Master's Thesis of Medicine

Measurement of infarct volumes in CT perfusion maps using different commercial software: quantitative analysis by using identical source data of acute stroke patients

상이한 상용 소프트웨어를 사용한 CT 관류 맵에서의 경색 용적 측정: 급성 뇌졸중 환자에서 동일한 소스 데이터를 사용한 정량적 분석

August 2021

Graduate School of Medicine
Seoul National University
Radiology Major

Chuluunbaatar Otgonbaatar

Measurement of infarct volumes in CT perfusion maps using different commercial software: quantitative analysis by using identical source data of acute stroke patients

지도교수 손철호

이 논문을 의학 석사 학위논문으로 제출함

2021년 08월

서울대학교 대학원
의학과 영상의학전공
Chuluunbaatar Otgonbaatar

Chuluunbaatar Otgonbaatar의
석사 학위 논문을 인준함

2021년 08월

위 원 장 _____
부위원장 _____
위 원 _____

Abstract

Measurement of infarct volumes in CT perfusion maps using different commercial software: quantitative analysis by using identical source data of acute stroke patients

Chuluunbaatar Otgonbaatar
Department of Radiology
The Graduate School
Seoul National University

Purpose: Although using Computed Tomography Perfusion (CTP) for selecting and guiding decision-making processes of a patient with acute ischemic stroke has its advantages, there is no clear standardization of the optimal threshold and parameters used to predict infarct core volume accurately. Nowadays, infarct core volume with a rCBF<30% threshold is commonly used. However, several studies have been performed to assess the volumetric agreement of CTP infarct core volume with follow-up Diffusion-Weighted Imaging (DWI); the time between CTP and DWI was within 24 hours. In this study, we aimed to assess the volumetric agreement of estimated infarct core volume with different

deconvolution methods, parameters, and thresholds on CTP software programs, including: RAPID, singular value decomposition plus (SVD+) VITREA, BAYESIAN VITREA, and also the final infarct volume on DWI with an especially short interval time (within 60 min) between CTP and follow-up DWI.

Materials and methods: Forty-two acute ischemic stroke patients with occlusion of a large artery in the anterior circulation were included in the study. The CT perfusion maps were processed with different CT perfusion software, including SVD+ and Bayesian algorithms in VITREA and RAPID. The RAPID identified infarct core as tissue rCBF < 20-38% and rCBV < 34-42%. The SVD+ VITREA defined infarct core as CBV reduction of 26% - 56%. The Bayesian VITREA quantified infarct core as tissue CBV reduction of 28% - 48%. Olea Sphere was used to measure the infarct core volume on DWI. The CTP infarct core volume measurements were compared with the final infarct volume, which was determined on DWI.

Results: The CTP was performed before DWI in all patients, and the median time between CTP and DWI was 37.5 minutes, with an interquartile range (IQR) of 20 – 44. In 42 patients, the median final infarct volume was 19.50 ml (IQR 6.91 – 69.72) with DWI. The most commonly used thresholds for each kind of CTP software,

including RAPID rCBF<30%, resulted in a median infarct volume difference (IQR) of 8.19 ml (3.95 – 30.70), spearman's correlation coefficient (r) = 0.759; SVD+ VITREA CBV reduction of 41% demonstrated a median infarct volume difference (IQR) of 3.82 ml (−2.91 – 20.95), r = 0.717; and BAYESIAN VITREA CBV reduction of 38% resulted in a median infarct volume difference (IQR) of 8.16 ml (1.58 – 25.46), r = 0.754. On the other hand, the optimal thresholds for each kind of software ended up estimating infarct core volume more accurately than the commonly used thresholds with lower infarct core volume differences. The most accurate and optimal infarct core volume thresholds for each kind of software were as follows: median infarct core volume difference (IQR) for RAPID rCBF<38% was 4.87 ml (0.84 – 23.51), r = 0.752; SVD+ VITREA CBV reduction of 26% was −1.05 ml (−12.26 – 14.58), r = 0.679; BAYESIAN VITREA CBV reduction of 28% was 5.23 ml (−2.90 – 22.91), r = 0.685.

Conclusions: Our study found that the CBV thresholds provide a more accurate parameter to predict infarct core volume in acute ischemic stroke patients compared with the CBF thresholds.

Keyword: Computed Tomography Perfusion, acute ischemic stroke, stroke core volume, RAPID, Vitrea, Bayesian, DWI

Student Number: 2019−24153

Contents

Tables

Figures

Chapter 1. Introduction

1.1. Study Background

A stroke is defined by the World Health Organization (WHO) as a “rapidly developing clinical sign of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer to death, with no apparent cause other than of vascular origin” [1]. Overall, most strokes are caused by insufficient blood flow to the brain tissue while the remainders are caused by hemorrhagic in origin. Acute ischemic stroke (AIS) remains a leading cause of disability and mortality worldwide. There are various etiologies for acute ischemic stroke. According to the Trial of Acute Stroke Treatment (TOAST) classification [2], there are five subtypes of ischemic strokes, including large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.

The non-contrast computed tomography (NCCT) is the first-line imaging that can be performed to exclude hemorrhage [3]. The findings of stroke on CT included hypodensity, loss of grey and white matter differentiation, loss of insular ribbon sign, loss of

cortical sulci, and hyperattenuating artery sign [4]. Magnetic resonance imaging (MRI) is also a helpful imaging technique for acute ischemic stroke diagnosis with more specificity and sensitivity than CT. Imaging parameters including T2-weighted imaging (T2WI), Fluid-Attenuated inversion-recovery (FLAIR), T2*-weighted gradient recalled echo (GRE), susceptibility-weighted imaging (SWI), MR angiography (MRA), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), ASL (arterial spin labeling) - perfusion-weighted imaging (PWI) achieves reliable information about the acute ischemic stroke and helpful for exclusion of differential diagnosis. Ischemic lesions appear as hyperintense areas in T2WI and FLAIR images within the first 3-8 hours of symptom onset [5, 6]. The GRE and SWI are sensitive for detecting the thrombus. The DWI is sensitive to changes in microcirculation disturbance, cell swelling [7], and provides trustworthy information on ischemic brain changes. The rate of water molecular diffusion decreased in acute stroke due to cytotoxic edema. Therefore the normal motion of water molecules (Brownian motion) is restricted in the affected tissue whereas lesion appears as hyperintense on DWI and hypointense on ADC within as early as 30 minutes after symptom onset [8, 9]. It allows early identification of lesion site, size, and time especially to the

hyperacute phase, with its specificity and sensitivity of 86–100% and 88–100% [10–13].

The Computed Tomography Perfusion (CTP) is the modern imaging technique that describes the cerebral tissue's hemodynamics and can be performed for evaluating acute stroke patients. CTP is widely used practically for selecting patients with acute ischemic stroke, guiding decision–making, and it has its advantages, including cost effectivity, availability, ease of patient monitoring, fast scanning, dynamic and angiographic imaging. Unfortunately, it has variability in quantification based on different underlying post–processing technique and thresholds applied by various software [14–16]. Brain perfusion maps can describe the brain tissue flow with several parameters, including the time to maximum peak (Tmax), cerebral blood volume (CBV), mean transit time (MTT), and cerebral blood flow (CBF). The CBV is defined as the volume of flowing blood in a given volume of the brain and is measured in units of milliliters of blood per 100 g of the brain. The CBF is defined as the volume of blood moving through a given volume of the brain in a specific amount of time and is measured in units of blood per 100 g of brain tissue per minute. The MTT is defined as the average amount of time of blood through the given volume of the brain and is measured in seconds [17]. The infarct

core is typically defined as the decreased CBF and CBV with increased MTT that suggests irreversible loss of function. The penumbra is defined as the decreased CBF with maintained CBV, indicating potentially salvageable tissue [18]. The basis of CTP is the intravascular tracer system. The entire volume of interest is supplied with blood by a single artery and drained by a single vein. Blood cells can take various paths through the capillary bed with different transit time depending on the chosen way. Therefore, local contrast agent concentration in the arterial, venous side and within the volume of interest can be measured in the time−concentration curves.

The residue function can be calculated by using the tissue concentration curve as follows:

Ctissue (t) = CBF x R (t) Ø AIF (t)

Ctissue (t) − tissue concentration curve

R(t) − residue function

AIF (t) − arterial input function

Ø – convolution operator.

Ctissue (t) and AIF (t) can be measured directly from the time−

attenuation curve from CTP, but the residue function's calculation becomes a problem. Several methods have been presented to deconvolute the tissue concentration curve [19]. There are two main deconvolution methods, including 1) model-dependent and 2) model-independent approach. Deconvolution is a standard methods employed for postprocessing CTP, and the singular value decomposition method, a model-independent, nonparametric deconvolution method, which are widely used in clinical practice [20]. Another alternative deconvolutions include Fourier transform-based deconvolution, nonlinear stochastic regularization [21], wavelet thresholding, Gaussian process deconvolution [22], and maximum likelihood estimation have been used for perfusion data [23-25]. There are several variants in the singular value decomposition included standard SVD (sSVD), block-circulant SVD (bSVD) or oscillation index SVD (oSVD) [26]. SVD+ is a tracer delay-insensitive singular value decomposition deconvolution algorithm known as being sensitive to noise. Theoretically, singular value decomposition is a matrix factorization method used to decompose matrix into the following three other matrices [27] (Figure 1):

$A = U\sum V^T$; whereas

A – real matrix of m x n

U – orthonormal (m x m matrix); right singular vector of A

$\sum$ – rectangular diagonal (m x n matrix)

V^T – conjugate transpose (n x n matrix; left singular vector of A.

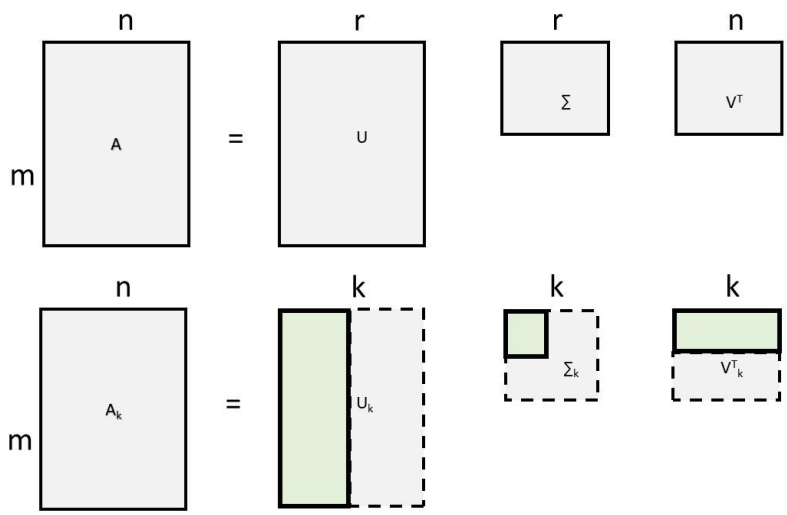


Figure 1. The architecture of the singular value decomposition

In other word, it is a linear system that transform the original data into a lower rank matrix. SVD+ uses an innovative preconditioning technique to minimize noise and stabilizes the algorithm to ensure fast calculation times. SVD+ is similar to randomized SVD which can be used to obtain rank−k singular value decomposition. When the original data (A) is large, matrices can be reduced in size, which would be similarly to original data(A) through randomized singular value decomposition [28]. Randomized singular value decomposition

algorithm uses random projection (**Ω**) to input original A into the reduced matrix. Then low-rank factorization could be obtained by manipulating the reduced matrix [29] (Figure 2).

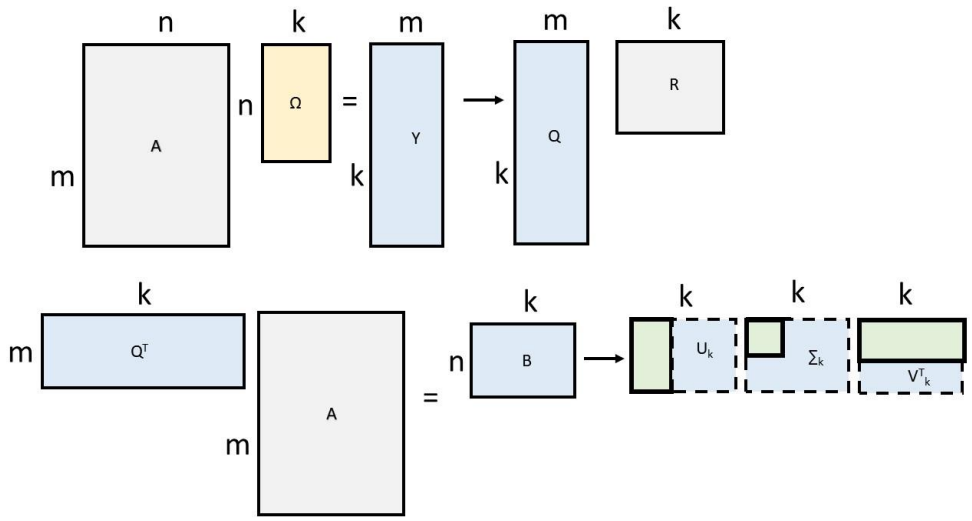


Figure 2. The architecture of the randomized singular value decomposition

Several trials [30-33] selected patients based on CTP infarct core volumes, which were calculated by using RAPID software and concluded that rCBF < 30% is a reliable threshold for infarct core volume prediction. The RAPID (iSchema View, Menlo Park, CA, USA) relies on the CBF parameters, while the Bayesian VITREA and SVD+VITREA depend on the CBV to identify the infarct volume. The Bayesian method [26], which is delay insensitive and uses a probabilistic approach that reduces the

oscillation and noise for estimating CBF, CBV and MTT maps [25], was introduced recently. The Bayes theorem is the basis of Bayesian method and it describes the outcome probabilities of related events or condition with conditional probability [34]. Therefore, the posterior probability of an event or conditions are calculated based on the current knowledge. The posterior probability is determined by updating the prior probability by the Bayes theorem. (Figure 3)

$$P(A|B) = \frac{P(B|A) \times P(A)}{P(B)}$$

P (A) marginal or prior probability of A

P (B) marginal or prior probability of B

P (B|A) likelihood function for B given A

P (A|B) posterior probability of A given B.

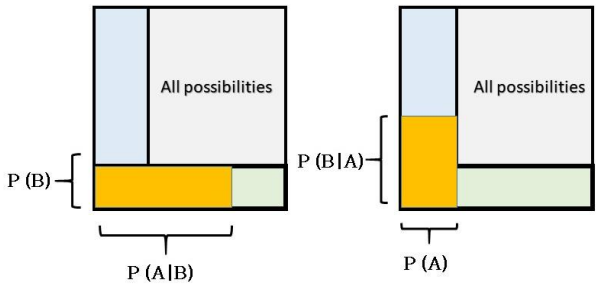


Figure 3. Bayes theorem algorithm

This technique has fewer errors on all parameters and is considered

the most accurate method without tracer-delay effect [26]. The precise estimation of perfusion yielded better results in the previous phantom [35] and clinical studies [36, 37]. Unfortunately, there is no clear standardization of the optimal threshold and parameters for predicting accurate infarct core volume.

Thrombolytic therapy is an effective treatment for acute ischemic stroke, and the US Food and Drug Administration (FDA) approved the intravenous tissue plasminogen activator (tPA) within three hours after stroke in 1996 [38]. The Multicenter RCT of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) [39] reported that the result of 500 patients who had an arterial occlusion in the anterior cerebral circulation and treated intraarterially within 6 hours after symptom onset. 32.6% of patients achieved good primary outcomes (modified Rankin scale at 90 days) with thrombectomy than the control group (19%). SWIFT PRIME [32] trial compared intravenous t-PA to endovascular thrombectomy using a stent retriever within 6 hours after the onset of stroke. Similarly, the rate of functional independence was significantly higher in the thrombectomy group (60%) than the intravenous t-PA group (35%), and there was no significant difference in the 90-day mortality between the two groups. The

Endovascular Treatment for Small Core and Anterior Circulation Proximal occlusion with Emphasis on Minimizing Computed Tomography to Recanalization Times (ESCAPE) [40] and The Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) [41] trials showed that the thrombectomy resulted in better clinical outcome compared with the medical management for patients with anterior circulation acute ischemic stroke up to 8 hours. DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) and DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) trials both demonstrated the benefits of mechanical thrombectomy for patients with AIS within 16h [31] and 24h [30] respectively based on CTP or MRI.

CT ASPECTS ≥ 6 score, moderate to good collateral (>50% MCA territory) on multiphase CTA, DWI ASPECTS ≥ 5, infarct volume ≤ 50 to 70 ml, and penumbra to core mismatch on perfusion imaging have been used for imaging selection criteria for thrombectomy within < 6 hours after the onset of stroke [42]. The radiographic selection criteria of DEFUSE 3 trial was ischemic core

volume < 70 ml, mismatch volume > 15 ml (Tmax > 6 sec) on CT or MRI perfusion. The DAWN trial defined the mismatch group into age < 80 years, infarct core ≤ 30 ml or age < 80 years, infarct core 31 – 51 ml or age ≥ 80 years, infarct core 0 – 20 ml on CT or MRI perfusion imaging. The selection of ideal patients for treatment requires quantification of the ischemic core and penumbra volume accurately on admission [43].

Accurate and rapid identification of the salvageable brain tissue resulted from ischemic changes is crucial for decision-making in intervention. In previous studies, the importance of measuring the size of the infarct core and penumbra area has shown a positive correlation with clinical outcome and predicting the efficiency of the treatment [44]. A large lesion volume greater than approximately 70 ml is associated with poor outcome and hemorrhage risk [45, 46]. However, several studies have been performed to assess the volumetric agreement of CTP infarct core volume with follow-up diffusion-weighted imaging (DWI); the time between CTP and DWI was within 24 hours.

1.2. Purpose of Research

Aimed to assess the volumetric agreement of estimated infarct core volume with different deconvolution methods, parameters, and thresholds on CTP software programs, including: RAPID, singular value decomposition plus (SVD+) VITREA, BAYESIAN VITREA, and also the final infarct volume on DWI with an especially short interval time (within 60 min) between CTP and follow-up DWI.

Chapter 2. Materials and methods

2.1. Patient selection

This is a retrospective study that included patients who met the following inclusion criteria from Apr. 2017 to Jan. 2021. The inclusion criteria were the following: 1) diagnosis of an acute ischemic stroke, 2) baseline DWI and CTP, 3) DWI within 1 hour after CTP, 4) occlusion of the large artery in the anterior circulation including middle cerebral artery, anterior cerebral artery, and internal carotid artery terminus. The study was approved by the institutional review board of the hospital. The exclusion criteria included motion artifacts, unmatching the location of infarct core volume between CTP and DWI. The clinical information including the history of the disease, time from onset to the emergency department door, National Institutes of Health Stroke Scale (NIHSS) at admission, methods of treatment, and the DWI time interval followed by CTP were collected.

2.2. Imaging protocol

All CT scans were performed on a 320-detector row scanner (Aquilion ONE, Toshiba Medical System) with imaging protocols including tube voltage 80 kVp, tube current 150 mA, thickness of 5 mm, number of slices 29. 50 ml non-ionic contrast material (Iomeron 400 ml; Brocca, Milan, Italy) was injected into the antecubital vein at the rate of 5ml/sec via a power injector, followed by a 30 ml saline flush at the same rate before the dynamic scanning was obtained. The CT perfusion maps were processed with different CT perfusion softwares including singular value decomposition plus (SVD+) and Bayesian algorithm in VITREA (Vital Images, MN, USA) and RAPID (iSchema View, Menlo Park, CA). The region of interest of the arterial input function (AIF) was automatically applied on the insular segment of the middle cerebral artery on the contralateral side and the region of interest of the venous output function (VOF) from the superior sagittal sinus. For each patient, all parameters, including the mean transit time (MTT), time to peak (TTP), relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and a delay map were obtained. The mean transit time (MTT) was calculated as a first moment of the residue function by delay-compensated SVD+, a theoretically

delay-insensitive. The CBV was obtained as the ratio of the area under the curve of the brain tissue and the area under the curve of the venous output function. According to the central volume principle, the CBF value was calculated as follows: CBF = CBV / MTT. The acute stroke protocols in our institute included axial T2WI, axial FLAIR, SWI, DWI, and time of flight brain and neck MR angiography. MRI DWI was performed using the 1.5T and 3T MRI with parameters involved TR 8990, TE 73, FOV 240 x 240, number of slices 40, matrix size 160x160, slice thickness 3 mm with a 1 mm slice gap.

2.3. CTP and DWI image analysis

The CTP maps were post-processed by VITREA and iSchema View. The criteria for the infarct core was determined as CBV reduction of 26% – 56% with interval of 3% on singular value decomposition plus VITREA and CBV reduction of 28% – 48% with interval of 2% on the Bayesian algorithm VITREA. iSchema View conducted RAPID analysis and the infarct core was determined as relative CBF (rCBF) < 20% – 38% and relative CBV (rCBV) < 34% – 42%. The most commonly used thresholds to quantify infarct core for each kind of CTP software were as follows: RAPID rCBF<30%,

SVD+ VITREA CBV reduction of 41%, and Bayesian CBV reduction of 38%. The maximum and minimum values are supplied within the software.

The Olea Sphere software (Olea Medical, LA Ciotat, France) was used to measure the infarct core volume on DWI (the region of restricted diffusion). The CTP core volume measurements were compared with the infarct volume, which was determined on DWI. According to the infarct core volume within DWI, we analyzed CTP core volume measurements with the following thresholds: 1) infarct core volume ≤ 20 ml, ≤ 30 ml, ≤51 ml, ≤70 ml, and more than 70 ml. The thresholds of 20, 30, and 51 ml were chosen based on DEFUSE 3 trial [31], and the threshold of 70 ml was based on DAWN [30], EXTEND-IA [45] trial.

2.4. Statistical analysis

The continuous variables were represented by median and interquartile range (IQR). The Kolmogorov-Smirnov test was used to evaluate normality. The infarct core volumes by DWI and CTP were compared with the Wilcoxon signed-rank test. The Spearman's correlation coefficient (r) and Bland-Altman analysis with 95% limits of agreement were performed between the CTP and DWI. r values less than 0.5 indicate fair, r values from 0.5 to 0.7 indicate moderate, r values from 0.7 to 0.9 indicate very strong, and r values more than 0.9 indicate perfect correlation between the variables. $p < 0.05$ indicated a significant difference. Statistical analysis was performed using the SPSS statistical software ver. 25.0 (IBM, Armonk NY, USA).

Chapter 3. Results

The baseline characteristics are shown in Table 1. A total of 42 patients were included in our study. At baseline, the median initial NIHSS score was 10.5 with IQR of 4 – 14.25; the median age was 70 years with IQR of 58.75 – 77. The CTP was performed before DWI in all patients and the median time between CTP and DWI was 37.5 minutes (IQR 20 – 44) ranging from 12 – 60 min. The large vessel occlusions involved were the following: 35 (83.33%) middle cerebral artery (MCA), 12 (28.67%) internal carotid artery (ICA), and 1 (2.38%) anterior cerebral artery (ACA). Thrombectomy was performed in six out of the 42 patients while four patients underwent treatment with IV thrombolysis and one patient underwent both IV thrombolysis and thrombectomy.

The median infarct core volume with different thresholds of various CTP software including SVD+ VITREA, BAYESIAN VITREA and RAPID are shown in Table 2. The median infarct core volumes (IQR) with use of the most commonly settings for RAPID rCBF < 30% [5.5 ml (0 – 24.50); $p < 0.001$], SVD+ VITREA CBV reduction of 41% [12.09 ml (4.40 – 27.54); $p < 0.001$], and BAYESIAN VITREA CBV reduction of 38% [4.15 ml (0 – 17.37); $p < 0.001$] were significantly lower compared with DWI [19.50 ml (6.91 – 69.72)]. On the other hand, no significant difference

observed in the median infarct core volume (IQR) by SVD+ VITREA CBV reduction of 35% [15.14 ml (6.14 – 36.60); p = 0.120], 32% [16.36 ml (7.18 – 41.22); p = 0.302], 29% [18.19 ml (8.67 – 44.48); p = 0.536], 26% [20.69 ml (10.07 – 48.58); p = 0.896] and DWI.

The median infarct core volume differences estimated by SVD+ VITREA, BAYESIAN VITREA, and RAPID are listed in Table 3. The median infarct core volume difference for the most commonly used settings of SVD+ VITREA CBV reduction of 41% was lower [3.82 ml (IQR, −2.91 to 20.95] than those of BAYESIAN VITREA CBV reduction of 38% [8.16 ml (IQR, 1.58 to 25.46)] and RAPID rCBF < 30% [8.19 ml (IQR, 3.95 – 30.70)] thresholds. Among the different thresholds for each kind of CTP software, RAPID rCBF < 38%, SVD+ VITREA CBV reduction of 26%, and BAYESIAN VITREA CBV reduction of 28% were optimal threshold to estimate the infarct core volume with lowest median infarct core volume difference as follows: the CBV reduction of 26% for SVD+ VITREA [−1.05 ml (IQR, −12.26 to 14.58)], CBV reduction of 28% for BAYESIAN VITREA [5.23 ml (IQR, −2.90 to 22.91)], and RAPID rCBF < 38% [4.87 ml (IQR, 0.84 to 23.51)]. The individualized error bars for infarct core volume difference between the RAPID rCBF < 38%, SVD+ VITREA CBV reduction of 26%,

BAYESIAN VITREA CBV reduction of 28% and the currently used thresholds of RAPID rCBF < 30%, SVD+ VITREA CBV reduction of 41%, BAYESIAN VITREA CBV reduction of 38% are shown in Figure 4.A–D.

Table 1. Baseline characteristics

Clinical characteristics	N=42
Age, median (IQR)	70 (58.75 – 77)
Initial NIHSS, median (IQR)	10.5 (4 – 14.25)
Onset time to door min, median (IQR)	351.5 (105 – 647.75)
Levels of occlusions, n (%)	
MCA	
M1	14 (33.33%)
M2	17 (40.76%)
M3	3 (7.14%)
M4	1 (2.38%)
ACA	
A2	1 (2.38%)
ICA	
Proximal	7 (16.67%)
Distal	5 (11.90%)
Time interval	
CTP to DWI time, median (IQR)	37.5 (20 – 44)
Medical history	
Atrial fibrillation	6 (14.29%)
Hypertension	22 (52.38%)
DM	18 (42.86%)
Cancer	9 (21.43%)
Hyperlipidemia	4 (9.52%)
Treatment	
IV thrombolysis alone, n (%)	4 (9.52%)
Thrombectomy alone, n (%)	6 (14.29%)
IV thrombolysis + Thrombectomy, n (%)	1 (2.38%)

Note – IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; MCA, Middle cerebral artery; ACA, Anterior cerebral artery; ICA Internal carotid artery; CTP, Computed tomography perfusion; DWI, diffusion–weighted imaging

Table 2. The median infarct core volume with different thresholds of various CTP software

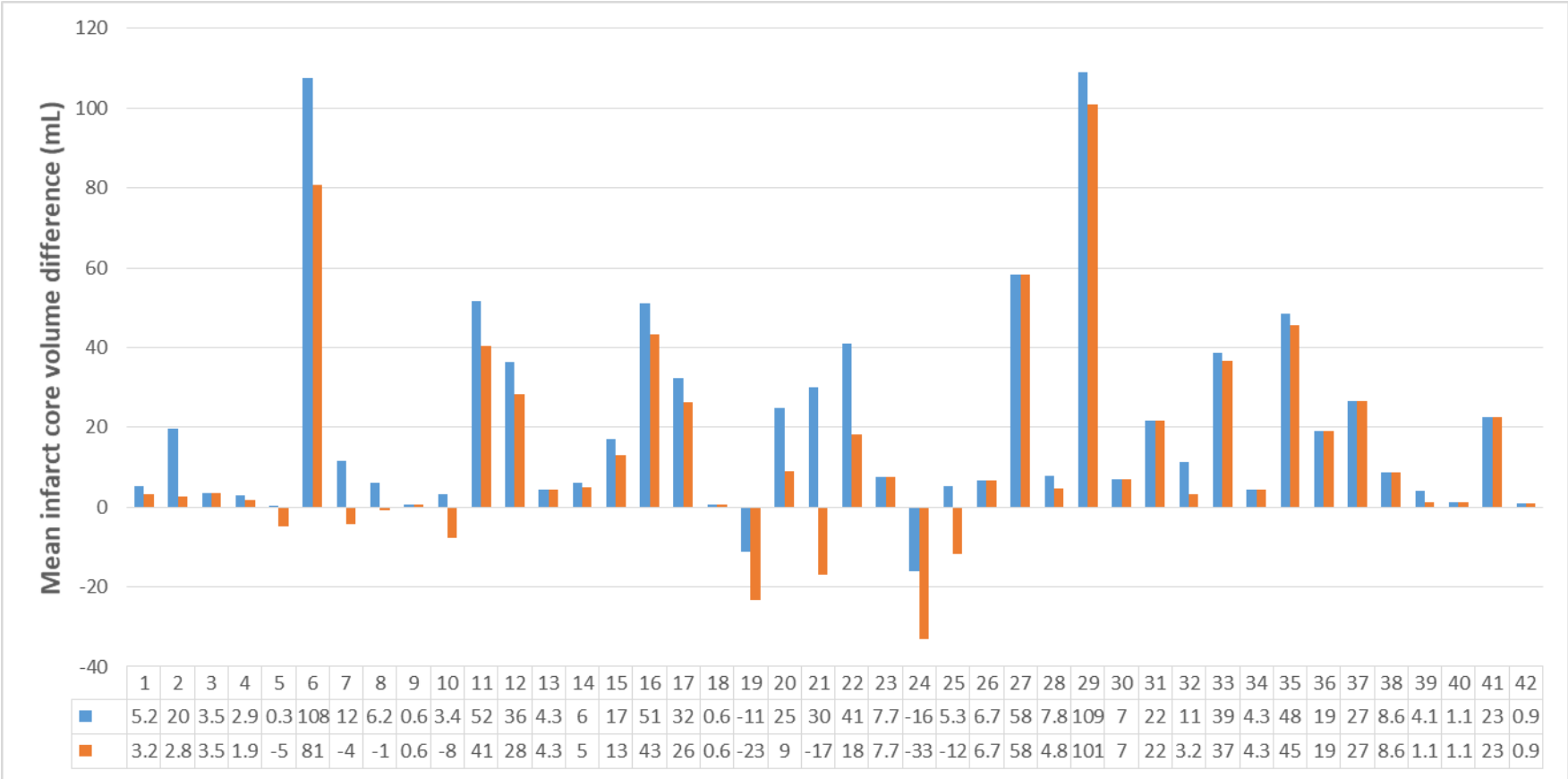
		Median infarct core volume, mL (IQR)	P value
DWI		19.50 (6.91 – 69.72)	
RAPID, rCBF	<20%	0 (0 – 7)	0.001
	<30%	5.5 (0 – 24.50)	0.001
	<34%	7.5 (0 – 35.25)	0.001
	<38%	9.0 (0 – 40.75)	0.001
RAPID, rCBV	<34%	0 (0 – 16.0)	0.001
	<38%	3.5 (3.5 – 16.25)	0.001
	<42%	4.5 (0 – 17.50)	0.001
BAYESIAN VITREA, CBV reduction	48%	1.78 (0 – 9.27)	0.001
	46%	2.36 (0 – 10.29)	0.001
	44%	2.89 (0 – 11.77)	0.001
	42%	3.21 (0 – 13.30)	0.001
	40%	3.53 (0 – 15.16)	0.001
	38%	4.15 0 – 17.37)	0.001
	36%	4.83 (0 – 20.79)	0.001
	34%	5.54 (0.75 – 23.93)	0.001
	32%	6.85 (1.58 – 25.99)	0.001
	30%	8.35 (2.43 – 27.49)	0.004
	28%	9.94 (3.32 – 31.51)	0.010
SVD+ VITREA, CBV reduction	56%	5.27 (0 – 16.07)	0.001
	53%	6.39 (1.08 – 17.87)	0.001
	50%	7.71 (1.97 – 19.77)	0.001
	47%	9.17 (2.71 – 21.34)	0.001
	44%	10.42 (3.31 – 23.33)	0.002
	41%	12.09 (4.40 – 27.54)	0.015
	38%	13.61 (5.19 – 31.79)	0.040
	35%	15.14 (6.14 – 36.60)	0.120
	32%	16.36 (7.18 – 41.22)	0.302
	29%	18.19 (8.67 – 44.48)	0.536
	26%	20.69 (10.07 – 48.58)	0.896

Note – IQR, interquartile range; DWI, Diffusion-weighted imaging; rCBV, relative cerebral blood volume, rCBF, relative cerebral blood flow; CBV, cerebral blood volume

Table 3. The median infarct core volume differences estimated by SVD+ VITREA, BAYESIAN VITREA, and RAPID

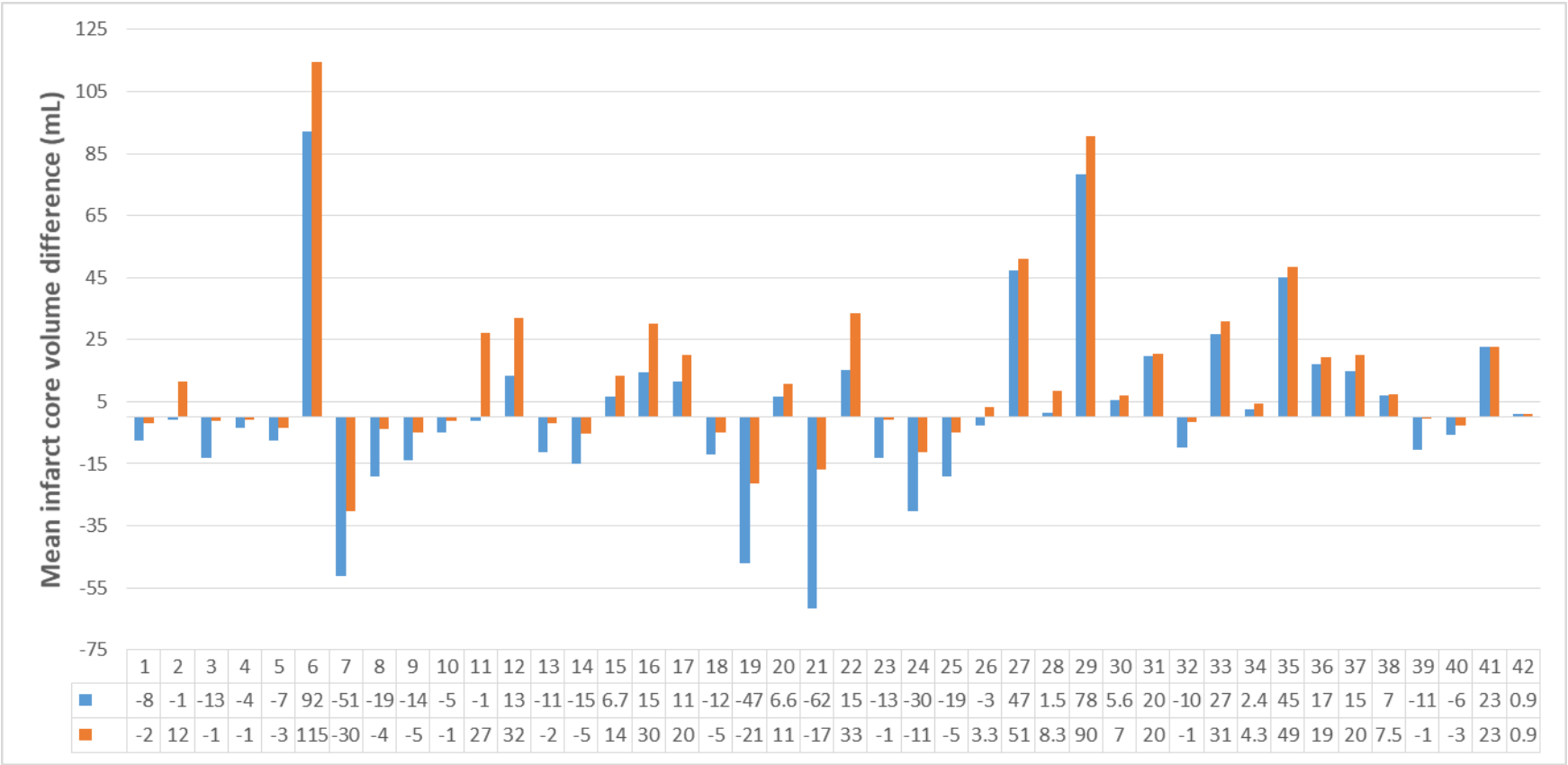
		Median difference (IQR)
RAPID, rCBF	<20%	17.44 (5.73 – 41.24)
	<30%	8.19 (3.95 – 30.70)
	<34%	6.21 (2.5 – 26.72)
	<38%	4.87 (0.84 – 23.51)
RAPID, rCBV	<34%	11.00 (4.24 – 31.79)
	<38%	9.19 (3.43 – 26.77)
	<42%	8.16 (2.51 – 26.77)
BAYESIAN VITREA, CBV reduction	48%	11.25 (5.42 – 37.43)
	46%	10.26 (4.42 – 35.78)
	44%	9.65 (4.11 – 32.95)
	42%	9.04 (3.55 – 30.46)
	40%	8.58 (2.85 – 25.89)
	38%	8.16 (1.58 – 25.46)
	36%	8.15 (0.65 – 25.00)
	34%	7.03 (−0.47 – 24.55)
	32%	6.57 (−1.62 – 24.05)
	30%	6.22 (−2.25 – 23.54)
	28%	5.23 (−2.90 – 22.91)
SVD+ VITREA, CBV reduction	56%	10.70 (4.11 −30.25)
	53%	8.48 (3.34 −25.06)
	50%	6.22 (1.81 – 23.55)
	47%	4.61 (0.85 – 22.87)
	44%	4.26 (−0.96 – 22.20)
	41%	3.82 (−2.91 – 20.95)
	38%	3.32 (−3.93 – 20.40)
	35%	2.19 (−5.6 – 19.38)
	32%	1.94 (−8.04 – 19.34)
	29%	1.39 (−10.44 – 17.36)
	26%	−1.05 (−12.26 – 14.58)

Note – IQR, interquartile range; rCBV, relative cerebral blood volume, rCBF, relative cerebral blood flow; CBV, cerebral blood volume



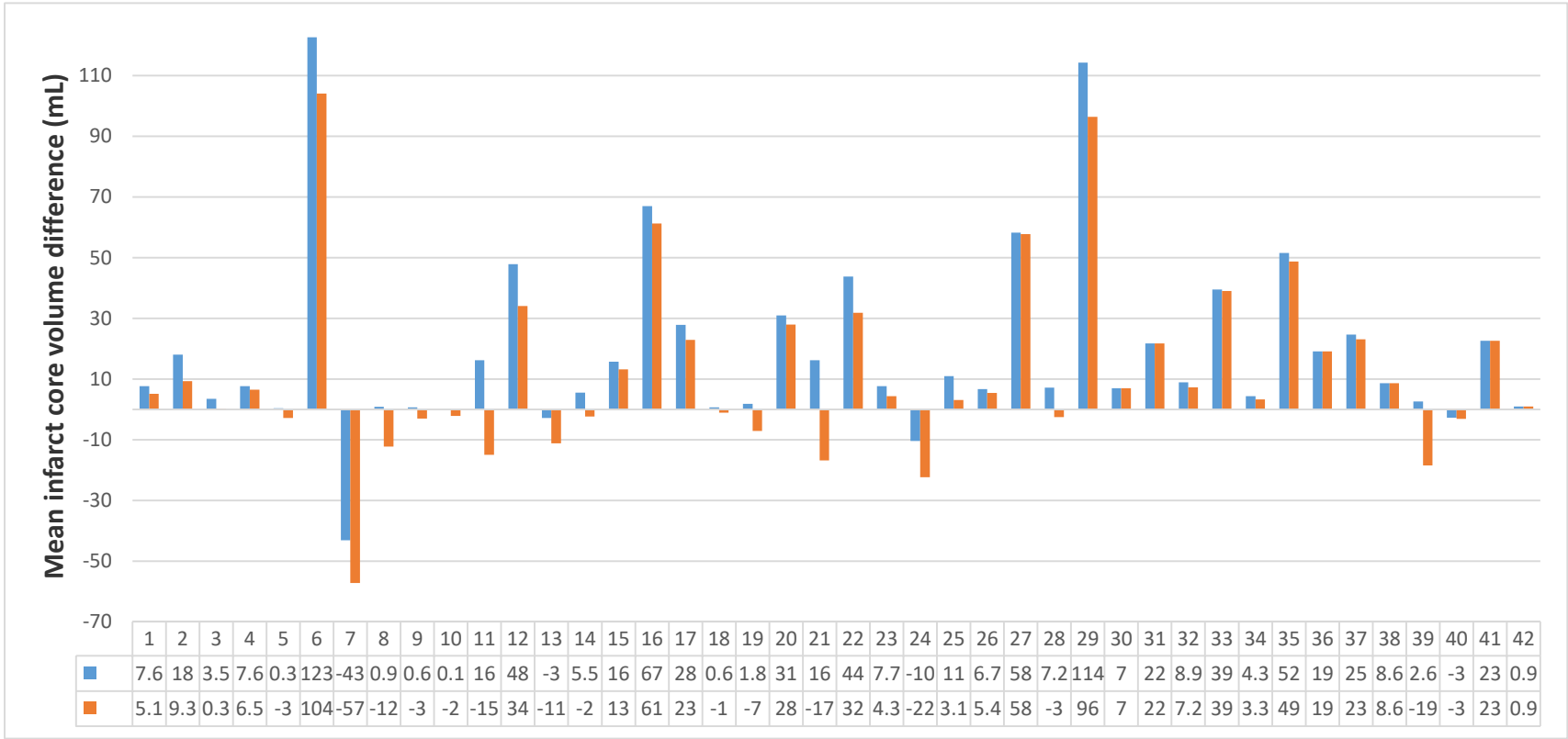
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
■	5.2	20	3.5	2.9	0.3	108	12	6.2	0.6	3.4	52	36	4.3	6	17	51	32	0.6	-11	25	30	41	7.7	-16	5.3	6.7	58	7.8	109	7	22	11	39	4.3	48	19	27	8.6	4.1	1.1	23	0.9
■	3.2	2.8	3.5	1.9	-5	81	-4	-1	0.6	-8	41	28	4.3	5	13	43	26	0.6	-23	9	-17	18	7.7	-33	-12	6.7	58	4.8	101	7	22	3.2	37	4.3	45	19	27	8.6	1.1	1.1	23	0.9

Figure 4.A. Stacked bar graph of mean infarct core volume difference in RAPID. The graph shows the infarct core volume using rCBF<38% (orange) and rCBF<30% (blue) thresholds



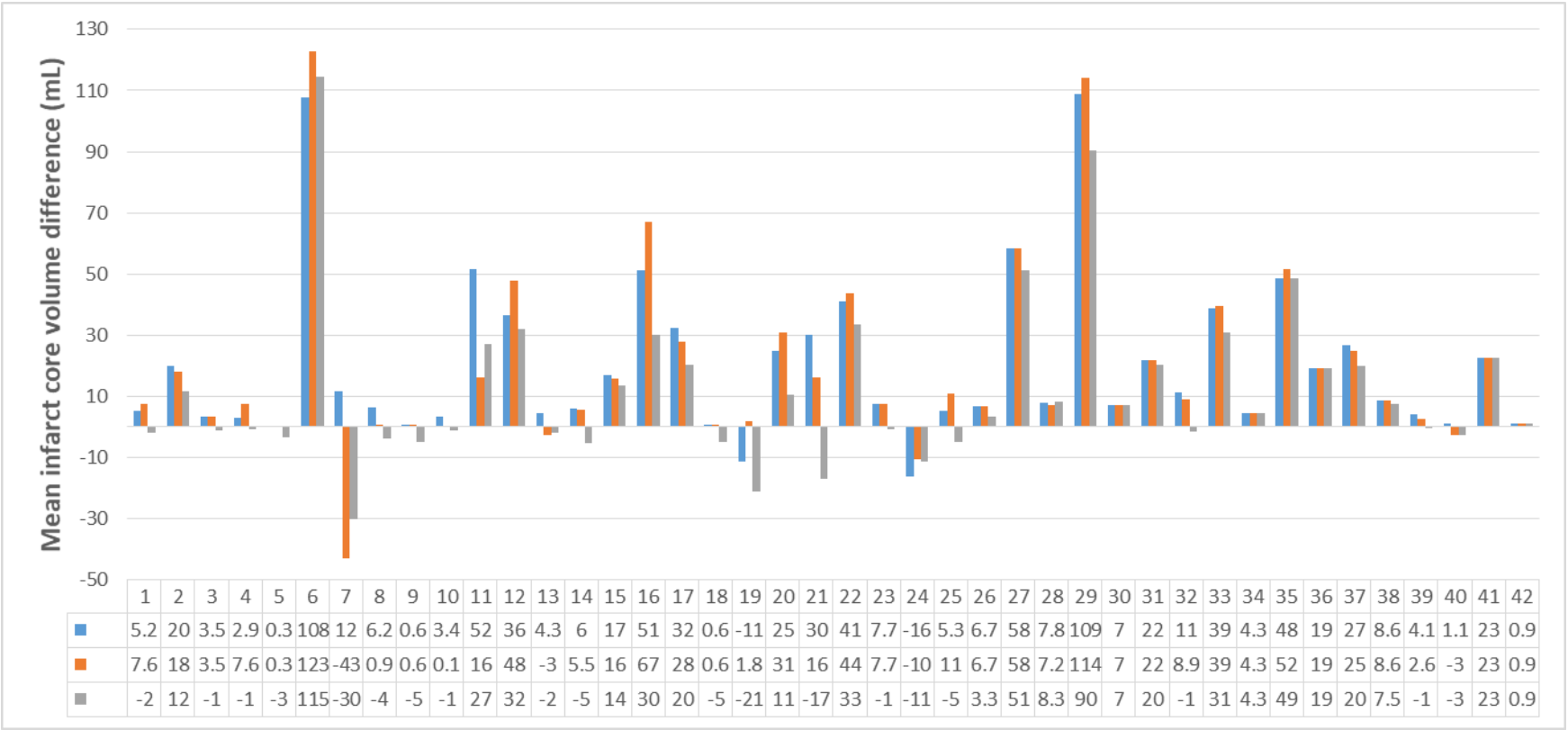
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
■	-8	-1	-13	-4	-7	92	-51	-19	-14	-5	-1	13	-11	-15	6.7	15	11	-12	-47	6.6	-62	15	-13	-30	-19	-3	47	1.5	78	5.6	20	-10	27	2.4	45	17	15	7	-11	-6	23	0.9
■	-2	12	-1	-1	-3	115	-30	-4	-5	-1	27	32	-2	-5	14	30	20	-5	-21	11	-17	33	-1	-11	-5	3.3	51	8.3	90	7	20	-1	31	4.3	49	19	20	7.5	-1	-3	23	0.9

Figure 4.B. Stacked bar graph of mean infarct core volume difference in CTP SVD+ VITREA. The graph shows the infarct core volume using CBV reduction of 26% (blue) and CBV reduction of 41% (orange) thresholds



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
	7.6	18	3.5	7.6	0.3	123	-43	0.9	0.6	0.1	16	48	-3	5.5	16	67	28	0.6	1.8	31	16	44	7.7	-10	11	6.7	58	7.2	114	7	22	8.9	39	4.3	52	19	25	8.6	2.6	-3	23	0.9
	5.1	9.3	0.3	6.5	-3	104	-57	-12	-3	-2	-15	34	-11	-2	13	61	23	-1	-7	28	-17	32	4.3	-22	3.1	5.4	58	-3	96	7	22	7.2	39	3.3	49	19	23	8.6	-19	-3	23	0.9

Figure 4.C. Stacked bar graph of mean infarct core volume difference in CTP BAYESIAN VITREA. The graph shows the infarct core volume using CBV reduction of 28% (orange) and CBV reduction of 38% (blue) thresholds



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
■	5.2	20	3.5	2.9	0.3	108	12	6.2	0.6	3.4	52	36	4.3	6	17	51	32	0.6	-11	25	30	41	7.7	-16	5.3	6.7	58	7.8	109	7	22	11	39	4.3	48	19	27	8.6	4.1	1.1	23	0.9
■	7.6	18	3.5	7.6	0.3	123	-43	0.9	0.6	0.1	16	48	-3	5.5	16	67	28	0.6	1.8	31	16	44	7.7	-10	11	6.7	58	7.2	114	7	22	8.9	39	4.3	52	19	25	8.6	2.6	-3	23	0.9
■	-2	12	-1	-1	-3	115	-30	-4	-5	-1	27	32	-2	-5	14	30	20	-5	-21	11	-17	33	-1	-11	-5	3.3	51	8.3	90	7	20	-1	31	4.3	49	19	20	7.5	-1	-3	23	0.9

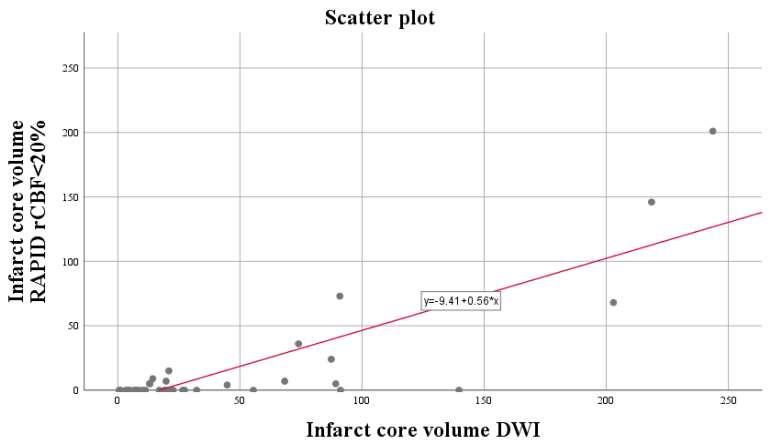
Figure 4.D. Stacked bar graph of mean infarct core volume difference in SVD+ VITREA, BAYESIAN VITREA, and RAPID. The graph shows the infarct core volume using SVD+ VITREA CBV reduction of 41% (grey), BAYESIAN CBV reduction of 38% (orange) and RAPID rCBF < 30% (blue) thresholds.

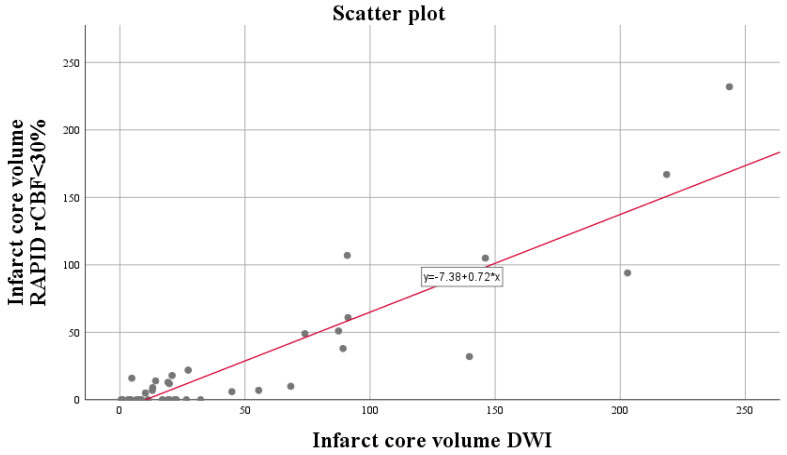
The Spearman's correlation coefficients (r) on infarct core volume with different thresholds of various CTP software against DWI infarct core volume are shown in Table 4. Figure 5 illustrates the scatterplots of infarct core volume for each kind of CTP software with different thresholds. Generally, a moderate to very strong correlation was found between all different thresholds of various CTP software and DWI including: RAPID rCBF threshold and DWI, SVD+ VITREA and DWI as well as BAYESIAN VITREA and DWI. The correlation of infarct core volume between DWI and the most commonly used settings for SVD+ VITREA, RAPID and BAYESIAN VITREA for each kind of CTP software were as follows: SVD+ VITREA CBV reduction of 41% ($r = 0.717$); RAPID rCBF < 30% ($r = 0.759$); and BAYESAIN VITREA CBV reduction of 38% ($r = 0.754$).

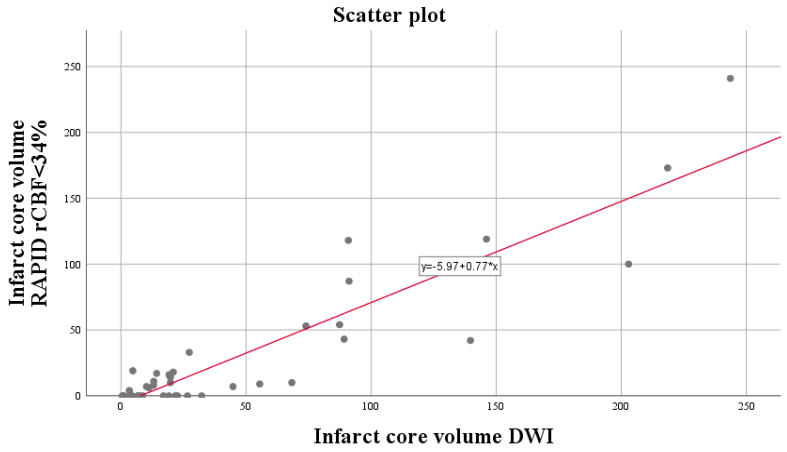
Table 4. The correlation on infarct core volume between different thresholds of various CTP software and DWI

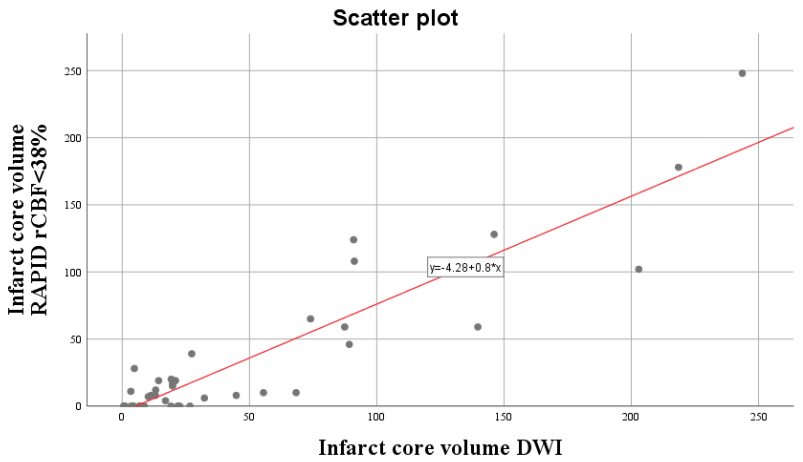
		SCC (r)
RAPID, rCBF	<20%	0.617
	<30%	0.759
	<34%	0.745
	<38%	0.752
RAPID, rCBV	<34%	0.663
	<38%	0.688
	<42%	0.682
BAYESIAN VITREA, CBV reduction	48%	0.702
	46%	0.717
	44%	0.742
	42%	0.733
	40%	0.734
	38%	0.754
	36%	0.745
	34%	0.731
	32%	0.717
	30%	0.712
	28%	0.685
SVD+ VITREA, CBV reduction	56%	0.748
	53%	0.724
	50%	0.725
	47%	0.722
	44%	0.719
	41%	0.717
	38%	0.713
	35%	0.710
	32%	0.700
	29%	0.681
	26%	0.679

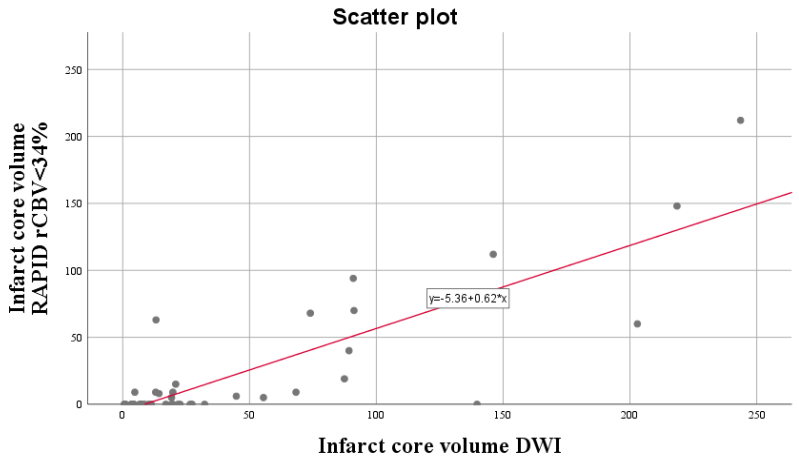
Note –rCBV, relative cerebral blood volume, rCBF, relative cerebral blood flow; CBV, cerebral blood volume; SCC, spearman's correlation coefficient

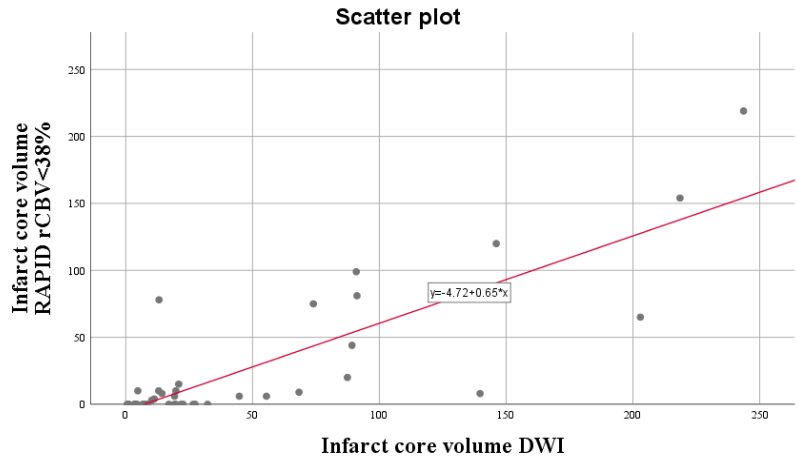

Scatter plot
Infarct core volume RAPID rCBF<20%
Infarct core volume DWI
y=-9.41+0.56*x
0
50
100
150
200
250

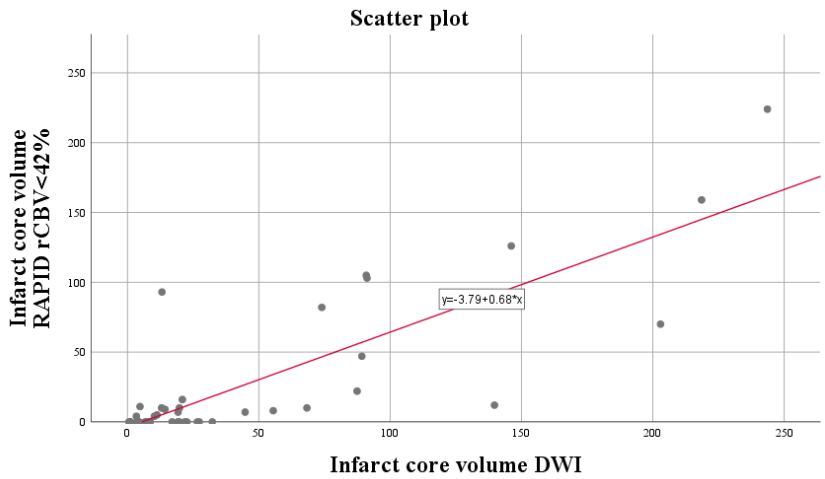

Scatter plot
Infarct core volume RAPID rCBF<30%
Infarct core volume DWI
y=-7.38+0.72*x
0
50
100
150
200
250

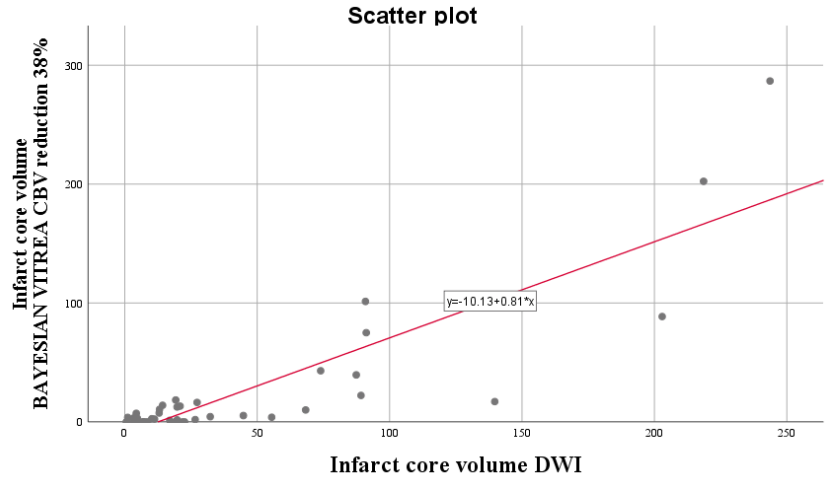

Scatter plot
Infarct core volume RAPID rCBF<34%
Infarct core volume DWI
y=-5.97+0.77*x
0
50
100
150
200
250

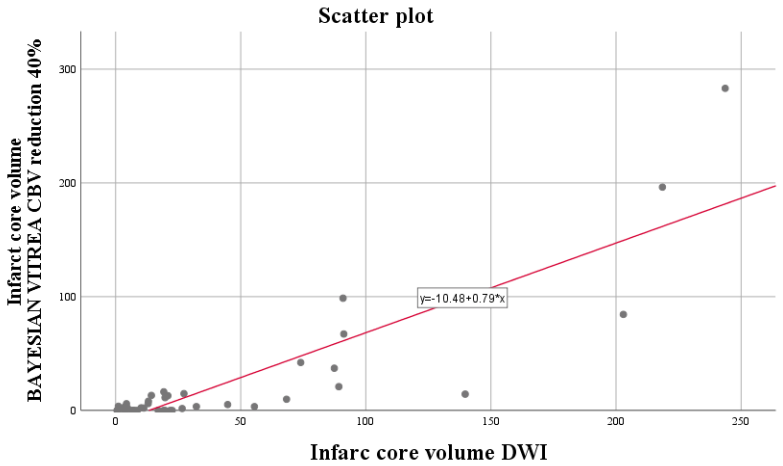

Scatter plot
Infarct core volume RAPID rCBF<38%
Infarct core volume DWI
y=-4.28+0.8*x
0
50
100
150
200
250

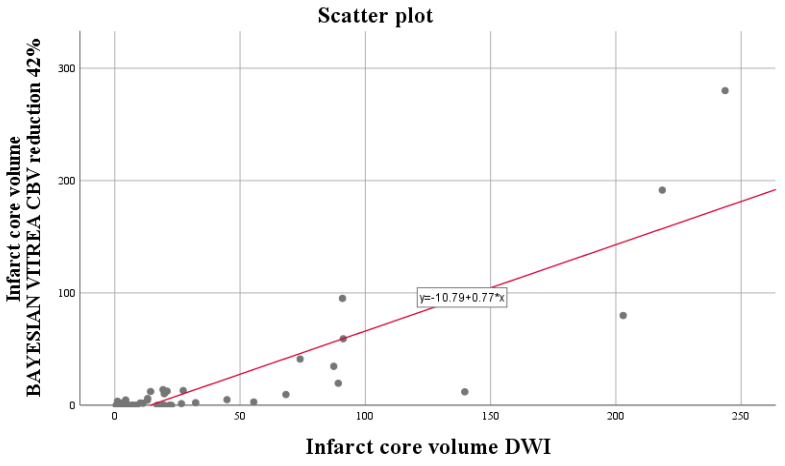

Scatter plot
Infarct core volume RAPID rCBV<34%
Infarct core volume DWI
y=-5.36+0.62*x
0
50
100
150
200
250

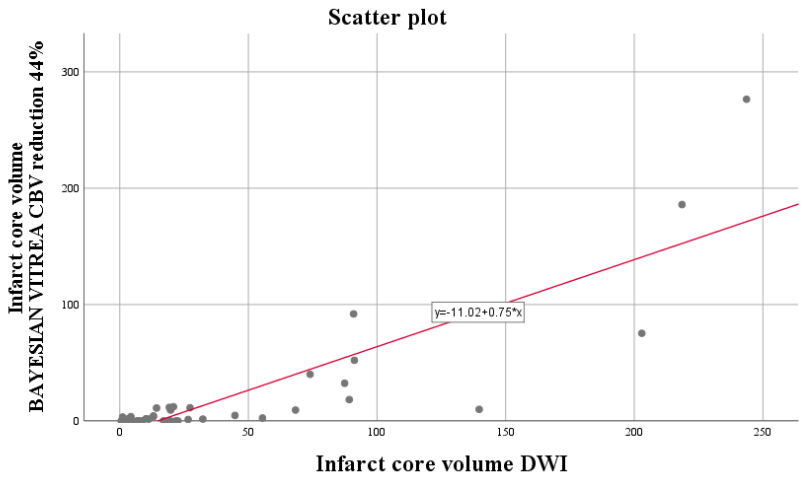

Scatter plot
Infarct core volume RAPID rCBV<38%
Infarct core volume DWI
y=-4.72+0.65*x
0
50
100
150
200
250

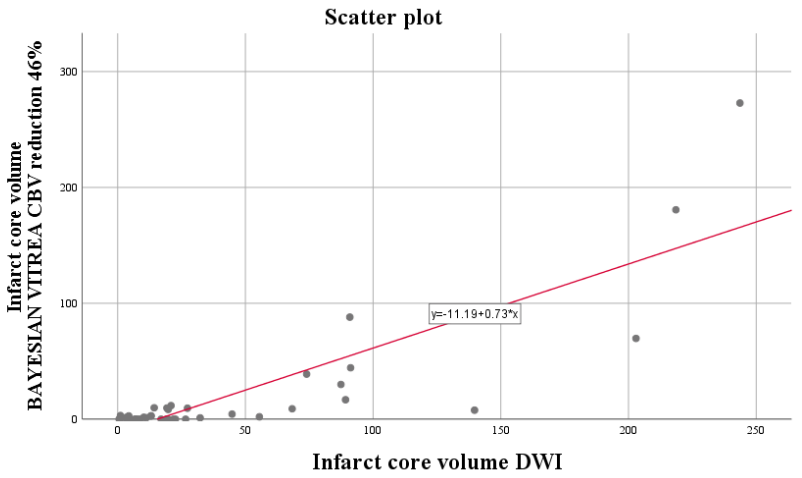

Scatter plot
Infarct core volume RAPID rCBV<42%
Infarct core volume DWI
y=-3.79+0.68*x
0
50
100
150
200
250

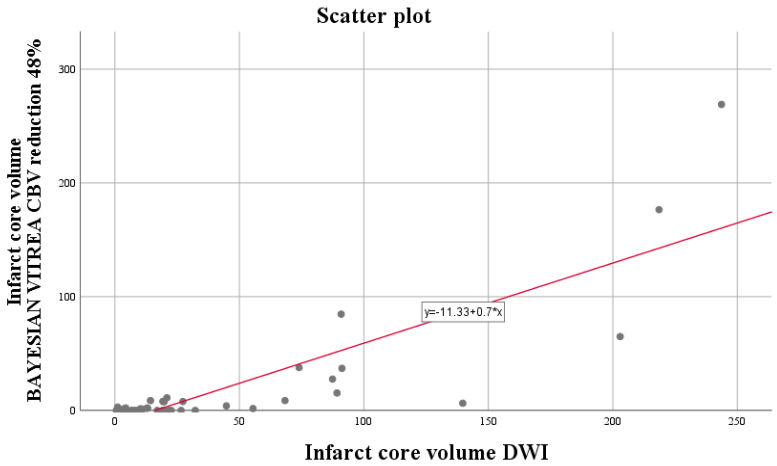

Scatter plot
Infarct core volume BAYESIAN VITREA CBV reduction 38%
Infarct core volume DWI
y=-10.13+0.81*x
0
100
200
300
50
150
250

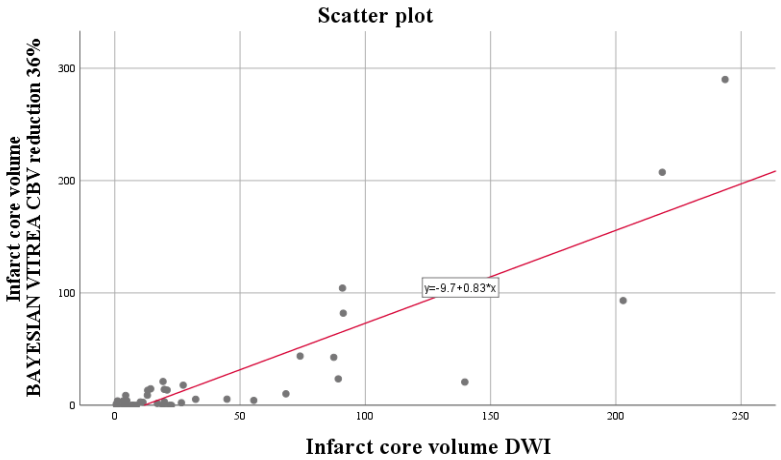

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 40%
y=-10.48+0.79*x
Infarc core volume DWI

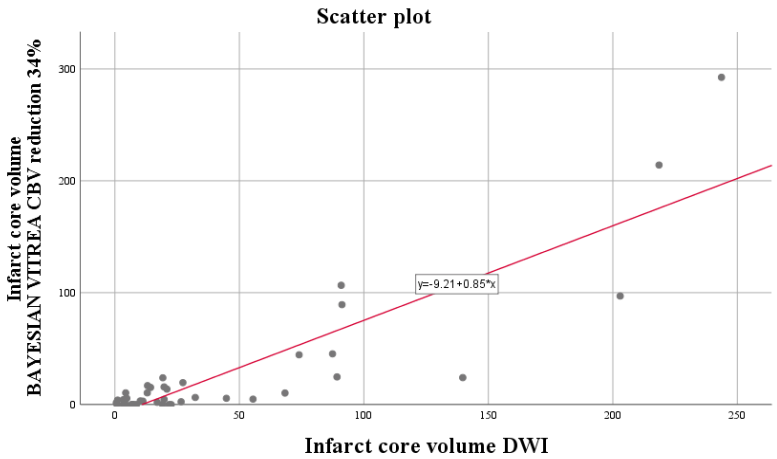

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 42%
y=-10.79+0.77*x
Infarct core volume DWI

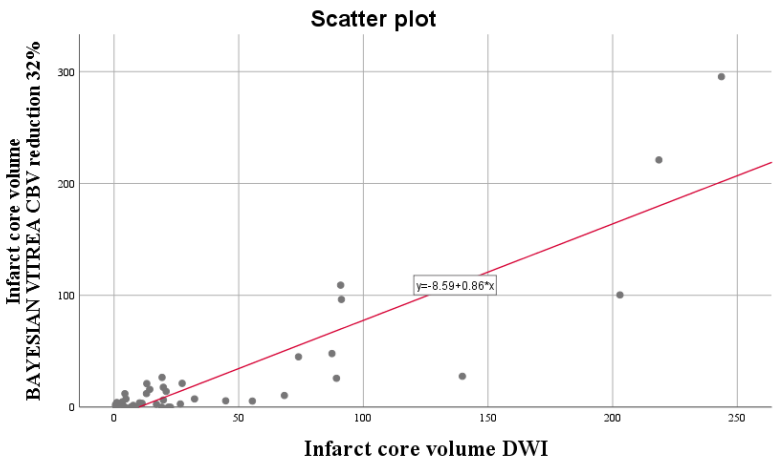

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 44%
y=-11.02+0.75*x
Infarct core volume DWI

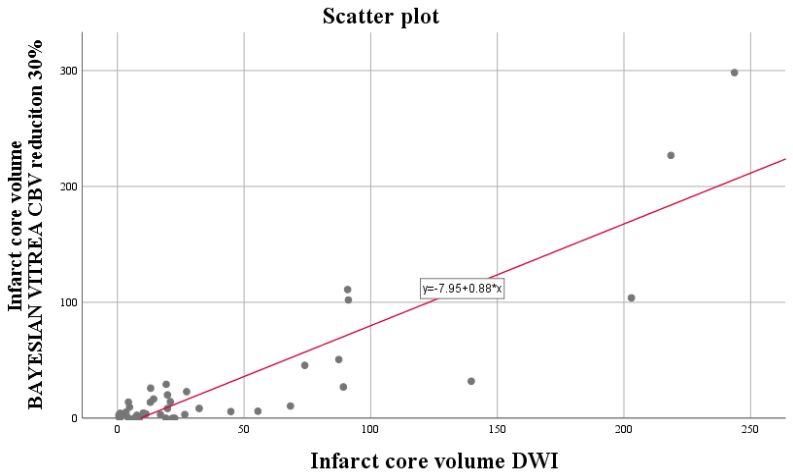

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 46%
y=-11.19+0.73*x
Infarct core volume DWI

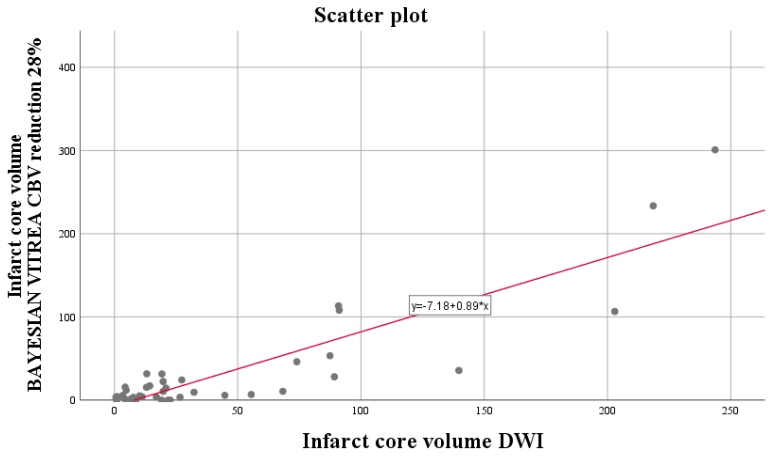

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 48%
y=-11.33+0.7*x
Infarct core volume DWI

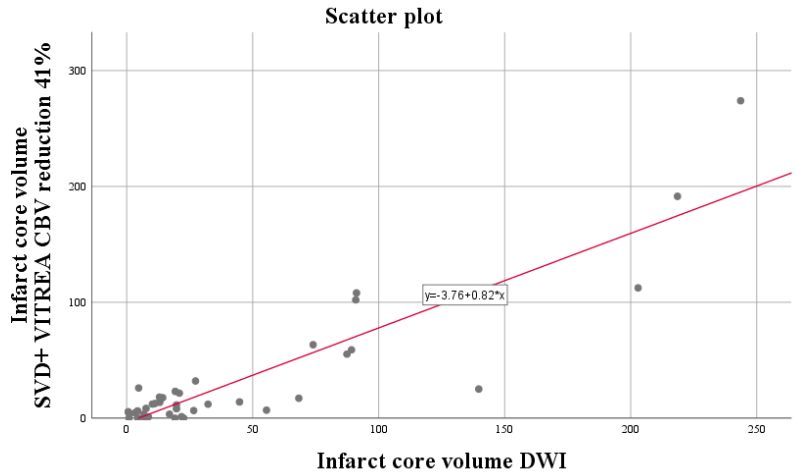

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 36%
y=-9.7+0.83*x
Infarct core volume DWI

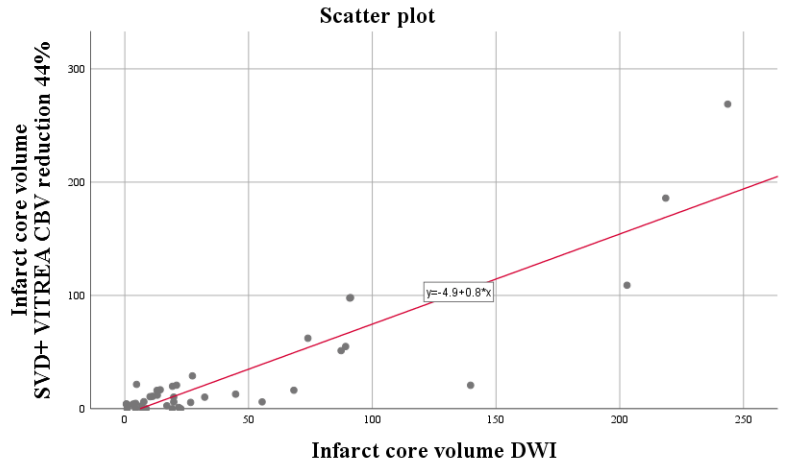

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 34%
y=-9.21+0.85*x
Infarct core volume DWI

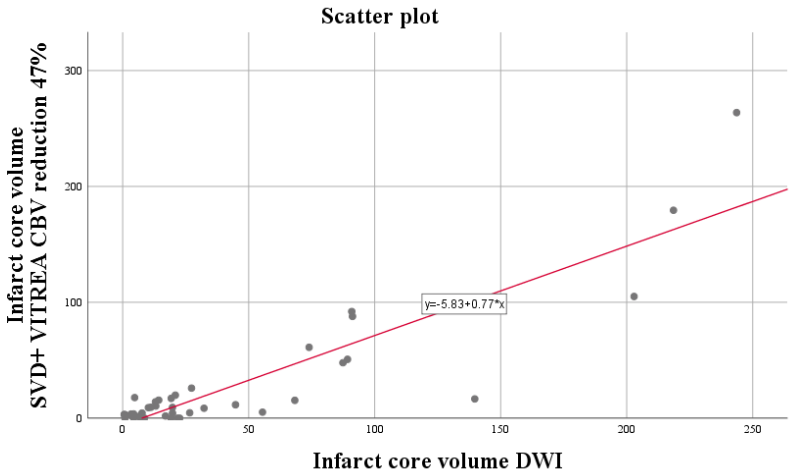

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 32%
y=-8.59+0.86*x
Infarct core volume DWI

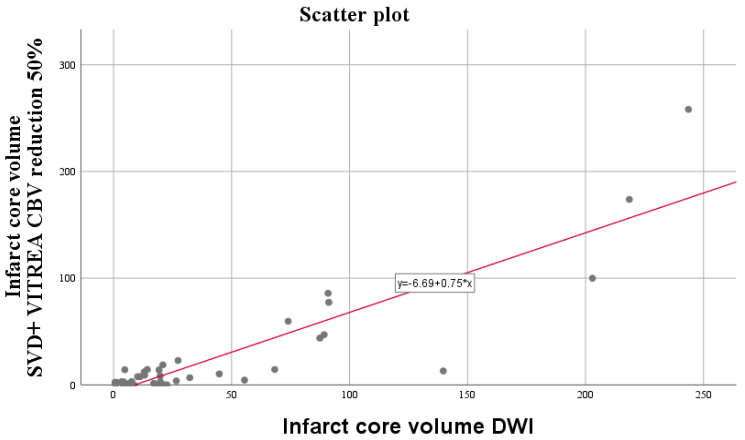

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduciton 30%
y=-7.95+0.88*x
Infarct core volume DWI

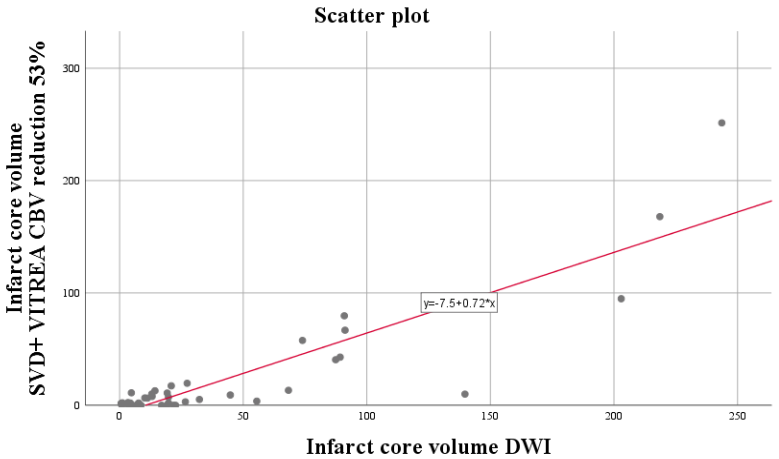

Scatter plot
Infarct core volume
BAYESIAN VITREA CBV reduction 28%
y=-7.18+0.89*x
Infarct core volume DWI

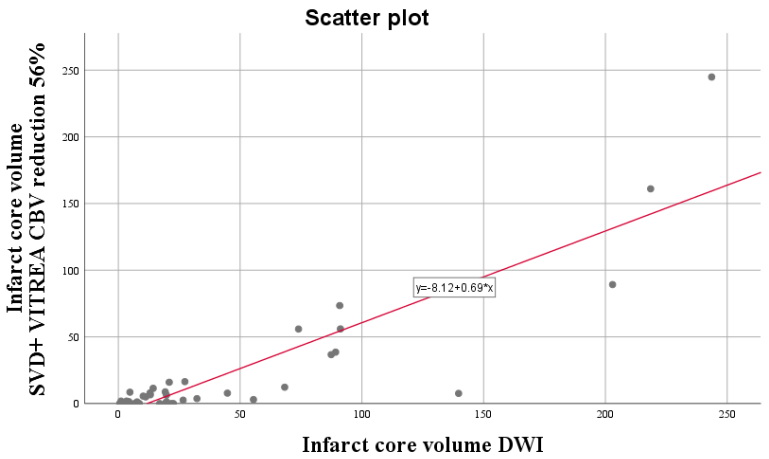

Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 41%
y=-3.76+0.82*x
Infarct core volume DWI

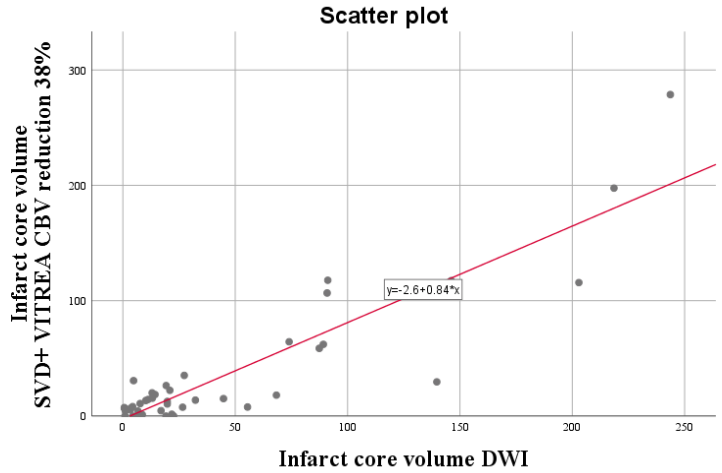

Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 44%
y=-4.9+0.8*x
Infarct core volume DWI

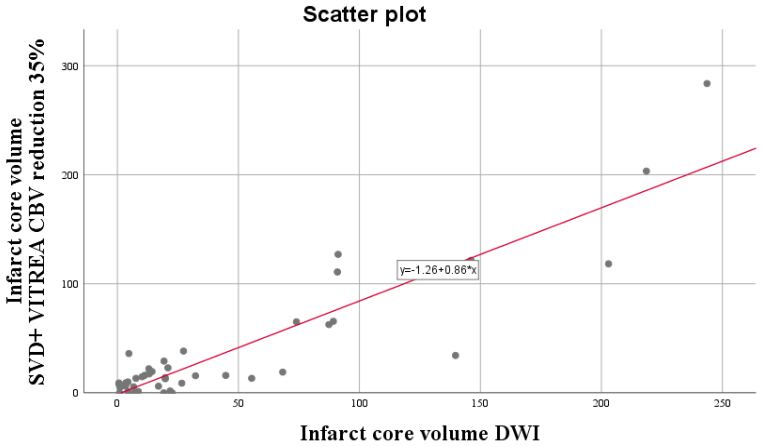

Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 47%
y=-5.83+0.77*x
Infarct core volume DWI

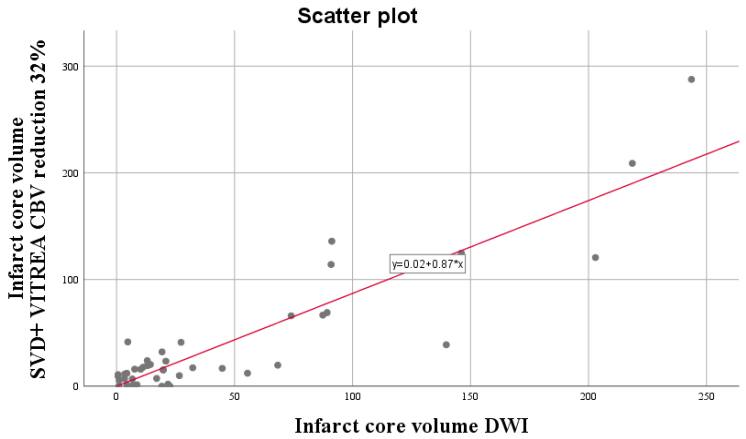

Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 50%
y=-6.69+0.75*x
Infarct core volume DWI

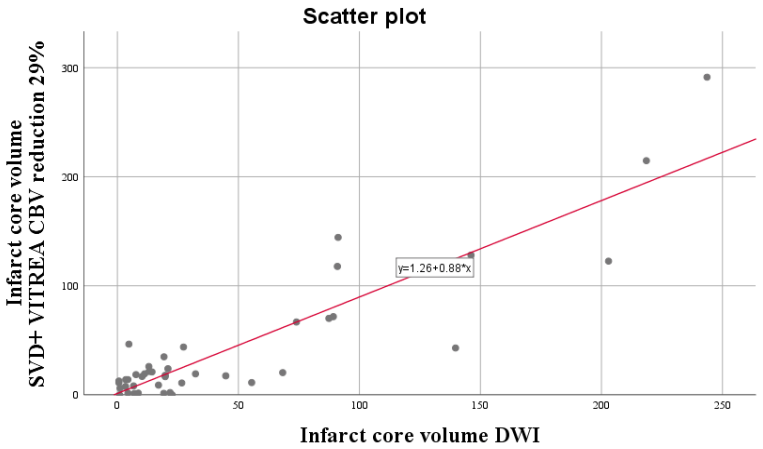

Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 53%
y=-7.5+0.72*x
Infarct core volume DWI


Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 56%
y=-8.12+0.69*x
Infarct core volume DWI


Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 38%
y=-2.6+0.84*x
Infarct core volume DWI


Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 35%
y=-1.26+0.86*x
Infarct core volume DWI


Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 32%
y=0.02+0.87*x
Infarct core volume DWI


Scatter plot
Infarct core volume
SVD+ VITREA CBV reduction 29%
y=1.26+0.88*x
Infarct core volume DWI

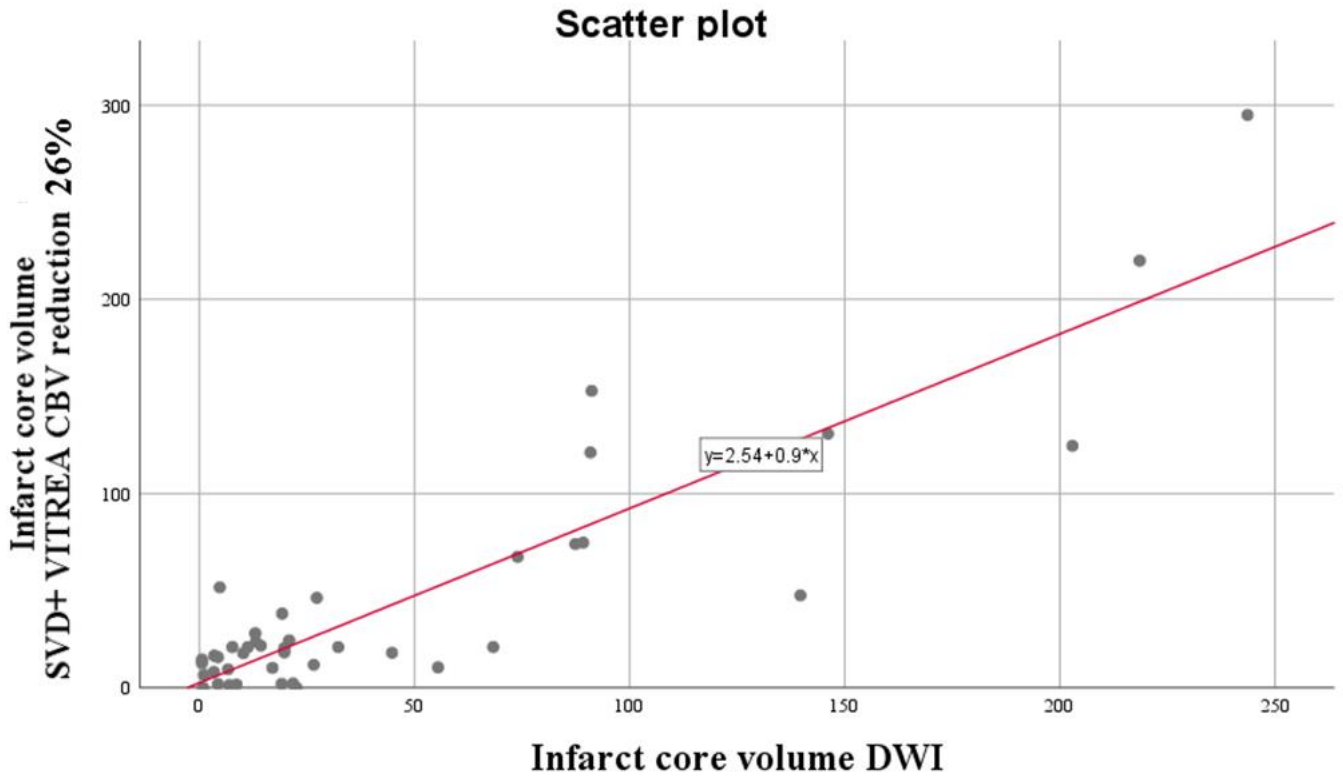
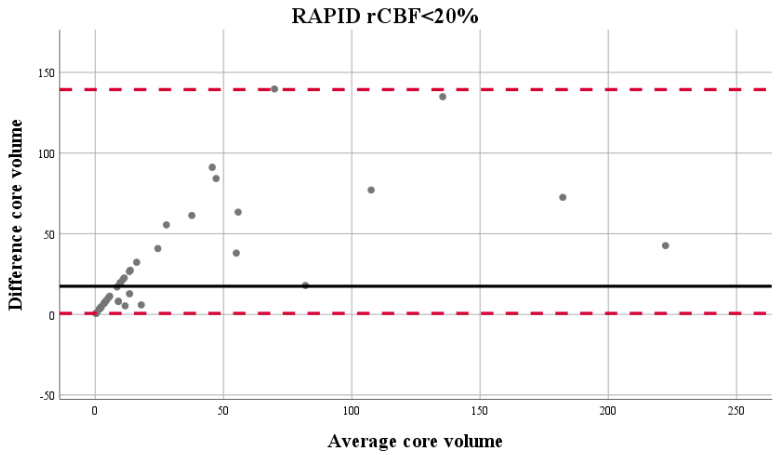
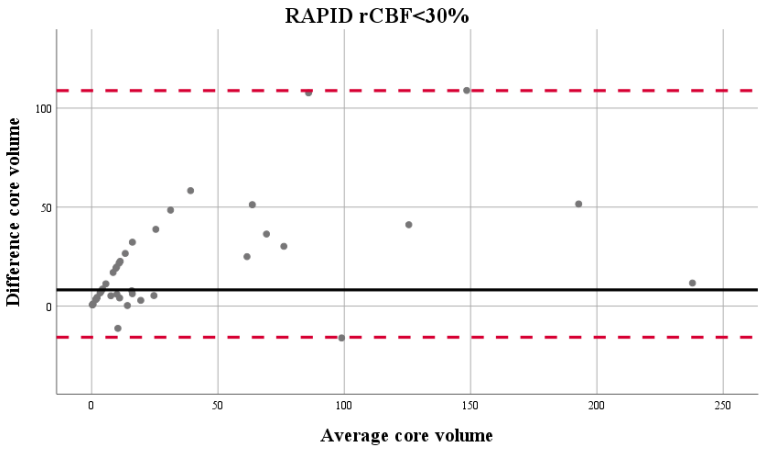
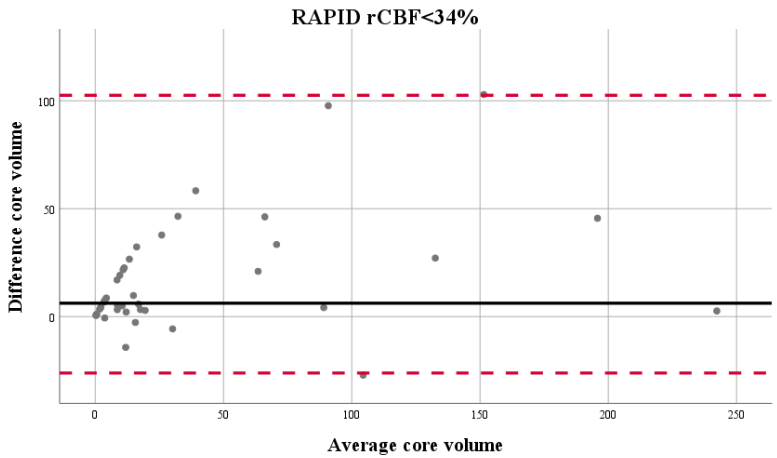


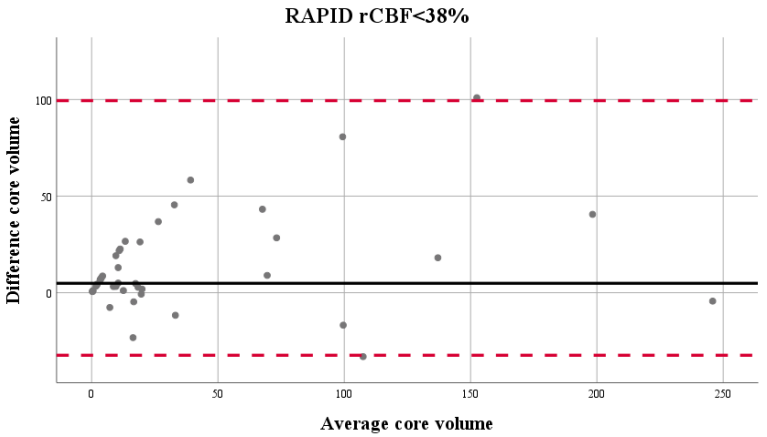
Figure 5. The scatterplot shows the correlation between the infarct core volume estimated with different thresholds and software including SVD+ VITREA, BAYESIAN VITREA, RAPID and infarct core volume estimated with DWI.

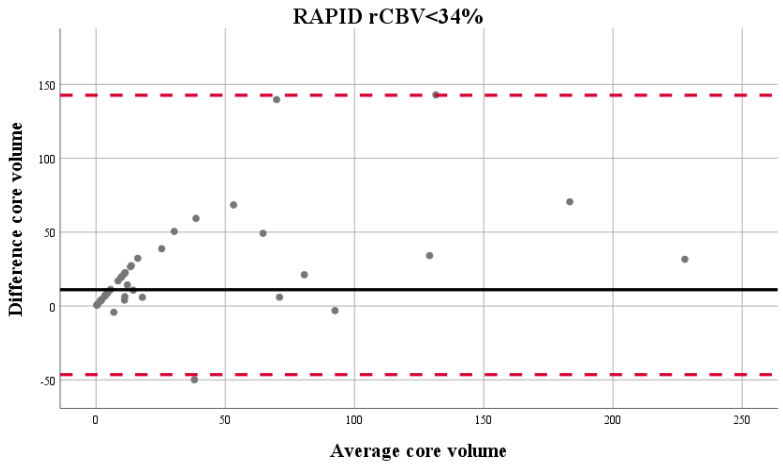
The Bland-Altman limits of agreement for infarct core volume by each kind of CTP software and DWI is illustrated on Figure 6. The Bland-Altman limits of agreement for the most commonly used settings for each kind of CTP software were as follows: RAPID rCBF < 30% -15.75 to 108.83 ml; SVD+ VITREA CBV reduction of 41% -29.63 to 112.78 ml; and BAYESIAN VITREA CBV reduction of 38% -40.67to 122.04 ml. Among the most commonly used settings, the limits of agreement for infarct core volume were smaller with SVD+ VITREA compared to those of the RAPID and BAYESIAN VITREA. Compared to the commonly used settings for CTP software, the limits of agreement were smallest with RAPID rCBF < 38% -32.17 to 99.40 ml; SVD+ VITREA CBV reduction of 26% -60.90 to 91.12 ml; and BAYESIAN VITREA CBV reduction of 28% -54.61 to 103.61 ml.

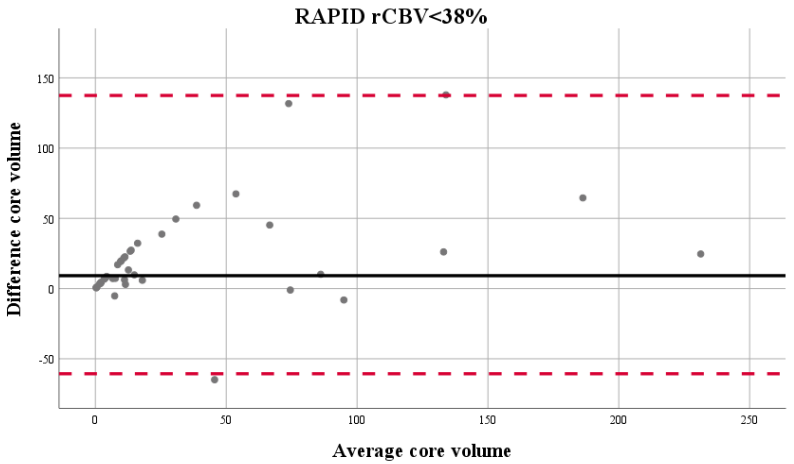

RAPID rCBF<20%
Difference core volume
Average core volume

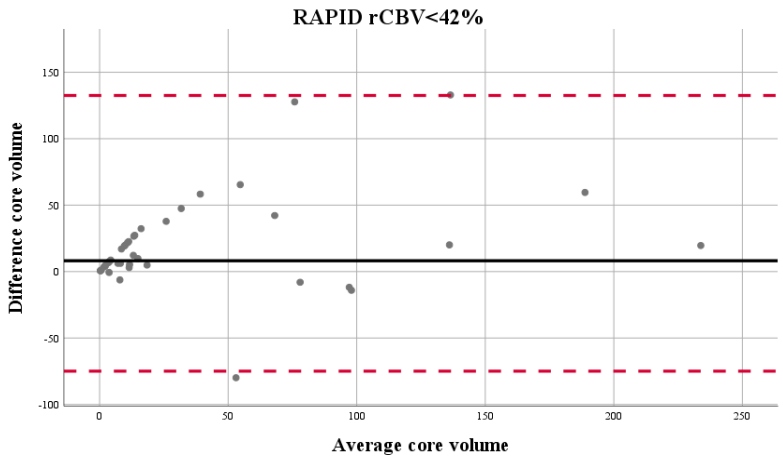

RAPID rCBF<30%
Difference core volume
Average core volume

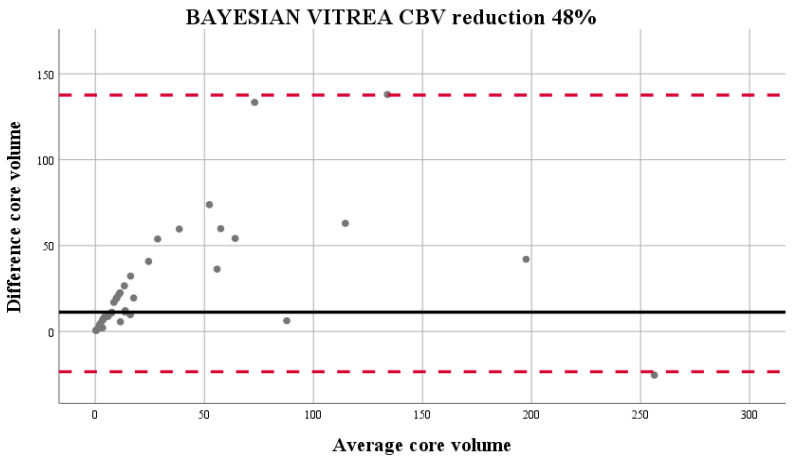

RAPID rCBF<34%
Difference core volume
Average core volume

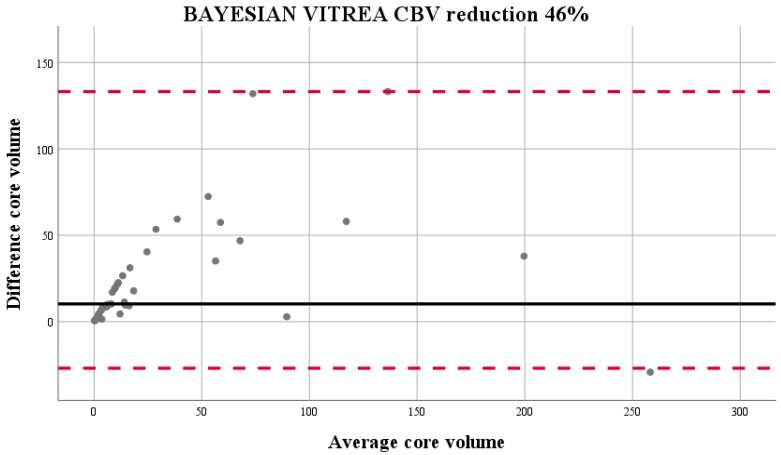

RAPID rCBF<38%
Difference core volume
Average core volume

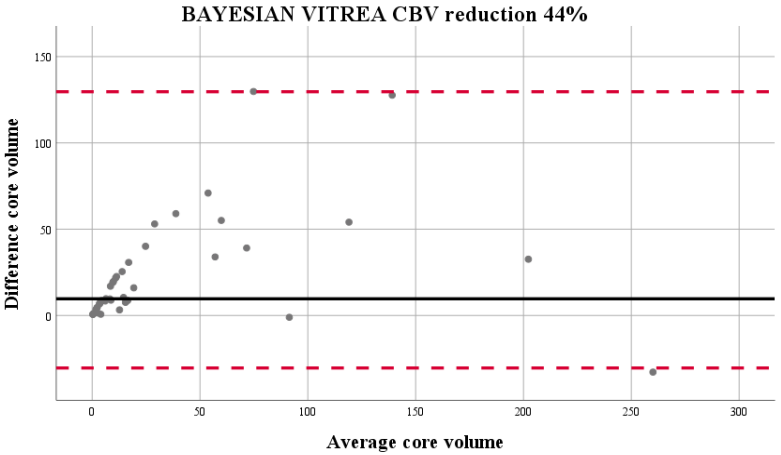

RAPID rCBV<34%
Difference core volume
Average core volume
150
100
50
0
-50
0
50
100
150
200
250

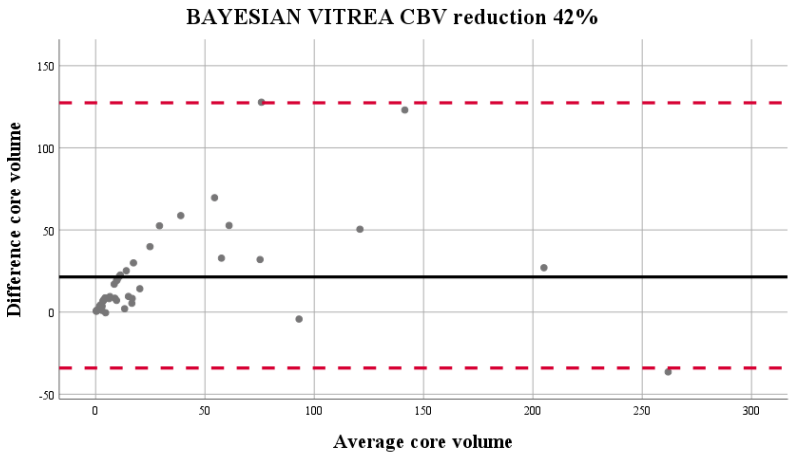

RAPID rCBV<38%
Difference core volume
Average core volume
150
100
50
0
-50
0
50
100
150
200
250

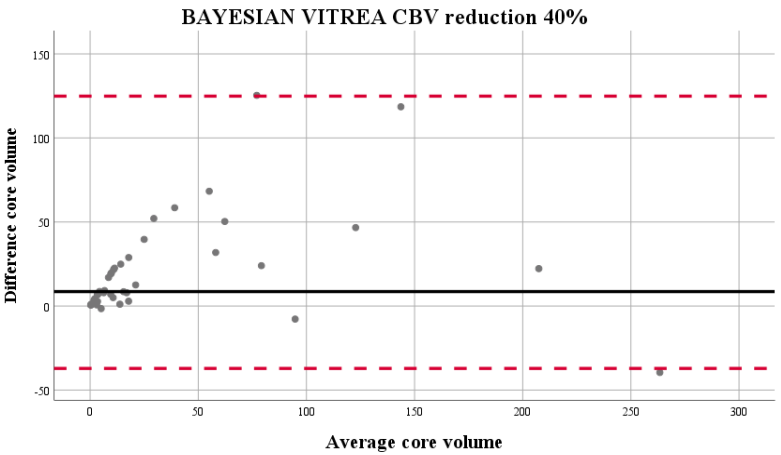

RAPID rCBV<42%
Difference core volume
Average core volume
150
100
50
0
-50
-100
0
50
100
150
200
250

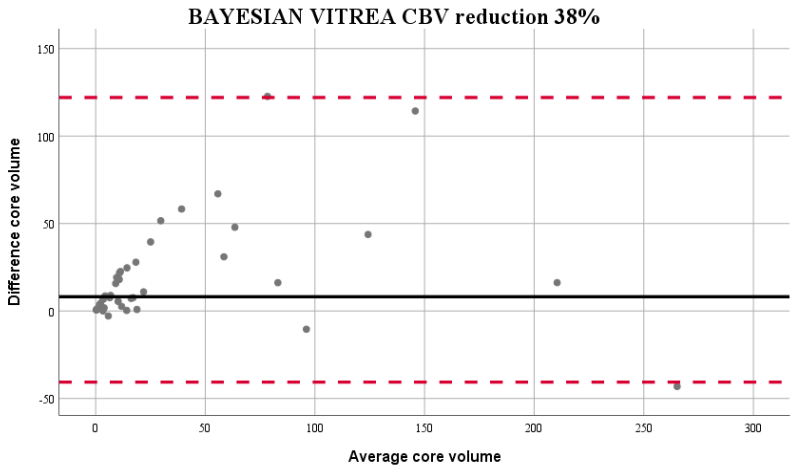

BAYESIAN VITREA CBV reduction 48%
Difference core volume
Average core volume
150
100
50
0
0
50
100
150
200
250
300

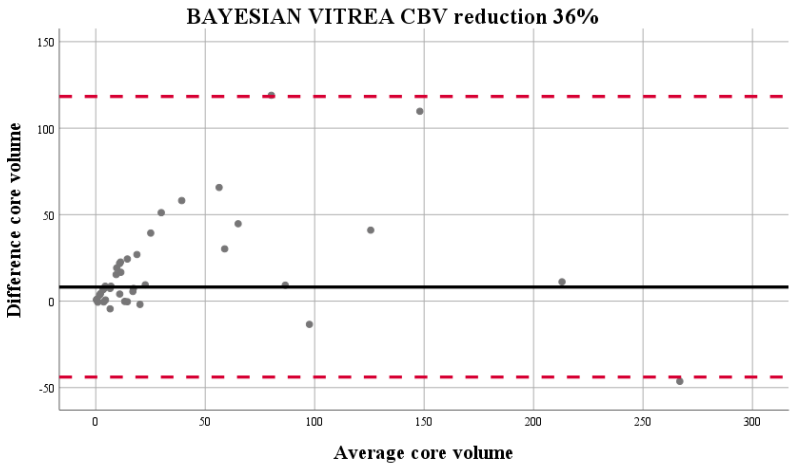

BAYESIAN VITREA CBV reduction 46%
Difference core volume
Average core volume

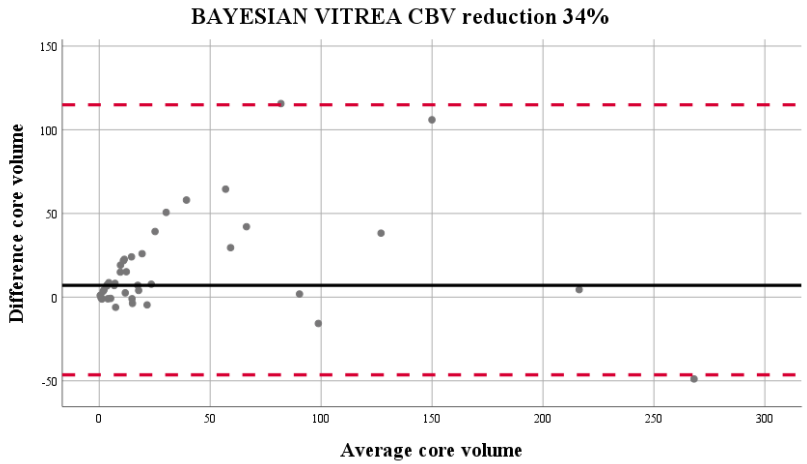

BAYESIAN VITREA CBV reduction 44%
Difference core volume
Average core volume

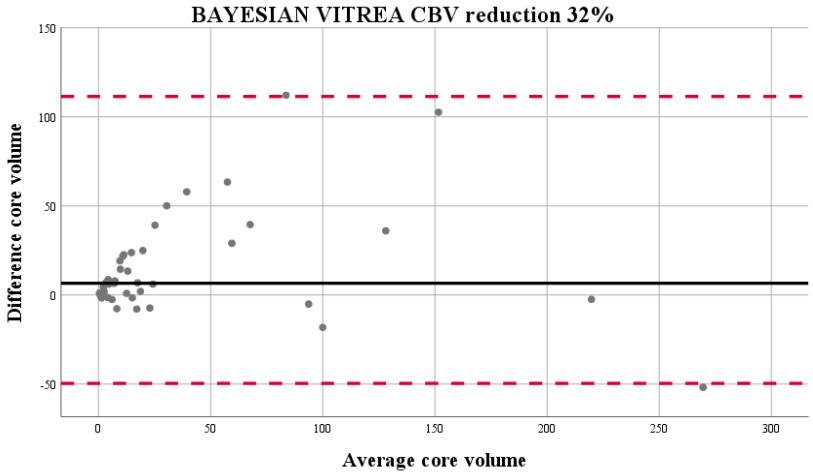

BAYESIAN VITREA CBV reduction 42%
Difference core volume
Average core volume

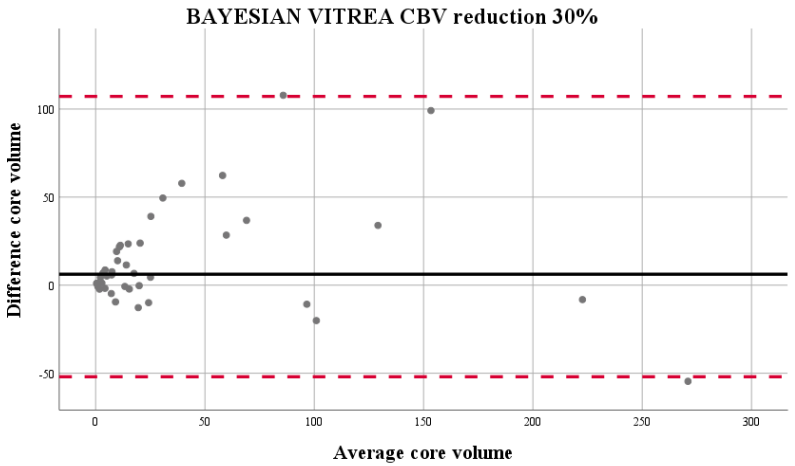

BAYESIAN VITREA CBV reduction 40%
Difference core volume
Average core volume

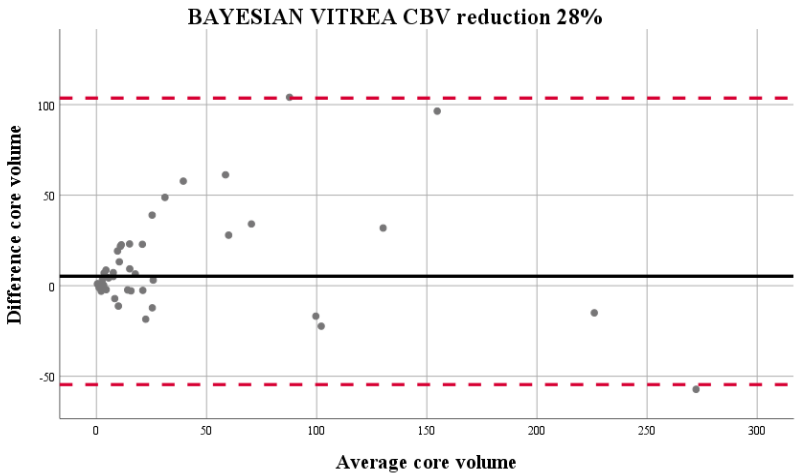

BAYESIAN VITREA CBV reduction 38%
Difference core volume
Average core volume

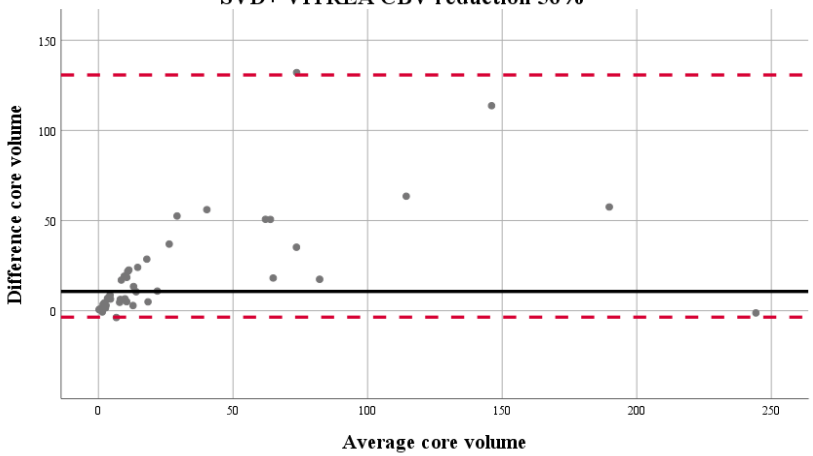

BAYESIAN VITREA CBV reduction 36%
Difference core volume
Average core volume

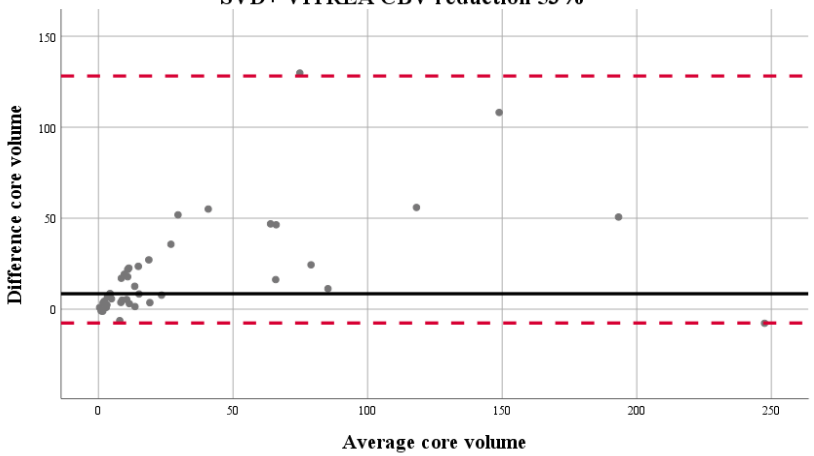

BAYESIAN VITREA CBV reduction 34%
Difference core volume
Average core volume

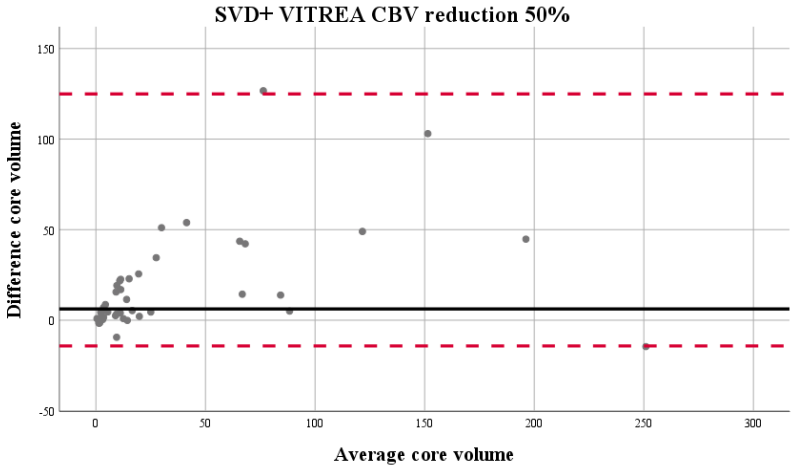

BAYESIAN VITREA CBV reduction 32%
Difference core volume
Average core volume

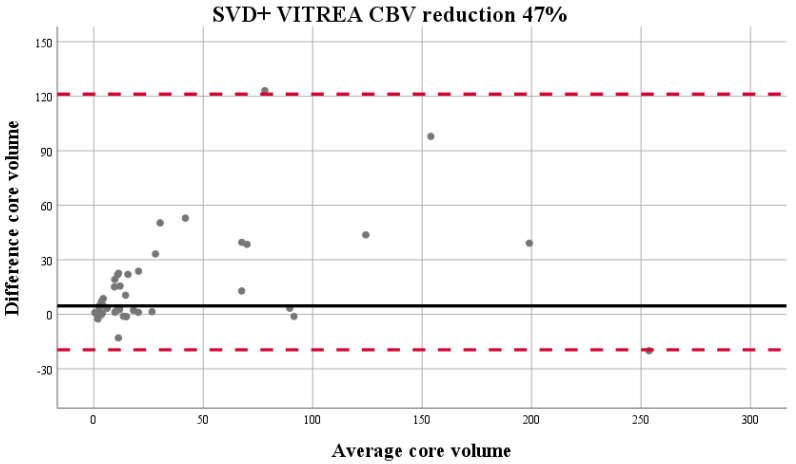

BAYESIAN VITREA CBV reduction 30%
Difference core volume
Average core volume
100
50
0
-50
0
50
100
150
200
250
300

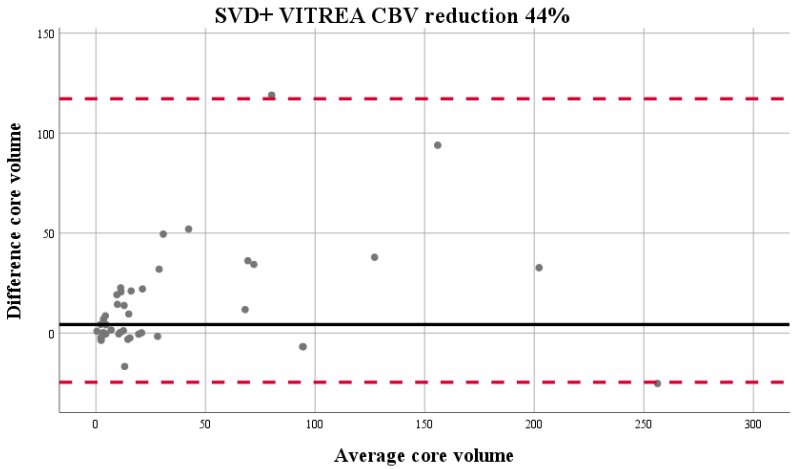

BAYESIAN VITREA CBV reduction 28%
Difference core volume
Average core volume
100
50
0
-50
0
50
100
150
200
250
300

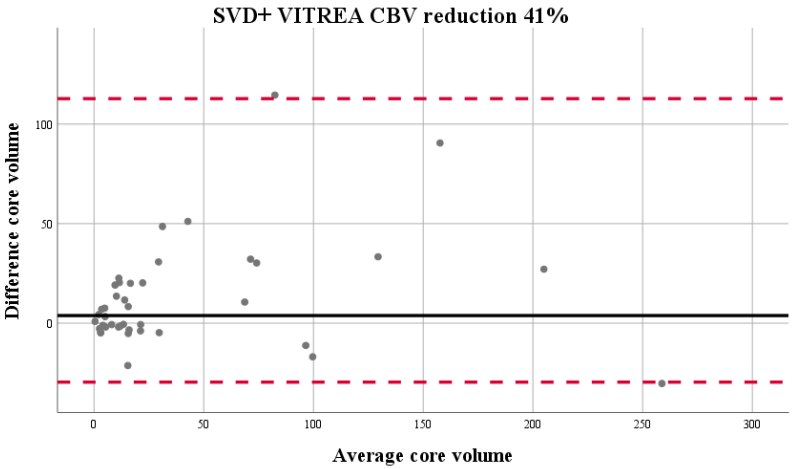

SVD+ VITREA CBV reduction 56%
Difference core volume
Average core volume
150
100
50
0
0
50
100
150
200
250

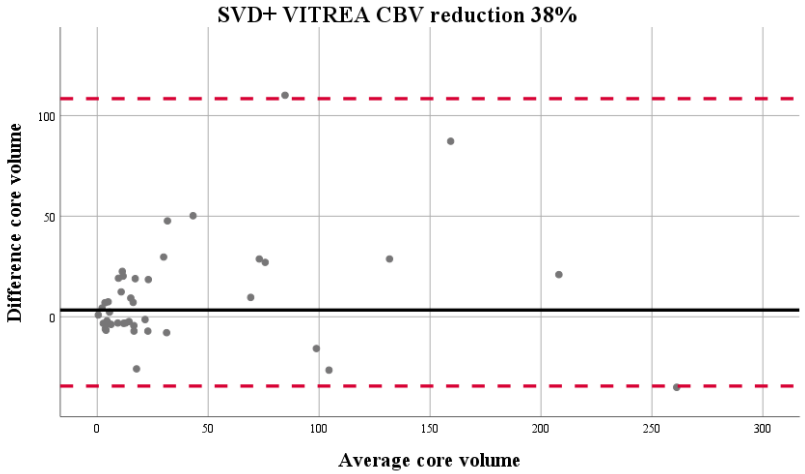

SVD+ VITREA CBV reduction 53%
Difference core volume
Average core volume
150
100
50
0
0
50
100
150
200
250

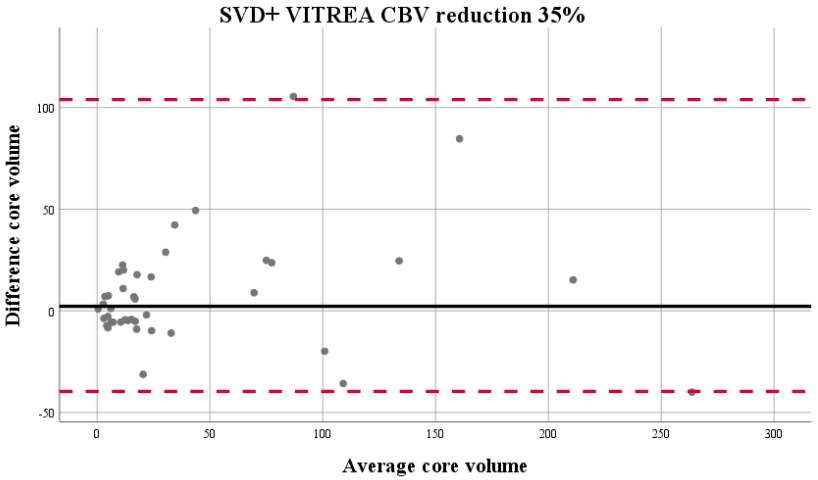

SVD+ VITREA CBV reduction 50%
Difference core volume
Average core volume

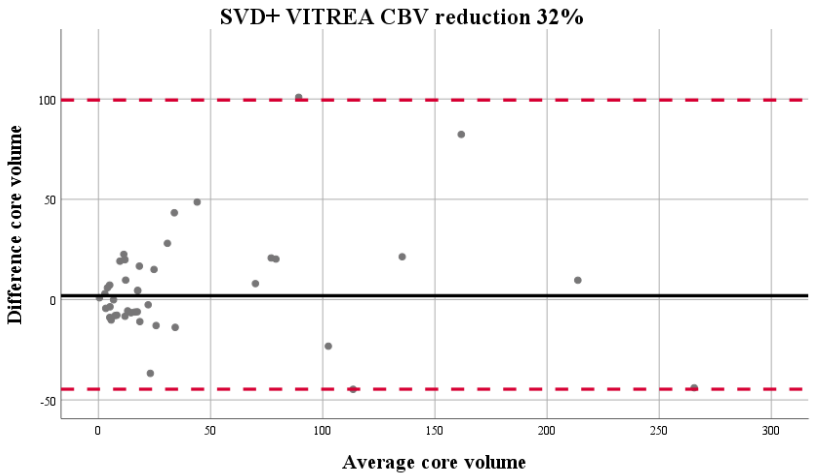

SVD+ VITREA CBV reduction 47%
Difference core volume
Average core volume

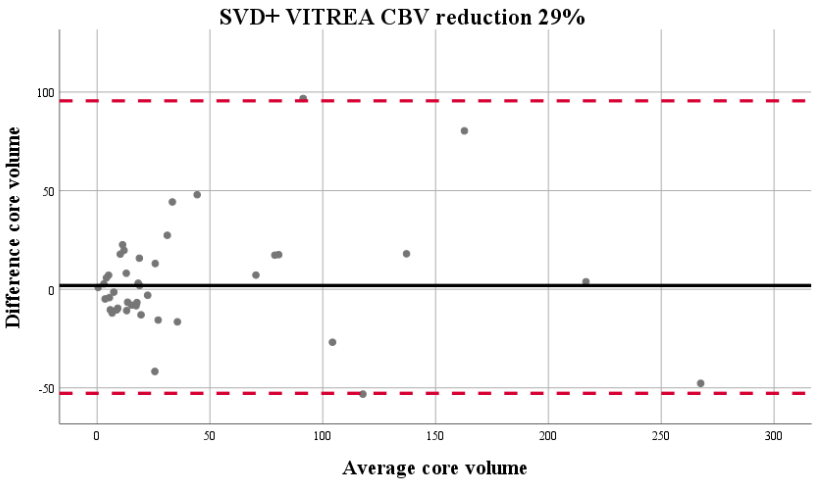

SVD+ VITREA CBV reduction 44%
Difference core volume
Average core volume


SVD+ VITREA CBV reduction 41%
Difference core volume
Average core volume


SVD+ VITREA CBV reduction 38%
Difference core volume
Average core volume
100
50
0
0
50
100
150
200
250
300


SVD+ VITREA CBV reduction 35%
Difference core volume
Average core volume
100
50
0
-50
0
50
100
150
200
250
300


SVD+ VITREA CBV reduction 32%
Difference core volume
Average core volume
100
50
0
-50
0
50
100
150
200
250
300


SVD+ VITREA CBV reduction 29%
Difference core volume
Average core volume
100
50
0
-50
0
50
100
150
200
250
300

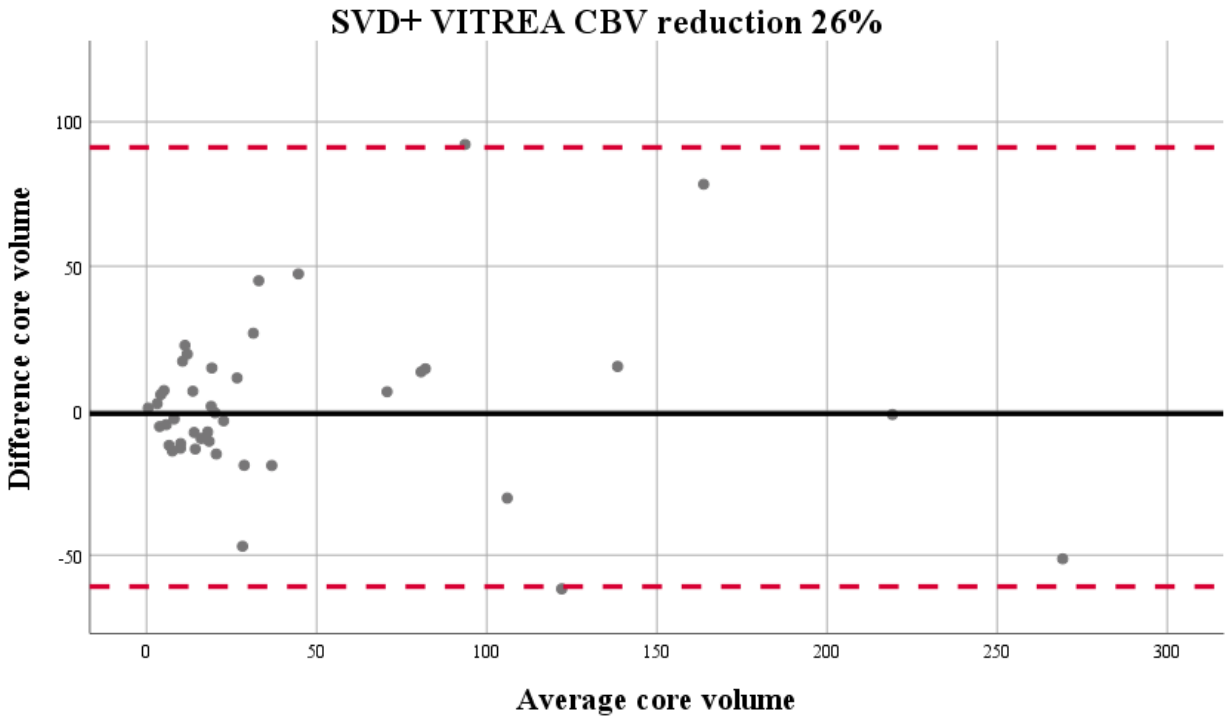


Figure 6. The Bland–Altman plot for the agreement on infarct core volume by each kind of CTP software (SVD+ VITREA, BAYESIAN VITREA, RAPID) with different thresholds against DWI infarct core volume. The dotted line demonstrates the 25th and 75th quartiles while the solid line shows the median difference.

The median infarct core volume difference for each kind of CTP software with different thresholds based on DWI infarct core volume is shown in Table 5. The percentage of incorrectly categorization (Table 6.A–C) according to the DWI based infarct core estimate ≤20 ml, ≤30 ml, ≤50 ml, ≤70 ml, and >70 ml; SVD+ VITREA CBV reduction of 26% threshold with 2/10 (20%), 6/32 (18.75%), 6/30 (20%), 6/28 (21.43%), 4/23 (17.39%), BAYESIAN VITREA CBV reduction of 28%, threshold with 4/10 (40%), 9/32 (28.15%), 9/30 (30%), 9/28 (32.14%), 7/23 (30.43%), and RAPID rCBF<38% threshold with 4/10 (40%), 17/32 (53.13%), 17/30 (56.68%), 17/28 (60.71%), 13/23 (56.52%). Illustration of representative cases on estimation of infarct core volume in two different CTP software with different thresholds are shown in Figure 7–11.

Table 5. The median core volume difference with different thresholds and software for CTP according to the DWI derived infarct core volume with thresholds of ≤20 ml, ≤30 ml, ≤50 ml, ≤70 ml, and >70 ml

Infarct core volume difference from DWI, median (IQR)			>70ml	≤70ml	≤50ml	≤30ml	≤20ml
RAPID	rCBF	<20%	74.83 (41.46 – 102.12)	8.37 (4.44 – 21.26)	8.05 (4.33 – 19.37)	7.83 (4.33 – 18.61)	6.98 (3.45 – 11.24)
		<30%	38.75 (21.63 – 65.59)	6.46 (3.38 – 19.61)	6.11 (3.24 – 17.53)	5.65 (3.00 – 10.59)	5.21 (1.09 – 7.75)
		<34%	30.25 (3.79 – 59.08)	5.11 (1.34 – 18.61)	4.66 (1.04 – 11.57)	4.33 (0.95 – 8.39)	4.33 (0.91 – 6.98)
		<38%	23.25 (-7.48 – 52.58)	4.33 (0.95 – 17.61)	3.89 (0.84 – 9.72)	3.35 (0.70 – 7.51)	3.24 (0.63 – 6.68)
	rCBV	<34%	41.65 (17.38 – 87.84)	8.16 (3.58 – 21.26)	7.33 (3.43 – 19.31)	6.83 (3.38 – 16.30)	6.28 (1.09 – 10.75)
		<38%	35.65 (7.38 – 83.47)	7.23 (3.38 – 21.26)	7.10 (3.27 – 19.31)	6.83 (3.08- 16.05)	6.28 (1.09 – 8.63)
		<42%	31.15 (-8.98 – 80.98)	6.83 (3.10 – 21.26)	6.46 (2.51 – 19.31)	6.23 (1.56 – 15.80)	5.28(0.91 – 8.63)
Bayesian VITREA	CBV reduction of	48%	57.02 (28.79 – 88.75)	9.96 (4.44 – 19.70)	9.28 (4.11 – 19.24)	8.71 (3.67 – 15.77)	6.98 (2.13 – 11.20)
		46%	52.14 (27.02 – 87.31)	9.40 (4.36 – 19.61)	8.92 (4.11 – 18.18)	8.62 (3.67- 15.58)	6.98 (1.80 – 10.24)
		44%	46.59 (24.19 – 85.11)	8.69 (3.67 – 19.61)	8.50 (3.39 – 17.53)	8.02 (3.29 – 14.65)	6.98 (1.45 – 9.58)
		42%	41.63 (19.20 – 82.98)	8.24 (3.48 – 19.61)	7.92 (3.10 – 17.53)	7.38 (2.39 – 13.04)	6.68 (1.03 – 8.63)
		40%	39.27 (14.75 – 80.87)	7.79 (2.76 – 19.61)	7.34 (2.31 – 17.53)	9.99 (1.49 – 11.71)	4.98 (0.91 – 8.53)
		38%	37.36 (9.53 – 78.80)	7.39 (1.13 – 18.87)	7.08 (0.90 – 16.29)	6.83 (0.89 - 10.44)	4.34 (0.63 – 7.68)
		36%	35.61 (3.56 – 76.72)	7.15 (0.63 – 18.53)	6.83 (0.43 – 15.69)	6.13 (0.02 – 9.23)	4.11 (-0.35 – 7.68)
		34%	33.88 (-2.53 – 74.88)	6.97 (-0.68 – 18.16)	6.81 (-0.83 – 14.99)	5.51 (0.93 – 8.54)	3.45 (-0.99 – 7.68)
		32%	32.49 (-8.36 – 73.20)	6.28 (-1.21 – 17.98)	6.08 (-1.47 – 13.65)	5.20 (-1.56 – 8.45)	1.89 (-1.67 – 6.98)
		30%	31.17 (-13.15 – 71.50)	5.49 (-1.57 – 17.84)	4.83 (-1.91 – 12.06)	4.40 (-2.12 – 8.37)	0.91 (-2.29 -6.98)

	28%	29.88 (−18.21 – 70.02)	4.70 (−2.53 – 17.66)	3.80 (−2.65 – 10.26)	3.18 (−2.78 – 8.28)	0.28 (−3.06 – 6.98)
SVD+ VITREA	56%	50.67 (17.95 – 76.06)	6.62 (3.09 – 18.98)	6.51 (2.95 – 17.35)	6.36 (2.90 – 12.78)	5.02 (1.55 – 8.63)
	53%	46.64 (14.99 – 68.96)	6.17 (2.52 – 18.81)	5.48 (2.12 – 17.19)	5.12 (1.65 – 11.58)	4.34 (0.95 – 8.33)
	50%	42.87 (11.65 – 62.50)	4.55 (1.08 – 18.59)	4.42 (0.90 – 15.92)	4.16 (0.88 – 10.76)	3.51 (0.42 – 6.98)
	47%	38.80 (2.22 – 57.24)	2.96 (0..74 – 18.25)	2.42 (0.47 – 15.21)	1.99 (0.05 – 10.03)	1.84 (−1.08 – 6.98)
	44%	33.50 (−6.82 – 51.91)	1.33 (−0.68 – 17.95)	1.03 (−0.96 – 13.93)	0.62 (−1.43 – 9.31)	0.32 (−2.24 – 6.98)
	41%	28.67 (−12.62 – 47.64)	0.16 (−2.55 – 17.75)	−0.63 (−2.91 – 12.12)	−0.70 (−3.22 – 8.13)	−1.14 (−3.38 – 6.98)
	38%	24.00 (−18.46 – 43.36)	−0.24 (−3.66 – 16.98)	−1.71 (−3.93 – 10.06)	−2.20 (−4.23 – 7.37)	−3.10 (−4.38 – 6.98)
	35%	19.41 (−23.89 – 39.78)	−0.56 (−5.61 – 15.23)	2.42 (−5.62 – 8.25)	−3.30 (−5.63 – 6.96)	−4.26 (−5.63 – 5.82)
	32%	14.93 (−28.39 – 36.60)	−1.34 (−7.9 – 13.68)	−3.07 (−8.04 – 7.87)	−3.97 (−8.22 – 5.58)	−5.63 (−8.31 – 4.47)
	29%	12.24 (−32.074 – 33.57)	−2.24 (−10.24 – 11.82)	−3.63 (−10.44 – 7.37)	−4.56 (−10.45 – 5.09)	−6.58 (−10.45 – 2.70)
	26%	9.98 (−35.52 – 31.07)	−3.20 (−11.85 – 10.25)	−4.18 (−12.26 – 6.80)	−5.16 (−12.78 – 4.78)	−7.38 (−13.04 – 1.51)

CBV reduction of

Note – DWI, Diffusion-weighted imaging; rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow; CBV, cerebral blood volume

Table 6.A. The number of misclassification group with RAPID according to the DWI derived infarct core volume with thresholds of ≤20 ml, ≤30 ml, ≤50 ml, ≤70 ml, and >70 ml

DWI volume	RAPID						
	rCBF				rCBV		
	<20%	<30%	<34%	<38%	<34%	<38%	<42%
>70 ml (n=10)	7	5	4	4	5	4	3
≤70 ml (n=32)	25	21	18	17	23	21	20
≤51 ml (n=30)	24	21	18	17	23	21	20
≤30 ml (n=28)	23	20	17	17	22	20	19
≤20 ml (n=23)	19	16	13	13	18	16	15

Note – DWI, Diffusion-weighted imaging; rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow;

Table 6.B. The number of misclassification group with BAYESIAN VITREA according to the DWI derived infarct core volume with thresholds of ≤20 ml, ≤30 ml, ≤50 ml, ≤70 ml, and >70 ml

DWI volume	BAYESIAN VITREA										
	CBV reduction of										
	48%	46%	44%	42%	40%	38%	36%	34%	32%	30%	28%
>70 ml (n=10)	6	6	5	5	5	4	4	4	4	4	4
≤70 ml (n=32)	17	16	15	14	14	12	12	11	10	10	9
≤51 ml (n=30)	17	16	15	14	14	12	12	11	10	10	9
≤30 ml (n=28)	16	16	15	14	14	12	12	11	10	10	9
≤20 ml (n=23)	13	13	13	12	12	10	10	9	8	8	7

Note – DWI, Diffusion-weighted imaging; CBV, cerebral blood volume;

Table 6.C. The number of misclassification group with SVD+ VITREA according to the DWI derived infarct core volume with thresholds of ≤20 ml, ≤30 ml, ≤50 ml, ≤70 ml, and >70 ml

DWI volume	SVD+ VITREA										
	CBV reduction of										
	56%	53%	50%	47%	44%	41%	38%	35%	32%	29%	26%
>70 ml (n=10)	5	5	4	4	4	4	4	4	4	2	2
≤70 ml (n=32)	12	10	7	7	7	8	8	8	8	7	6
≤51 ml (n=30)	12	10	7	7	7	8	8	8	8	7	6
≤30 ml (n=28)	12	10	7	7	7	8	8	8	8	7	6
≤20 ml (n=23)	10	8	5	5	6	6	6	6	6	5	4

Note – DWI, Diffusion-weighted imaging; CBV, cerebral blood volume

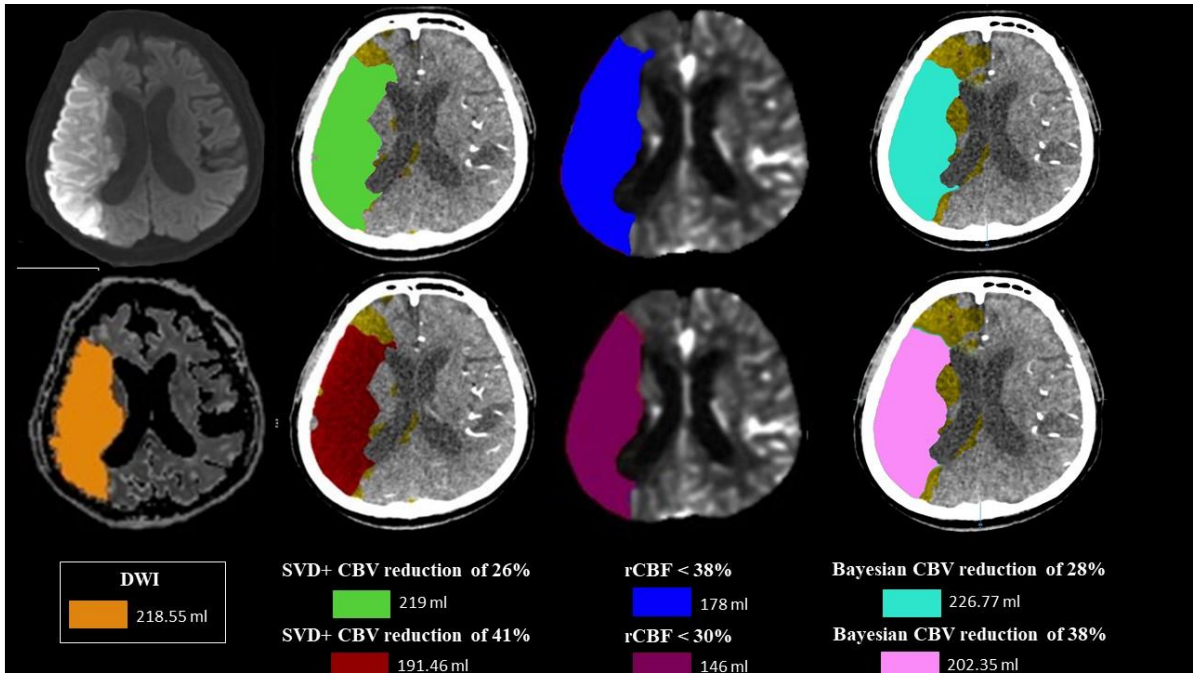


Figure 7. A 75 year-old man with left hemispheric stroke. The infarct core volume was estimated 218.55 ml with DWI-ADC (orange color). The NCCT revealed acute infarction in the right middle cerebral artery territory caused by occlusion of right proximal ICA. The initial NIHSS score was 21 and the time between CTP to MRI was 40 min. The infarct core volume was measured 191.46 ml on SVD+ VITREA CBV reduction of 41% (red color), 219 ml on SVD+ VITREA CBV reduction of 26% (green color). On the other hand, RAPID rCBF < 30% (purple color) threshold estimated infarct core volume 146 ml and 178 ml on rCBF < 38% (blue color). The infarct core volume was estimated 202.35 ml on Bayesian VITREA CBV reduction of 38% (pink color), 233.54 ml on BAYESIAN VITREA CBV reduction of 28% (turquoise color).

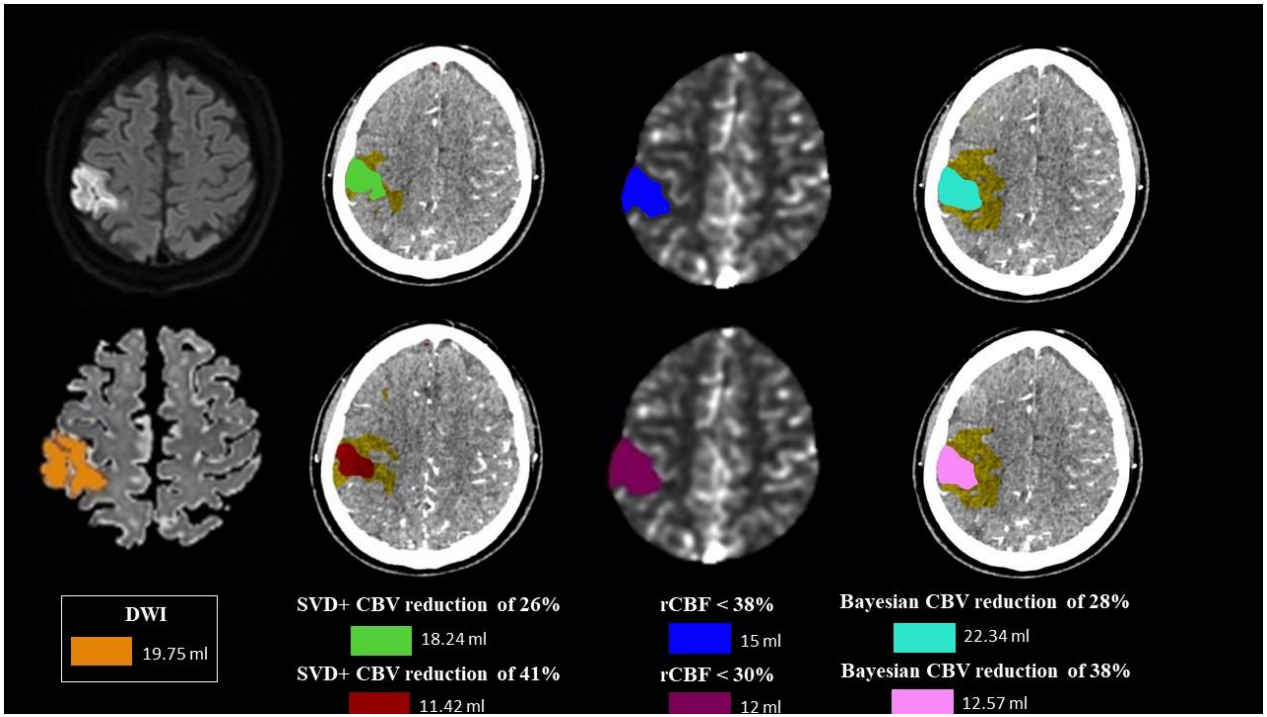


Figure 8. A 74 year-old man with left hemispheric stroke. The initial NIHSS score was 6 and the time between CTP to MRI was 29 min. The infarct core volume was estimated 19.75 ml with DWI-ADC (orange color). The CTA demonstrates occlusion of the right proximal ICA and M3 distal branch of MCA. The infarct core volume was estimated 11.42 ml on SVD+ VITREA CBV reduction of 41% (red color), 18.24 ml on SVD+ VITREA CBV reduction of 26% (green color), 12.57 ml on BAYESIAN VITREA CBV reduction of 38% (pink color), 22.34 ml on BAYESIAN VITREA CBV reduction of 28% (turquoise color), 12 ml on RAPID rCBF < 30% (purple color), and 15 ml on RAPID rCBF < 38% (blue color).

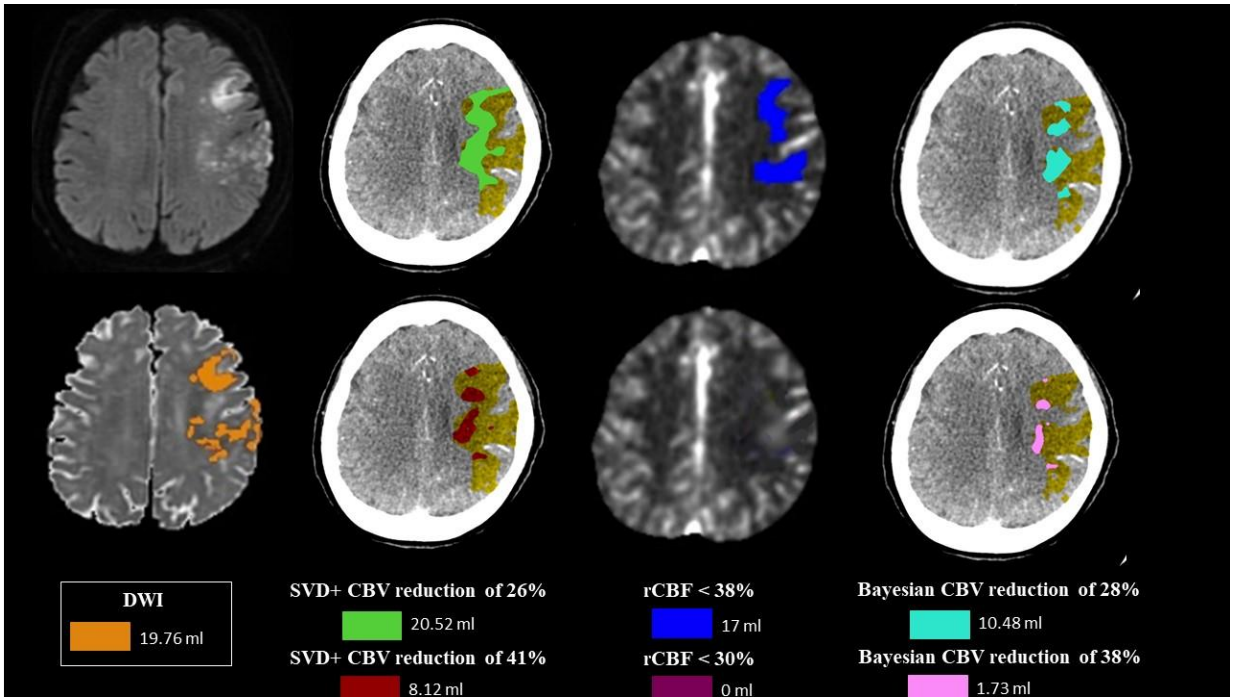


Figure 9. A 74 year-old woman with right hemispheric stroke. The initial NIHSS score was 17 and the time between CTP to MRI was 37 min. The infarct core volume was estimated 17.76 ml with DWI-ADC (orange color). The CTA demonstrates occlusion of the left M1 MCA. The infarct core volume was calculated 8.17 ml on SVD+ VITREA CBV reduction of 41% (red color), 20.52 ml on SVD+ VITREA CBV reduction of 26% (green color), 1.73 ml on BAYESIAN VITREA CBV reduction of 38% (pink color), 10.48 ml on BAYESIAN VITREA CBV reduction of 28% (turquoise color), 0 ml on RAPID rCBF < 30% (purple color), and 17 ml on RAPID rCBF < 38% ml (blue color).

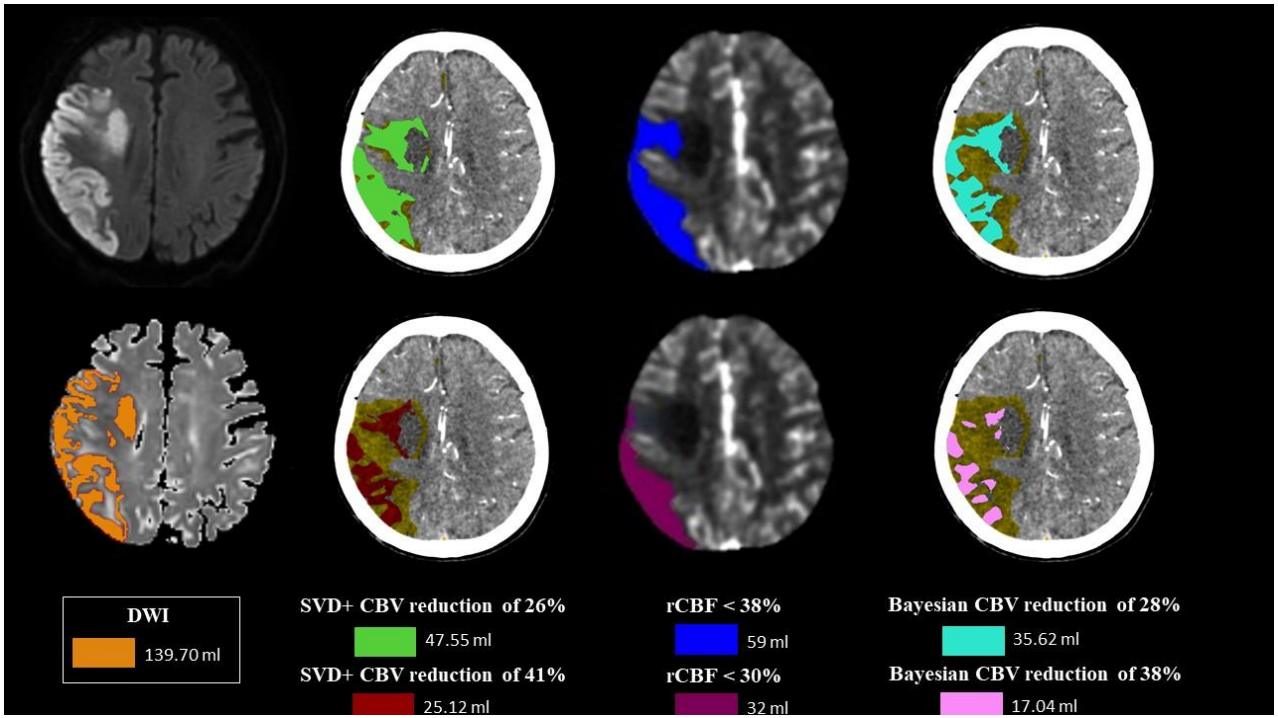


Figure 10. A 85 year-old woman with left hemispheric stroke. The initial NIHSS score was 12 and the time between CTP to MRI was 20 min. The infarct core volume was estimated 139.70 ml with DWI-ADC (orange color). The CTA demonstrates occlusion of the right M1 MCA. The infarct core volume was calculated 25.12 ml on SVD+ VITREA CBV reduction of 41% (red color), 47.55 ml on SVD+ VITREA CBV reduction of 26% (green color), 17.04 ml on BAYESIAN VITREA CBV reduction of 38% (pink color), 35.62 ml on BAYESIAN VITREA CBV reduction of 28% (turquoise color), 32 ml on RAPID rCBF < 30% (purple color), and 59 ml on RAPID rCBF < 38% ml (blue color).

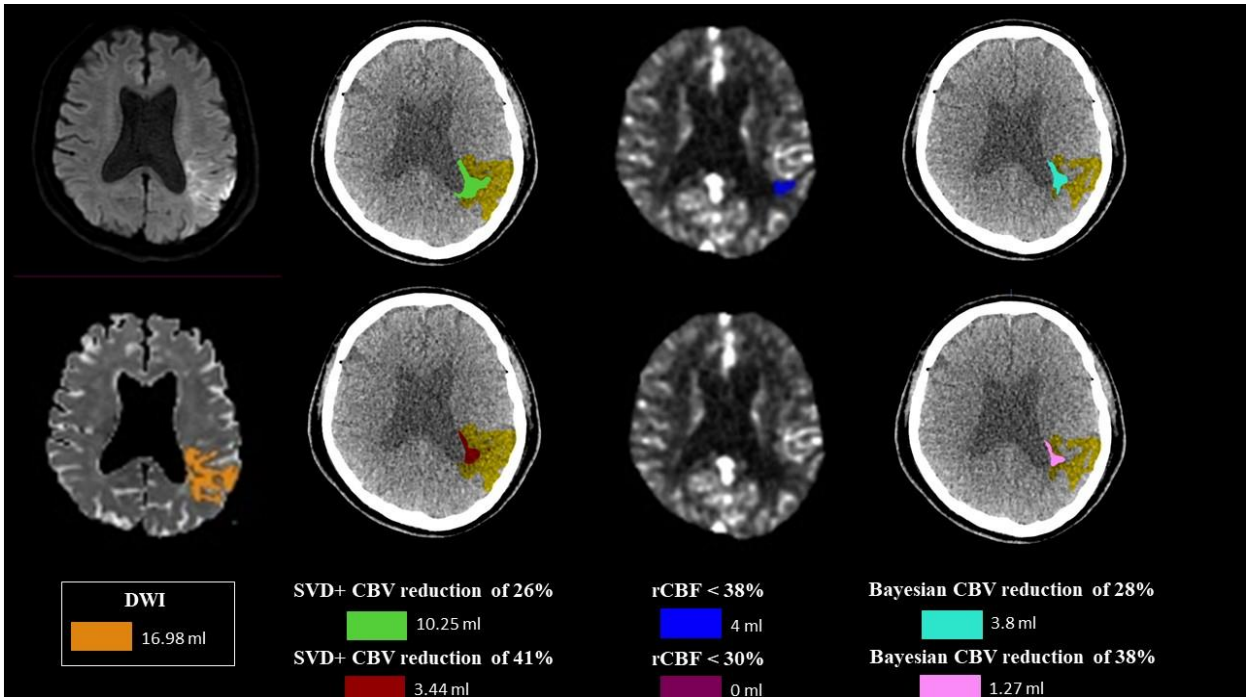


Figure 11. A 77 year-old man with right hemispheric stroke. The initial NIHSS score was 9 and the time between CTP to MRI was 35 min. The infarct core volume was estimated 16.98 ml with DWI-ADC (orange color). The CTA demonstrates occlusion of the left M2 division. The infarct core volume was calculated 3.44 ml on SVD+ VITREA CBV reduction of 41% (red color), 10.25 ml on SVD+ VITREA CBV reduction of 26% (green color), 1.27 ml on BAYESIAN VITREA CBV reduction of 38% (pink color), 3.8 ml on BAYESIAN VITREA CBV reduction of 28% (turquoise color), 0 ml on RAPID rCBF < 30% (purple color), and 4 ml on RAPID rCBF < 38% ml (blue color).

Chapter 4. Discussions

In this study we aimed to assess the volumetric agreement of estimated infarct core with different CTP software (SVD+, Bayesian algorithm within VITREA and RAPID) and final infarct volume on DWI in patients with an especially short interval times (less than 60 minutes) from CTP to DWI. The study was conducted in a population (n=42) of patients with an occlusion in the large artery of anterior circulation including middle cerebral artery, anterior cerebral artery, and internal carotid artery terminus. The advantage of this study was the short time [median 37.5 minutes (IQR, 20–44), ranging 12−60 min between CTP and DWI. All CTP and DWI−derived infarct core volumes were measured prior to endovascular procedures, which could be another strength. We found that RAPID rCBF<38%, SVD+ VITREA CBV reduction of 26%, and BAYESIAN VITREA CBV reduction of 28% were the optimal threshold to estimate the infarct core volume in patients with an occlusion in large artery of anterior circulation compared with the most commonly used settings for each kind of CTP software. In our study, all optimal thresholds of different CTP software demonstrated an moderate to very strong correlation (r value more than 0.617) against DWI infarct core volume.

The SWIFT PRIME [32], EXTEND-IA [33], DAWN [30] and DEFUSE 3 [31] trials have demonstrated that there was an accurate final infarct volume correlation using the RAPID (rCBV < 30%). Authors reported that RAPID estimates the infarct core volume more accurately compared with other CTP software [47, 48]. Hoving [49] et al. investigated the volumetric agreement of estimated ischemic core on CTP with 24 hours of follow-up infarct on DWI. Their study showed that the infarct core volume estimated using rCBF<30% on RAPID was smaller than 24h follow up-infarct core volume with moderate - poor spatial agreement. Austein [47] et al. studied the accuracy of different CTP software packages including Brain CT perfusion package (Philips Healthcare), Syngo volume perfusion CT Neuro (Siemens Healthcare), and RAPID (iSchemaView Inc). They reported that the RAPID (rCBF<30%) resulted in high accuracy, best correlation and smaller infarct volume difference rather than Brain CT perfusion package (Philips Healthcare – CBV < 2.0 ml/100g and rMTT > 145%) and Syngo volume perfusion CT Neuro (Siemens Healthcare – CBV < 1.2 ml/100ml). However, the final infarct volume was assessed based on NCCT or DWI up to 8 days after CTP. In our study, rCBF < 38% demonstrated a smaller difference in the median infarct core volume than those of the rCBF < 30% with higher correlation. The Bland-

Altman limits of agreements were larger in rCBF<30% compared with rCBF < 38%. Our results showed that applying rCBF<38% is a reliable threshold in estimating infarct core volume, as it was confirmed by a study of Cereda [50] despite the 27 hours follow-up infarct volume measurement. In addition, we found that according to the DWI-derived infarct core volume ≤20 ml, ≤30 ml, ≤50 ml, ≤70 ml, and >70 ml, the number of incorrectly categorization was higher when using rCBF<30% threshold compared with rCBF<38%.

In our study, the most commonly used threshold for Bayesian VITREA CBV reduction of 38% estimated infarct core volume more accurately with smaller median infarct core volume differences than those of RAPID rCBF < 30%. Our results are consistent with the previous study of Rava [37] as reported that default Bayesian Vitrea CTP software, which characterized on adjacent perfusion to detect the infarction core (CBV reduction of 38%), showed a smaller infarct volume difference than RAPID rCBF < 30%. However, this study was conducted with limited thresholds and a 24-hour delay between MRI and CTP, which could allow the tissue to convert from penumbra to infarct. The current study demonstrated that BAYESIAN VITREA CBV reduction of 28% is more accurate in estimation of infarct core volume in comparison to the most commonly used settings for BAYESIAN VITREA CBV

reduction of 38%. The 95% limits of agreements in Bland-Altman analysis were wider for BAYESIAN VITREA CBV reduction of 38% compared with BAYESIAN VITREA CBV reduction of 28%.

Authors of a previous study [51] highlighted the better performance of Bayesian method than the SVD on the estimation of infarct core volume. Ichikawa et al. [51] compared CT perfusion data analyzed with the Bayesian (CBV < 38%) and singular value decomposition (CBV < 41%) algorithm. There was no significant difference in the median infarct volume on SVD+ and Bayesian algorithm and MRI-derived infarct volume. The infarct volume agreement between CTP and the follow up MRI was good correlation in both SVD+ and Bayesian algorithm. Our results did not support these results. In our results, the commonly used settings for SVD+ VITREA CBV reduction of 41% demonstrated better performance on the estimation of infarct core volume in comparison to BAYESIAN VITREA CBV reduction of 38%. The median core volume difference was smaller when using SVD+ VITREA CBV reduction of 41% compared with BAYESIAN VITREA CBV reduction of 38%. This may be relevant to the MRI-derived infarct core volume follow-up time. The infarct core volume with MRI was obtained in 24h follow up with previous study [51] while

the median time of MRI was obtained only 37.5 min after CTP in our study. These results were supported by a previously conducted study [52] which reported that the average infarct core volume difference was smaller in the SVD+ VITREA compared with BAYESIAN VITREA for the patient with acute ischemic stroke who underwent endovascular treatments.

Even though the CBF threshold correlates more than CBV threshold with final infarct core volume by DWI was reported in some literature [53, 54]. In our study, SVD+ VITREA CBV reduction of 26% resulted in more accurate estimation of infarct core volume than CBF thresholds. This result was concordant with another study [52] which reported that CBV reduction of 26% is the optimal threshold for infarct volume prediction in the non-intervention group. We found that there was no statistically significant difference between SVD+ VITREA CBV derived infarct core volume and DWI-derived infarct core volume while different rCBF thresholds resulted significantly smaller in the estimation of infarct core volume compared with DWI-derived infarct core volume. The Bland-Altman limits of agreements for infarct core volume were smaller in SVD+ VITREA CBV reduction of 26% while it was larger in SVD+ VITREA CBV reduction of 41%. The current

study showed that 95% limits of agreements in Bland-Altman analysis were narrow for CBV threshold derived infarct core volume than CBF thresholds. The percentage of incorrectly categorization based on DWI derived infarct core volume ≤70 ml was lower in the SVD+ VITREA CBV reduction of 26% (18.75%) compared with SVD+ VITREA CBV reduction of 41% (25%), RAPID rCBF < 30% (65.63%), RAPID rCBF < 38% (53.15%), BAYESIAN VITREA CBV reduction of 38% (37.5%), BAYESIAN VITREA CBV reduction of 28% (28.13%). The underestimation and overestimation measurement by different software could exclude or select the patient for endovascular treatment differently and directly associate with the clinical outcome of the patient. In our study, SVD+ VITREA CBV reduction of 26% was ideal for infarct core volume measurement.

There were several limitations in our study. It is a retrospective study and there was a small sample size used for our study. The small sample size was a consequence of inclusion criteria including short interval time (within 60 min) between CTP and DWI, and occlusion of the large artery in the anterior circulation. We did not evaluate the FLAIR/T2 derived late follow-up. Hence, we hypothesized short time follow-up DWI-derived infarct core

volume could reflect the true infarct core volume and vasogenic edema could overestimate the true infarct volume in late follow-up. The maximum and minimum threshold with fixed intervals are supplied within the software and we did not analyze the overlap of locations between different thresholds on CTP software (RAPID, SVD+ VITREA, BAYESIAN VITREA) and infarct core volume estimated with DWI. Regardless, our results showed that the CBV threshold is more accurate than the CBF threshold for infarct core volume measurements and the optimized thresholds estimated infarct core volume more accurately than the most commonly used settings.

Chapter 5. Conclusions

Our study found that the CBV thresholds provide a more accurate parameter to predict infarct core volume in acute ischemic stroke patients compared with the CBF thresholds.

Bibliography

1. *The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators.* J Clin Epidemiol, 1988. **41**(2): p. 105-14.
2. Adams, H.P., Jr., et al., *Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).* Neurology, 1999. **53**(1): p. 126-31.
3. Wintermark, M., et al., *Imaging recommendations for acute stroke and transient ischemic attack patients: A joint statement by the American Society of Neuroradiology, the American College of Radiology, and the Society of NeuroInterventional Surgery.* AJNR Am J Neuroradiol, 2013. **34**(11): p. E117-27.
4. Provenzale, J.M., et al., *Assessment of the patient with hyperacute stroke: imaging and therapy.* Radiology, 2003. **229**(2): p. 347-59.
5. Mohr, J.P., et al., *Magnetic resonance versus computed tomographic imaging in acute stroke.* Stroke, 1995. **26**(5): p. 807-12.
6. Leiva-Salinas, C. and M. Wintermark, *Imaging of acute ischemic stroke.* Neuroimaging Clin N Am, 2010. **20**(4): p. 455-68.
7. Gersing, A.S., et al., *Mapping of cerebral metabolic rate of oxygen using dynamic susceptibility contrast and blood oxygen level dependent MR imaging in acute ischemic stroke.* Neuroradiology, 2015. **57**(12): p. 1253-61.
8. Schaefer, P.W., P.E. Grant, and R.G. Gonzalez, *Diffusion-weighted MR imaging of the brain.* Radiology, 2000. **217**(2): p. 331-45.
9. Srinivasan, A., et al., *State-of-the-art imaging of acute stroke.* Radiographics, 2006. **26 Suppl 1**: p. S75-95.
10. Oppenheim, C., et al., *Is there an apparent diffusion coefficient threshold in predicting tissue viability in hyperacute stroke?* Stroke, 2001. **32**(11): p. 2486-91.

11. Sunshine, J.L., et al., *Hyperacute stroke: ultrafast MR imaging to triage patients prior to therapy.* Radiology, 1999. **212**(2): p. 325-32.
12. Gonzalez, R.G., et al., *Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset.* Radiology, 1999. **210**(1): p. 155-62.
13. Lovblad, K.O., et al., *Clinical experience with diffusion-weighted MR in patients with acute stroke.* AJNR Am J Neuroradiol, 1998. **19**(6): p. 1061-6.
14. Koopman, M.S., et al., *Comparison of three commonly used CT perfusion software packages in patients with acute ischemic stroke.* J Neurointerv Surg, 2019. **11**(12): p. 1249-1256.
15. Fahmi, F., et al., *Differences in CT perfusion summary maps for patients with acute ischemic stroke generated by 2 software packages.* AJNR Am J Neuroradiol, 2012. **33**(11): p. 2074-80.
16. Kudo, K., et al., *Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients.* Radiology, 2010. **254**(1): p. 200-9.
17. Konstas, A.A., et al., *Theoretic basis and technical implementations of CT perfusion in acute ischemic stroke, part 2: technical implementations.* AJNR Am J Neuroradiol, 2009. **30**(5): p. 885-92.
18. Lui, Y.W., et al., *Evaluation of CT perfusion in the setting of cerebral ischemia: patterns and pitfalls.* AJNR Am J Neuroradiol, 2010. **31**(9): p. 1552-63.
19. Forkert, N.D., et al., *Comparison of 10 TTP and Tmax estimation techniques for MR perfusion-diffusion mismatch quantification in acute stroke.* AJNR Am J Neuroradiol, 2013. **34**(9): p. 1697-703.
20. Kudo, K., et al., *Difference in tracer delay-induced effect among deconvolution algorithms in CT perfusion analysis: quantitative evaluation with digital phantoms.* Radiology, 2009. **251**(1): p. 241-9.
21. Zanderigo, F., et al., *Nonlinear stochastic regularization to characterize tissue residue function in bolus-tracking MRI:*

assessment and comparison with SVD, block-circulant SVD, and Tikhonov. IEEE Trans Biomed Eng, 2009. **56**(5): p. 1287-97.

22. Andersen, I.K., et al., *Perfusion quantification using Gaussian process deconvolution.* Magn Reson Med, 2002. **48**(2): p. 351-61.
23. Gobbel, G.T. and J.R. Fike, *A deconvolution method for evaluating indicator-dilution curves.* Phys Med Biol, 1994. **39**(11): p. 1833-54.
24. Rempp, K.A., et al., *Quantification of regional cerebral blood flow and volume with dynamic susceptibility contrast-enhanced MR imaging.* Radiology, 1994. **193**(3): p. 637-41.
25. Boutelier, T., et al., *Bayesian hemodynamic parameter estimation by bolus tracking perfusion weighted imaging.* IEEE Trans Med Imaging, 2012. **31**(7): p. 1381-95.
26. Kudo, K., et al., *Bayesian analysis of perfusion-weighted imaging to predict infarct volume: comparison with singular value decomposition.* Magn Reson Med Sci, 2014. **13**(1): p. 45-50.
27. Santos, A.R., et al., *A singular value decomposition approach for improved taxonomic classification of biological sequences.* BMC Genomics, 2011. **12 Suppl 4**: p. S11.
28. Wei, W., et al., *Randomized Generalized Singular Value Decomposition.* Communications on Applied Mathematics and Computation, 2021. **3**(1): p. 137-156.
29. Erichson, N.B., et al., *Randomized Matrix Decompositions Using R.* Journal of Statistical Software; Vol 1, Issue 11 (2019), 2019.
30. Nogueira, R.G., et al., *Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct.* N Engl J Med, 2018. **378**(1): p. 11-21.
31. Albers, G.W., et al., *Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging.* N Engl J Med, 2018. **378**(8): p. 708-718.
32. Saver, J.L., et al., *Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke.* N Engl J Med, 2015. **372**(24): p. 2285-95.

33. Campbell, B.C., et al., *Endovascular therapy for ischemic stroke with perfusion-imaging selection.* N Engl J Med, 2015. **372**(11): p. 1009-18.
34. Lopez Puga, J., M. Krzywinski, and N. Altman, *Points of significance: Bayes' theorem.* Nat Methods, 2015. **12**(4): p. 277-8.
35. Sasaki, M., et al., *Assessment of the accuracy of a Bayesian estimation algorithm for perfusion CT by using a digital phantom.* Neuroradiology, 2013. **55**(10): p. 1197-203.
36. Nael, K., et al., *Defining Ischemic Core in Acute Ischemic Stroke Using CT Perfusion: A Multiparametric Bayesian-Based Model.* AJNR Am J Neuroradiol, 2019. **40**(9): p. 1491-1497.
37. Rava, R.A., et al., *Assessment of a Bayesian Vitrea CT Perfusion Analysis to Predict Final Infarct and Penumbra Volumes in Patients with Acute Ischemic Stroke: A Comparison with RAPID.* AJNR Am J Neuroradiol, 2020. **41**(2): p. 206-212.
38. Adams, H.P., Jr., et al., *Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association.* Circulation, 1996. **94**(5): p. 1167-74.
39. Berkhemer, O.A., et al., *A randomized trial of intraarterial treatment for acute ischemic stroke.* N Engl J Med, 2015. **372**(1): p. 11-20.
40. Goyal, M., et al., *Randomized assessment of rapid endovascular treatment of ischemic stroke.* N Engl J Med, 2015. **372**(11): p. 1019-30.
41. Jovin, T.G., et al., *Thrombectomy within 8 hours after symptom onset in ischemic stroke.* N Engl J Med, 2015. **372**(24): p. 2296-306.
42. Mokin, M., et al., *Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee.* J Neurointerv Surg, 2019. **11**(3): p. 215-220.
43. Lansberg, M.G., et al., *MRI profile and response to endovascular*

reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol, 2012. **11**(10): p. 860-7.

44. Xie, Y., et al., *Pretreatment lesional volume impacts clinical outcome and thrombectomy efficacy.* Ann Neurol, 2018. **83**(1): p. 178-185.
45. Parsons, M.W., et al., *Pretreatment diffusion- and perfusion-MR lesion volumes have a crucial influence on clinical response to stroke thrombolysis.* J Cereb Blood Flow Metab, 2010. **30**(6): p. 1214-25.
46. Yoo, A.J., et al., *MRI-based selection for intra-arterial stroke therapy: value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization.* Stroke, 2009. **40**(6): p. 2046-54.
47. Austein, F., et al., *Comparison of Perfusion CT Software to Predict the Final Infarct Volume After Thrombectomy.* Stroke, 2016. **47**(9): p. 2311-7.
48. Kudo, K., et al., *Accuracy and reliability assessment of CT and MR perfusion analysis software using a digital phantom.* Radiology, 2013. **267**(1): p. 201-11.
49. Hoving, J.W., et al., *Volumetric and Spatial Accuracy of Computed Tomography Perfusion Estimated Ischemic Core Volume in Patients With Acute Ischemic Stroke.* Stroke, 2018. **49**(10): p. 2368-2375.
50. Cereda, C.W., et al., *A benchmarking tool to evaluate computer tomography perfusion infarct core predictions against a DWI standard.* J Cereb Blood Flow Metab, 2016. **36**(10): p. 1780-1789.
51. Ichikawa, S., H. Yamamoto, and T. Morita, *Comparison of a Bayesian estimation algorithm and singular value decomposition algorithms for 80-detector row CT perfusion in patients with acute ischemic stroke.* Radiol Med, 2021.
52. Rava, R.A., et al., *Effect of computed tomography perfusion post-processing algorithms on optimal threshold selection for final infarct volume prediction.* Neuroradiol J, 2020. **33**(4): p. 273-285.
53. Kamalian, S., et al., *CT cerebral blood flow maps optimally correlate*

with admission diffusion-weighted imaging in acute stroke but thresholds vary by postprocessing platform. Stroke, 2011. **42**(7): p. 1923-8.

54. Bivard, A., et al., *Defining the extent of irreversible brain ischemia using perfusion computed tomography.* Cerebrovasc Dis, 2011. **31**(3): p. 238-45.

국문 초록

Measurement of infarct volumes in CT perfusion maps using different commercial software: quantitative analysis by using identical source data of acute stroke patients

연구 목적: CT 관류 영상 (CT Perfusion map, CTP) 급성 허혈성 뇌졸중 환자의 치료 여부의 선택 결정과정에 실제로 널리 사용되고 있지만, 정확한 경색 중심부 용적을 예측하는 데 사용되는 최적의 임계값과 매개 변수에 대해서는 명확한 표준이 없다. 현재 rCBF <30 %의 임계값을 가진 경색 중심부(Infarct core) 용적이 일반적으로 사용되고 있다. 그러나 Follow-up diffusion-weighted imaging (DWI)와 경색 중심부(Infarct core) 용적의 일치를 평가하기 위해 CTP와 DWI 사이의 시간간격이 24 시간 이내인 여러 연구가 진행되었다. 본 연구의 목적은 RAPID, singular value decomposition+ (SVD+) VITREA, BAYESIAN VITREA 등의 CTP 소프트웨어 프로그램에서 다양한 Deconvolution 방법, 매개 변수, 임계값에 따라 측정된 경색 중심부 용적과 짧은 시간 간격으로 (60분 이내) 시행된 DWI에서 측정된 경색 중심부용적과의 일치율을 평가한다.

연구 방법: 전방 순환에 있어서 큰 혈관의 폐색증을 가진 42명의 급성 허혈성 뇌졸중 환자가 포함되었다. CT 관류 영상은 VITREA 및 RAPID의 SVD +와 Bayesian 알고리즘을 포함한 다양한 CT 관류 소프트웨어로 처리되었다. RAPID는 경색 중심부를 rCBF <20 % −38 %, rCBV <34 % −42 %을 가진 조직으로 식별하였다. SVD+ VITREA에서는 경색 중심부를 CBV의 26−56 % 감소로 정의하였다. BAYESIAN VITREA에서는 경색 중심부를 CBV의 28−48% 감소로 정의하였다. Olea Sphere는 DWI 경색 중심부 용적을 측정하는 데 사용되었다. CTP 중심부 용적의 측정값은 DWI에서 결정된 최종 경색 용적과 비교되었다.

연구 결과: CTP는 모든 환자에서 DWI 전에 실시되었고, CTP와 DWI 사이의 시간의 중앙값은 37.5 분(min)이었다 interquartile range (IQR) 20 −44. 42 명의 환자에서는 최종 경색 중심부 용적의 중앙값은 DWI에서 19.50 ml (IQR 6.91 − 69.72) 였다. RAPID rCBF <30% 기본 설정값에서 경색 중심부 용적 차이의 중앙값은 (IQR) 8.19 ml (3.95 – 30.70), spearman's correlation coefficient (r) = 0.759를 얻을 수 있었으며; SVD+ VITREA CBV의 41% 감소 시 경색 중심부 용적 차이의 중앙값은 (IQR) 3.82 ml (−2.91 – 20.95), r = 0.717로, BAYESIAN VITREA CBV의 38% 감소 시 경색 중심부 용적 차이의 중앙값은 (IQR) 8.16 ml (1.58 – 25.46), r = 0.754이었다. 반면 각 소프트웨어에 대한 최적의 임계값은 경색 중심부 용적을 기본 설정보다 정확하게 추정하는 것으로 입증되었다. 각 소프트웨어의 가장 정확하고 최

적의 경색 중심부 용적 차이의 임계값은 다음과 같았다: RAPID rCBF <38 % 경색 중심부 용적 차이는 4.87 ml (0.84 – 23.51), r = 0.752; SVD + VITREA CBV이 26 % 감소 시 경색 중심부 용적의 용적 차이가 −1.05 ml (−12.26 – 14.58), r = 0.679로 나타났으며; BAYESIAN VITREA CBV의 28 % 감소는 경색 중심부 용적 차이가 5.23 ml (−2.90 – 22.91), r = 0.685였다.

결론: 본 연구에서는 CBV 임계값은 CBF 임계값과 비교하여 급성 허혈성 뇌졸중 환자의 경색 중심부 용적을 예측하는 더 정확한 매개변수를 제공하는 것으로 나타났다.

주요어: CT 관류 영상 (Computed Tomography Perfusion), 급성 허혈성 뇌졸중, 경색 용적 차이, RAPID, Vitrea, Bayesian, DWI

학번: 2019-24153

"본 논문작성자는 한국정부초청장학금(Global Korea Scholarship)을 지원받은 장학생임"