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Malignant infarction after endovascular treatment: Incidence and prediction

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Abstract

Background: Early prediction of malignant infarction may guide treatment decisions. For patients who received endovascular treatment, the risk of malignant infarction is unknown and risk factors are unrevealed.

Aims: The objective of this study is to estimate the incidence of malignant infarction after endovascular treatment in patients with an occlusion of the anterior circulation, to identify independent risk factors, and to establish a model for prediction.

Methods: We analyzed patients who received endovascular treatment for a large vessel occlusion in the anterior circulation within 6.5 h after symptom onset, included in the Dutch MR CLEAN Registry between March 2014 and June 2016. We compared patients with and without malignant infarction. Candidate predictors were incorporated in a multivariable binary logistic regression model. The final prediction model was established using backward elimination. Discrimination and calibration were evaluated with the area under the receiver operating characteristic curve (AUROC) and the Hosmer-Lemeshow test.

Results: Of 1445 patients, 82 (6%) developed malignant infarction. Independent predictors were lower age, higher National Institutes of Health Stroke Scale (NIHSS), lower alberta stroke program early CT score (ASPECTS), internal carotid artery occlusion, lower collateral score, longer times from onset to groin puncture, and unsuccessful reperfusion. The AUROC of a prediction model combining these features was 0.83 (95% confidence interval (CI): 0.79–0.88) and the Hosmer-Lemeshow test indicated appropriate calibration ($P = 0.937$).

Conclusion: The risk of malignant infarction after endovascular treatment started within 6.5 h of stroke onset is approximately 6%. Successful reperfusion decreases the risk. A prediction model combining easily retrievable measures of age, ASPECTS, collateral status, and reperfusion shows good discrimination between patients who will develop malignant infarction and those who will not.

Keywords

Stroke, reperfusion, therapy, intervention, treatment, ischaemic stroke

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Introduction

Malignant infarction, characterized by severe space-occupying edema formation, is a life-threatening complication of ischemic stroke, with case fatality rates of up to 78%.[1] The reported incidence depends on the definition of malignant infarction and the study population, and varies between 2% in unselected cohorts of patients with ischemic stroke and 30% in patients with an occlusion of the middle cerebral artery (MCA).[2–6]

The only treatment option of proven benefit is surgical decompression through a large hemicraniectomy and duraplasty.[7,8] This treatment is beneficial if applied within 48 h of stroke onset, possibly with greater benefit after earlier treatment.[7,9] Only few factors allow reliable prediction of life-threatening edema formation.[10] Lesion volume of >82 cc on diffusion-weighted imaging within 6 h after symptom onset predicted a "malignant" evolution with 98% specificity, but with low sensitivity.[11]

As the risk of malignant infarction seems to increase with infarct size,[10] a relatively high incidence is expected in patients with occlusions of the proximal segments of the anterior circulation who present with severe neurological deficit. A large reduction of the need for surgical decompression has been described after endovascular treatment (EVT) with a stent retriever[12] and successful reperfusion has been associated with reduced midline shift in the MR CLEAN Trial,[13] which suggests that malignant infarction can be prevented with early recanalization.[14] Still, even patients with successful EVT may develop malignant infarction.[15] Size of the ischemic area, timing and degree of reperfusion, and collateral status may affect this risk.[4]

Aims

We aim to estimate the incidence of malignant infarction in patients with ischemic stroke in the anterior circulation who undergo EVT, identify predictors of malignant infarction after EVT, and develop a prediction model.

Methods

Design

We analyzed patients who were included in the MR CLEAN Registry.[16] The MR CLEAN Registry is a prospective, observational study in all centers that perform EVT in the Netherlands. In this registry, all patients who underwent EVT (defined as entry into the angiography suite and arterial puncture) after 16 March 2014 were included. Patients included up to 15 June 2016 were used in the current analysis.

Patients

Inclusion criteria for the present study were age 18 years and older, intracranial arterial occlusion in the anterior circulation (internal carotid artery (ICA), ICA terminus (ICA-T) or middle (M1/M2) or anterior (A1/A2) cerebral artery), and groin puncture within 6.5 h of symptom onset.

Identification of patients with malignant infarction

The primary outcome measure was malignant infarction based on clinical and radiological reports. Patients who underwent hemicraniectomy or died because of life-threatening edema formation were classified as having "malignant infarction." First, we selected patients who died within one week after stroke onset and patients who underwent hemicraniectomy. Subsequently, from this subgroup, letters of discharge in combination with scan reports (if available) were used to identify the cause of death or reason for hemicraniectomy. Letters of discharge were screened for indications of malignant infarction such as decreased arousal, pupillary changes and a (rapid) decline in neurological status. Scan reports were screened for marks of space occupying edema such as midline shift > 5 mm, if midlineshift was not measured, we relied on other parameters such as herniation. Patients with symptomatic intracranial hemorrhage or another known cause of death, such as infection, myocardial infarction, pulmonary embolism, were classified as "no malignant infarction." Patients with an unknown cause of death were excluded from further analysis.

Treatment

Patients were treated according to national guidelines for the treatment of acute ischemic stroke, including intravenous thrombolysis, if indicated.

The necessity of decompressive surgery was left to the judgment of the attending stroke team.

Imaging

ASPECTS was graded from 0 to 10, with 1 point subtracted for any evidence of early ischemic changes in each defined region on the non contrast computed tomography (NCCT).[17]In our study proximal occlusion site was defined as an ICA or ICA-T occlusion. Collaterals were graded on a four-point scale ranging from 0 (absent collaterals) to 3 (excellent collaterals).[18] The expanded Treatment In Cerebral Ischemia (eTICI) score ranges from 0 (no antegrade reperfusion of the territory of the occluded artery) to 3 (complete antegrade reperfusion). Successful reperfusion was defined

as eTICI 2B-3. Intracranial hemorrhage was classified on follow-up imaging according to the Heidelberg criteria and was considered symptomatic if the patient had died or had deteriorated neurologically.[19]

Candidate predictors

Candidate predictors were selected based on the available literature and results of univariable analysis.[11,14,20–23] These included age, history of hypertension, statin use, baseline NIHSS, admission glucose level, ASPECTS, proximal occlusion site, collateral score, time from onset to groin puncture, and reperfusion grade.

Statistical analyses

Baseline characteristics are presented in a descriptive way for patients with and those without malignant infarction. Differences between groups were tested with Pearsons chi-square test in case of ordinal/nominal variables and Mann–Whitney–U or unpaired t-test in case of continuous variables.

We performed a multivariable binary logistic regression analysis. All candidate predictors were included and backward elimination was applied to identify the most efficient final model. We used a P-value of 0.05 as the cutoff value. The collinearity assumption was not violated according to the variance inflation factors. The discriminative ability and calibration of the model were evaluated with the area under the receiver operating characteristic curve (AUROC) and the Hosmer-Lemeshow test, respectively. With the Hosmer-Lemeshow test, a non-significant P-value reflects appropriate calibration.

Missing values

Missing NIHSS scores were retrospectively scored with a standardized score chart based on information from the reported neurological examination. If successful reperfusion was not achieved during EVT, the time of last contrast bolus injection was used as a proxy for time of duration of procedure.[24] In order to make unbiased estimates of associations between imaging and clinical parameters and the development of space-occupying edema, multiple imputation was performed. All descriptive analyses include all patients without imputation of the data.

Standard protocol approvals, registrations

The MR CLEAN Registry was approved by the ethics committee of the Erasmus University MC, Rotterdam, The Netherlands (MEC-2014-235). With this approval, it was approved by the research board of each participating center.

Results

Of the 1628 patients who were registered in the MR CLEAN Registry, 140 patients were excluded, mainly because of an occlusion in the posterior circulation or because the time from onset to EVT was longer than 6.5 h. From the included 1488 patients, 82 (6%, 95% confidence interval (CI) 4–7%) patients were classified as having a malignant infarction. Patients with an unknown cause of death (n = 43) were excluded from further analysis (Figure 1).

Baseline characteristics

Patients who developed malignant infarction were younger and had a more severe deficit at the time of presentation (Table 1). They less often had hypertension and used statin less frequently, had a more proximal occlusion (ICA or ICA-T) on baseline computed tomography angiography (CTA), more extensive early signs of ischemia (lower ASPECTS score), and lower collateral scores. Also, these patients had longer times of onset to groin puncture and onset to reperfusion/last contrast bolus, a longer duration of the procedure and more often unsuccessful reperfusion (Table 1).

Model development

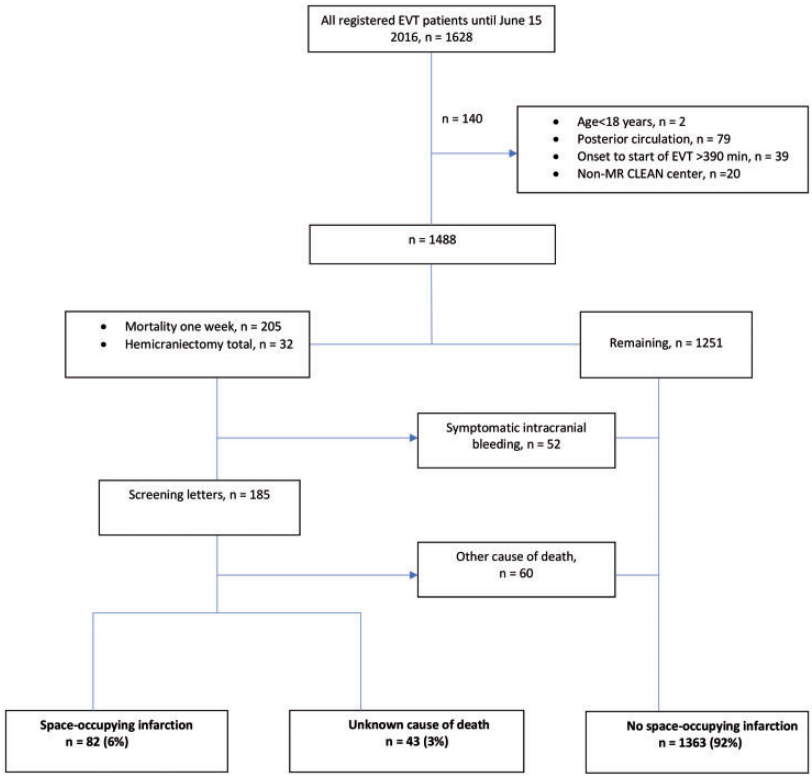
The following factors were independently associated with malignant infarction: higher age, higher baseline NIHSS, lower ASPECTS, proximal occlusion site (ICA or ICA-T), lower collateral score, longer time from onset to groin puncture, and unsuccessful reperfusion (Table 2, Figure 2). The AUROC of a prediction model combining these factors was 0.83 (95% CI 0.79–0.88). The Hosmer-Lemeshow test showed that the calibration of the model was appropriate (P = 0.937).

Discussion

In patients who had anterior circulation occlusions and received EVT, the risk of malignant infarction was 6%. This risk was higher with younger age, higher baseline NIHSS, proximal occlusion, lower ASPECTS, worse collateral filling, longer time from onset to groin puncture and unsuccessful reperfusion. A prediction model combining these factors had high discriminative ability and was well calibrated.

Before the implementation of EVT, the reported incidence of malignant infarction in patients with ischemic stroke ranged between 2 and 30%, with higher incidence in case of larger infarcts.[2–4] In this study, we found a relatively low incidence of 6% in patients with large infarcts. This can partly be explained by the fact that all patients in this study received EVT and thereby achieving higher rates of recanalization.[13,14]

Figure 1. Flow of patients through this study.



Some previous studies have reported on associations between reperfusion therapies and malignant infarction.[3,25,26] In these studies, reperfusion injury was put forward as a possible causal factor. By contrast, Gauberti et al. showed no significant increase of edema after complete reperfusion in patients who received EVT for ischemic stroke.[27] We found a lower risk of malignant infarction with successful reperfusion. Longer time from symptom onset to groin puncture was independently related to larger risk of malignant infarction. A large study with more than 2000 patients treated over a course of nine years suggested that EVT reduces the risk of malignant MCA infarctions considerably. The researchers report an incidence of malignant infarction of 32% in patients who received IVT alone and of 24% in patients who received EVT.[28] Even lower rates of malignant infarction after EVT have been reported in the REVASCAT (11%) and ESCAPE (5%) trials. However, from these studies, patients with (extensive) signs of ischemia on baseline computed tomography (CT) were excluded.[28,29]

Our predictors are in line with reports on malignant infarction in the absence of EVT. Lower age is a well-established predictor.[30] The ratio between the extracellular space and intracranial volume is lower in younger patients, probably providing less buffering capacity for brain swelling.[31] NIHSS is a measure of stroke severity and high NIHSS has also been associated with malignant infarction.[30] The presence of early ischemic changes on admission CT is a harbinger of malignant infarction and can be evaluated with ASPECTS, which is a widely used tool to assess early ischemic changes.[17] In our study, lower ASPECTS was indeed associated with malignant infarction. In line with other studies, ICA/ICA-T occlusions were associated with higher rates of malignant infarction.[20] This is probably explained by infarct size, which is larger with more proximal occlusions.

Collateral pathways include the circle of Willis, leptomeningeal vessels, the ophthalmic artery, and connections between distal segments of the large cerebral arteries. In our study, a lower collateral score was associated with a larger probability of malignant infarction. With poor collateral status more tissue is subjected to hypoperfusion in an early phase, causing more extensive infarcts.[32] This is in line with previous reports, where poor collaterals were associated with malignant infarction.[6,18]

Several models have been developed for predicting malignant infarction; however, these models predate the introduction of EVT and their validity in the setting of current standard care is unknown.[30] Most models

Table 1. Baseline characteristics.

	No malignant infarction, (n = 1363)	Malignant infarction, (n = 82)	P-value
Demographics			
Age, median (IQR)	70 (59–79)	61 (52–75)	<0.001
Male, n (%)	718 (53)	47 (57)	0.428
NIHSS baseline, median (IQR)	16 (11–20)	19 (16–22)	<0.001
Medical history, n (%)			
Previous stroke	230 (17)	8 (10)	0.121
Myocardial infarction	212 (16)	9 (11)	0.343
Peripheral arterial disease	127 (10)	4 (5)	0.232
Atrial fibrillation	306 (23)	13 (16)	0.172
Cardiovascular risk factors, n (%)			
Hypertension	692 (51)	29 (36)	0.008
Hypercholesterolemia	397 (30)	19 (24)	0.258
Diabetes mellitus	230 (17)	12 (15)	0.651
Current smoking	310 (23)	18 (22)	0.532
Medication, n (%)			
Antiplatelet use	450 (34)	22 (5)	0.229
Statin	485 (36)	20 (24)	0.032
Stroke characteristics, n (%)			
Treatment with IVT	1077 (79)	61 (74)	0.328
Glucose levels at admission, median (IQR)	6.7 (6–8)	7.2 (6–9)	0.159
Most proximal level of occlusion			<0.001
ICA/ICA-T	336 (25)	42 (55)	
MCA-M1	774 (60)	31 (40)	
MCA-M2	168 (13)	4 (5)	
Other	18 (1)	0 (0)	
ASPECTS subgroups			<0.001
0–4	73 (6)	17 (22)	
5–7	301 (23)	29 (37)	
8–10	932 (71)	33 (42)	
Collaterals			<0.001

(continued)

Table 1. Continued

	No malignant infarction, (n = 1363)	Malignant infarction, (n = 82)	P-value
0 = Absent collaterals	69 (6)	22 (29)	
1 = Filling <50% of occluded area	408 (32)	38 (50)	
2 = >50% but less than 100%	514 (41)	8 (11)	
3 = Filling 100% of the occluded area	274 (22)	8 (11)	
Workflow			
Onset to groin puncture in minutes, median (IQR)	205 (160–262)	220 (180–295)	0.009
Onset to reperfusion/last contrast bolus in minutes, median (IQR)	264 (157–260)	324 (180–294)	<0.001
Duration of procedure in minutes, median (IQR)	62 (40–89)	85 (58–121)	<0.001
General anesthesia	339 (27)	28 (37)	0.063
Post EVT eTICI, n (%)			0.048
0	226 (17)	19 (24)	
1	42 (3)	3 (4)	
2 A	274 (20)	24 (30)	
2B	251 (19)	15 (19)	
2 C	130 (10)	5 (6)	
3	421 (31)	14 (18)	
Successful reperfusion (eTICI 2B-3), n (%)	802 (60)	34 (43)	0.003

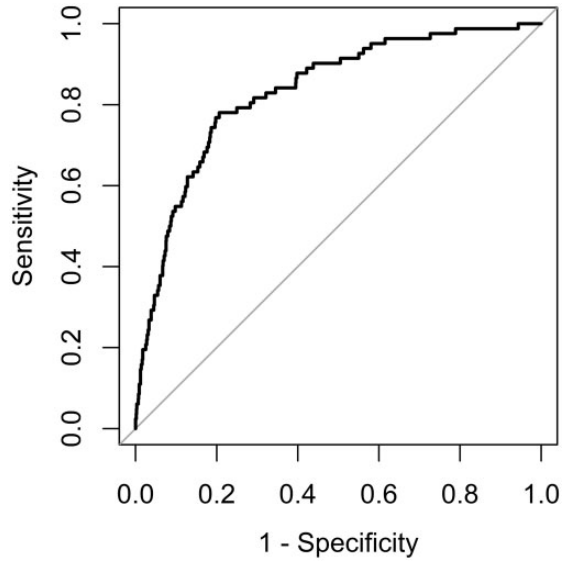
IQR: interquartile range; IVT: intravenous trombolysis; ICA: internal carotid artery; ICA-T: internal carotid artery terminus; MCA-M: middle cerebral artery – segment; ASPECTS: alberta stroke program early CT score; EVT: endovascular treatment; eTICI: expanded treatment in cerebral ischemia.

Table 2. Associations between baseline factors and malignant infarction

	Crude OR	(95% CI)	P-value cOR	Adjusted OR	(95% CI)	P-value aOR
Age (per 10 years older)	0.8	(0.7–0.9)	<0.001	0.7	(0.6–0.8)	<0.001
Baseline NIHSS (per point higher)	1.1	(1.1–1.2)	<0.001	1.1	(1.0–1.1)	<0.001
ASPECTS (per point lower)	1.3	(1.2–1.4)	<0.001	1.1	(1.0–1.3)	0.017
Proximal occlusion site (ICA/ICA-T)	3.2	(2.0–5.1)	<0.001	2.2	(1.3–3.5)	0.002
Collateral score (per point lower)	2.8	(2.1–3.8)	<0.001	2.5	(1.8–3.4)	<0.001
Onset to groin puncture (per 60 min longer)	1.3	(1.1–1.5)	0.010	1.3	(1.1–1.6)	0.015
Unsuccessful reperfusion (eTICI 2B-3)	1.9	(1.2–3.0)	0.006	1.8	(1.1–2.9)	0.017

OR: odds ratio; CI: confidence interval; cOR: crude odds ratio; aOR: adjusted odds ratio; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: alberta stroke program early CT score; ICA: internal carotid artery; ICA-T: internal carotid artery terminus; eTICI: expanded Treatment In Cerebral Ischemia.

Figure 2. Receiver operated characteristic curve for the prediction of space occupying edema by the combined predictors (age, NIHSS baseline, ICA/ICA-T occlusion, ASPECTS baseline score, collateral score, time from onset to groin puncture, and TICI 2B-3). The area under the curve is 0.83 (95% CI: 0.79–0.88).



include the following predictors: younger age, higher NIHSS, larger parenchymal hypoattenuation on CT (aka lower ASPECTS), and lack off revascularization.[30] Most of the earlier prediction models are based on relatively small numbers of patients.[22,33] Shimoyama et al. used magnetic resonance imaging (MRI) to assess ASPECTS, which is thought to be more accurate than using CT.[23] This was reflected in the observed c-statistic of 0.88. However, MRI is not routinely conducted in stroke care in most centers and therefore generalizability to other centers seems limited. The EDEMA score, consisting of basal cistern effacement, serum glucose, no tPA or thrombectomy, midline shift, and prior stroke, showed an acceptable predictive value, which improved by adding the baseline NIHSS score (c-statistic 0.76).[33] Other than previous reports, we only included patients who received EVT. In this well-defined subgroup, our final prediction model was superior to most of the previously developed models, which makes it a promising prediction tool for future use.

Implications

Our prediction model shows good discrimination between patients who will develop malignant infarction after EVT and those who do not, using easily retrievable parameters. The results from this study are generalizable for patients with an occlusion in the anterior circulation who received EVT. For reliable derivation of predictive values for individual patient outcomes, the model needs validation, preferably in an external cohort.

Strengths and limitations

One of the strengths of this study is the prospective registry design, minimizing concern of several sorts of bias. Furthermore, a large group of patients was analyzed and by using multiple imputation, we prevented bias caused by missing data.

The most important limitation of our study is the identification of patients with malignant infarction, which was done retrospectively. With our current definition of malignant infarction, and with the screening of discharge letters from selected patients, we are confident to have reached a high specificity for the final diagnosis of (severe) malignant infarction. Since we wanted to reduce the risk of ''missing'' patients with malignant infarction who died at day 6 or 7, we chose to select patients who died within seven days. We also aimed to reduce the risk of misclassifying malignant infarction in case of death by other causes. For that reason, we limited ourselves to the first seven days after symptom onset. We may however have misclassified patients that survived malignant infarction without hemicraniectomy, leading to an underestimation of the incidence. Additionally, 43 patients were excluded from our analysis, because the cause of death was unclear.

Conclusion

Younger age, higher baseline NIHSS, proximal occlusion, lower ASPECTS, poor collateral status, longer time from onset to groin puncture, and unsuccessful reperfusion are independent predictors of malignant infarction in patients who had anterior circulation occlusions and received EVT. A prediction model combining these easily retrievable parameters shows good discrimination between patients who develop malignant infarction and those who do not.

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Data availability statement

Descriptive data that support the findings of this study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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