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ORIGINAL ARTICLE

Predicting cerebral edema in ischemic stroke patients

Antonio Muscari[1,2] · Luca Faccioli[3] · Maria Vittoria Lega[2] · Andrea Lorusso[2] · Marco Pastore Trossello[3] · Giovanni M. Puddu[1] · Luca Spinardi[3] · Marco Zoli[1,2]

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Abstract

Objectives To produce a scoring system for predicting the development of edema in ischemic stroke patients without edema on admission.

Methods This retrospective study included 572 ischemic stroke patients (73.3 ± 13.0 years, 300 male) without signs of cerebral edema on the first CT scan, which was performed on admission. Another scan was normally performed 3 days later, and subsequently whenever needed. Edema was defined as cerebral hypodensity with compression of lateral ventricles. The main clinical, laboratory, and instrumental variables obtained during the first 24 h were related to the appearance of edema on the CT scans performed after the first one.

Results Cerebral edema occurred in 158 patients (27.6%) after a median time of 4 days. The variables independently associated with edema development were (odds ratio, 95% CI) the following: (1) total anterior circulation syndrome (4.20, 2.55–6.93; $P < 0.0001$), (2) hyperdense appearance of middle cerebral artery (4.12, 2.03–8.36; $P = 0.0001$), (3) closed eyes (2.53, 1.39–4.60; $P = 0.002$), (4) vomiting (3.53, 1.45–8.60; $P = 0.006$), (5) lacunar cerebral syndrome (0.36, 0.17–0.77; $P = 0.008$); and (6) white matter lesions (0.53, 0.33–0.86; $P = 0.01$). Counting one positive point for the first four variables and one negative point for the last two variables, a scoring system (E-score) was built. Cerebral edema could be predicted when the score was ≥ 1 (positive predictive value 61.6%, specificity 85.3%, sensitivity 62.0%). The area under the receiver operating characteristic curve was 0.78.

Conclusions In ischemic stroke patients, six variables obtained during the first 24 h of hospitalization were predictive of subsequent cerebral edema development.

Keywords Brain CT scan · Cerebral edema · Determinants · Ischemic stroke · Predictors

Introduction

The cerebral ischemic lesions of largest size can be associated with edema of variable entity, which usually develops after a few hours or days after the onset of symptoms. Independent of lesion size, patient's death often does not occur for the neurological deficit directly caused by cerebral ischemia, but for the endocranial hypertension caused by edematous swelling. This

✉ Antonio Muscari
antonio.muscari@unibo.it

Luca Faccioli
luca.faccioli@aosp.bo.it

Maria Vittoria Lega
mariavittoria.lega@gmail.com

Andrea Lorusso
andrea.lorusso3@studio.unibo.it

Marco Pastore Trossello
marco.pastoretrossello@aosp.bo.it

Giovanni M. Puddu
giovapu@libero.it

Luca Spinardi
luca.spinardi@aosp.bo.it

Marco Zoli
marco.zoli@unibo.it

[1] Stroke Unit – Medical Department of Continuity of Care and Disability, S.Orsola-Malpighi Hospital, Bologna, Italy

[2] Department of Medical and Surgical Sciences, Stroke Unit, S.Orsola-Malpighi Hospital, University of Bologna, Via Albertoni, 15, 40138 Bologna, Italy

[3] Diagnostic and Interventional Neuroradiology Unit, S.Orsola-Malpighi Hospital, Bologna, Italy

reverberates at all levels within the skull box, with possible midline shift, cerebral herniation, impairment of brainstem reticular formation, and state of coma.

Thus, every effort should be made to promptly recognize malignant cerebral edema, in order to plan decompressive hemicraniectomy. However, surgical therapy is demolitive and hazardous and can be performed only in selected cases [1], while medical therapy cannot yet rely on means of proven efficacy [2–5]. Nevertheless, the venous administration of hyperosmotic substances, such as mannitol or hypertonic saline solution, which favor the drainage of fluid from cerebral tissue to the vascular compartment, is commonly accepted. The most recent guidelines suggest employing these means only for patients with clinical deterioration from cerebral swelling, while an indiscriminate prophylactic use of anti-edema treatment is not recommended [6].

Ideally, the best choice would be to preventively intervene not in all cases of ischemic stroke, but only in the subgroup with the highest risk of developing edema. This would be an extension of present guidelines: instead of treating with hyperosmotic substances only patients with cerebral edema in progress, also patients at risk of developing edema would be treated. This strategy could possibly prevent edema formation, or prevent edema from becoming malignant. At present, the results of a few studies are available concerning attempts to predict which patients with cerebral edema are at highest risk of death, to promptly perform decompressive hemicraniectomy [7–11]. Two studies have found some predictors of cerebral edema, among baseline variables, in patients undergoing thrombolysis [12, 13]. However, no study has tried to identify, during the first day of stroke, the patients at risk of developing edema independently of the attempts of revascularization with thrombolysis or thrombectomy.

Aim of the present investigation was therefore to identify some variables, among those obtained during the first 24 h of hospitalization, which are associated with the subsequent appearance of cerebral edema in ischemic stroke patients. These variables were then included in a scoring scale allowing the stratification of the risk of cerebral edema.

Methods

We retrospectively assessed 643 patients consecutively admitted to our stroke unit for ischemic stroke within 24 h from the onset of symptoms, from January 2011 to January 2014.

The study was intended to predict the appearance of cerebral edema using a series of factors obtained during the first 24 h of stay. Thus, the patients with already visible edema on the first CT scan performed at the emergency department were excluded ($N = 56$). In fact, although this may be considered an interesting group of patients, any "predictor" found in this group could be caused by, rather than being an antecedent of, edema. In addition, the patients who had not undergone at least two CT scans were also excluded ($N = 15$). Eventually, 572 patients (mean age 73.3 ± 13.0 years, 300 male) participated in the study.

Because this was a retrospective study including many patients who had died after the acute phase of stroke, an informed consent could not be obtained. However, the study protocol was approved by our joint university-hospital ethics committee.

All main clinical, laboratory, and instrumental data were recorded in an electronic duplicate of our clinical record and were then retrospectively used for statistical analysis.

Stroke severity was clinically assessed by the National Institutes of Health Stroke Scale (NIHSS) [14] and the Oxfordshire Community Stroke Project (OCSP) classification [15]. The impairment of consciousness was assessed by the Glasgow Coma Scale (GCS) [16].

The patients with known arterial hypertension or under anti-hypertensive treatment were considered hypertensive. The patients under anti-diabetic treatment, or with fasting blood glucose ≥ 1.26 g/l, were considered diabetic. The patients under statin treatment, or with serum total cholesterol ≥ 200 mg/dl, were considered hypercholesterolemic. The patients who referred to drink any amount of alcohol in a non-occasional manner were considered alcohol drinkers. The presence of fever (body temperature > 37 °C) during the first 24 h was also recorded. Furthermore, previous myocardial infarction or stroke, the occurrence of current or previous atrial fibrillation, and treatment with i.v. thrombolysis were recorded (thrombectomy not available at that time). The main routine laboratory variables obtained in the morning following admission were also considered.

In our hospital, routine stroke imaging is performed by brain CT scans, as suggested by current guidelines [6]. We considered the following possible findings on the first CT scan (which was normally performed in the emergency department after a median time of 3.2 h from stroke onset): (1) white matter lesions (diffuse hypodensity of white matter denoting chronic microvascular disease; this was defined as any degree ≥ 1 according to van Swieten, which means any periventricular hypodensity in the anterior or posterior region of three reference CT slices [17]) and (2) hyperdense appearance of middle cerebral artery suggesting possible occlusion.

The study end-point was cerebral edema. Initially, ischemic stroke is associated with cytotoxic edema, which on CT scan is hardly distinguishable from the ischemic area [18]. In this first stage, CT may show mild hypodensity, with loss of differentiation between gray and white matter at the level of both the cortex and the basal ganglia. In the second stage, edema can increase and become vasogenic (i.e., caused by blood–brain barrier disruption), with more evident hypodensity and swelling of gyri and decrease of sulci and cerebrospinal spaces. Finally, in the third stage, a further increase of swelling

can lead to compression and displacement of lateral ventricles (mass effect, sometimes associated with midline shift towards the contralateral hemisphere) [19].

In the present study, we considered only edema at the third stage, namely the one most clearly identifiable being associated with mass effect on lateral ventricles. The appearance of cerebral edema was sought in all CT scans performed after the first one. The median number of CT scans was 2 (interquartile range 2–3; overall range 2–11). On average, the second CT scan was performed 3 days after the first one. The subsequent possible CT scans were performed in relation to clinical needs. All CT scans were re-assessed and agreed by two expert neuroradiologists (L.F. and L.S.).

Statistical analysis

All clinical and laboratory variables were obtained during the first 24 h of hospitalization. Continuous normal variables were described with mean and SD, while the variables with non-gaussian distribution were described with median and interquartile range. Means were compared with Student's t test, medians with Mann-Whitney's U test, and percentages with χ^2. The multivariable analysis was performed by logistic regression, with cerebral edema as dependent variable and backward elimination procedure. The model with dichotomous variables provided the coefficients for calculating odds ratios and relative 95% confidence intervals. The scoring scale for cerebral edema prediction was obtained counting one positive point for each variable directly associated with edema, and one negative point for each variable inversely associated. To establish the validity of the scoring system, the area under the receiver operating characteristic (ROC) curve was calculated, together with its 95% confidence interval.

Two-tailed tests were used throughout, and P values < 0.05 were considered significant.

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Results

In 158 out of 572 patients (27.6%), cerebral edema was detected after a median time of 4 days from admittance (interquartile range 2–5; overall range 2–19). Midline shift was documented in 44 out of 158 patients with edema (27.8%).

Table 1 reports the list of the main baseline clinical variables and risk factors, separately for the patients with and without subsequent development of cerebral edema. The most significant univariate associations with cerebral edema ($P \leq$ 0.0001) concerned atrial fibrillation, high NIHSS score, low GCS score (both total and referred to each of its three components), fever, total anterior circulation syndrome (TACS), and lacunar circulation syndrome (LACS, inverse association). TACS is a severe neurological syndrome with both cortical and subcortical involvement, usually due to occlusion of a middle cerebral artery; it is characterized by the simultaneous presence of hemiplegia, hemianopsia, hemineglect, and/or aphasia according to the hemisphere involved. LACS is a mild sensory-motor syndrome without involvement of important cortical functions, usually due to small infarcts confined to the territory of deep perforating arteries. Other less significant associations concerned partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS) (both inverse association), and vomiting. There was no relationship, instead, with cardiovascular risk factors, previous major vascular events (stroke and myocardial infarction), and measured blood pressure.

The baseline laboratory and instrumental variables are reported in Table 2. The significant direct associations with cerebral edema concerned acute phase markers (leukocytes, C-reactive protein, and blood glucose) and the hyperdense appearance of middle cerebral artery on first CT scan. Instead, white matter lesions were inversely associated with cerebral edema: they had therefore an apparent protective effect.

To establish which associations with cerebral edema were independent, a multiple logistic regression was performed in which cerebral edema (dependent variable) was related to the 17 variables associated with P values < 0.05 in Tables 1 and 2 (atrial fibrillation, NIHSS score, LACS, PACS, TACS, POCS, GCS, GCS-eye response < 4, GCS-verbal response < 5, GCS-motor response < 6, vomiting, fever, leukocytes, C-reactive protein, blood glucose, white matter lesions, and hyperdense middle cerebral artery). After backward elimination of the nonsignificant associations, the following variables remained independently associated with the subsequent development of cerebral edema (Table 3, in decreasing order of significance): TACS, hyperdense appearance of middle cerebral artery, white matter lesions (inverse association), NIHSS score, closed eyes at GCS (any degree in the scale from 3 to 1), vomiting, LACS (inverse association), and GCS score.

To construct a scoring scale predictive of cerebral edema of easy application in the clinical ambit, we dichotomized the two continuous variables (NIHSS score and GCS score). For these two variables, among all possible cutoffs, we chose the one that allowed the best identification of edema patients, namely the one associated with the maximum $\chi 2$ value. In this way, the patients with NIHSS score ≥ 15 and the patients with GCS score ≤ 14 were considered at risk of cerebral edema. The logistic regression was then repeated using the same variables in Table 3, but with the dichotomized version of NIHSS and GCS scores (Table 4). After backward elimination procedure, the two dichotomized variables were eliminated from the model. Thus, only TACS, hyperdense appearance of middle cerebral artery, closed eyes, vomiting, LACS, and white matter lesions were included in the scoring scale

Table 1 Baseline clinical variables and risk factors in patients with and without subsequent development of cerebral edema

Baseline variable	Edema with mass effect		*P* value
	Absent (*N* = 414)	Present (*N* = 158)	
Age (years)	73.2 ± 13.2	73.5 ± 12.6	0.83
Male	224 (54.1)	76 (48.1)	0.20
Hypertension	331 (80.0)	135 (85.4)	0.13
Ex-smoker	92 (22.2)	29 (14.4)	0.31
Current smoker	93 (22.5)	38 (24.1)	0.69
Diabetes	93 (22.5)	28 (17.7)	0.21
Hypercholesterolemia	244 (58.9)	97 (61.4)	0.59
Alcohol	37 (8.9)	22 (13.9)	0.08
Atrial fibrillation	117 (28.3)	71 (44.9)	0.0001
Previous stroke	60 (14.8)	22 (13.9)	0.86
Previous myocardial infarction	55 (13.3)	23 (14.6)	0.69
NIHSS score	5 [3–10]	15 [7–20]	< 0.0001
OCSP classification [15]			
LACS	128 (30.9)	9 (5.7)	< 0.0001
PACS	166 (40.1)	48 (30.4)	0.03
TACS	54 (13.0)	86 (54.4)	< 0.0001
POCS	66 (15.9)	15 (9.5)	0.048
GCS	15 [14–15]	14 [11–15]	< 0.0001
GCS, eye response < 4	30 (7.2)	48 (30.4)	< 0.0001
GCS, verbal response < 5	129 (31.2)	80 (50.6)	< 0.0001
GCS, motor response < 6	20 (4.8)	30 (19.0)	< 0.0001
Vomiting	13 (3.1)	12 (7.6)	0.02
Fever	125 (30.2)	77 (48.7)	< 0.0001
Average SBP (mmHg)	143.2 ± 22.4	143.7 ± 19.0	0.83
Average DBP (mmHg)	78.2 ± 11.4	77.0 ± 9.9	0.22
Thrombolysis	57 (13.8)	29 (18.4)	0.17

DBP diastolic blood pressure, *GCS* Glasgow Coma Scale, *LACS* lacunar circulation syndrome, *NIHSS* National Institutes of Health Stroke Scale, *OCSP* Oxfordshire Community Stroke Project, *PACS* partial anterior circulation syndrome, *POCS* posterior circulation syndrome, *SBP* systolic blood pressure, *TACS* total anterior circulation syndrome

predictive of cerebral edema (E-score). In particular, the score was obtained by algebraically summing one positive point for the variables TACS, hyperdense appearance of middle cerebral artery, closed eyes and vomiting, and one negative point for the variables LACS and white matter lesions.

Table 2 Laboratory and neuroradiologic variables in patients with and without subsequent development of cerebral edema

Baseline variable	Edema with mass effect		*P value*
	Absent (*N* = 414)	Present (*N* = 158)	
Leucocytes (× 10^3/mmc)	8.07 [6.62–9.85]	9.48 [7.85–11.95]	< 0.0001
Hemoglobin (g/dl)	13.8 [18.3–14.9]	13.7 [12.4–14.5]	0.27
Hematocrit (%)	41.7 [38–45]	41.0 [37.6–43.9]	0.13
C-reactive protein (mg/dl)	0.63 [0.26–2.15]	0.96 [0.45–3.26]	0.0006
Blood glucose (g/l)	0.92 [0.81–1.14]	0.99 [0.86–1.25]	0.006
Cholesterol (mg/dl)	197.3 ± 45.4	190.3 ± 40.0	0.10
Creatinine (mg/dl)	0.91 [0.78–1.09]	0.88 [0.74–1.06]	0.25
White matter lesions	160 (38.6)	37 (23.4)	0.0006
Hyperdense middle cerebral artery	15 (3.6)	40 (25.3)	< 0.0001

Table 3 Baseline variables independently associated with subsequent development of cerebral edema ($N = 136/515$)

Variable	Beta ± S.E.	Wald	*P* value
TACS	1.146 ± 0.321	12.7	0.0004
Hyperdense middle cerebral artery	1.247 ± 0.392	10.1	0.002
White matter lesions	− 0.835 ± 0.276	9.2	0.003
NIHSS score	0.078 ± 0.028	7.7	0.006
GCS, eye response < 4	0.985 ± 0.368	7.1	0.008
Vomiting	1.261 ± 0.529	5.7	0.02
LACS	− 1.013 ± 0.433	5.5	0.02
GCS score	0.173 ± 0.084	4.3	0.04
Intercept	− 4.479 ± 1.330	11.3	0.0008

Final result of multiple logistic regressions with backward elimination procedure of nonsignificant associations. The initial model included all the variables associated with cerebral edema with *P* values < 0.05 in previous tables. Cases with missing data were excluded ($N = 57$). Total $R^2 = 0.26$

GCS Glasgow Coma Scale, *LACS* lacunar circulation syndrome, *NIHSS* National Institutes of Health Stroke Scale, *S.E.* standard error, *TACS* total anterior circulation syndrome

Table 5 shows a progressive increase in the frequency of cerebral edema as the E-score increased. At one end of the scale, among 57 patients with a score of − 2, there was only one patient with cerebral edema (1.7%). At the other extreme, all of the 13 patients with 3 or 4 points had cerebral edema (100%). The area under the ROC curve, derived from the sensitivity and specificity values associated with each score, was 0.78 (95% CI 0.74–0.83) (Fig. 1). The probability of developing cerebral edema exceeded 50% with 1 or more points. Among 159 patients with 1 or more points (27.8% of all patients), 98 developed cerebral edema (positive predictive value 61.6%, specificity 85.3%, sensitivity 62.0%). On the other hand, only 60 patients out of 413 with a score lower than 1 developed cerebral edema (negative predictive value 85.5%).

Table 4 Baseline variables, dichotomous or dichotomized, independently associated with subsequent development of cerebral edema ($N = 158/572$)

Variable	O.R. [95% C.I.]	*P* value
TACS	4.20 [2.55–6.93]	< 0.0001
Hyperdense middle cerebral artery	4.12 [2.03–8.36]	0.0001
Closed eyes	2.53 [1.39–4.60]	0.002
Vomiting	3.53 [1.45–8.60]	0.006
LACS	0.36 [0.17–0.77]	0.008
White matter lesions	0.53 [0.33–0.86]	0.01

Final result of multiple logistic regressions with backward elimination procedure of non-significant associations. The initial model included the eight variables of Table 3, with NIHSS dichotomized at ≥ 15, and GCS dichotomized at < = 14. Overall $R^2 = 0.24$

C.I. confidence interval, *GCS* Glasgow Coma Scale, *LACS* lacunar circulation syndrome, *NIHSS* National Institutes of Health Stroke Scale, *O.R.* odds ratio, *TACS* total anterior circulation syndrome

Table 5 Frequency of cerebral edema according to the E-score

E-score	*N*	With edema	%
4	1	1	100.0
3	12	12	100.0
2	50	34	68.0
1	96	51	53.1
0	198	42	21.2
− 1	158	17	10.8
− 2	57	1	1.7

The E-score was obtained by algebraically summing a positive point for the variables TACS, hyperdense middle cerebral artery, closed eyes and vomiting, and a negative point for the variables LACS and white matter lesions

Discussion

This study has shown that, in patients with ischemic stroke, six clinical and radiological parameters easily available within the first 24 h of hospitalization were predictive of the subsequent development of cerebral edema with mass effect.

The E-score derived from this study was obtained summing one point for TACS, hyperdense appearance of middle

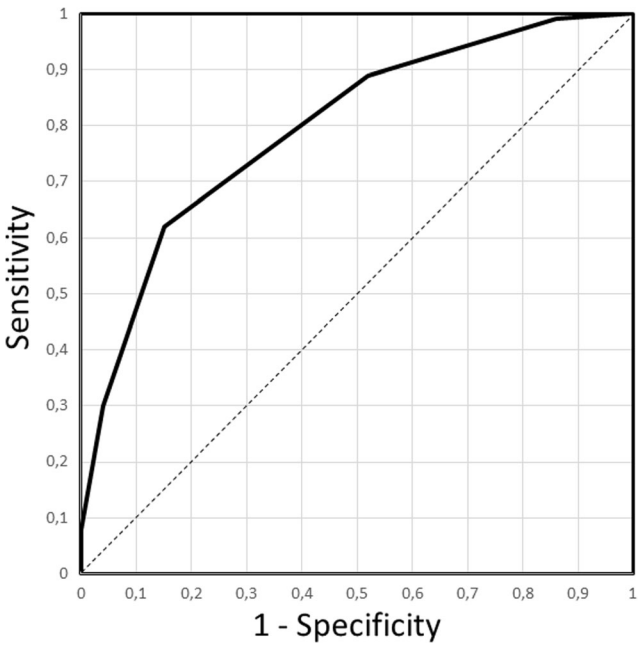

Fig. 1 Receiver operating characteristic (ROC) curve obtained from specificity and sensitivity values in predicting cerebral edema, considering as cutoffs all possible E-score values. Area under the ROC curve 0.78 (95% C.I. 0.74–0.83)

cerebral artery, closed eyes and vomiting, and subtracting one point for LACS and white matter lesions. The score of 1 was sufficient to predict a probability of edema development exceeding 50%. The probability further increased as the score increased.

Total anterior circulation syndrome (TACS) and the hyperdense appearance of middle cerebral artery were the most predictive factors (odds ratio > 4 and $P \leq 0.0001$). The hyperdense appearance of middle cerebral artery had already been shown as possible predictor of cerebral edema [12, 13]. Both factors are usually associated with the impairment of the whole vascular territory of middle cerebral artery, which is the maximum lesion obtainable with the occlusion of a cerebral artery. The great predictive ability of these two elements is therefore not surprising, as it is well known that the size of cerebral lesion is the main factor favoring edema formation [7]. Nevertheless, no direct measurement of infarct size was included, in the present study, among the possible edema predictors. On non-contrast CT scans performed on admission, infarct size can be assessed by the Alberta Stroke Program Early CT Score (ASPECTS) [20]. This score provides a reliable estimation of infarct size when it is obtained using imaging techniques based on CT perfusion or magnetic resonance [21]. In fact, DWI ASPECTS has been used in the DASH score [9] to assess the risk of development of malignant infarction in patients with documented proximal vessel occlusion. However, we did not consider the ASPECTS because, when the ASPECTS is based on early non-contrast CT, it is poorly reproducible and slightly reliable in outcome prediction [22–24]. In addition, it is only applicable to infarcts in the middle cerebral artery territory.

NIHSS score, an important indicator of stroke severity, was also associated with the development of cerebral edema, as shown by others [12, 13]. However, this association was less strong than the association between TACS and cerebral edema, and disappeared in multivariable analysis when NIHSS was dichotomized.

Other variables were predictive of edema only in univariate analysis, probably because they are often associated with large cerebral lesions, such as atrial fibrillation, fever [25], and markers of inflammation [26]. Also, in other studies, blood glucose had been found to be associated with cerebral edema [9, 11, 13, 27], but in the present study, this association was significant only in univariate analysis.

One of the characteristic symptoms of cerebral edema with endocranial hypertension is the impairment of the state of consciousness, which is commonly assessed with the GCS. In this study, the GCS was also predictive of the subsequent development of edema. Its most relevant feature was vigilance loss (closed eyes), and in fact, the inclusion of this element in the logistic model led to the exclusion of the dichotomized GCS score. Vigilance loss was found to be associated with cerebral edema also in other studies [13]. Another characteristic symptom of endocranial hypertension is vomiting, which was also found to be predictive of the subsequent development of edema.

Lacunar syndromes are usually characterized by a mild symptomatology. They are caused by the occlusion of a perforating arteriole in a deep site determining a cerebral lesion of small size (typically, < 1.5 cm) [28]. It is therefore reasonable that this type of clinical presentation, which is evidently alternative to TACS, may suggest disregarding the hypothesis of edema formation.

White matter lesions are often associated with lacunar lesions [29], as they also are the expression of small vessel disease, although of smaller caliber. However, this association does not entirely justify the "protective" significance of white matter lesions on cerebral edema development (a novel finding of this study). In fact, in multivariable analysis, they remained associated with cerebral edema independently of LACS. White matter lesions might be associated with a certain degree of cerebral atrophy, which could reduce the increment of endocranial pressure caused by edema, thus limiting its mass effect.

Finally, it is noteworthy the absence of association with cerebral edema of several variables, including cardiovascular risk factors, measured blood pressure, renal function, and other laboratory investigations. Some studies had shown that previous stroke might have a protective effect on the appearance of cerebral edema [11, 13]. In the present study, previous stroke was found to be less frequent in the patients with edema, but not significantly.

This study has all the main limitations of retrospective studies. Among them, the most important concerns the fact that only the available data could be collected. Thus, for example, among the patients considered free of cerebral edema, there could be some in whom a late edema was not detected because not enough CT scans were performed. In addition, some potentially relevant variables, such as those derived from more sophisticated imaging techniques, were not available among the routine investigations. Finally, these results need to be validated in a different cohort of patients.

Keeping in mind these limitations, the six parameters identified in this study may allow an early assessment of the risk of cerebral edema in ischemic stroke patients. The rapid detection of malignant cerebral edema is of paramount importance to perform decompressive hemicraniectomy promptly. In addition, in the hope of counteracting or even preventing the appearance of this dangerous complication of stroke, high-risk patients might be selected for close monitoring and, possibly, for immediate treatment with hyperosmotic substances. This would concern nearly a quarter of all ischemic strokes, although, before routinely doing this, prospective studies should confirm our results.

Hyperosmotic substances are presently the main anti-edema medical therapy recognized by guidelines, even if their

efficacy is not yet adequately demonstrated. Hopefully, other possibilities of medical therapy of cerebral edema will be available in the future. In this regard, the E-score could also prove useful to select patients to be randomized for assessing the efficacy of the new therapies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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References

1. Brogan ME, Manno EM (2015) Treatment of malignant brain edema and increased intracranial pressure after stroke. Curr Treat Options Neurol 17:327
2. Grände PO, Romner B (2012) Osmotherapy in brain edema: a questionable therapy. J Neurosurg Anesthesiol 24:407–412
3. Bereczki D, Fekete I, Prado GF, Liu M (2007) Mannitol for acute stroke. Cochrane Database Syst Rev:CD001153. https://doi.org/10.1002/14651858.CD001153.pub2
4. Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S (2004) Glycerol for acute stroke. Cochrane Database Syst Rev: CD000096. https://doi.org/10.1002/14651858.CD000096.pub2
5. Diringer MN, Scalfani MT, Zazulia AR, Videen TO, Dhar R (2011) Cerebral hemodynamic and metabolic effects of equi-osmolar doses mannitol and 23.4% saline in patients with edema following large ischemic stroke. Neurocrit Care 14:11–17
6. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL, American Heart Association Stroke Council. 2018 (2018) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 49:e46–e110
7. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB (2008) Predictors of life-threatening brain edema in middle cerebral artery infarction. Cerebrovasc Dis 25:176–184
8. Thomalla G, Hartmann F, Juettler E, Singer OC, Lehnhardt FG, Köhrmann M, Kersten JF, Krützelmann A, Humpich MC, Sobesky J, Gerloff C, Villringer A, Fiehler J, Neumann-Haefelin T, Schellinger PD, Röther J, for the Clinical Trial Net of the German Competence Network Stroke (2010) Clinical trial net of the German competence network stroke. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. Ann Neurol 68:435–445
9. Shimoyama T, Kimura K, Uemura J, Yamashita S, Saji N, Shibazaki K, Iguchi Y (2014) The DASH score: a simple score to assess risk for development of malignant middle cerebral artery infarction. J Neurol Sci 338:102–106
10. Kim H, Jin ST, Kim YW, Kim SR, Park IS, Jo KW (2015) Predictors of malignant brain edema in middle cerebral artery infarction observed on CT angiography. J Clin Neurosci 22:554–560
11. Ong CJ, Gluckstein J, Laurido-Soto O, Yan Y, Dhar R, Lee JM (2017) Enhanced detection of edema in malignant anterior circulation stroke (EDEMA) score: a risk prediction tool. Stroke 48:1969–1972
12. Strbian D, Meretoja A, Putaala J, Kaste M, Tatlisumak T, Helsinki Stroke Thrombolysis Registry Group (2013) Cerebral edema in acute ischemic stroke patients treated with intravenous thrombolysis. Int J Stroke 8:529–534
13. Thorén M, Azevedo E, Dawson J, Egido JA, Falcou A, Ford GA, Holmin S, Mikulik R, Ollikainen J, Wahlgren N, Ahmed N (2017) Predictors for cerebral edema in acute ischemic stroke treated with intravenous thrombolysis. Stroke 48:2464–2471
14. Lyden P, Lu M, Jackson C, Marler J, Kothari R, Brott T, Zivin J (1999) Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke 30:2347–2354
15. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C (1991) Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 337:1521–1526
16. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84
17. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J (1990) Grading white matter lesions on CT and MRI: a simple scale. J Neurol Neurosurg Psychiatry 53:1080–1083
18. Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease et al (2009) Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. Stroke 40:3646–3678
19. Osborn AG, Salzman L, Barkovich AJ (2009) Acute cerebral ischemic infarction. In: Diagnostic imaging: brain, 2nd edn. Lippincott, Philadelphia, pp 108–111
20. Barber PA, Demchuk AM, Zhang J, Buchan AM (2000) Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 355:1670–1674
21. Luo S, Yang L, Luo Y (2018) Susceptibility-weighted imaging predicts infarct size and early-stage clinical prognosis in acute ischemic stroke. Neurol Sci 39:1049–1055
22. Naylor J, Churilov L, Chen Z, Koome M, Rane N, Campbell BCV (2017) Reliability, reproducibility and prognostic accuracy of the Alberta Stroke Program Early CT Score on CT perfusion and non-contrast CT in Hyperacute stroke. Cerebrovasc Dis 44:195–202
23. Demeestere J, Scheldeman L, Cornelissen SA, Heye S, Wouters A, Dupont P et al (2018) Alberta Stroke Program Early CT Score versus computed tomographic perfusion to predict functional outcome after successful reperfusion in acute ischemic stroke. Stroke 49:2361–2367
24. Kong WY, Tan BYQ, Ngiam NJH, Tan DYC, Yuan CH, Holmin S, Andersson T, Lundström E, Teoh HL, Chan BPL, Rathakrishnan R, Ting EYS, Sharma VK, Yeo LLL (2017) Validation of Serial Alberta Stroke Program Early CT Score as an outcome predictor in thrombolyzed stroke patients. J Stroke Cerebrovasc Dis 26: 2264–2271
25. Muscari A, Puddu GM, Conte C, Falcone R, Kolce B, Lega MV, Zoli M (2015) Clinical predictors of fever in stroke patients: relevance of nasogastric tube. Acta Neurol Scand 132:196–202
26. Muscari A, Collini A, Fabbri E, Giovagnoli M, Napoli C, Rossi V, Vizioli L, Bonfiglioli A, Magalotti D, Puddu GM, Zoli M (2014)

Changes of liver enzymes and bilirubin during ischemic stroke: mechanisms and possible significance. BMC Neurol 14:122

27. Kasner SE, Demchuk AM, Berrouschot J et al (2001) Predictors of fatal brain edema in massive hemispheric ischemic stroke. Stroke 32:2117–2123
28. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 24:35–41
29. Muscari A, Faccioli L, Ghinelli M, Napoli C, Pirazzoli E, Puddu GM, Spinardi L, Trossello MP, Zoli M (2016) Hypertension and other determinants of white matter lesions in stroke patients. J Clin Hypertens (Greenwich) 18:907–912