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Cerebral arterial collateral status, but not venous outflow profiles, modifies the effect of intravenous tissue plasminogen activator in acute ischemic stroke

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Abstract:

BACKGROUND: The role of arterial collateral and venous outflow status on the response to intravenous tissue plasminogen activator (IV-tPA) has not been sufficiently clarified in acute major cerebral occlusions.

PATIENTS AND METHODS: A total of 130 patients (mean age: 71 years; 73 females) with acute middle cerebral artery M1/M2 segment or terminal internal carotid artery occlusion treated solely with IV-tPA were analyzed. Regional leptomeningeal score (rLMC) was used for cerebral arterial collateral scoring, and the cortical vein opacification score (COVES) and modified Prognostic Evaluation based on Cortical vein score difference In Stroke (PRECISE) superficial and deep scores were used for venous outflow profile. Exploratory logistic models for response to IV-tPA [positive response: National Institutes of Health Stroke Scale (NIHSS) decrease 4 (or decrease to 0) at 24 h; dramatic response: NIHSS decrease ≥8 (or decrease to 0 or 1)], functional outcome (modified Rankin's score 0–1 as "excellent" and 0–2 "good") and tPA-associated hemorrhagic transformation were constructed.

RESULTS: IV-tPA efficacy was positive in 47% and dramatic in 32%. Dramatic response was linked to better arterial collateral status (exp[B] =1.115 [95% confidence interval (CI), 1.016–1.223]). Excellent outcome was noted in 26% and good in 45%. One-point increase in rLMC score independently increased good prognosis (exp[B] =1.209 [1.034–1.412]). Patients with good prognosis had higher (by 0.5 points) modified PRECISE deep score (P = 0.047) and less frequent nonsufficient modified PRECISE deep score (0–2) (P = 0.017) in univariate analyses. However, these associations failed to survive in multiple regression. Any type tPA-associated cerebral hemorrhagic transformation was observed in 23% and parenchymal hemorrhage type 2 in 5.4%. While rLMC score showed a borderline strength correlation to hemorrhage (exp[B] =0.899 [95% CI, 0.808–1.001]), outflow scores not.

CONCLUSION: While arterial collateral status modifies the effect of tPA in acute anterior circulation major artery occlusions, venous outflow capacity is not so critical.

Keywords:

Collateral, outflow, penumbra, stroke, thrombolysis, venous

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Introduction

Intravenous (IV) tissue plasminogen activator (tPA) is a standard treatment in the management of acute ischemic stroke and is used in combination with thrombectomy, which is the primary treatment modality in large cerebral arterial occlusions.[1,2] Sufficient collateral

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circulation in the ischemic penumbral tissue is essential for the success of both IV tPA and thrombectomy.[3] The effect of arterial collateral circulation in salvaging the ischemic penumbra has long been investigated. The consensus has reached that improved collateral circulation promotes the response to both thrombolysis and thrombectomy in patients with acute ischemic stroke and is even associated with better clinical outcomes in patients managed conservatively.[4,5] The role of cerebral venous outflow in the efficacy of acute ischemic stroke recanalization treatments has recently become the focus of attention. Studies showed that functional outcomes with thrombectomy improved as venous outflow improved, and some complications such as cerebral edema development decreased.[6-9] In this study, we presented in detail the effect of venous outflow on functional outcomes in patients who received only IV tPA due to acute ischemic stroke.

Patients and Methods

A total of 130 patients (mean age: 71 ± 14 years; 73 females) with middle cerebral artery (MCA M1 or M2 segment) or terminal internal carotid artery occlusion who were consecutively recorded in the Hacettepe acute stroke prospective database in the last 15 years (between 2008 and 2023) and treated with IV tPA but did not undergo neurothrombectomy were included in the study. Computed tomography (CT) angiography (CTA) was performed before IV tPA in all patients. The stroke database and study protocol were approved by the Hacettepe University noninterventional ethics committee (Project No.: GO 22/427, Decision No.: 2022/07-48). Due to the retrospective design and anonymized data nature of the study, informed consent was waived. Patients were routinely examined in detail in terms of cardiac and vascular diseases in order to determine stroke etiology. Details on the protocols of the database are available elsewhere.[10] The causative stroke classification algorithm was used for the etiological subclassification of acute stroke.[11]

The National Institutes of Health Stroke Scale (NIHSS)[12] was used to measure the clinical severity of stroke on admission, at the 24th h, and at discharge. Disability level was quantified with the modified Rankin scale (mRS)[13] at 3 months. mRS 0 and 1 was categorized as "excellent" outcome and 0, 1, and 2 as "favorable (or good)." A "positive" response to IV tPA was defined as a decrease in NIHSS of at least 4 points or to 0 at 24 h after IV tPA administration. A decrease of 8 or more points or to 0 or 1 in the NIHSS was considered a "dramatic" response to IV tPA.[14,15]

Imaging

Technical details of CTA and noncontrast CT used can be found elsewhere.[10,16] In short, multi-detector line scanners (SOMATOM "Emotion Duo," "Sensation-16," or "Perspective with 64 slice configurations," Siemens, Erlangen, Germany) were used in spiral mode at 5 mm slice thickness with reconstruction with 1 mm, 120–130 kV, and 200 mAs as image acquisition parameters. CTA was performed by helical scanning after antecubital vein injection (at a rate of 4 ml/s with a start delay of 3 s) of 100 ml nonionic contrast media. Acquisition timing was defined as per dynamic contrast bolus detection method (Care Bolus; Siemens Medical Systems, Erlangen, Germany). CTA parameters used were as follows: SOMATOM Emotion Duo: Slice thickness 1 mm, 130 kV foramen magnum to apex, 50 mAs, reconstruction increment 7 mm; SENSATION-16: 120 kV aortic arch to vertex, slice collimation 75 mm, 100 mAs and slice-width 1 mm.

Terminology (Fiorelli's classification) was used to diagnose and classify post-IV tPA cerebral hemorrhagic complications. Hemorrhages that occupy more than 30% of the infarct area, have an obvious mass effect, or located in extra-infarct areas were classified as parenchymal hematoma type 2.[17]

Parenchymal hypodensity was quantified using the Alberta Stroke Program Early CT Score (ASPECTS) on pretreatment brain CT. In the ASPECTS evaluation made out of 10 points, scores 8 and above were categorized as "low" and seven and below as "significant" hypodensity.[18]

The regional leptomeningeal score (rLMC) was used for cerebral arterial collateral scoring. In this system, a total score of pial and lenticulostriate arteries is obtained by scoring 6 ASPECTS regions (M1–6), together with the anterior cerebral artery, basal ganglia, and Sylvian sulcus regions as compared to the corresponding regions in the opposite hemisphere (A score of 0 is given for "absent", 1 for "relatively decreased", and 2 for "identical or more prominent". Pial vessels of the same grade in the Sylvian sulcus are scored as 0, 2, and 4). A rLMC score of 17–20 was grouped as "good," 11–16 as "medium," and 0–10 as "poor."[19]

The venous outflow profile was scored in two ways. The first, the cortical vein opacification score (COVES) (0–6),[20] was used in its original form by quantifying opacification of the vein of Labbé (VoL), sphenoparietal sinus (SPS), and superficial middle cerebral vein (SMCV). "0" was given if the vein cannot be identified, "1" if it is decreased relative to the contralateral counterpart, and "2" if it is normal. If the total COVES score is 2 and below, it is defined as "unfavorable," and if it is 3 and above, it is considered "favorable" venous outflow. The second, a modification of the Prognostic

Evaluation based on cortical vein score difference In Stroke (PRECISE)[21] score, was used. While taking into account the interhemispheric difference of the veins scored in their original form, we compared them individually with the opposite side, similar to the COVES, and made our rating as 0, 1, and 2 for each vein included. While SMCV, VoL, vein of Trolard (VoT), and basal vein of Rosenthal (BVR) were included in the PRECISE superficial score (mPRECISE superficial, 0–8), thalamostriate vein and internal cerebral vein were scored for the PRECISE deep score (mPRECISE deep, 0–4). The direction of the mPRECISE superficial/deep and COVES is the same [Figure 1].

ASPECTS, arterial and venous opacification scores were performed by ESG and EY, and in cases of disagreement, consensus was reached by the study's senior neuroradiologist, RG.

Statistics

All values were presented as "mean ± standard deviation", "mean (95% confidence interval [95% CI])", "percentage" and "median (maximum-minimum)" depending on their characteristics. Normality of distribution was examined appropriately with Kolmogorov–Smirnov and Shapiro–Wilk tests. Mann–Whitney *U*/Student's *t* and Chi-square/Fisher's exact tests were used to assess differences between the groups appropriately. To ascertain the independent importance of arterial collateralization and venous outflow scores on positive and dramatic response to IV tPA, outstanding and good 3-month functionality, and any tPA-related or symptomatic bleeding, exploratory multivariable logistic regression models were built. Factors with $P < 0.1$ in the univariate steps were included in the multivariate stage. The threshold for statistical significance was established at $P < 0.05$. Every computation was performed (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).

Clinical trial registry

Not applicable. The study was based on retrospective data gathering from a prospectively-designed/proceed hospital database.

Results

IV tPA efficacy was positive in 47% of the patients and excellent in 32% [Table 1]. Effective response to IV tPA was only affected by symptom onset to needle time on univariate comparisons and not further analyzed. Dramatic response to IV tPA was significantly linked to arterial collateral status. After adjustment with admission NIHSS, rLMC score persisted as a significant determinant of excellent tPA response (per 1 point, exp[B] =1.115 [95% CI, 1.016–1.223]).

At the end of the 3rd month, excellent results were recorded in 26% of the patients and favorable outcomes were in 45% [Table 2]. In univariate analysis, younger age and less severe stroke clinical severity were associated with good outcomes. The rLMC score was significantly higher in these patients. In

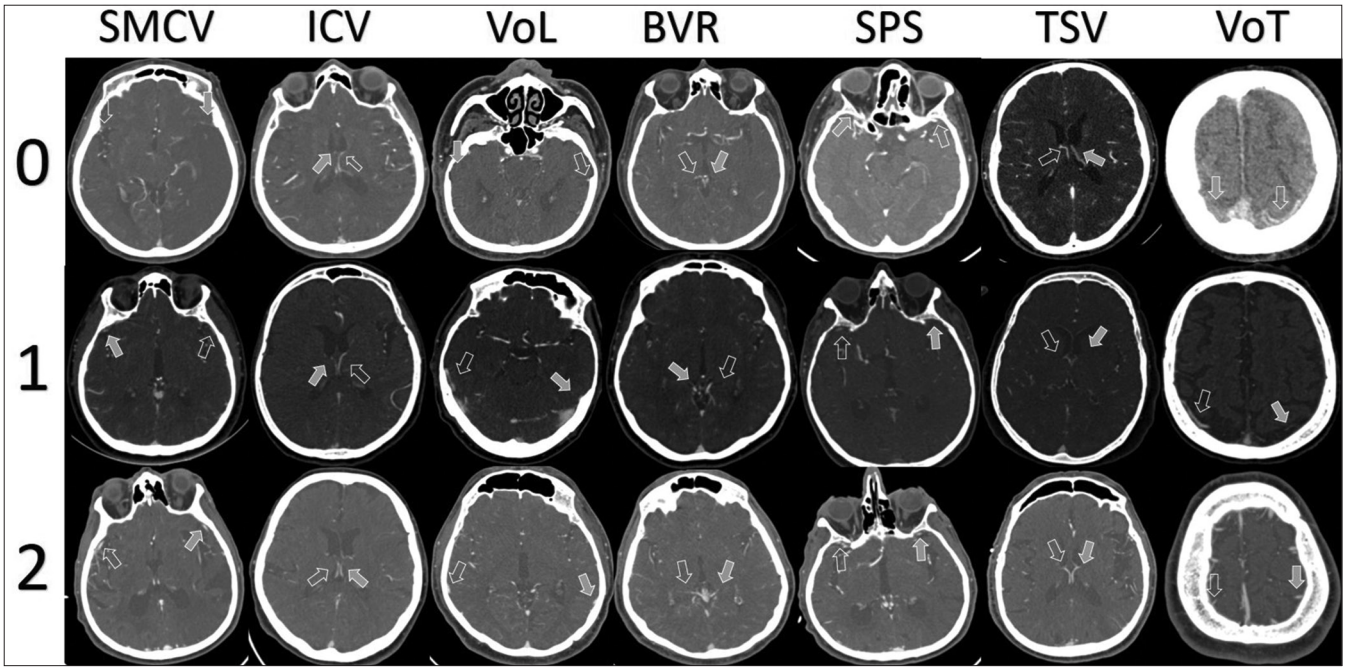

Figure 1: The vein opacification scoring system is summarized in the Figure 0: Complete absence of vein opacification, 1: Moderate opacification, and 2: Full opacification. The vessel in the affected hemisphere is shown with a gray arrow, and the vessel on the unaffected side is shown with a blank arrow. SMCV: Superficial middle cerebral vein, ICV: Internal cerebral vein, VoL: Vein of Labbe, BVR: Basal vein of Rosenthal, SPS: Sphenoparietal sinus, TSV: Thalamostriate vein, VoT: Vein of Trolard

Table 1: Response to intravenous tissue plasminogen activator

	Positive response			Dramatic response		
	Yes (*n*=61)	No (*n*=69)	*P*	Yes (*n*=41)	No (*n*=89)	*P*
Age	70±16	72±13	0.563	69±17	71±13	0.601
Female (%)	59	53	0.488	66	51	0.117
BMI	27±5	28±5	0.631	28±7	27±4	0.223
Hypertension (%)	66	72	0.427	61	73	0.179
Diabetes mellitus (%)	30	32	0.727	22	35	0.129
Atrial fibrillation (%)	23	29	0.406	17	31	0.102
NIHSS (admission)	13±5	13±6	0.843	12±6	14±6	0.093
Symptom onset to tPA (min)	166±65	189±55	0.033	186±73	175±54	0.329
Any bleeding (%)	16	28	0.080	7	30	0.004
PH type 2 (%)	2	9	0.074	0	8	0.062
Length of hospital stay (days)	15±24	18±17	0.631	9±9	20±23	0.005
ASPECTS 8-9-10 (%)	89	91	0.617	88	91	0.247
ASPECTS median	10 (6–10)	10 (5–10)	0.871	10 (6–10)	10 (5–10)	0.247
rLMC median	15 (2–20)	16 (2–20)	0.864	18 (2–20)	15 (2–20)	0.005
rLMC poor (%)	30	41	0.210	16	43	0.018
rLMC medium (%)	45	30		47	33	
rLMC good (%)	25	29		37	24	
COVES median	3.5 (1–6)	4 (0–6)	0.507	4 (1–6)	4 (0–6)	0.804
COVES 0 (%)	2	7	0.282	0	7	0.603
COVES 0–2 (%)	40	37	0.646	33	39	0.215
mPRECISE superficial median	5 (1–8)	6 (0–8)	0.178	5 (1–8)	6 (0–8)	0.703
mPRECISE deep median	4 (1–4)	4 (1–4)	0.578	4 (1–4)	4 (1–4)	0.858

ASPECTS: Alberta Stroke Program Early Computed Tomography Score, COVES: Cortical vein opacification score, NIHSS: National Institutes of Health Stroke Scale, PH: Parenchymal hematoma, PRECISE: Prognostic Evaluation based on Cortical vein score difference In Stroke, rLMC: Regional leptomeningeal score, tPA: Tissue plasminogen activator, BMI: Body mass index

multivariate analysis, one-point increase in rLMC score independently increased good prognosis (mRS 0–2) (exp[B] =1.209 [1.034–1.412], P = 0.017) while NIHSS (1 point, exp[B] =0.857 [0.756–0.973], P = 0.016) and age (1 year, exp[B] =0.953 [0.909–0.999], P = 0.046) decreased significantly favorable prognosis. Similarly, a poor RLMC score (0–10) significantly reduced the chance of a good prognosis compared to higher (11–16 and 17–20) rLMC scores (exp[B] =0.077 [0.009–0.679], P = 0.048) independently of age and NIHSS. While no relationship was found between the modified PRECISE superficial score and the prognosis in the univariate analysis, patients with good prognosis (mRS 0–2) had higher (by 0.5 points) modified PRECISE deep score (3.5 ± 1 vs. 3 ± 1, P = 0.047) and lower frequency of nonsufficient modified PRECISE deep score (0–2) (19% vs. 48%, P = 0.017). However, these associations failed to survive in multiple regression (exp[B] =0.629 [95% CI, 0.261–1.517], P = 0.302).

Any tPA-associated cerebral hemorrhagic transformation was observed in 23% and PH type 2 in 5.4% [Table 3]. In the univariate analysis, patients who developed any type of cerebral hemorrhagic complication had a lower rLMC score (poor arterial collateralization; 10.5 vs. 16.5, P = 0.001) and a higher rate of poor rLMC (58% vs. 28%, P = 0.004). The modified PRECISE deep score was also lower in these patients (2.7 ± 1.1 vs. 3.4 ± 1, P = 0.039). In addition, the rate of poor rLMC was higher in patients with PH type 2 (79% vs. 33%, P = 0.056). Modified PRECISE deep score showed no correlation in multivariate analysis (exp[B] =0.879 [95% CI, 0.548–1.411], P = 0.594), while rLMC score showed a borderline strength correlation (exp[B] =0.899 [0.808–1.001], P = 0.051). The PH type 2 outcome did not allow multivariate analysis due to low patient numbers.

Discussion

In this study, we confirmed that an adequate level of territorial arterial collateralization in acute ischemic stroke is related to a significant improvement in the efficiency of IV thrombolysis.[22] Early dramatic response to IV tPA and good long-term functional outcome at mRS 0–1 and mRS 0–2 levels increase in patients with good rLMC scores. In addition, good outcome rate decreased with low arterial collateral scores. This effect is independent of other factors including age and stroke severity.

The interplay between the sufficiency of collateral circulation and ischemic stroke outcome has been evaluated from multiple aspects in the literature. Essentially, the effect of collateral circulation is to prolong the therapeutic time window for beneficial reperfusion to occur. Better pre-tPA collateral status was shown to be associated with smaller infarct size, lower rate of

Table 2: Prognosis

	Excellent outcome (mRS ≤1)			Favorable outcome (mRS ≤2)		
	Yes (*n*=34)	No (*n*=96)	*P*	Yes (*n*=58)	No (*n*=72)	*P*
Age	62±16	74±13	<0.001	64±16	76±10	<0.001
Female	65	52	0.203	57	54	0.756
BMI	28±5	27±6	0.762	29±7	26±4	0.013
Hypertension (%)	56	75	0.037	36	25	0.166
Diabetes mellitus (%)	29	32	0.756	31	32	0.912
Atrial fibrillation (%)	24	27	0.685	17	33	0.046
NIHSS (admission)	10±5	14±5	<0.001	10±5	16±5	<0.001
Symptom onset to tPA (min)	188±75	176±57	0.361	178±68	180±58	0.878
Any bleeding (%)	9	28	0.020	14	31	0.021
PH type 2 (%)	0	7	0.111	0	10	0.016
Length of hospital stay (days)	7±4	20±23	<0.001	8±8	24±25	<0.001
ASPECTS 8-9-10 (%)	91	89	0.670	90	89	0.889
ASPECTS median	10 (7–10)	10 (5–10)	0.276	10 (6–10)	9 (5–10)	0.059
rLMC median	18 (8–20)	15 (2–20)	0.002	17.5 (5–20)	14 (2–20)	<0.001
rLMC poor (%)	10	43	0.007	16	48	0.001
rLMC medium (%)	54	33		48	31	
rLMC good (%)	36	24		36	21	
COVES median	4 (0–6)	4 (0–6)	0.874	4 (0–6)	4 (0–6)	0.672
COVES 0 (%)	5	5	0.956	5	5	0.986
COVES 0–2 (%)	27	39	0.298	36	38	0.852
mPRECISE superficial median	5 (2–8)	5 (0–8)	0.699	5 (1–8)	6 (0–8)	0.870
mPRECISE deep median	4 (1–4)	4 (1–4)	0.199	4 (1–4)	4 (1–4)	0.039

ASPECTS: Alberta Stroke Program Early Computed Tomography Score, COVES: Cortical vein opacification score, NIHSS: National Institutes of Health Stroke Scale, PH: Parenchymal hematoma, PRECISE: Prognostic Evaluation based on Cortical vein score difference In Stroke, rLMC: Regional leptomeningeal score, tPA: Tissue plasminogen activator, mRS: Modified Rankin Scale, BMI: Body mass index

Table 3: Post-tissue plasminogen activator cerebral hemorrhage

	Any cerebral hemorrhage			PH type 2		
	Yes (*n*=30) (*n**)	No (*n*=99) (*n**)	*P*	Yes (*n*=7) (*n**)	No (*n*=122) (*n**)	*P*
Age	70±13	70±15	0.992	70±12	70±15	0.871
Female (%)	60	54	0.533	57	55	0.857
BMI	26±5	28±6	0.201	25±4	28±6	0.311
Hypertension (%)	73	69	0.627	71	57	0.455
Diabetes mellitus (%)	33	31	0.753	43	30	0.486
Atrial fibrillation (%)	50	19	0.002	43	25	0.308
NIHSS (admission)	15±5	13±6	0.096	16±6	13±6	0.182
Symptom onset to tPA (min)	166±49	182±64	0.213	158±40	179±62	0.381
Length of hospital stay	21±12	15±23	0.230	21±12	16±21	0.582
ASPECTS 8-9-10	87	90	0.618	100	89	0.342
ASPECTS median	9 (5–10)	10 (6–10)	0.012	10 (8–10)	10 (5–10)	0.721
rLMC	10.5 (2–20)	16.5 (2–20)	0.001	13 (2–10)	15 (2–20)	0.416
rLMC poor (%)	58	28	0.004	70	33	0.056
rLMC medium (%)	28	40		10	39	
rLMC good (%)	14	32		20	28	
COVES median	3.5 (0–6)	4 (0–6)	0.385	4 (0–6)	4 (0–6)	0.853
COVES 0 (%)	10	3	0.128	0	5	0.573
COVES 0–2 (%)	17	38	0.285	35	38	0.727
mPRECISE superficial median	5.5 (0–8)	5 (1–8)	0.527	6 (0–8)	5 (1–8)	0.536
mPRECISE deep median	2 (1–4)	4 (1–4)	0.025	4 (2–4)	4 (1–4)	0.868

*There was no 24th h head CT in one case. CT: Computed tomography, ASPECTS: Alberta Stroke Program Early CT Score, COVES: Cortical vein opacification score, NIHSS: National Institutes of Health Stroke Scale, PH: Parenchymal hematoma, PRECISE: Prognostic Evaluation based on Cortical vein score difference In Stroke, rLMC: Regional leptomeningeal score, tPA: Tissue plasminogen activator, BMI: Body mass index

symptomatic intracranial hemorrhage, and higher rate of rapid positive response to IV thrombolysis.[23] Good collateralization in acute ischemic stroke also indicates benefit in mechanical thrombectomy. Good pretreatment collaterals enhance not only the rates of faster and more successful recanalization but also reperfusion,

both corresponding to better functional. outcome.[3] In addition, good collateral status is associated with lower rates of symptomatic reperfusion hemorrhage and overall mortality.[24] Furthermore, the positive effect of collateral circulation continues, albeit more limitedly, in patients who cannot achieve timely tissue-level reperfusion. In this regard, good collateral status leads to a reduction in the infarct size and a correspondingly better functional outcome in patients who are managed conservatively and reperfusion has never been attempted.[4,5,25,26] A sufficient collateral circulation is also related to milder admission neurological symptoms, while the time window for response to recanalization treatments is narrower in patients with severe clinical deficit and poor collateral circulation. All these findings highlight the necessity of developing effective methods that can be applied preferably in the field, to strengthen collateral status.[27,28]

Venous outflow has been studied in patients with acute ischemic stroke more recently. In this context, opacification of VoL, VoT, BVR, SPS, SMCV, thalamostriate vein, and internal cerebral vein is evaluated in pretreatment CTA source images. The COVES score, which is the most studied score, encodes VoL, SPS and SMCV. The PRECISE score, which is an older score, encodes VoL, SPS, VoT and BVR in the superficial vein category, and thalamostriate vein and internal cerebral vein in its deep category.[20,21] We could not detect any correlation between the COVES and PRECISE superficial scores and the effect of IV tPA. The effect of venous outflow on IV tPA activity has not been studied clearly in the literature. However, in thrombectomy patients, an independent positive association has been found by multiple groups between better outflow scores (e.g., COVES 3 or more) and favorable prognosis, faster recanalization, less reperfusion edema and bleeding.[6-9,20] Although no difference was found in our patients with dramatic tPA response, the suboptimal recanalization rates obtained with IV tPA in proximal occlusion may contribute to this difference in effect when compared to the thrombectomy studies.

The finding we observed was an increase in the good prognosis and a decreasing trend in hemorrhagic transformation with the increase in the modified PRECISE deep venous outflow score in anterior circulation major vessel occlusions. This score includes the thalamostriate vein and internal cerebral vein as mentioned above. The modified PRECISE deep score was 0.5 (out of 4) higher and the nonsufficient (0–2) deep outflow score rate was less in those with a good (mRS < 3) outcome. It was also noted that there was a positive correlation between high scores and bleeding (but not PH type 2). All of these were statistically at a trend level and did not reach significance in multiple regression analysis. In the literature, it was shown in a study that good response to IV tPA increased in patients with prominent internal cerebral veins.[29] Our findings partially support this observation. New studies are needed for its predictiveness of significant findings for the fate of mechanical thrombectomy[6,9,20] and CTA correlates of venous outflow changes observed on susceptibility-weighted imaging[30] in systemic thrombolysis.

It is appropriate to mention a few limitations of our study. Thin section and delayed CT angiographic imaging may be more favorable for venous outflow than the standard scans we used. We may have missed some important correlations because we only examined patients receiving IV tPA and excluded patients who underwent thrombectomy or received conventional supportive care. Recanalization rates could not be determined because vascular patency was not evaluated routinely after IV tPA. However, evaluation of both arterial and venous collaterals in pretreatment CT angiography is useful to some extent in predicting eventual prognosis and response to treatment. This can be useful even without knowing the recanalization status after treatment.

Author contributions

ESG and EY contributed equally. ESG, EY, EMA, RG and MAT contributed to the study concept, design and finalization of the manuscript. ESG, EY, EMA, RG and MAT contributed to the data collection, analysis and interpretation processes. MAT wrote the first version of the manuscript, and ESG, EY, EMA, and RG critically revised the manuscript for important intellectual content. MAT, ESG and EY are guarantors of the article and agree to be responsible for all aspects of the research.

Ethical policy and institutional review board statement

The study was approved by the Ethics Committee of Hacettepe University, Turkey (No. 2022/07-48, dated on 19-4-2022). All the human procedures were performed as per the revised Helsinki Declaration principles. Participants recruited provided written informed consent before enrolling in the study.

Data availability statement

The article presents the basic and detailed data needed for understanding. Further data may be provided upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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