RESEARCH ARTICLE

Prediction of poor clinical outcome in vascular cognitive impairment: TRACE-VCI study

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Abstract

Introduction: Prognostication in memory clinic patients with vascular brain injury (eg possible vascular cognitive impairment [VCI]) is often uncertain. We created a risk score to predict poor clinical outcome.

Methods: Using data from two longitudinal cohorts of memory clinic patients with vascular brain injury without advanced dementia, we created (n = 707) and validated (n = 235) the risk score. Poor clinical outcome was defined as substantial cognitive decline (change of Clinical Dementia Rating ≥1 or institutionalization) or major vascular events or death. Twenty-four candidate predictors were evaluated using Cox proportional hazard models.

Results: Age, clinical syndrome diagnosis, Disability Assessment for Dementia, Neuropsychiatric Inventory, and medial temporal lobe atrophy most strongly predicted poor outcome and constituted the risk score (C-statistic 0.71; validation cohort 0.78). Of note, none of the vascular predictors were retained in this model. The 2-year risk

of poor outcome was 6.5% for the lowest (0-5) and 55.4% for the highest sum scores (10-13).

Discussion: This is the first, validated, prediction score for 2-year clinical outcome of patients with possible VCI.

KEYWORDS

cognitive decline, death, major vascular event, memory clinic, poor clinical outcome, prediction score, prognosis, vascular cognitive impairment

1 | BACKGROUND

Patients presenting at a memory clinic with vascular cognitive impairment (VCI) encompass a heterogeneous population in terms of cognitive profile and severity of deficits, vascular brain injury, and co-occurring neurodegenerative pathology.[1] This diversity also translates into differences in prognosis between patients, making it difficult to provide patients with appropriate information.

Clinical outcome in patients with VCI is multifaceted, as patients with VCI may experience further cognitive decline, but also progressive vascular morbidity, mortality, and general deterioration of function. The prognosis of patients with VCI in a community- and institution-dwelling study population has previously been evaluated by the Canadian Study of Health and Aging, showing that rates of institutionalization and mortality for those with VCI were substantially higher than for people without cognitive impairment, with mortality rates similar to those of patients with Alzheimer's disease.[2,3] Factors influencing cognitive decline in patients with VCI have been studied more intensively, but not in a memory clinic setting.[4-7]

Heterogeneity and uncertainty about outcome in VCI also provide challenges for clinical trials, in which large interindividual differences in the rate of cognitive decline can obscure treatment effects. This may have contributed to the lack of success in previous trials in this field.[7-9] In this search for possible interventions, it is important to enrich trial populations with high-risk patients. Also, prognosis is not only relevant from a trials perspective, but also for the individual patient with VCI. However, individual risk scores to identify VCI patients at risk for poor clinical outcome are still lacking.

Therefore, this study aimed to create and externally validate a risk score to predict poor clinical outcome in the 2 years from the initial visit at a memory clinic in memory clinic patients with vascular brain injury. The risk score should be easily implementable in clinical practice.

2 | METHODS

2.1 | Study population

The longitudinal cohort of the TRACE-VCI study population was used for the development of the risk score. Memory clinic patients with vascular brain injury without advanced dementia (Mini-Mental State Examination [MMSE] score of ≥20 and/or a Clinical Dementia Rating [CDR] of ≤ 1 at baseline visit) were eligible (n = 707). The rationale and design of the TRACE-VCI study has been published previously.[10] In short, all patients had to have cognitive complaints for which they were referred to the clinic and evidence of vascular brain injury on magnetic resonance imaging (MRI), operationalized as the presence of at least one of the following: (1) mild deep white matter hyperintensities (WMH; Fazekas scale grade 1[11]) and an increased vascular risk defined as presence of ≥2 vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, current smoking, or a reported history of a vascular event other than stroke, based on medical history, medication use, and/or measurements[10]), (2) moderate to severe deep WMH (Fazekas scale grade ≥ 2), (3) ≥ 1 lacune of presumed vascular origin (from here on lacune(s)), (4) ≥ 1 non-lacunar (large vessel) infarct(s), (5) ≥ 1 cerebral microbleed(s), (6) ≥ 1 intracerebral hemorrhage(s) (ICH) /macrobleed(s). Patients were not primarily selected for inclusion in the TRACE-VCI cohort based on specific clinical diagnoses. The presence of co-occurring conditions, in addition to vascular injury, such as neurodegenerative pathology or depression, was accepted, in line with earlier proposed VCI criteria.[5] Patients with a presumed primary etiology other than vascular brain injury or neurodegeneration (eg, brain tumors, hydrocephalus, or excessive alcohol consumption) were excluded.

Each patient underwent a standardized extensive 1-day memory clinic evaluation including an interview, physical and (cognitive) neurological examination, laboratory testing, neuropsychological testing, and MRI scan of the brain. Lumbar puncture was performed in a subset of the study population.[10] The study was approved by the institutional review board of the VU Medical Center (VUMC) and the University Medical Center Utrecht (UMCU). All patients provided informed consent prior to research-related procedures.

2.2 | Cognitive and psychological assessment

We used the Dutch version of the MMSE (maximum score of 30) as a cognitive screening test.[12] Level of education was evaluated by years of completed education. The severity of cognitive impairment was assessed using the CDR (0-3) global score.[13]

Neuropsychiatric and behavioral symptoms were evaluated by the 15-item Geriatric Depression Scale (GDS)[14] and the Neuropsychiatric

Inventory (NPI; maximum score of 144).[15] The Disability Assessment for Dementia (DAD; maximum score of 100) questionnaire investigated functional decline.[16] The NPI and DAD were collected through the use of a proxy respondent. All participants underwent an extensive neuropsychological examination, with some variation between centers and over time.[9] These test results were used by the final conclusion regarding clinical syndrome diagnosis (no objective cognitive impairment, mild cognitive impairment [MCI], dementia). Patients were diagnosed with dementia if there was a clear decline in cognitive function defined as a deficit in ≥ 2 cognitive domains at neuropsychological testing and interference in daily living.[1] MCI was diagnosed in patients with complaints of deterioration in cognitive function with objective evidence of impairment in at least one cognitive domain and normal or only mildly impaired instrumental activities of daily living. Finally, no objective cognitive impairment was defined as having cognitive complaints, but no objective cognitive impairment on neuropsychological testing.

2.3 | MRI assessment

Details on MRI scanners and scan protocol were described previously.[10] Medial temporal lobe atrophy (MTA) was visually rated (possible range of scores for each site, 0-4) on reconstructions of the 3D T1-weighted images.[17] WMH were rated using the Fazekas scale (deep WMH grade 0-3) on fluid-attenuated inversion recovery (FLAIR) images.[11] Non-lacunar infarct(s) and lacune(s), microbleed(s) and intracerebral hemorrhage(s)/macrobleed(s) were all rated in line with the STRIVE (standards for reporting vascular changes on neuroimaging) criteria.[18] Ratings were performed by or under the supervision of a neuroradiologist.

2.4 | Laboratory testing

Cerebrospinal fluid (CSF) concentrations of amyloid beta$_{42}$ (Aβ_{42}), tau, and/or total tau phosphorylated at threonine 181 (p-tau) were measured at the neurochemistry laboratory at the Department of Clinical Chemistry of the Amsterdam UMC.[19] Patients with a ratio of total tau/Aβ_{42} > 0.52 were diagnosed as having a positive CSF biomarker Alzheimer profile.[20] Apolipoprotein E (APOE) genotyping was performed using a QIAxcel DNA Fast Analysis kit (Qiagen, Venlo, the Netherlands). Subjects were classified as APOE e4 carriers if they had one (heterozygous) or two (homozygous) e4 alleles and as noncarriers if they had no e4 alleles.

2.5 | Follow-up assessment

Follow-up data were collected during a visit at the outpatient clinic approximately 2 years from baseline visit. At the baseline visit, the doctor and patient decided if a follow-up visit at the clinic was necessary and in the best interest of the patient. All patients who did not attend the outpatient clinic after ≈2 years were contacted by phone and a close relative or friend was also contacted to complement information.

RESEARCH IN CONTEXT

1. Systematic review: We found no existing prognostic scores for memory clinic patients with possible vascular cognitive impairment (VCI). Existing risk scores for other groups of memory clinic patients focus on cognitive decline or institutionalization and not on cardiovascular events or death, which is also relevant in the context of VCI.

2. Interpretation: We report the first risk score for 2-year clinical outcome of patients with possible VCI at a memory clinic. The risk score showed a good discriminative ability (c-statistic of 0.71) for a clinically relevant outcome.

3. Future directions: This risk score could facilitate the selection of high-risk patients for early intervention studies or to enrich trial populations. Clinicians can use the score to guide their decisions in terms of clinical attention and more individually based prognostic information.

If patients were unreachable or gave no permission to contact them personally in the future, the general practitioner or doctor of the nursing home was contacted if permitted by available informed consent. Of note, the TRACE-VCI study design did not impose specific guidance for treatment of vascular risk factors. This was left to the discretion of the treating physicians.

2.6 | Outcome measures

Poor clinical outcome was defined as a composite of (1) substantial cognitive decline, (2) occurrence of a major cardiovascular event (MACE), (3) death, and/or (4) institutionalization due to other reasons than cognitive decline. Substantial cognitive decline was defined as a change in CDR of ≥ 1 and/or institutionalization due to cognitive dysfunction during the follow-up period, compared to baseline visit at the outpatient clinic. Occurrence of a MACE during follow-up was defined as a fatal or non-fatal myocardial infarct (excluding silent myocardial infarct) and/or stroke (not considering transient ischemic attack [TIA]).[21]

2.7 | Statistical analysis

Selection of predictors for the final risk score was done in three sequential steps.

Step 1: Twenty-four candidate predictors were identified based on the literature and expert opinion, including demographics, cognitive and psychological assessments, vascular risk factors, forms of vascular brain injury, severity of cognitive impairment, clinical diagnosis, CSF biomarker analysis, MTA score, and APOE genotyping. First missing
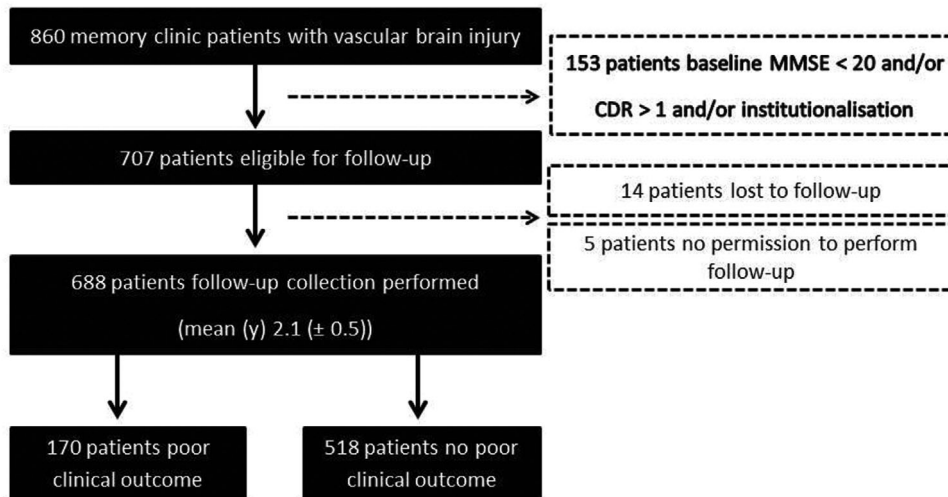
FIGURE 1 Flowchart of patients eligible for follow-up and primary outcome measures. MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating

values were analyzed with the missing completely at random (MCAR) test in parameters with missing data in >5% of the study population. Imputation was used for variables with at random missing data. Next the candidate predictors were evaluated against two main criteria: (1) present in at least 5% of the poor outcome group and (2) significantly associated with 2-year risk of poor clinical outcome in Cox proportional hazard models, adjusting for age, sex, and education. Step 2: Eligible candidate predictors were also examined in multivariable models of groups of related predictors (eg, CDR, MMSE, and clinical syndrome diagnosis), to select the strongest independent predictor. Step 3: The remaining candidate predictors were evaluated in multivariable Cox proportional hazard models and the predictive ability was analyzed.

Discrimination was used to assess the predictive accuracy of the models. Discrimination refers to the model's ability to distinguish between individuals with and without a poor clinical outcome after 2 years, and was assessed by using Harrell's c-statistics. The risk score was created by substitution of the β coefficients of the final prediction model with points. The β coefficient of 10 years of age (continuous variable) was used as a reference standard and assigned 2 points. In other words, all predictors with a (rounded) β coefficient that was the equivalent of 5 years of aging qualified for inclusion in the final model.

Kaplan-Meier estimates were used to calculate the actual 2-year poor clinical outcome risk per sum score. Additionally, the mean time to incident poor clinical outcome per sum score was estimated. A Cox proportional hazard model with the sum score as the only variable was fitted to compare the increase in risk by each level of the sum score.

All analyses were done with the use of SPSS (version 21; SPSS, Chicago, IL, USA), and associations were judged to be significant at the 0.05 level.

2.8 | External validation

For external validation, we used a cohort of 214 patients from the ongoing Singapore Harmonization project. The same inclusion criteria were used as for the development cohort. There were two minor differences. First, obesity was defined as a body mass index (BMI) of 27.5 kg/m^2 or higher, because Asians have a higher percentage of body fat.[22] Second, instead of the mean left/right MTA, only the most severe MTA score was available and used in the evaluation of the prediction score in this validation cohort. Outcome at 2 years was defined in the same way as for the development cohort.

3 | RESULTS

3.1 | Characteristics of the study population

Of the 707 eligible patients, 14 patients were lost to follow-up and 5 patients withdrew permission to perform follow-up (Figure 1 . Hence, follow-up was obtained from 97.3% of eligible patients, with a mean follow-up time of 2.1 (standard deviation [SD] 0.5) years. More information on all collected parameters is presented in Table S1 in supporting information. Poor clinical outcome occurred in 170 (25%) patients (Figure 2a with the following first event: 64 (38% of first events) had a change in CDR of $\geq$ 1, 36 (21%) were institutionalized due to cognitive decline, 37 (22%) died, 20 (12%) had a MACE, and 13 (8%) patients were institutionalized due toother reasons. Mean time to the first event was 1.7 (SD 0.7) years. Some patients had multiple events, the total number of events was 212; this distribution is shown in Figure 2b.
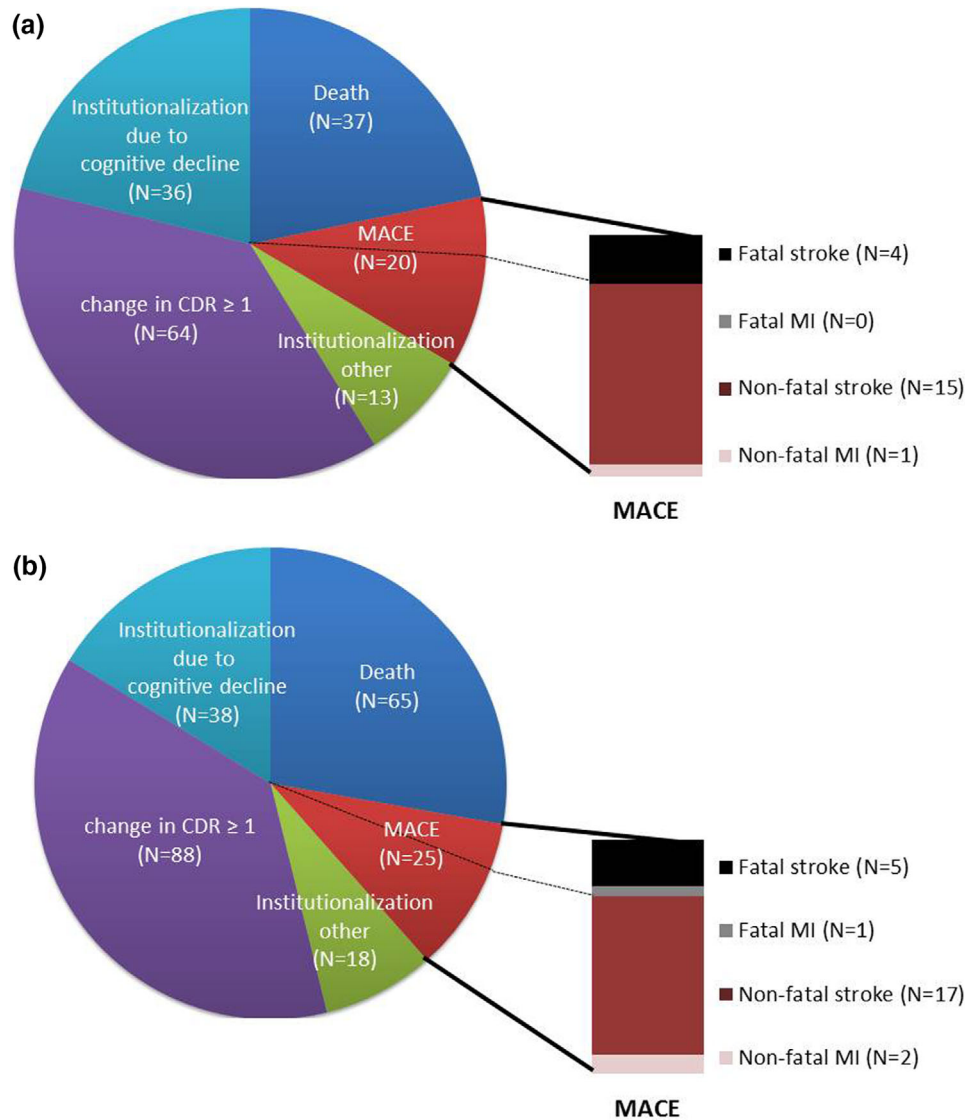
FIGURE 2 2a, TRACE-VCI patients with poor clinical outcome (n = 170), first events. 2b, TRACE-VCI patients with poor clinical outcome, total events (including first events + events after first event but within 2 years of follow-up [n = 212]) in terms of cognitive decline, major cardiovascular event (MACE), death, and institutionalization due to other reasons (n = 212)

3.2 | Prediction model

Table 1 shows the baseline characteristics of all patients and the subgroups with and without poor clinical outcome. Candidate predictors with missing data in >5% of the study population were analyzed and included DAD, NPI scores, and the collection of CSF biomarkers. There was a significant Little's MCAR test. However, further evaluation showed that the DAD and NPI scores were both missing if a proxy-respondent was not available. This was mostly the case if a patient was diagnosed with no objective cognitive impairment. For instance, 58% of patients with a missing NPI score showed no objective cognitive impairment compared to 21% of patients with no missing NPI scores (P value = .00). There was no difference in demographics and cognitive impairment between patients with and without CSF biomarker analysis. However, the CSF biomarkers were not

missing not at random, due to different criteria for collection of CSF between centers.

Of the initial 24 candidate predictors, seven were significantly different (adjusted for age, sex, and education) between patients with and without poor clinical outcome. Three of the seven predictors were interrelated (CDR, MMSE, and clinical syndrome diagnosis [ie, no objective cognitive impairment, MCI, and dementia]). We therefore explored these three candidate predictors together in multivariable models. The strongest independent predictor was clinical syndrome diagnosis, which was selected for the final model. As a result, the final multivariable model included the following five variables: age, DAD, NPI, clinical syndrome diagnosis, and MTA score. The final multivariate model included 539 patients with 141 first events because of missing values in any of the predictors in 149 patients. Table 2 shows the β coefficients, hazard ratios, and 95% confidence intervals. The c-statistic for

TABLE 1 Baseline characteristics

	Total (n = 688)	Poor clinical outcome (n = 170)	No poor clinical outcome (n = 518)	Adjusted HR (95%CI)[b]
Demographics				
Age (years)	67.8 ± 8.6	71.6 ± 8.4	66.6 ± 8.3	
<60	127 (18)	13 (8)	114 (22)	ref
60-69	281 (41)	59 (35)	222 (43)	2.25 (1.23-4.11)[a]
70-79	229 (33)	69 (41)	160 (31)	3.34 (1.84-6.04)[a]
≥8	51 (7)	29 (17)	22 (4)	6.76 (3.51-13.03)[a]
Female	300 (44)	65 (38)	235 (45)	1.26 (0.92-1.71)
Education[c]	684 (99)	170 (100)	514 (99)	
0-6	29 (4)	9 (5)	20 (4)	Ref
7-9	205 (30)	50 (29)	155 (30)	1.02 (0.50-2.06)
>9	450 (66)	111 (65)	339 (66)	0.83 (0.42-1.63)
Follow-up duration (years)	2.1 ± 0.5	2.0 ± 0.6	2.1 ± 0.4	
Cognitive and psychological assessment at baseline visit				
CDR score	0.5 [0.5-0.5]	0.5 [0.5-1.0]	0.5 [0.0-0.5]	
0	155 (23)	16 (9)	139 (27)	ref
0.5	370 (54)	75 (44)	295 (57)	1.92 (1.11-3.32)[a]
1	163 (24)	79 (46)	84 (16)	4.41 (2.53-7.70)[a]
DAD, median [IQR]	92 [78-100]	85 [69.-95]	94 [82-100]	
Number available	584 (85)	152 (89)	432 (84)	
51-100	547 (94)	137 (90)	410 (95)	ref
≤50	37 (6)	15 (10)	22 (5)	1.88 (1.09-3.24)[a]
MMSE, median [IQR]	26 [24-28]	25 [23-27]	27 [24-29]	
Number available	683 (99)	167 (98)	516 (100)	
26-30	403 (59)	71 (43)	332 (64)	Ref
20-25	280 (41)	96 (57)	184 (36)	1.87 (1.36-2.57)[a]
GDS, median [IQR]	3 [2-5]	2 [1-5]	3 [2-5]	
Number available	656 (95)	158 (93)	498 (96)	
0-5	504 (77)	126 (80)	378 (76)	ref
≥6	152 (23)	32 (20)	120 (24)	1.06 (.71-1.57)
NPI, median [IQR]	9 [3-19]	12 [5-21]	8 [3-18]	
Number available	578 (84)	151 (89)	427 (82)	
0-10	315 (54)	66 (44)	249 (58)	ref
≥11	263 (46)	85 (56)	178 (42)	1.58 (1.14-2.18)[a]
Vascular risk factors (VRF)				
Hypertension[d]	589 (86)	153 (90)	436 (84)	1.35 (0.81-2.24)
Hypercholesterolemia[e]	315 (46)	76 (45)	239 (46)	0.95 (0.70-1.28)
Diabetes mellitus[f]	126 (18)	30 (18)	96 (19)	0.92 (0.62-1.37)
Current smoker** (n = 683)	135 (20)	30 (18)	105 (20)	0.95 (0.64-1.43)
Obesity[g] (BMI ≥ 30) (n = 680)	139 (20)	27 (16)	112 (22)	0.79 (0.52-1.21)

(Continues)

TABLE 1 (Continued)

	Total (n = 688)	Poor clinical outcome (n = 170)	No poor clinical outcome (n = 518)	Adjusted HR (95%CI)[b]
History vascular events				
Reported stroke	68 (10)	12 (7)	56 (11)	0.87 (0.48-1.57)
Others[h]	68 (10)	21 (12)	47 (9)	
Number of VRF([d e f ** g h]),				
median (IQR)	2 [1-3]	2 [1-3]	2 [1-3]	1.01 (0.88-1.16)
MRI characteristics: vascular brain injury and MTA score				
WMH				
None	57 (8)	11 (6)	46 (9)	ref
Mild	319 (46)	64 (38)	255 (49)	0.94 (0.49-1.80)
Moderate/severe	312 (45)	95 (56)	217 (42)	1.13 (0.59-2.17)
Lacune(s)	155 (23)	43 (25)	112 (22)	1.08 (0.76-1.52)
Non-lacunar infarct(s)	80 (12)	23 (14)	57 (11)	1.15 (0.74-1.79)
Microbleed(s) (n = 679)	291 (42)	70 (41)	221 (43)	1.02 (0.75-1.40)
Lobar	185	47	138	
Deep	46	12	34	
Mixed (lobar/deep)	60	11	49	
Number ≥5	65	19	46	1.17 (0.72-1.89)
Macrobleed(s)	14 (2)	2 (1)	12 (2)	0.83 (0.21-3.36)
Multiple forms of vascular				
brain injury	287 (42)	76 (45)	211 (41)	1.05 (0.88-1.27)
MTA score (n = 677)	1.0 ±88	1.6 ± 90	0.88 ± 81	
Number available	677 (98)	167 (98)	510 (98	
<1.5	432 (64)	69 (41)	363 (71)	ref
≥1.5	245 (36)	98 (59)	147 (29)	2.16 (1.53-3.06)[a]
Severity of cognitive impairment and clinical diagnosis				
no objective cognitive impairment	189 (27)	11 (6)	178 (34)	ref
MCI	204 (30)	30 (18)	174 (34)	2.66 (1.32-5.37)[a]
Dementia	295 (43)	129 (76)	166 (32)	7.25 (3.85-13.7)[a]
Vascular	30 (10)	8 (6)	22 (13)	
Neurodegenerative	248 (84)	112 (87)	136 (82)	
AD	185 (75)	85 (76)	100 (74)	
FTD	21 (8)	9 (8)	12 (9)	
DLB	15 (6)	5 (4)	10 (7)	
Others[i]	27 (11)	13 (12)	14 (10)	
Unknown etiology[j]	17 (6)	9 (7)	8 (5)	
CSF biomarker analysis[k]	419 (61)	97 (57)	322 (62)	
Positive biomarker Alzheimer profile[l]	202 (48)	58 (60)	144 (45)	1.40 (0.92-2.13)
APOE genotyping[m]	573 (83)	146 (86)	427 (82)	
e4 noncarrier	284 (50)	69 (47)	215 (50)	ref

(Continues)

TABLE 1   (Continued)

	Total (n = 688)	Poor clinical outcome (n = 170)	No poor clinical outcome (n = 518)	Adjusted HR (95%CI)[b]
e4 heterozygous	230 (40)	57 (39)	173 (41)	1.07 (0.75-1.52)
e4 homozygous	59 (10)	20 (14)	39 (9)	1.42 (0.86-2.35)

Data are presented as mean ± standard deviation, median [interquartile range] or number (%).Abbreviations: AD, Alzheimer's disease; BMI, body mass index; CDR: Clinical Dementia Rating scale; CSF, cerebrospinal fluid; DAD, Disability Assessment for Dementia; DLB, Lewy body dementia; FTD, frontotemporal dementia; GDS, geriatric depression scale; IQR, interquartile range; MACE, major cardiovascular event; MCI, mild cognitive impairment; MI, myocardial infarct; MMSE, Mini-Mental State Examination; MTA, medial temporal atrophy; NPI, Neuropsychiatric Inventory; VRF, vascular risk factors; WMH, white matter hyperintensities.

[a]P-values of < .05, adjusted for age, sex, and education.

[b]The hazard ratio was adjusted for age, sex, and education.

[c]Education in years.

[d]Determined based on a self-reported medical history, use of antihypertensive drugs, or a newly diagnosed hypertension (> 140/90 mmHg).[38]

[e]Hypercholesterolemia was determined based on medical history or medication use.

[f]Diabetes mellitus was based on medical history, medication use, or dysglycemia (non-fasting glucose of $\geq$ 11.1 mmol/L or an HbA1c $\geq$ 48 mmol/mol [or $\geq$ 6.5%]).[38]

[g]Obesity was defined as a baseline body mass index (BMI) $\geq$ 30, calculated as weight in kilograms divided by height in meters squared.

[h]A vascular event other than stroke was defined as a history of ischemic heart disease (myocardial infarction, surgery, or endovascular treatment for coronary artery disease), peripheral arterial disease (any arterial occlusion or surgical intervention of a peripheral artery such as an abdominal or leg artery), or carotid artery intervention (stenting or endarterectomy).

[i]Such as primary progressive aphasia, cortical basal syndrome, and progressive supranuclear palsy.

[j]Dementia of unknown origin, further examination needed to state diagnosis.

[k]CSF biomarker analysis was performed in 419 (61%) patients.

[l]Defined as a ratio tau/Aβ_{42} > 0.52.

[m]APOE genotyping was performed in 573 (83%) patients.

TABLE 2   Multivariable model of poor clinic outcome risk score

N = 539 patients (141 first events)[a]	N (total)	N (events)	β	HR (95% CI)	Risk-score
Age (years)					
< 60	85	10	0	1	0
60-69	224	51	0.37	1.45 (0.73-2.88)	1
70-79	185	55	0.52	1.68 (0.84-3.34)	2
≥80	45	25	1.02	2.77 (1.29-5.98)	4
DAD percentage					
51-100	504	127	0	1	0
≤50	35	14	0.20	1.22 (0.68-2.19)	1
NPI score					
0-10	288	62	0	1	0
≥11	251	79	.23	1.25 (0.88-1.78)	1
Cognitive impairment					
No objective cognitive impairment	117	6	0	1	0
MCI	168	25	0.98	2.67 (1.08-6.58)	3
Dementia	254	110	1.85	6.34 (2.71-14.82)	6
MTA score					
< 1.5	332	61	0	1	0
≥1.5	207	80	0.29	1.33 (0.92-1.93)	1

Abbreviations: β, beta coefficient from Cox proportional hazard models; CI, confidence interval; DAD, disability assessment for dementia; HR, hazard ratio; MCI, mild cognitive impairment; MTA, medial temporal atrophy; NPI, neuropsychiatric inventory.

[a]The total study population includes 688 patients of whom 170 patients had poor clinical outcome. The multivariate model presented in the table concerns only 539 patients with 141 first events because patients with missing values on any of the predictors dropped out of the model.

TABLE 3 Risk of poor clinical outcome by each level of risk score

Sum score	Number at risk[a]	Poor clinical outcome[b]	Hazard ratio[c]	Mean time to event	Observed 2-year risk[d]		Incidence rate			
	N (%)	N (%)	Nature first event	HR (95%CI)	Mean y (± SD)	%	Per 1000			
			A	B	C	D				Persons-years
Overall	539 (%)	141 (%)	83	17	31	10				
0-5	214 (40)	14 (10)	4	4	6	0	Ref	1.7 (± 0.7)	6.5	31.4
6	50 (9)	9 (6)	3	3	3	0	2.9 (1.3-6.7)	1.7 (± 0.7)	18	88.8
7	51 (9)	14 (10)	7	1	6	0	4.6 (2.2-9.7)	1.7 (± 0.6)	27.5	140.4
8	81 (15)	32 (23)	22	2	6	2	6.7 (3.6-12.6)	1.9 (± 0.5)	39.5	195.7
9	78 (14)	36 (26)	23	6	4	3	7.9 (4.3-14.7)	1.6 (± 0.7)	46.2	248.6
≥10	65 (12)	36 (26)	24	1	6	5	8.6 (4.6-15.9)	1.7 (± 0.7)	55.4	285.3

Abbreviations: CI, confidence interval; DAD, Disability Assessment for Dementia; HR, hazard ratio; MTA, medial temporal atrophy; NPI, Neuropsychiatric Inventory; SD, standard deviation.

Notes: The nature of the first event that was observed is indicated: A = substantial cognitive decline, B = MACE (major cardiovascular event), C = death, D = institutionalization due to other reasons

[a]Number at risk: number of subjects within each sum score group, with percentage of the total cohort in parentheses.

[b]Number of subjects with poor clinical outcome (only included if all data of the included parameters (age, DAD, NPI, cognitive impairment, MTA score) were available) in this sum score group: the percentage is the proportion of persons with poor clinical outcome in that particular sum group.

[c] From Cox proportional hazard models.

[d]Based on Kaplan-Meier estimates.

FIGURE 3 Summary of poor clinical outcome risk score

age alone was 0.62 (N = 688). The c-statistic for the final multivariate model was 0.71. In post hoc analysis only including patients with no objective cognitive impairment and MCI (n = 284), poor clinical outcome was predicted with a similar c-statistic of 0.71. The same c-statistic was found in the evaluation of only the outcome substantial cognitive (n = 104) decline instead of total poor clinical outcome.

Table 3 shows the risk of poor clinical outcome, according to each sum score. Sum scores lower than 5 (0-5) and ≥10 (10-13) were fairly rare and were collapsed into one category for the Kaplan-Meier-estimated dementia risk and Cox proportional hazard model. The c-statistic of this point model was the same as the final multivariate model. There was a nine times difference in poor clinical out-

come risk between the lowest sum scores (0-5) (associated Kaplan-Meier estimate 6.5%) and the highest sum scores of ≥10 (associated Kaplan-Meier estimate 55.4%; Table 3 . Figure 3 shows the final risk score model.

The external validation cohort consisted of 214 patients (see flowchart in Figure S1 in supporting information) with average age of 71 (SD 8.3) years. Poor clinical outcome occurred in 31 (14.5%) patients, during a mean follow-up in the total study population of 1.9 (SD 0.4) years. There were several differences in baseline characteristics compared to the development cohort. Patients were older, showed lower GDS and NPI scores, and higher rates of hypercholesterolemia and diabetes mellitus. MRI less commonly showed

microbleed(s), but lacune(s) were more common and the burden of WMH was higher (Table S2 in supporting information). In this validation cohort, the c-statistic for the final risk score was 0.78. In this model, 22 cases dropped out due to missing values of predictors. Hence, the model included 192 patients of whom 27 patients had poor clinical outcome. The risk of poor clinical outcome is reported for each sum score in Table S3 in supporting information. Because of small numbers in the lowest and highest sum score groups, the lowest sum scores were merged into one category of 0 until 7 and the highest sum scores were merged into one category of 10 or higher. In the validation cohort there was six times difference in poor clinical outcome risk between the lowest sum score (0-7; associated Kaplan-Meier estimate 6.4%) and the highest sum score of 10 or higher (associated Kaplan-Meier estimate 37.9%; Table S3).

4 | DISCUSSION

The risk score we developed predicts the 2-year risk of poor clinical outcome in memory clinic patients with vascular brain injury. The score is based on age, DAD percentage, NPI score, clinical syndrome diagnosis, and MTA score. The prediction model stratifies individuals into six categories and showed a nine times difference in risk of poor clinical outcome between the lowest and highest sum scores. Validation of the prediction score in an independent cohort showed comparable predictive ability.

Previously published prediction models for use in memory clinic settings primarily aimed to predict progression from MCI to dementia (c-statistic 0.74 to 0.80).[23] These models exclude patients with no objective cognitive impairment and only evaluated cognitive decline. Our risk score also predicts cognitive decline as an outcome (c-statistic 0.71), but has a similar predictive accuracy for institutionalization, major cardiovascular event(s), and death. These are all relevant outcomes for patients with possible VCI. We are not aware of reported (predictive abilities of) risk scores for memory clinic patients to predict these other outcomes. The predictive ability of commonly used risk scores to predict only cardiovascular disease, such as the Framingham risk score, was comparable to ours (c-statistics 0.68-0.71).[24]

The strongest predictor of poor outcome was older age. This is in line with the current body of literature, showing that age is the most well-known risk factor for dementia,[25] also at a memory clinic.[23] In addition, higher age is also related to higher risk of institutionalization and death.[26] Yet, the other predictors do add to the predictability; the c-statistic for age alone was 0.62 and for the risk score 0.71. These other included predictors have previously been associated with poor clinical outcome in patients with dementia. Several studies have shown that worse cognitive impairment on baseline level, greater functional impairment in daily living, and worse behavioral disturbance NPI, independently predict institutionalization in the following 2-3 years in patients with dementia.[27,28] In addition, worse behavioral disturbance NPI is a predictor of conversion from MCI to dementia.[29] Furthermore, MTA score has been shown to predict cognitive decline in memory clinic patients, also in patients with a diagnosis of vascular dementia.[30,31]

Somewhat counterintuitively, none of the vascular risk factors or manifestations of vascular brain injury were part of the final risk model. Several explanations may underlie this observation. First, by design, all subjects from the cohort had some form of vascular brain injury, because the risk score was developed for patients with possible VCI. Perhaps, among patients selected for presence of vascular brain injury, burden of vascular risk factors and lesions do not discriminate as much for clinical outcomes as they would in comparison to people without these abnormalities. Indeed, a previous study on dementia prediction in patients with reported stroke[32] also found that cognitive impairment was, but vascular risk factors and vascular co-morbidity were not, predictive of dementia. Second, although vascular injury is predictive of cognitive decline in the general population, it may be less predictive in people with a higher burden of pathologies, such as those visiting a memory clinic. Previous studies[33] have for instance shown that WMH load is a predictor of all types of dementia in the general population and in memory clinic patients with subjective memory complaints, but not in memory clinic patients with MCI.[30] The role of cardiovascular risk factors in dementia prediction may diminish with age, as is also seen for these factors in coronary heart disease prediction in the elderly.[34] Interestingly, more patients with severe WMH scores had poor clinical outcome, although this association was not statistically significant. The same was found for *APOE* e4 homozygous carriers and a positive biomarker Alzheimer's disease profile. Consequently, addition of these parameters to our prediction model did not add further predictive ability.

Our study has several strengths. The major strengths are the large and detailed cohort of memory clinic patients with possible VCI and the high percentage of follow-up performance 2 years from baseline visit. The composite primary outcome measure is robust and clinically relevant, including cognitive as well as vascular outcome measurements. Also, all five predictors of the final risk score (age, DAD percentage, NPI score, cognitive impairment, and MTA score) can readily be obtained in a memory clinic setting. The DAD and NPI are well-known and - validated questionnaires. The external validation in another cohort of VCI patients in a different geographical location corroborated the findings. The differences in distribution of the predictors in the development and validation cohort did not affect the predictive accuracy of the prediction score in the validation cohort.

There are several limitations to our study. Most importantly, there were missing values of candidate predictors, the most relevant of which were DAD score, NPI score, and CSF biomarker analysis. The DAD and NPI scores were collected through the use of a proxy respondent and were both missing if a proxy respondent was not available. This was mostly the case if a patient was diagnosed with no objective cognitive impairment. Still, 117 patients with no objective cognitive impairment were included in the final analysis. The missing CSF biomarker analysis was different by center; either it was standard for research purposes or at the discretion of the doctor and the patient. However, there was no difference in demographics and cognitive impairment between patients with and without CSF biomarker analysis. We

therefore assume that less missing values would not have resulted in the inclusion of CSF biomarker profile in the risk score. Another possible limitation of our study is the unrestricted inclusion criteria for possible VCI. We did not exclude co-occurring etiologies, such as AD. Vascular brain injury on MRI is a very common finding in memory clinic patients and uncertainty can exist about its clinical and prognostic relevance. The inclusion of mixed pathology increases the clinical applicability of the risk score. Furthermore, we did not define a minimal threshold for severity of cognitive dysfunction for inclusion in our cohort. By contrast, most diagnostic criteria for VCI state that this construct only applies to patients with MCI or dementia.[35,36] The rationale for our approach is that some patients with cognitive decline as result of vascular brain injury may not present with cognitive deficits that are severe enough to be classified as MCI.[10] The setting and design of our study likely affect the predictive ability of our model. While the model did validate well in an independent memory clinic cohort, predictive ability in other settings, such as a stroke clinic, might be different. Longer follow-up might also affect predictive ability. Finally, although vascular risk factors are generally well controlled in Dutch patients,[37] our protocol did not include standardized guidance on treatment and we did not follow-up risk factor control over time. Hence, predictive ability of the score might be different if vascular risk factors were treated more (or less) strictly in our cohort.

To the best of our knowledge, this study is the first to describe a risk score of poor clinical outcome in memory clinic patients with possible VCI, also with external validation. The prediction of poor outcome by means of a combined outcome measure of either cognitive decline, institutionalization, major cardiovascular event(s), or death, makes the risk score highly clinically relevant. The main use of a risk score is to target measures to those most at risk. Therefore, this risk score could be of great benefit in the selection of high-risk patients for early intervention studies or to enrich trial populations. Also, clinicians can use the score to guide their decisions in terms of clinical attention and more individually based prognostic information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.