Materiales y métodos: Se analizaron datos de pacientes con accidente cerebrovascular isquémico con menos de 24 horas de evolución. Se utilizó una regla de predicción previamente desarrollada basada en la escala NIHSS para estimar el volumen de tejido hipo-

perfundido con Tmax>6s, un marcador de elegibilidad para los criterios de tratamiento DEFUSE 3. Este volumen estimado se comparó con los volúmenes de perfusión reales obtenidos por resonancia magnética o tomografía computarizada con segmentación de inteligencia artificial. Se calcularon la sensibilidad, especificidad y valores predictivos para determinar la elegibilidad de DEFUSE 3.

Resultados: Se incluyeron 61 pacientes (edad: 71.9 ± 14.8 años, mujeres: 60%, NIHSS: 16.5 ± 7.4 puntos). La regla de predicción mostró una alta precisión en la determinación de la elegibilidad de DEFUSE 3 con una sensibilidad de 0.96, especificidad de 0.93, valor predictivo positivo de 0.98 y valor predictivo negativo de 0.87.

Discusión: Estimar el volumen de hipoperfusión directamente a partir de la escala NIHSS utilizando una regla de predicción simple proporciona un método confiable y fácilmente disponible para identificar a los pacientes potencialmente elegibles para el tratamiento DEFUSE 3. La estimación rápida y confiable del volumen de hipoperfusión podría mejorar el acceso a la atención avanzada del accidente cerebrovascular en entornos con recursos de imágenes limitados.

Palabras clave: ACV isquémico, imagen de perfusión, trombectomía mecánica

KEY POINTS
Current knowledge

- Extended window mechanical thrombectomy improves neurological outcomes in ischemic stroke with large vessel occlusion. Patient selection for endovascular treatment often relies on advanced neuroimaging, which may be limited. Past research suggests clinical data can estimate parameters derived from advanced neuroimaging.

Contribution of the article to current knowledge

- In our study, we validated a clinical prediction rule that allows estimating eligibility based on DEFUSE 3 criteria for patient selection for extended window mechanical thrombectomy.
- These results suggest that it might be possible to select patients in the extended window without the need for advanced neuroimaging studies.

The selection of patients with acute ischemic stroke (IS) due to proximal large vessel occlusion (LVO) for mechanical thrombectomy (MT) depends on the time that has elapsed since the event. Within the first six hours of symptom onset, a National Institute of Health Stroke Scale (NIHSS) and an Alberta stroke program early CT score (ASPECTS) greater than 6 are adequate to establish the indication[1].

In patients within 6 to 24 hours since last known to be well, on the other hand, it is necessary to demonstrate the presence of ischemic penumbra through the mismatch (MM) between the ischemic core and the NIHSS (DAWN criteria)[2] or between the ischemic core and the perfusion defect (DEFUSE 3 criteria)[3]. For the latter, the use of advanced neuroimaging and complex post-processing software is necessary. The ischemic core volume can be estimated without the need for perfusion studies in a semiquantitative manner by means of the CT-ASPECTS[4], CTA-ASPECTS[5] scale or measured in the diffusion weighted image (DWI) sequence in magnetic resonance image (MRI). While the determination of the perfusion defect, whether for the estimation of the ischemic core volume or the penumbra, necessarily implies the implementation of advanced acquisition and post-processing techniques[6]. The availability of these techniques, particularly in emerging countries, is limited[7]. This means that a significant number of patients with ischemic stroke due to LVO and evolution time greater than 6 hours who are admitted to centers with MT availability cannot access this therapy because this diagnostic technology is not available and they cannot be referred to nearby centers because they do not have it either. In recent years, interest has arisen in the study of these patients with non-advanced imaging using surrogates capable of providing data on stroke evolution, information on the ischemic core and more recently, information on the perfusion status.

It has been suggested that the quantification of the clinical severity of a stroke event through the NIHSS can be used to estimate the perfusion defect in patients. This serves as a surrogate for the hypoperfusion volume, specifically Tmax>6s volume[8].

In this regard, Desai et al developed a model that can estimate the volume of hypoperfused tissue by using the Clinical Approximated Hypoperfused Tissue Volume (CAT) derived from the NIHSS score and a multiplication factor (MF). Consequently, the Tmax>6s volumes can be predicted accurately from the NIHSS[8]. Our aim was to validate this predictive rule in a population of patients with LVO stroke at our center.

Materials and methods

Six hundred and sixty-four patients admitted for ischemic brain events were screened in the stroke unit of the comprehensive stroke center *Clínica La Sagrada Familia* (Buenos Aires - Argentina) between May 1, 2020, and April 30, 2022. Four hundred and forty-six patients were excluded for not presenting LVO, 20 for receiving a final diagnosis of stroke mimic, and 77 for a final diagnosis of TIA. Sixty patients were excluded for not having adequate perfusion studies (poor technical quality, not having undergone perfusion studies, not artificial intelligence [AI] post processed).

Final analysis included 61 patients who presented with anterior circulation LVO strokes up to 24 hours (internal carotid and middle cerebral artery in segments M1 and M2) who had perfusion studies available either by magnetic resonance or computed tomography with the subsequent calculation of the Tmax>6s volume obtained by post-processing the images with the RAPID AI iSchemaView software.

Both demographic and clinical data (sex, age, NIHSS at admission, time since last known to be well) were obtained, as well as variables provided by neuroimaging that corresponded to the determination of the ischemic core by perfusion in CT [volume with an rCBF (relative cerebral blood flow) < 30%] or in the DWI on MRI [volume with an ADC <620] and of the perfusion defect on either CT or MRI [volume with a Tmax (time to peak residual function) >6 seconds]). These data were obtained from the patients' medical records.

It was determined that patients met DEFUSE 3 criteria if they had an ischemic core less than 70 mL, MM ratio greater than or equal to 1.8 (Tmax volume>6/ischemic core volume), and a penumbra volume greater than or equal to 15 mL (volume difference Tmax>6-core ischemic). DEFUSE 3 eligibility determined in this way was considered the gold standard[3].

The Tmax>6e volume was calculated through the NIHSS according to the model proposed by Desai et al as follows[8,9].

Tmax>6e volume = NIHSS * MF

If →NIHSS < a 10 → Tmax>6e volume = NIHSS * 15

If →NIHSS ≥ a 10 → Tmax>6e volume = NIHSS * 6

Further, eligibility was determined by DEFUSE 3 criteria according to the MM core penumbra based on the calculated CAT volume (Tmax>6e) and the core volume determined by the rCBF <30% from the CT perfusion study or the MRI diffusion sequence as the volume with an ADC <620, with the ischemic core values provided by the RAPID AI iSchemaView analysis.

Statistical analysis

Continuous variables were expressed as mean and standard deviation or median and interquartile range, depending on their distribution (assessed by the Kolmogorov-Smirnov normality test). Categorical variables were expressed as percentages.

The linear correlation between NIHSS and Tmax volume >6s was estimated with Pearson's coefficient. To determine the agreement between Tmax volume >6s and estimated Tmax>6s volume the intraclass correlation coefficient for absolute agreement was used[9]. Additionally, a Bland-Altman plot was generated to assess the agreement between Tmax>6 and Tmax>6e[10,11].

We evaluated the sensitivity, specificity, positive predictive value, and negative predictive value, with their respective 95% confidence interval, for the detection of eligibility by DEFUSE 3 criteria[12].

Statistical analysis was performed with IBM SPSS statistics version 25 for macOS and MedCalc for Bland-Altman plot.

Ethical approval

Ethics approval was obtained from the Ethic Committee of *Clínica La Sagrada Familia* (SF//0053).

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. All patients gave their written informed consent for habeas data.

Results

Sixty-one patients were included in the analysis (Table 1). The mean age was 71.8 ± 14.8 years, 59% were female. Vascular occlusion was at the level of the middle cerebral artery in segments M1 (68.9%), M2 (4.9%) and in the terminal carotid artery (26%). Endovascular treatment was received in 98.4%. The mean NIHSS at admission was 16.5 ± 7.4 points. The median time from symptom onset to perfusion imaging was 499 minutes (IQR 306-798) and 66.1% of patients presented beyond 360 minutes. Forty-seven (77%) of patients met DEFUSE 3 criteria.

The mean Tmax>6s volume was 156 ± 79 ml and the core had a median of 22 ml (IQR 0 to 59). The mean Tmax>6e volume was 107 ± 37 ml.

Albeit weak, a significant correlation was found between NIHSS on admission and Tmax>6s volume measured by perfusion (r=0.32 p=0.007) (Figure 1). This was similar when the correlation between Tmax>6s volume and Tmax>6e volume was evaluated (r=0.34 p=0.007) (Figure 2). The intraclass correlation coefficient was 0.33 (p=0.019) suggesting low agreement. The Bland-Altman plot revealed an average bias of 49.2 ml with limits of agreement between -97.4 and 195.7 ml (Figure 3).

The sensitivity, specificity, positive predictive value, and negative predictive value of Tmax>6e volume for determining DEFUSE 3 eligibility criteria were 0.96 (IC 95% 0,90-0.99), 0.93 (IC 95% 0.72-0.99), 0.98(IC 95% 0.91-0.99), and 0.87 (IC 95% 0.64-0.97) respectively. As shown in Table 2 only two false negative results and one false positive were found.

A subanalysis was performed on patients with more than 6 hours of evolution obtaining similar findings (S: 0.96 [IC 95% 82-99%] E:0.91 [IC 95% 59-99%] PPV: 0.96 [IC 95% 81-99%] NPV 0.91 [IC 95% 83-99%]).

Table 1 | Characteristics of the study population

	n = 61
Female (%)	59
Age (mean +/- SD)	71.9 (14.8)
Median time from stroke onset to qualifying imaging (IQR) in minutes	499 (306-798)
More than 6hs of evolution (%)	63.9
Mechanical thrombectomy	98.4
Vessel occluded (%)	
MCA M1	68.9
MCA M2	4.9
ICA	26
NIHSS at admission (mean ± SD)†	16.5 (7.4)
Median volume of ischemic core (IQR) - mL	22 (0-59)
Tmax>6s volume (mean ± SD) in mL‡	156 (79)
Tmax>6e volume (mean ± DS) in mL§	107 (37)
Average bias* in mL (limit of agreement)	49.2 (-97.4 and 195.7)
Eligibility with DEFUSE 3 criteria with Tmax>6 seconds (%)	77
Eligibility with DEFUSE 3 criteria with Tmax>6e (%)	75.4

MCA M1: middle cerebral artery M1 segment; MCA M2: middle cerebral artery M2 segment; ICA: internal carotid artery

‡*Tmax>6s: time to peak residual function value)>6 seconds measured using RAPID, IschemiaView*

§*Tmax>6e: Tmax>6s estimated using NIHSS basal x Multiplication Factor*

**average bias of the mean of the difference between measured Tmax>6sec and estimated Tmax>6sec (in Bland-Altman plot)*

†*Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a greater deficit*

Figure 1 | Graph of scatter plot showing the relationship between NIHSS at admission and Tmax>6s volume, (r = 0.32 p = 0.007), n = 61

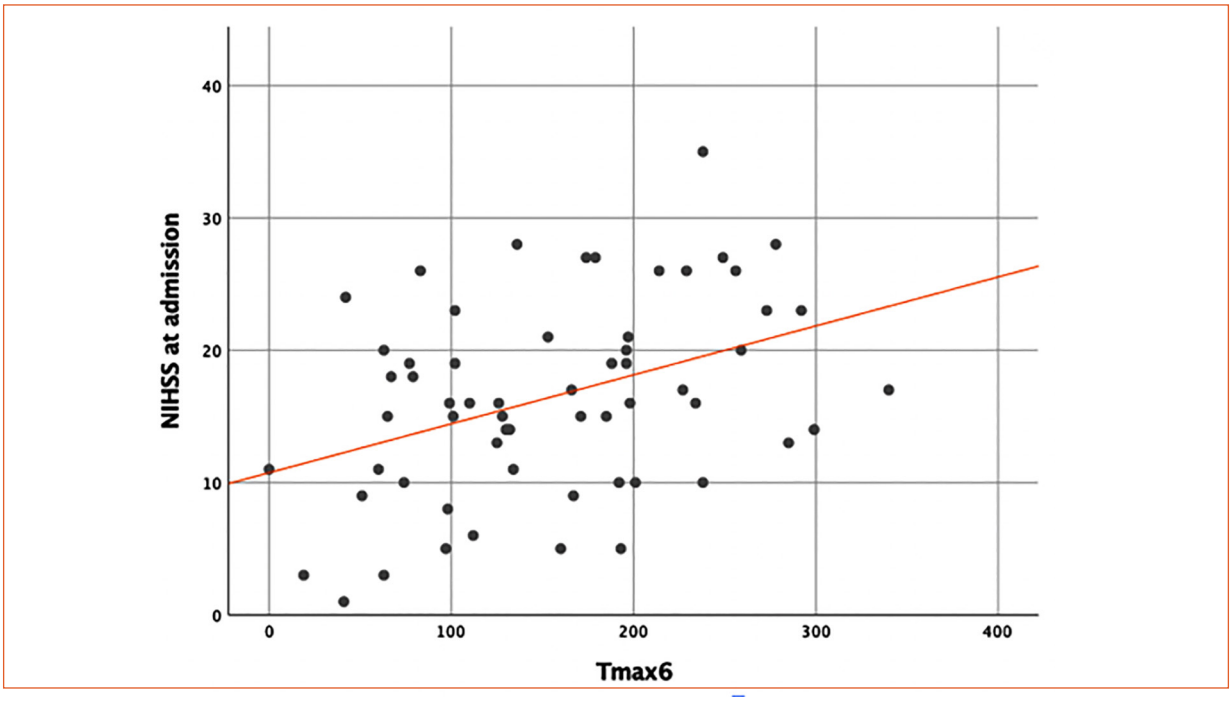

Figure 2 | Graph of scatter plot showing the relationship between the estimated Tmax>6s volume and the measured Tmax>6s volume, (r = 0.34 p = 0.007), n = 61

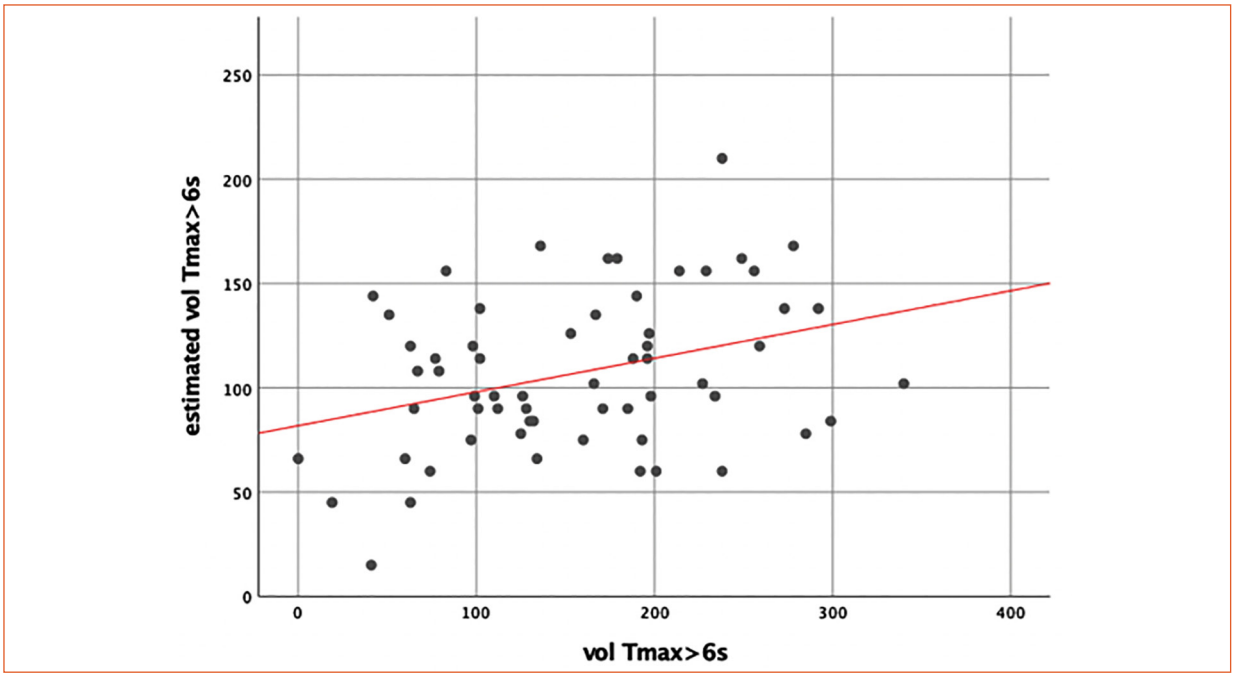

Figure 3 | Bland-Altman plot showing the agreement between Tmax6 and EstimatedTmax6. The x-axis represents the average of the two methods' measurements, and the y-axis represents the difference between the two methods' measurements. The solid line represents the mean difference (bias) of 49.2 ml, and the dashed lines represent the limits of agreement, which range from -97.4 ml to 195.7 ml

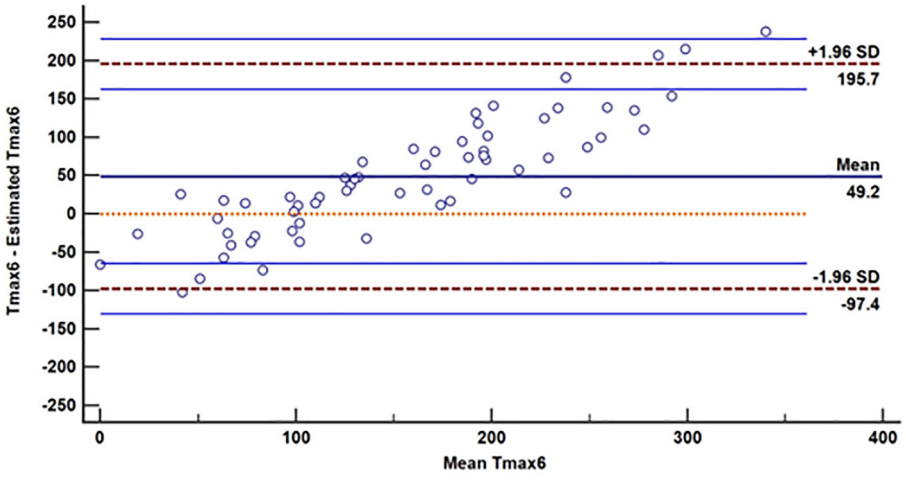

Table 2 | Diagnostic test performance

n=61		DEFUSE 3 con Tmax>6e[§]	
		-	+
DEFUSE 3 with Tmax>6s	-	TN = 13	FP = 1
measured[‡]	+	FN = 2	TP =4 5

TP: true positives; TN: true negatives; FN: false negatives; FP: false positives
The determination of DEFUSE 3 criteria by estimating the hypoperfusion volume from NIHSS at admission produces two false negative results and one false positive, which corresponds to a sensitivity, specificity, positive predictive value, and negative predictive value of 0.96 (IC 95% 0.90-0.99), 0.93 (IC 95% 0.72-0.99), 0.98(IC 95% 0.91-0.99), and 0.87 (IC 95% 0.64-0.97), respectively.
[‡]*Tmax>6s measured: Tmax>6s measured using RAPID, IschemiaView*
[§]*Tmax>6e: Tmax>6s estimated using NIHSS basal x Multiplication Factor*

Discussion

The main finding of our study is that eligibility by DEFUSE 3 criteria can be determined based on the estimation of the Tmax>6s volume using the clinical severity of the event determined by the NIHSS scale. Our results confirm those published by Desai[8].

Pivotal studies demonstrated the benefit of MT associated with intravenous thrombolysis in patients with acute ischemic stroke and proximal LVO when presented within 6 hours of the onset of the event[13]. Subsequently, the DAWN and DEFUSE 3 studies demonstrated the benefit of MT in windows of 6 to 24 h and 6 to 16 hours, respectively, in patients with limited ischemic core volume[2,3]. In both studies, a neuroimaging selection criterion was used to ensure the presence of salvageable tissue. In the case of DAWN, patients with clinical-core MM, that is, relatively high NIHSS values in relation to the core volume measured by MRI [volume with an ADC <620] or by CT perfusion [rCBF < 30%], were selected. A

similar criterion was used in DEFUSE 3, but the MM ratio between the volume of the perfusion defect (time to peak residual function value)>6 seconds [Tmax>6s volume]) in relation to the ischemic core volume was considered. In both studies, RAPID AI iSchemaView software was used for automatic processing and segmentation of the mentioned volumes.

Current American Stroke Association guidelines recommend the use of these technologies for the selection of patients in a late window (6 to 24 hours) to determine eligibility for MT[1]. At present, there are some limitations in the implementation of these criteria. Accessibility in our environment is limited, with few centers having this technology based on artificial intelligence[7], which is a limitation for access to reperfusion of patients with large vessel occlusion in windows longer than 6 hours.

Regarding the DAWN criteria, the ischemic core can be determined by CT perfusion or MRI diffusion as mentioned above without requiring the determination of the Tmax>6s volume and thus the MM is determined based on the patient's NIHSS as a surrogate for the total perfusion defect. However, it should be noted that the DAWN criteria are less inclusive than the DEFUSE 3 criteria and using only the former could unduly exclude patients who are candidates for reperfusion therapy[14].

The model developed by Desai et al to predict Tmax>6s volume from the patient's NIHSS follows the concept of clinical/perfusion correlation. Although the correlation between the two parameters was poor (r=0.168) they demonstrated that replacing the measured Tmax>6s volume with that estimated can determine eligibility with a sensitivity of 100% and a specificity of 92% when the DEFUSE 3 criteria determined with the volume provided by the automated analysis of Tmax>6s is taken as the gold standard, thus demonstrating the clinical applicability of Tmax>6e[8]. In the validation cohort of the original study, the determination of Tmax>6s volume was found to have a sensitivity of 100% and a specificity of 92% when used in conjunction with determination of the ischemic core to detect eligibility by DEFUSE 3 criteria[8].

Our findings are consistent with those of Desai et al. Although as in the original study the correlation values between measured and estimated Tmax>6s volume were weak (r=0.34 p=0.007) the sensitivity and specificity of the rule to determine eligibility by DEFUSE 3 criteria was high with only two false negatives and one false positive out of a total of 61 patients, which implies its clinical usefulness. The data extracted from the Bland-Altman plot suggest an overall trend towards underestimation of the hypoperfusion volume although a linear trend is also observed indicating overestimation with lower values of Tmax6 and underestimation when values are higher.

It is noteworthy that after determining the Tmax>6e volume according to NIHSS it is necessary to know the core volume to infer eligibility by DEFUSE 3 criteria. In the study by Desai et al and in the present study, the core volume determined by perfusion or diffusion and post-processing with RAPID AI, iSchemaView was used.

Currently the minimum technology necessary to implement this rule along with core estimation is widely available; recently, a freely available, open source, deep learning-based tool has been developed that allows automatic segmentation of ischemic core on diffusion-weighted MRI images[15]. In recent years, with the advance of knowledge that allows estimation of the ischemic core with non-advanced imaging studies, there is a tendency to simplify the selection of patients for endovascular treatment even in hyperextended windows and large-volume cores. In this way, manual segmentation of the core with freely available software[16] and estimation of core volume by means of the ABC/2 rule in MRI diffusion studies are possible[17]. It is also possible to use the ASPECTS scale as a surrogate for core volume[4].

A recent meta-analysis included four controlled studies and 28 uncontrolled studies to evaluate the efficacy of selecting patients for MT within a 6 to 24 hours' window using NCCT and the ASPECTS scale. The results of the meta-analysis indicated that this patient selection strategy showed no significant difference in terms of neurological disability compared to patients selected using advanced imaging studies[18].

More recently three randomized studies demonstrated the benefit of MT in patients with large ischemic core volumes corresponding to

low scores (3-5) on the ASPECTS scale in window of up to 24 hours[19-21]. The MR CLEAN-LATE study demonstrated the effectiveness of MT in patients with proximal occlusion when selected according to collateral circulation status on arterial phase angiotomography without perfusion studies[22].

There are some limitations to this external validation study. First, the retrospective nature of data collection must be considered. In addition, the inclusion of patients was performed in a specific referral center, which may generate a selection bias. Importantly, in our study population, a relatively high proportion of patients meeting DEFUSE 3 criteria was observed (77%). This may influence the overestimation of the sensitivity and specificity of the model, as it is possible that these selected patients have characteristics that better fit the model predictions. Therefore, these limitations need to be considered when interpreting the results and generalized to other clinical settings and populations.

Although its use could be useful to extend the indication of MT in centers without availability of advanced neuroimaging, it should be noted that the implementation of this prediction rule for the estimation of Tmax volume>6s is not currently recommended by clinical practice guidelines and its use should be carefully considered in institutional protocols. The use of this rule could generate the inappropriate inclusion or exclusion of patients. The sensitivity and specificity of the method both in its original description and in our population demonstrate that the greatest risk would be the exclusion of the treatment due to underestimation of the penumbra.

In summary, although the evaluation of patients with stroke has become ostensibly more complex since the publication of the DAWN and DEFUSE 3 studies, in recent years evidence has emerged to simplify the selection of patients to be treated, even in extended windows. In this context, our findings show that eligibility by DEFUSE 3 criteria can be rapidly inferred by estimating the hypoperfusion Tmax>6s volume from the NIHSS. Future work should study the relationship between Tmax>6e and an ischemic core surrogate such as the ASPECTS scale.

Conflict of interest: None to declare

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