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Predictors of Life-Threatening Brain Edema in Middle Cerebral Artery Infarction

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Key Words
Brain edema · Cerebral infarction · Middle cerebral artery infarction

Abstract
Background: We performed a systematic review to identify predictors of the development of life-threatening brain edema in patients with middle cerebral artery infarction. ***Methods:*** We searched Medline from January 1966 and Embase from January 1974 to April 2007 for cohort and case-control studies on predictors of life-threatening edema in patients with middle cerebral artery infarction. Crude data were used to calculate risk ratios, odds ratios, or weighted mean differences. ***Results:*** Infarct size was the major determinant of the development of life-threatening edema. Other associated determinants were early mass effect, involvement of other vascular territories, higher body temperature, internal carotid artery occlusion, and need for mechanical ventilation. However, predictive values were only moderate. ***Conclusions:*** The size of the ischemic area is the major determinant. Single predictors lack sufficient predictive value to select candidates for surgical decompression before the onset of clinical signs of herniation.

Large middle cerebral artery (MCA) infarcts may be complicated by space-occupying and life-threatening edema formation, usually between the 2nd and 5th day after stroke onset. Case fatality rates as high as 78% have been reported [1]. Fatal edema occurs in 1–5% of all patients with a supratentorial infarct [2, 3].

Because of the limitations of medical treatment strategies to reduce edema formation [4], there have been proposals for decompressive surgery consisting of a large hemicraniectomy and a duraplasty [5, 6]. In rats with MCA infarction, surgical decompression reduced infarct volume when performed early after the onset of ischemia, but not when start of treatment was delayed [7]. Although a recent systematic review of retrospective and uncontrolled clinical studies failed to show a significant effect of timing of surgery on outcome [8], a large prospective study not included in this review also suggested that functional outcome is better if treatment is started early, even before clinical deterioration [6]. If this suggestion is confirmed in ongoing clinical trials, patients at risk for developing fatal edema should be identified as early as possible.

Different early predictors of life-threatening edema are described, ranging from the presence of vomiting to infarct volume [9–30]. In this article, the results of a systematic review to identify predictors of the development of life-threatening brain edema in patients with MCA infarction are presented.

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Methods

Search Strategy and Selection Criteria

We searched Medline from January 1966 to April 2007 and Embase from January 1974 to August 2006 for cohort and case control studies on predictors of the development of life-threatening brain edema in patients with MCA infarction. The search terms we used were (predict* OR prognos*) AND (stroke OR (middle cerebral artery)) AND (oedema OR oedema OR swelling OR malignant OR herniation OR space-occupying). Publications were identified independently by the first and by the last author. Reference lists of all relevant publications were checked for additional articles. This method of cross-checking was continued until no further studies were found.

Inclusion Criteria

Criteria for inclusion of studies were (1) cohort or case-control studies conducted among patients with acute MCA infarction, published as full articles and written in English, French, or German; (2) clear description of the cohort in cohort studies and the control group in case-control studies; and (3) outcome defined as neurological deterioration with a decrease in consciousness and signs of cerebral herniation as a result of the development of life-threatening brain edema. Studies were also included if patients died or if invasive therapeutic procedures, such as decompressive surgery, were performed, after the above outcome criteria had been met. For inclusion in the meta-analysis, the studies had to present crude data to allow recalculations in our analyses. However, we were not able to use individual patient data. Studies were excluded if (1) only a radiological outcome was described, without clinical information, or if (2) brain imaging was not performed and patients with other lesions than MCA infarcts could therefore not be excluded. Data were included only once if used in multiple publications.

Data Extraction

Data were systematically extracted with use of a predefined data extraction form. Difficulties were resolved by consensus discussions between the first and the last author.

Data Analysis

Cochrane Collaboration's Review Manager software (version 4.2) was used for analysis. For analysis of crude data, data of at least two studies had to be available on the same potential risk factor. Crude dichotomous data were used to construct 2 × 2 tables and to calculate risk ratios (RRs) or odds ratios (ORs) where appropriate, as well as positive and negative predictive values. Data from cohort and case control studies were not combined. Crude continuous data were used to calculate weighted mean differences. If there was statistically significant heterogeneity among the results of included studies ($p < 0.05$), we used random- instead of fixed-effect models, because these include both within-study variance and between-study variation in the assessment of uncertainty of the meta-analysis [31]. Data are presented as point estimates with 95% confidence intervals. The boxes in the figures describe the study size, with larger boxes for larger studies.

Results

Of 955 citations identified after searching Medline and Embase with the above search terms, 23 were eventually included in the present review (fig. 1). Details of these studies are given in table 1.

We were able to perform a meta-analysis of crude data on the following potentially predictive factors: age, sex, gaze palsy on admission, need for mechanical ventilation, infarct size, early signs of infarction on CT, side of infarction, involvement of other vascular territories besides the MCA territory, results of perfusion-weighted imaging, thrombolysis, recanalization, hemorrhagic transformation, blood glucose on admission, diabetes mellitus, temperature on admission, infarct etiology, and the presence of MCA or ICA occlusion. Because of the use of different cut-off points, it was not possible to combine data for some other predictive factors, and for this reason, data on infarct severity, level of consciousness, blood pressure, fever, brain atrophy, neuromonitoring, cerebral perfusion, and midline shift are presented in a narrative synthesis. In 7 studies, some patients had subsequent surgical decompression, after the outcome criteria had been met [12, 17, 21, 24–26, 30].

Meta-Analysis

The results of the meta-analysis are summarized in table 2 and figures 1–5. We found a total of 27 factors evaluated for their relation with the development of life-threatening brain edema, of which 12 were statistically significant predictors of this complication. For infarct size, cut-off values of 50, 66 and 100% of the MCA territory were used [9, 18, 20, 21, 23, 26, 27, 29, 30], and for perfusion deficit a cut-off value of 66% of the MCA territory was used. A need for mechanical ventilation [RR 10 (2.1–51), $p = 0.004$], infarction of more than 66% of the MCA territory [RR 7.5 (3.9–14.3), $p < 0.0001$], and a perfusion deficit larger than 66% of the MCA territory [RR 7.7 (2.5–24), $p = 0.0004$] were found to be the strongest predictors in this meta-analysis. However, predictive values were only moderate, and highly dependent on the incidence of life-threatening edema, which ranged from 10 to 78% in the cohort studies included in this review (table 2). MCA occlusion was associated with a significantly reduced risk of the development of life-threatening brain edema [RR 0.5 (0.3–0.7), $p < 0.0001$].

Narrative Synthesis

The investigators of 11 studies reported on severity of the neurological deficits at admission and risk of the de-

Table 1. Details of included studies

	Year	Study design	Cohort	Total cases (proportion)	Controls	Consecutive	Incidence of life-threatening edema, %	Population	Onset of symptoms to assessment time, h	Outcome definition
Berrouschot [9]	1998	cohort	108	11 (10%)		yes	10	ICU	6	fatal edema formation
Berrouschot [10]	1998	cohort	53	37 (70%)		yes	70	ICU	12	fatal edema formation
Bosche [11] Dohmen [12] Heiss [17]	2003	cohort	31 34 34	14 (45%) 17 (50%) 16 (47%)		ND	45 50 47	ICU	12	signs of uncal herniation with space-occupying edema on imaging
Firlik [13]	1998	cohort	20	6 (30%)		no	30	new	6	signs of uncal herniation with space-occupying edema on imaging
Foerch [14]	2004	cohort	51	16 (31%)		yes	31	new	6	fatal edema formation or signs of uncal herniation with space-occupying edema on imaging
Gerriets [15]	2001	cohort	42	12 (29%)		yes	29	new	16	fatal edema formation
Hacke [1] Schwab [28]	1996	cohort cohort	55	43 (78%)		ND	78	ICU	12	fatal edema formation
Haring [16]	1999	case control		31	31	no		new	18	signs of uncal herniation with space-occupying edema on imaging
Kasner [18]	2001	cohort	201	94 (47%)		no	47	ICU	48	fatal edema formation
Krieger [19]	1999	case control		23	112	no		new	6	fatal edema formation
Kucinski [20]	1998	cohort	74	17 (23%)		ND	23	new	6	fatal edema formation
Lee [21]	2004	cohort	31	10 (32%)		ND	32	new	6	signs of uncal herniation with space-occupying edema on imaging
Limburg [22]	1990	cohort	26	6 (23%)		yes	23	new	24	fatal edema formation
Manno [23]	2003	cohort	36	22 (61%)		no	61	new	12	signs of uncal herniation with space-occupying edema on imaging
Maramattom [24]	2004	cohort	24	14 (58%)		yes	58	ICU	?	signs of uncal herniation with space-occupying edema on imaging
Mori [25]	2001	cohort	55	34 (62%)		ND	62	new	6	signs of uncal herniation with space-occupying edema on imaging
Oppenheim [26]	2000	cohort	28	10 (36%)		no	36	new	14	signs of uncal herniation with space-occupying edema on imaging
Ryoo [27]	2004	cohort	27	11 (41%)		yes	41	new	6	fatal edema formation
Stolz [29]	2002	cohort	21	9 (43%)		yes	43	new	120	fatal edema formation
Thomalla [30]	2003	cohort	37	11 (30%)		no	30	new	6	signs of uncal herniation with space-occupying edema on imaging

Variables were included only if studied by at least two authors. ND = Not derivable.

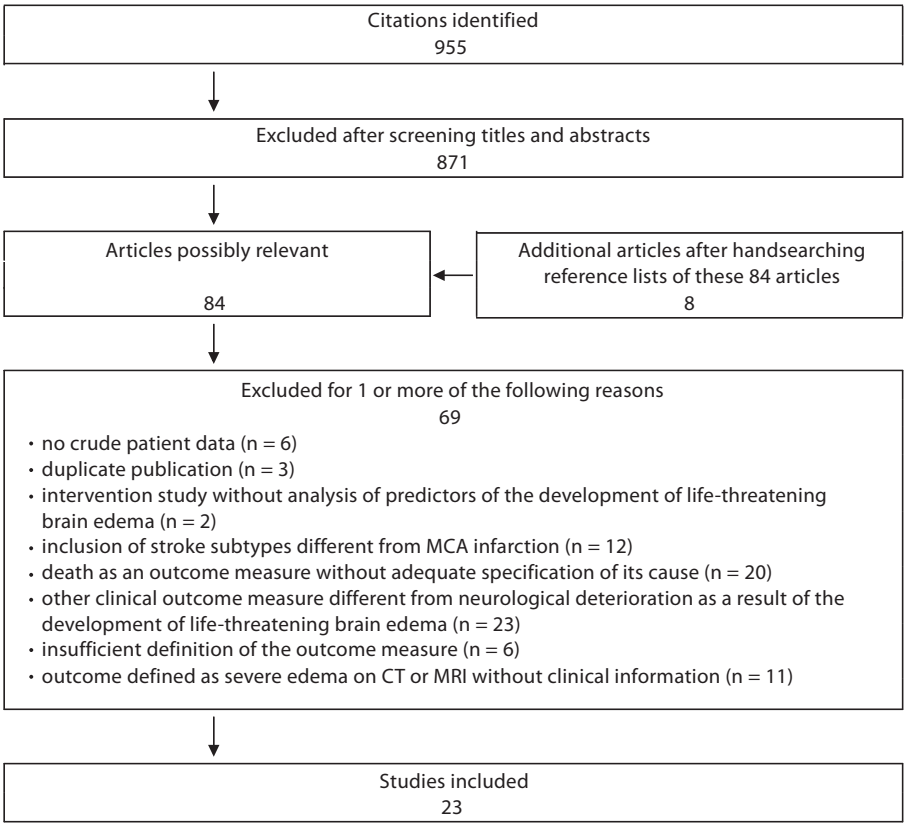

Fig. 1. Flow chart of study inclusion.

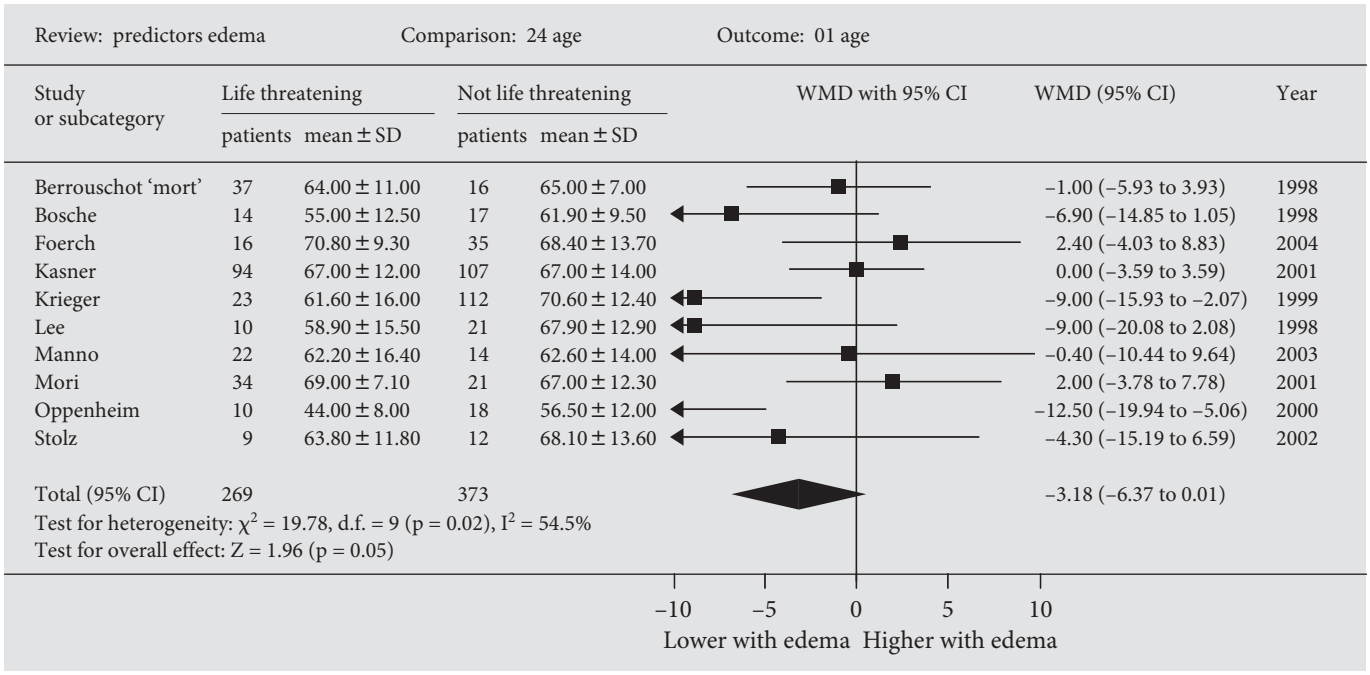

Fig. 2. Weighted mean differences (random) in age between patients with and without life-threatening edema.

Table 2. Results of the meta-analysis

Predictor	Estimates (95% CI)	p value for overall effect	p value for heterogeneity	Overall incidence malignant edema, %	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)
Age [10, 11, 14, 18, 19, 21, 23, 25, 26, 29]	WMD –3.2 (–6.4 to 0.0)[1]	0.05	0.02	42		
Men versus women [1, 11, 14, 18, 23–26, 29, 30]	RR 0.9 (0.8 to 1.1)	0.37	0.54	50	48 (42–53)	48 (42–54)
Conjugate gaze palsy on admission [10, 22, 24]	RR 1.2 (0.8 to 1.7)	0.45	0.25	55	60 (48–71)	55 (36–73)
Mechanical ventilation during admission [1, 14][2]	RR 10 (2.1 to 51)[3]	0.004	0.85	56	72 (61–81)	96 (80–99)
Infarct size larger than 50% of the MCA territory [18, 21, 23]	RR 2.0 (1.5 to 2.6)[3]	<0.00001	0.81	46	65 (56–74)	68 (60–75)
Infarct size larger than 50% of the MCA territory [16, 19]	OR 9.2 (4.0 to 20.9)[3]	<0.00001	0.21			
Infarct size larger than 66% of the MCA territory [9, 21, 27, 29]	RR 7.5 (3.9 to 14.3)[3]	<0.00001	0.12	22	86 (68–96)	90 (85–95)
Infarction of the complete MCA territory [9, 26, 29, 30]	RR 7.0 (2.5 to 19.4)[3]	0.0002	0.02	21	71 (54–85)	91 (85–95)
Obscuration of the lentiform nucleus on admission [18, 20]	RR 0.9 (0.7 to 1.2)	0.65	0.71	40	39 (32–46)	58 (47–68)
Early mass effect [18, 20][4]	RR 1.5 (1.2 to 2.0)[c]	0.002	0.89	40	51 (40–63)	64 (57–71)
Left-sided versus right-sided [1, 11, 10, 21, 23, 26, 30]	RR 1.1 (0.8 to 1.3)	0.68	0.3	47	47 (38–56)	53 (45–62)
Involvement of other vascular territories [14, 21, 24–27, 29][5]	RR 2.6 (2.0 to 3.2)[3]	<0.00001	0.03	44	86 (74–94)	69 (62–76)
Perfusion deficit larger than 66% of the MCA territory [21, 27]	RR 7.7 (2.5 to 24)[3]	0.0004	0.29	36	73 (50–89)	86 (71–95)
Low perfusion levels in other vascular territories [21, 27][5]	RR 3.7 (2.0 to 6.6)[3]	<0.001	0.12	36	85 (55–98)	78 (63–89)
Thrombolysis [11, 14, 18, 23, 25, 28, 30]	RR 0.8 (0.6 to 1.1)	0.24	0.03	50	43 (35–50)	47 (41–52)
Recanalization [20, 25, 28]	RR 0.9 (0.2 to 2.5)	0.56	0.0003	45	30 (19–42)	43 (32–55)
Hemorrhagic transformation [12, 13, 18, 25]	RR 1.8 (0.9 to 3.7)	0.10	0.05	49	75 (55–89)	54 (48–60)
Blood glucose levels on admission [10, 18, 19]	WMD 0.20 mM (–0.7 to 1.0)	0.64	0.39	40		
History of diabetes mellitus [14, 18]	RR 1.2 (0.9 to 1.6)	0.16	0.27	44	49 (39–60)	60 (52–67)
Body temperature on admission [10, 11]	WMD 0.3°C (0.0 to 0.6)[3]	0.03	0.31	61		
Athero-thrombotic infarction [14, 30]	RR 1.1 (0.5 to 2.3)	0.29	0.53	31	33 (13–59)	70 (57–80)
Cardioembolic infarction [14, 30]	RR 0.7 (0.4 to 1.2)	0.18	0.52	31	25 (14–40)	63 (46–77)
MCA occlusion [1, 20, 27, 30]	RR 0.5 (0.3 to 0.7)[3]	<0.0001	0.07	38	21 (14–29)	40 (29–52)
Hyperdense MCA sign on CT [18, 21, 23, 24]	RR 1.2 (0.9 to 1.5)	0.28	0.09	46	51 (42–61)	57 (51–64)
Hyperdense MCA sign on CT [16, 19]	OR 4.0 (0.5 to 35.7)	0.05	0.004			
ICA occlusion [1, 20, 26, 30]	RR 2.8 (1.9 to 4.1)[3]	<0.00001	0.09	37	63 (51–74)	82 (74–89)
Hyperdense ICA sign on CT [18, 21]	RR 1.0 (0.6 to 1.6)	0.99	0.12	45	42 (26–59)	55 (48–62)

Perfusion-weighted imaging was performed by CT [3, 13, 21], MRI [30], positron emission tomography [11, 12, 17], or single photon emission CT [9, 22]. Recanalization was measured by digital subtraction angiography (DSA). Hemorrhagic transformation had to be well defined and primary intraparenchymal hemorrhages had to be excluded. MCA occlusion was measured by DSA [1, 20], CT angiography [29], or MR angiography [30], and internal cerebral artery occlusion by DSA [1, 20] or MR angiography [26, 30].

[1] Indicates the mean age of patients with life-threatening edema was 3.2 years lower than the mean age of patients without.

[2] The time between the onset of symptoms and the need for ventilation was between 3 h and 5 days in one study [28].

[3] Statistically significant difference.

[4] Sylvian fissure obscuration, effacement of sulci, and lateral ventricle compression on admission.

[5] Anterior or posterior cerebral artery.

velopment of life threatening brain edema. Severity was expressed as a score on either the National Institutes of Health Stroke Scale [11, 12, 14, 21, 26, 27, 30] or the Scandinavian Stroke Scale [1, 10, 15, 29] and results were reported either on the basis of mean or median scores, or dichotomized with different cut-off points. This made a formal meta-analysis impossible. In general, patients with life-threatening edema had higher severity scores, either with statistical significance [26, 27, 30], or not [1, 11, 12, 14, 15, 21, 29]. Level of consciousness on admission was not significantly different in most studies [10, 22, 24, 25, 28]. In only one study, level of consciousness on admission was significantly lower in patients going on to develop life-threatening edema, but the definition of this factor was unclear [18].

Neither mean arterial pressure on admission [11], nor systolic blood pressure 12 h after the onset of symptoms [19], or peak or trough systolic pressure [18] was identified as a risk factor for life-threatening edema. Cerebral atrophy, a history of hypertension, fever on admission, and atrial fibrillation did not lead to significantly altered risk in one cohort [14], and one case-control [19] study.

Lower levels of extracellular nontransmitter amino acids were found in noninfarcted ipsilateral tissue in the first 12 h after the onset of symptoms in patients who de-

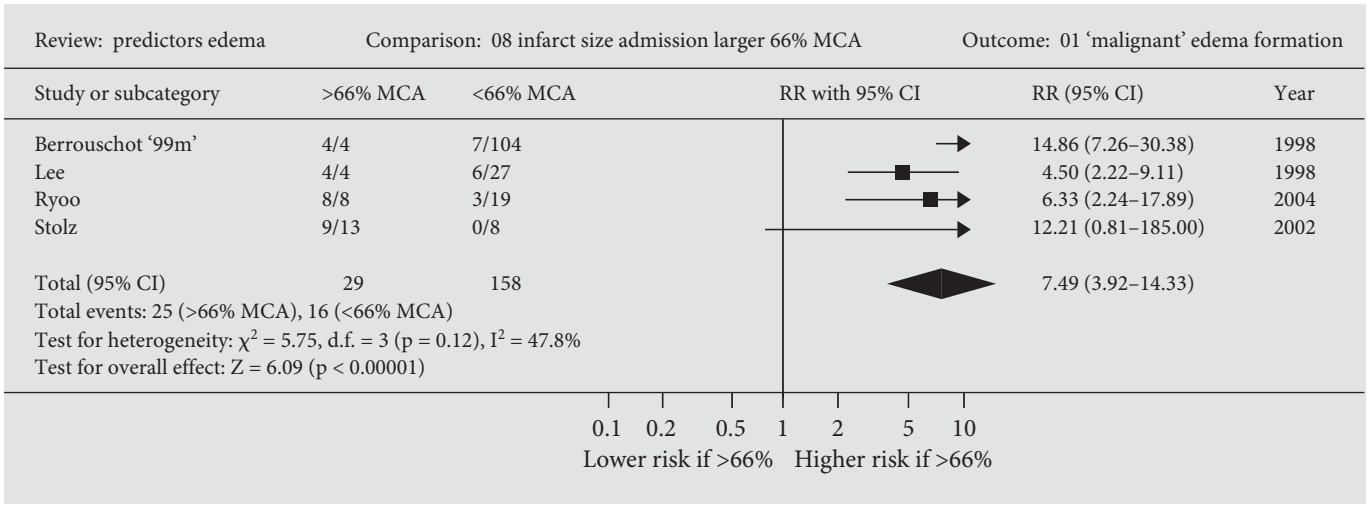

Fig. 3. Early infarct size and the RR (fixed) of developing life-threatening brain edema.

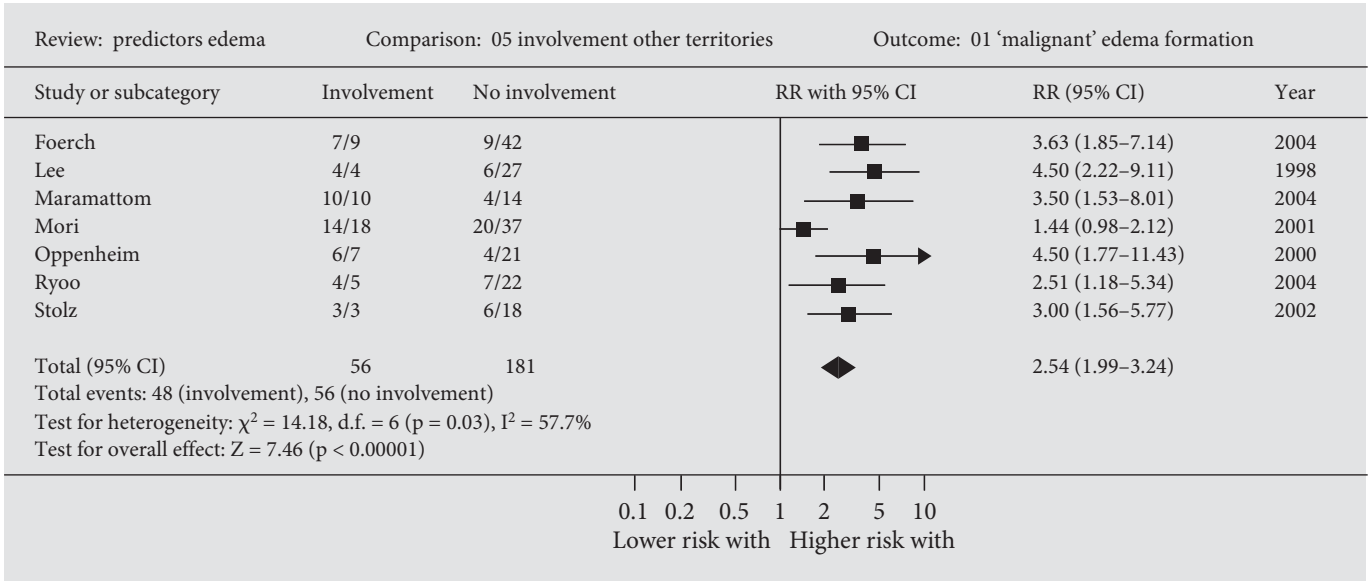

Fig. 4. Involvement of other vascular territories besides the MCA territory and the RR (fixed) of developing life-threatening brain edema.

veloped life-threatening edema [12, 17]. In the first 12 h after the onset of symptoms intracranial pressure (ICP) values could not discriminate between patients who did and did not go on to develop life-threatening edema [11, 17]. In one study, higher ICP values were found in patients with life-threatening edema, but it is unclear at what time points these ICP measurements were done [1]. Measurements of midline shift were presented in 5 cohort studies [1, 15, 24, 25, 29] and 1 case-control study [16]. However, measurements were performed at different time points and several landmarks for the measurements (such as the septum pellucidum [1, 25], the pineal body [1], and the third ventricle [15, 29]) and cut-off points were used. Generally, differences in midline shift between life-threatening and 'non-life-threatening' infarctions became statistically significant in the later stages of the dis-

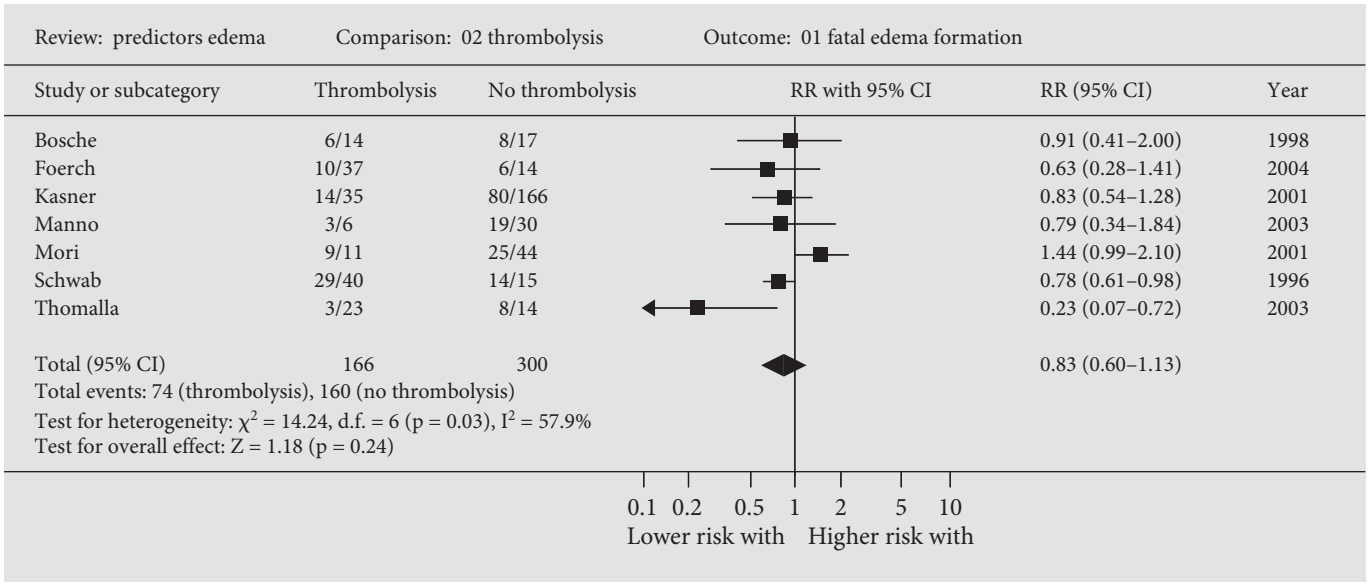

Fig. 5. Thrombolysis and the RR (random) of developing life-threatening brain edema.

Table 3. Variables found as independent predictors of malignant edema formation

Study	Interval from onset of symptoms to assessment, h	Predictor	Estimates (95% CI)
Berrouschot, 1998 [9]	6	SPECT activity deficit of the complete MCA territory	RR 40 (10–161)
		SPECT graded scale >140	RR 79 (11–569)
Haring, 1999 [16]	18	attenuated corticomedullary contrast	ND
Kasner, 2001 [18]	48	history of hypertension	OR 3.0 (1.2–7.6)
		history of congestive heart failure	OR 2.1 (1.5–3.0)
		WBC	OR 1.07/1,000 WBC/μl (1.01–1.14)
		WBC >10,000/μl	OR 3.9 (2.4–6.4)
		>50% MCA on CT	OR 6.3 (3.5–11.6)
		additional vascular territories on CT	OR 3.3 (1.2–9.4)
Krieger, 1999 [19]	24	nausea or vomiting	OR 5.1 (1.7–15.3)
	12	systolic BP >180	OR 4.2 (1.4–12.9)
Manno, 2003 [23]	12	hyperdense MCA sign	OR 29 (1.6–524)
		>50% MCA CT	OR 14 (1.04–189)
Oppenheim, 2000 [26]	14	volume DWI >145 cm^3	ND
Ryoo, 2004 [27]	6	hypoperfusion on CT time to peak map	OR 150 (ND)

SPECT = Single photon emission computed tomography; WBC = white blood cells; BP = blood pressure; ND = not derivable.

ease, after the onset of clinical signs of herniation. In one study, maximum midline shift was found earlier in patients with life-threatening edema than in patients without (day 2–4 vs. day 3–7) [1], and in another study the progression of midline shift was faster in patients with life-threatening edema than in patients without [29].

Independent Predictors of Life-Threatening Edema

Multivariate analysis of predictors of the development of life-threatening brain edema was performed in 9 studies [9, 10, 18, 19, 21, 23, 26, 27, 29]. Variables found as independent predictors are summarized in table 3.

Discussion

The major determinants of developing fatal brain edema after MCA infarction are the size of the infarct and the size of the area with perfusion deficit. In this systematic review, infarct size larger than 50% of the MCA territory and a perfusion deficit larger than 66% were identified as risk factors for the development of life-threatening brain edema. Involvement of additional vascular territories besides that of the MCA was significantly associated with the development of life threatening brain edema. However, positive and negative predictive values were too low to be useful in the clinic. To date, selection of patients for surgical decompression before the onset of clinical signs of herniation is not possible.

In two recent studies, lesion volume of more than 145 ml on diffusion-weighted imaging (DWI) within 14 h after the onset of symptoms [26] and more than 82 ml on apparent diffusion coefficient maps in the first 6 h [30] predicted the development of life-threatening brain edema with positive predictive values of 91 and 82%, and negative predictive values of 100 and 92%, respectively. These findings could not be subjected to meta-analysis, because they were not tested in different studies. Still, measurement of infarct volume with DWI is simple, reliable and promising, and should be used in future studies on the prediction of the development of life-threatening brain edema.

Several findings were anticipated. First, in general, greater stroke severity was associated with an increased risk of the development of life-threatening edema. Second, body temperature on admission was marginally higher (0.3°C) in patients with life-threatening edema, than in patients without. Stroke patients with fever have a worse prognosis than patients with a normal or low body temperature [32]. Moreover, it has been shown that moderate hypothermia can help to control critically elevated ICP values in severe space-occupying edema after MCA infarction [33].

Paradoxically, MCA occlusion was associated with a lower risk of life-threatening edema. This is probably a result of selection bias within the studies included in the meta-analysis, because the group of patients with an MCA occlusion consisted mainly of patients with distal MCA occlusions, whereas occlusions of the MCA trunk have been associated with poor outcome [34, 35]. The presence of a hyperdense MCA sign is usually indicative of MCA trunk occlusion [36] and in the present meta-analysis a hyperdense MCA sign on CT led to an increased RR and OR, but the results were not statistically significant [16, 18, 19, 21, 23, 24]. Patients with ICA occlusions had a higher risk of life-threatening edema. This group had mainly intracranial carotid occlusions, which is considered a poor prognostic sign [1, 20].

The association between levels of nontransmitter and transmitter amino acids in peri-infarct tissue and the development of life-threatening brain edema has been evaluated in two studies [12, 17]. Whereas levels of transmitter amino acids discriminated only in later stages of the disease, a statistically significant association was found between lower levels of extracellular nontransmitter amino acids within 12 h after stroke onset and the development of life threatening brain edema [11]. This is possibly a result of dilution of the extracellular compartment due to excessive vasogenic edema formation within the infarct, spreading into the extracellular space of peri-infarct tissue [11]. Sensitivities and specificities of approximately 80% were found at specific cut-off values. These observations may emphasize the relevance of vasogenic edema in peri-infarct zones, but it is unlikely that invasive neuromonitoring will be used on a large scale in future stroke units, because of its invasive character and costs. For this reason, the clinical applicability of these results is probably low.

The most important limitation of this systematic review and meta-analysis is the large variety of inclusion criteria and methods of analysis among the included studies, although we studied only articles on severe MCA infarction. The variation in incidence of life-threatening brain edema in the cohort studies reflects the large differences in inclusion criteria of these studies. As compared with newly admitted patients, predictive values in patients admitted to a neurocritical care unit were higher, because a priori chances of developing life-threatening edema were higher (tables 1 and 2). Moreover, signs that are directly related to the development of life-threatening brain edema, such as raised ICP, midline shift, and need for mechanical ventilation, are late rather than early outcome predictors. To be able to perform invasive treatment options, such as surgical decompression, as soon as possible, even before the onset of clinical signs of herniation, early predictors are relevant.

Early prediction of the development of life-threatening brain edema and selection of patients for decompressive surgery is difficult in patients with MCA infarction. The size of the ischemic area appears to be the major determinant. DWI may prove to be the most reliable tool but further studies are required. However, none of the clinical and radiological variables were sufficiently predictive of life-threatening brain edema to be used in iso-

lation for the selection of patients for prophylactic surgical decompression. Prediction would probably improve if combinations of symptoms and signs were used [18]. Future studies should aim for consistency in the clinical and radiological factors studied in order to allow inter-study comparisons and meta-analyses.

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