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REVIEW

What predicts a poor outcome in older stroke survivors? A systematic review of the literature

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Abstract

Purpose: To identify factors in the early post-stroke period that have a predictive value for a poor outcome, defined as institutionalization or severe disability. *Methods:* MEDLINE, PSYCINFO, EMBASE and CINAHL were systematically searched for observational cohort studies in which adult and/or elderly stroke patients were assessed $\leq$1 month post-stroke and poor outcome was determined after a follow-up of $\geq$3 months. *Results:* Thirty three articles were selected from 4063 records, describing 27 independent cohort studies. There are rather consistent findings that greater age, a more severe stroke (measured through a clinical evaluation scale), the presence of urinary incontinence (with impaired awareness) and a larger stroke volume (measured through brain imaging techniques) predict poor stroke outcome. In contrast to clinical expectations, the prognostic value of ADL-dependency and impaired cognition remains unclear, and factors in the domains of emotional and communicative functioning rarely feature. Studies using a selected group of stroke patients tended to identify different predictors. *Conclusions:* The current evidence is insufficient for the development of a clinical prediction tool that is better than physicians' informal predictions. Future research should focus on the selection of optimal screening instruments in multiple domains of functioning, including the timing of assessment. We suggest developing prediction tools stratified by more homogeneous, clinically distinguished stroke subtypes.

Keywords

Elderly, outcome, predictors, stroke

History

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➤ Implications for Rehabilitation

- A reliable prognosis soon after a stroke is highly relevant to patients who ultimately have a poor outcome, because it enables early planning of care tailored to their needs.
- In view of the development of a clinical prediction tool that is better than physicians' informal predictions, future research should focus on optimal screening instruments in multiple domains of functioning, including emotional and communicative functioning.
- Clinical prediction tools stratified by more homogeneous, clinically distinguished stroke subtypes, could enable more accurate prognosis in individual stroke patients.

Introduction

Previous studies of prognostication after an acute stroke have focused mainly on the prediction of a favorable outcome. In contrast, the objective of this literature review is to identify factors in acute stroke patients that have a predictive value for a poor outcome. Poor outcome, defined here as institutionalization or severe disability, occurs frequently. Previous research with large cohorts showed that approximately 15–20% of stroke survivors in developed countries are dependent on institutional long-term care [1–3]. This proportion seems to be rather persistent at different times post-stroke, ranging from ''completed rehabilitation'' after 37 ± 41 d [3] to 5 years post-stroke [1]. A reliable prognostication soon after the stroke is highly relevant to patients with a poor outcome of this nature, their relatives and their multidisciplinary stroke teams. It enables early planning of care tailored to their needs, while unrealistic expectations may be avoided by focusing consultation on acceptance of the stroke consequences.

There were some reviews several years ago dealing with the prognosis for institutionalization after stroke rehabilitation [4–6], but they all found insufficient evidence for an evidence-based prediction of the future residence of patients with an acute stroke. Previous reviews of prognoses after strokes for the recovery of functioning [4,7,8] did not focus on severe disability as an outcome measure. They included many studies that focused on the prediction of a favorable outcome, such as independence in activities of daily living (ADL) versus lack of independence. Prediction models based on this dichotomy do not fit with clinical practice, which has more categories ranging from full recovery of functioning through partial recovery with moderate disability, to severe disability and institutionalization.

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In this literature review, we intend to identify factors in the early post-stroke period that have a predictive value for a poor outcome, defined as institutionalization or severe disability. A clinical prediction tool that is simple to use and better than physicians' informal predictions [9] would be very desirable and helpful for the management of individual patients. We therefore, focus on factors that can easily be determined in clinical practice.

Methods

Search strategy

We searched MEDLINE, PSYCINFO, EMBASE and CINAHL for articles published up to March 2011, in English, German, French, Dutch or Spanish. The search was carried out with the help of a medical information specialist, using the following terms (with synonyms and closely related words): ''stroke'', and ''prognosis'' or ''prospective studies'' or ''risk factors'', and ''chronic disease'' or ''recovery of function'' or ''convalescence'' or ''rehabilitation'' or ''treatment outcome'' or ''disability evaluation''. The full search strategy is available from the authors. We also reviewed the reference lists of the articles we selected.

Selection criteria

Study design

We searched for observational cohort studies, both prospective and retrospective, and both community-based and hospital-based.

The prognostic factors had to have been assessed within 1 month of stroke onset. We included both stroke patients assessed in the acute phase on stroke units in hospitals and patients discharged to rehabilitation units or other post-stroke discharge destinations.

The follow-up period had to be 3 months at least. In this follow-up period, majority of patients reach their best level in functional recovery, even patients with severe and very severe strokes [10].

Patient population

We searched for studies that included elderly patients, or a mixed population of adult and elderly patients, with an ischemic, hemorrhagic (intracerebral or subarachnoid) or unclassifiable stroke, either for the first time or recurrent. We excluded studies that included patients with a transient ischemic attack (TIA).

Outcomes

We searched for studies that used institutionalization (long-term care setting) or severe disability as an outcome measure. The Barthel Index (BI) [11], the modified Rankin Scale (mRS) [12], the Glasgow Outcome Scale (GOS) [13] and the motor component of the Functional Independence Measure (FIM) [14] are the most commonly used scales to measure disability or dependence in ADL in stroke victims. We defined severe disability according to these scales as BI <60 (using the 100-point scale) or BI <12 (when the 20-point scale is used), mRS >3 [15] or GOS $<$ IV (or GOS $>$ II when the modified version is used that places the scores in reverse order, see http://www.strokecenter.org). All relevant studies that measured post-stroke disability through the FIM used the FIM as a continuous outcome measure (i.e. without a cut-off point to define severe disability).

Analyses

We only included studies with $\geq$50 patients. Multivariable regression analyses had to have been used to identify independent prognostic factors, with effects given by point estimates and confidence intervals (CI). These analyses are used in studies designed to develop an association or explanatory model (to explore the causality of the association between one central determinant and the outcome variable, corrected for confounding and effect modification), as well as in studies designed to develop a prediction model (to search for a combination of factors that are associated as strongly as possible with the outcome variable, often using stepwise regression analyses) [16].

Review procedure

All articles were reviewed by two reviewers independently (SA, MS). The first step in the selection was based on the title, the second on the abstract and the third on the full text, according to the selection criteria. Methodological aspects of the selected studies that were not defined in the selection criteria – such as the risk of bias in selection, selective loss-to-follow-up, the presence of important predictors in the study design and the external validity of the study results – were evaluated by two reviewers independently (SA, MS/MD) using the Dutch Cochrane Centre's assessment form for evaluating scientific publications. Disagreements were resolved in a consensus meeting.

The identified prognostic factors in the selected studies were categorized into patient characteristics, stroke characteristics, biological measures and clinical functioning measures. If a study presented a statistical model for a *favorable* outcome, the inverse of the point estimates and 95% CIs were taken to get the values for a *poor* outcome. We were not able to provide pooled estimates because there was much variation in patient populations, the variables assessed and the measurement instruments used. To summarize the findings for each variable, we assessed the number of independent studies that identified it as a prognostic factor (a), in relation to the number of independent studies that investigated the variable but found it *not* to have a predictive value (b). This proportion will be presented as a:b.

Results

The electronic search strategy resulted in 3971 titles (after removing duplicates) from which we selected 28 studies. A review of the reference lists in these selected articles resulted in 92 titles, from which we selected another five articles. The reasons for exclusion in the selection process of the 4063 records are presented in Figure 1. The final selection of 33 articles described 27 independent cohort studies, of which 15 studies involved ischemic strokes (IS) [17–35], one study hemorrhagic strokes (HS) [36] and 11 studies both IS and HS [2,37–48]. Articles that derived data of a same cohort were references [24,34] (TOAST Study), [27,32] (Northern Manhattan Study), [28,30,33] (GAIN International Trial), [39,48] (Copenhagen Stroke Study) and [40,41] (studies by Pettersen et al.). The number of patients included in the studies ranged from 60 [26] to 19 547 [2], the mean age ranged from 60.3 [23] to 83 [29] years. The participants' age was not reported in a number of studies [17,22,24,34,36].

The identified prognostic factors in the first month after stroke for a poor outcome are presented in Tables 1–4, together with point estimates and 95% CIs. The studies that investigated a variable but found it *not* to have predictive value are described in the following sections.

Prognostic factors in patient characteristics predicting a poor outcome

Greater age was identified as a prognostic factor in 12 [2,23,25,32,34–37,39/48,41,45,46]:4 [38,40,43,44] studies (i.e. age was identified as a prognostic factor in 12 independent

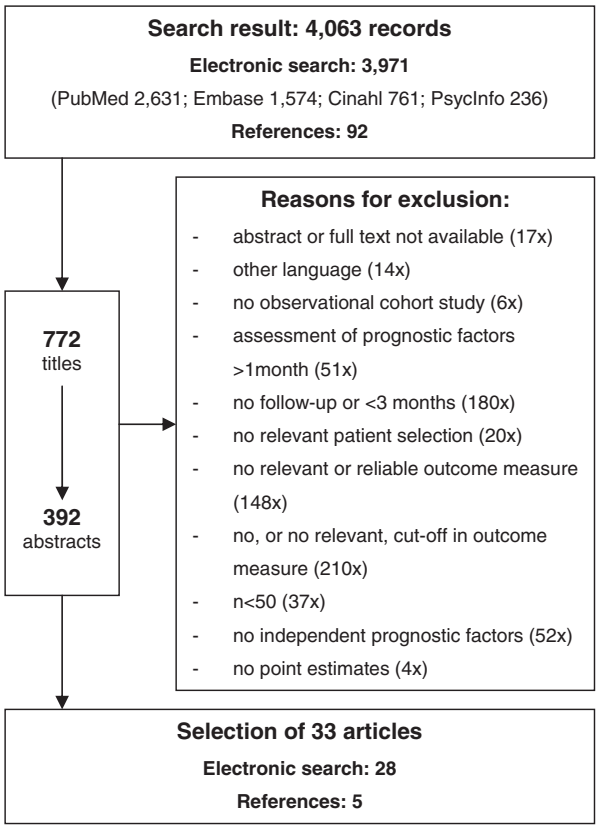

Figure 1. Reasons for exclusion in the systematic literature search.

studies and was found not to be a prognostic factor in four independent studies), both for IS and HS and in a wide range of follow-up periods (Table 1). The largest effects were found in the studies by Kammersgaard et al. [39], Glader et al. [2] and Rost et al. [36], which all assessed age as a categorical variable including very great ages ($\geq$80 or $\geq$85).

Living alone was identified as a prognostic factor in 2 [2,48]:6 [32,38,39,40/41,44,46] studies; a stronger effect was found in a selected cohort of severe stroke patients [48]. Female gender was identified as prognostic factor in 1 [2]:12 [17,32,34,36–38,39/48,40/41,43–46] and non-white race in 1 [34]:1 [32] studies. An interaction effect of insurance status and time of follow-up was found in 1 [32]:0 studies; there was an annual decline in functional status among patients with a low insurance status (i.e. no insurance or basic state insurance) in particular.

Finally, level of education (0:3 [32,44,46]) and having an occupation (0:2 [44,48]) were not identified as predictors of a poor outcome.

Prognostic factors in stroke characteristics predicting a poor outcome

A total or partial anterior circulation syndrome according to the Oxfordshire Community Stroke Project (OCSP) classification [49] was identified as a prognostic factor in 1 [40]:2 [38,41] studies (i.e. these syndromes were identified as a prognostic factor in one study but not in two other independent studies) (Table 2). Intracerebral HS, as opposed to IS, was identified as a prognostic factor in 1 [2]:6 [38,39/48,40,44–46] studies. Non-lacunar infarcts according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification in IS [50] were identified as a prognostic factor in 2 [20,34]:1 [25] studies and cardioembolic infarcts in 1 [20]:1 [46] studies, all with large effects. Adams et al. [34] also found an interaction effect of lacunar infarcts with baseline stroke severity, implying that more severe lacunar infarcts have a worse outcome than other stroke subtypes of the same severity. Intracerebral HS that is lobar in location was identified as a prognostic factor in 1 [36]:0 studies, with a large effect.

An increase in stroke volume was identified as a prognostic factor in 3 [23,25,36]:0 studies, both in IS and HS. The largest effect was found in the study by Rost et al. [36], which assessed stroke volume in (intracerebral) HS as a categorical variable. With respect to the side of the lesion, left-sided [32] and bilateral strokes [44] were both identified as a prognostic factor in 1:0 studies.

Stroke characteristics that were not identified as prognostic factors were: the presence of asymptomatic hemorrhagic transformation of infarction (0:1 [31]), a visible infarction on CT scans in lacunar stroke patients compared with those in whom no such lesion had been identified (0:1 [35]) and intraventricular hemorrhage in HS (0:1 [36]).

Prognostic factors in biological measures predicting a poor outcome

Blood pressure (BP) values in IS were identified as a prognostic factor in 4 [19,22,24,28/30]:2 [21,48] studies (i.e. BP values were identified as a prognostic factor in four independent studies but not in two other independent studies) (Table 3). Many different measurements were studied, all with a follow-up period of 3 months. Taking the first 24 h after the stroke, extremely low or high night-time BP values [19], significant falls in BP [22] and elevated baseline pulse pressure [30] were all identified as prognostic factors. A higher BP [24,28,30] or a spontaneous BP decrease [19] in the following week was also identified as prognostic factor.

With respect to comorbidity, chronic kidney disease was identified as a prognostic factor in 1 [42]:0 studies, ''other disabling diseases'' in 1 [39]:2 [38,48] studies and atrial fibrillation in 1 [39]:2 [32,48] studies. Diabetes mellitus was identified as a prognostic factor in 2 [2,17]:7 [23,25,32,36,39/48,44,45] studies; one of these two studies was restricted to first lacunar stroke patients [17]. The unexpected factor of ''never smoked'' (in a selected study population of men with anterior circulation stroke) was identified as a prognostic factor in 1 [23]:2 [32,39] studies. Other comorbidities that are known to be risk factors for strokes were not identified as prognostic factors for a poor outcome: a history of strokes (0:9 [2,23,25,34,39/48,40/41,43,44,46]), a history of hypertension (0:7 [17,23,32,36,39/48,44,45], although in some studies this variable was combined with hypertension during hospital stay), a history of heart disease (0:6 [17,32,36,39,44,45]) and a history of hypercholesterolemia (0:2 [23,32]).

With respect to other biological measures, infectious complications (pneumonia and urinary tract infection) were identified as a prognostic factor in 1 [33]:1 [43] studies, body temperature in 1 [48]:0 studies (in a selected cohort of severe stroke patients) and leukoaraiosis in 1 [17]:1 [26] studies (in a selected cohort of patients with a first lacunar stroke). Variables that were not identified as prognostic factors were serum insulin-like growth factor (0:1 [29]) and APOE genotype (0:1 [18]).

Prognostic factors in clinical functioning measures predicting a poor outcome

A more severe stroke at baseline (as an ''overall'' measure of clinical functioning) was identified as a prognostic factor in 8 [23,25,32,34,39/48,43,46,47]:0 studies (i.e. this factor was identified in all eight independent studies that assessed stroke severity), both in IS and HS (Table 4). The largest effect was

Table 1. Prognostic factors in the first post-stroke month for poor outcome: patient characteristics.

	Reference	*N*	Poor outcome	Follow up (m)	Factor category/value	OR	95% CI
Age							
IS + HS	39[a]	1197	IN+	84	≥85	3.90	2.10–7.30
	37	171	IN	12	<75 (ref) versus 75–79 versus ≥80[b]	3.13	1.45–6.67
	41	234	IN+	12	≥80	2.40	1.00–5.60
	45	752	IN	12	<65 (ref) versus 65–74 versus 75–84 versus ≥85[c]	2.00	1.40–2.80
	48[a]	84	SD	3	Per 10-year increase[d]	2.00	1.01–4.00
	46	165	IN	36	Per 1-year increase	1.08	1.03–1.15
	2	11 041	IN	3	• ≥85	ref	
					• versus 75–84	0.62	0.53–0.73
					• versus 65–74	0.36	0.29–0.44
					• versus <65	0.15	0.11–0.21
IS	25	256	SD+	3	Per 1-year increase	2.28[e]	1.22–4.28
	35	404	IN+	6	Per 10-year increase[f]	1.92	1.41–2.56
	32	525	SD	60	Per 1-year increase[c]	1.08	1.05–1.11
	34	1268	SD+	3	Per 1-year increase	1.06	1.05–1.09
	23	476	SD+	6	Per 1-year increase[g]	1.06	1.02–1.09
HS	36	418	SD+	3	≥80 (ref) versus <70[h]	0.12	0.05–0.24
Living status							
IS + HS	48	84	SD	3	Living single[d]	3.10	1.10–8.80
	2	11 041	IN	3	Living alone	2.28	2.28–3.05
Gender							
IS + HS	2	11 041	IN	3	Female	1.18	1.01–1.38
Race							
IS	34	1268	SD+	3	Non-white	1.56	1.12–2.13
Insurance status							
IS	32	525	SD	60	Time of follow-up per 1-year increase, for people with no insurance or Medicaid (United States)[c]	1.19	1.06–1.33

[a]References [39,48], Copenhagen Stroke Study.
[b]Only patients in rehabilitation departments.
[c]Only first stroke.
[d]Only patients with Scandinavian Stroke Scale <15.
[e]Only results for outcome measured with BI are presented.
[f]Only first lacunar stroke.
[g]Only men with anterior circulation stroke.
[h]Only primary intracerebral hemorrhage.
IN, institutionalization; SD, severe disability; +, including death; IS, ischemic stroke; HS, hemorrhagic stroke; OR, odds ratio; CI, confidence interval.

Table 2. Prognostic factors in the first post-stroke month for poor outcome: stroke characteristics.

	Reference	*N*	Poor outcome	Follow up (m)	Factor category/value	OR	95% CI
Stroke subtype							
IS + HS	40	222	IN+	3	Partial or total anterior (OCSP)	3.60	1.40–9.00
	2	11 041	IN	3	Intracerebral hemorrhage	1.27	1.02–1.58
IS	20	159	SD+	6	Cardioembolic infarct (TOAST)	RR 7.10	1.00–50.30
					Lacunar infarct (TOAST)	RR 0.07	0.01–0.50
					Other determined etiology (TOAST)	RR 0.07	0.01–0.50
	34	1268	SD+	3	Lacunar infarct (TOAST)	0.15	0.05–0.44
					• Interaction with baseline NIHSS	1.16	1.03–1.32
HS	36	418	SD+	3	Lobar versus infratentorial[a]	0.15	0.05–0.43
Lesion volume							
IS	25	256	SD+	3	Change from 0 to 63 cm^3 (CT scan)	2.70[b]	1.74–4.19
	23	476	SD+	6	Per 1 ml increase (DWI)[c]	1.01	1.00–1.02
HS	36	418	SD+	3	• >60 cm^2 (CT scan)[a]	ref	
					• 30–60 cm^2	0.12	0.02–0.59
					• <30 cm^2	0.02	0.00–0.09
Side of lesion							
IS + HS	44	151	IN	6	Bilateral[d]	4.44	1.45–13.6
IS	32	525	SD	60	Left-sided[e]	0.53	0.30–0.93

[a]Only primary intracerebral hemorrhage.
[b]Only results for outcome measured with BI are presented.
[c]Only men with anterior circulation stroke.
[d]Only patients in rehabilitation departments.
[e]Only first stroke.
IN, institutionalization; SD, severe disability; +, including death; IS, ischemic stroke; HS, hemorrhagic stroke; OR, odds ratio; CI, confidence interval; OCSP, Oxfordshire Community Stroke Project classification; TOAST, Trial of ORG 10172 in Acute Stroke Treatment classification; NIHSS, National Institute of Health Stroke Scale; DWI, diffusion-weighted imaging; RR, relative risk.

Table 3. Prognostic factors in the first post-stroke month for poor outcome: biological measures.

	Reference	*N*	Poor outcome	Follow up (m)	Factor category/value	OR	95% CI
Blood pressure (BP)					First 24 h:		
IS	19	403	SD+	3	Low night-time diastolic BP (≤60 mmHg)[a]	8.13	1.13–58.28
					High night-time systolic BP (≥165 mmHg)[a]	2.76	1.12–6.79
	30[b]	1455	SD+	3	Elevated pulse pressure	1.06	1.00–1.12
	22	551	SD+	3	Substantial decline in overall systolic BP (≥50 mmHg)	>1	NA
					Substantial decline in short-term systolic BP (≥30 mmHg)	>1	NA
					Following week:		
	19	403	SD+	3	First 5 d: decrease in daytime diastolic BP (≥10 mmHg)[a]	2.97	1.11–7.94
	28[b]	1455	SD+	3	First 2.5 d: substantial increase from baseline mean arterial BP (30%)	2.39	1.42–4.03
	24	1281	SD+	3	First 7 d: increase in weighted average mean arterial BP (per 10 mmHg)	1.19	1.02–1.39
	30[b]	1455	SD+	3	First 2.5 d: elevated weighted average pulse pressure	1.13	1.05–1.22
	24	1281	SD+	3	First 7 d: increase in weighted average systolic BP (per 10 mmHg)	1.12	1.02–1.23
Comorbidity							
IS + HS	42	821	IN+	12	Chronic kidney disease (eGFR 15–40)	4.6	1.6–13.2
	39	1197	IN+	84	Disabling diseases other than stroke	2.8	1.8–4.3
					Atrial fibrillation	2.2	1.20–3.80
	2	11041	IN	3	Diabetes mellitus	1.34	1.14–1.56
IS	17	333	SD+	24	Diabetes mellitus[c]	2.33	1.21–4.14
	23	476	SD+	6	Current smoker versus never smoked[d]	0.29	0.12–0.67
Complications							
IS	33	1455	SD	3	Aspiration pneumonia in first 7 d	3.8	2.20–6.70
					Urinary tract infection in first 7 d	1.9	1.20–2.90
Other							
IS + HS	48	84	SD	3	Body temperature: per 1 °C decrease[e]	0.56	0.32–0.91
IS	17	333	SD+	24	Leukoaraiosis[c]	3.02	1.95–5.75

[a]Only first stroke.
[b]References [28,30], GAIN International Trial.
[c]Only first lacunar stroke.
[d]Only men with anterior circulation stroke.
[e]Only patients with Scandinavian Stroke Scale <15.
IN, institutionalization; SD, severe disability; +, including death; IS, ischemic stroke; HS, hemorrhagic stroke; OR, odds ratio; CI, confidence interval; eGFR, estimated Glomerular Filtration Rate (Mayo Clinic).

found in the study by Dhamoon et al. [32] in which stroke severity was assessed as a categorical variable: a severe stroke gave a much greater likelihood of a poor stroke outcome than a moderate stroke. The study by Jorgensen et al. [48], which included only patients with a severe stroke on admission, still found a considerable predictive effect for stroke severity measured after one week, reflecting the amount of neurological recovery in the first post-stroke week.

Urinary incontinence (UI) was identified as a prognostic factor in 4 [32,37,40/41,45]:0 studies. The largest effect was found in the studies by Pettersen et al. [40,41], who defined this factor as UI with impaired awareness (patients with a reduced ability to be aware of bladder signals before leakage, to notice leakage when it takes place, or both) as opposed to urge UI (patients with frequent micturitions, a strong urge to urinate and subsequent leakage, and who are aware of and embarrassed about their problem).

A low level of consciousness was identified as a prognostic factor in 2 [2,36]:1 [48] studies, a high degree of dependency in basic ADLs in 4 [38,40/41,43,45]:3 [37,38,47] studies, a lower level of pre-stroke physical functioning in 3 [25,41,43]:2 [32,40] studies, impaired cognition in 3 [41,44,47]:2 [37,40] studies and pre-stroke cognitive impairment in 2 [36,46]:1 [40/41] studies. The measurement instrument used for these variables varied, with the exception of the measurement of levels of consciousness and pre-stroke cognitive impairment.

With respect to emotional functioning, an effect was found in 1 [27]:1 [47] study: an early depressed mood was identified as a prognostic factor for a poor outcome at 6 months through to 2 years after the stroke. A depressed mood before the stroke was not identified as a prognostic factor (0:1 [32]). Finally, we found no studies that identified prognostic factors in the domain of communicative functioning.

Discussion

A reliable prognostication soon after the stroke is highly relevant to patients with a poor outcome after a stroke, defined as institutionalization and/or severe disability. It enables early planning of care tailored to their needs, while unrealistic expectations may be avoided by focusing consultation on acceptance of the stroke consequences. We carried out this literature review with the aim of identifying factors in the first month after a stroke that have a predictive value for a poor outcome. The selection criteria led to a result of less than 1% of the almost 4000 titles screened. The major reason for exclusion of studies was the lack of a relevant cut-off point in the outcome measure, which emphasizes the huge gap in research focus on a poor outcome of this nature. The majority of the articles finally selected (18 out of 33) date from 2005 or later, which might indicate that the interest in this topic is hopefully growing.

Table 4. Prognostic factors in the first post-stroke month for poor outcome: clinical functioning measures.

	Reference	*N*	Poor outcome	Follow up (m)	Factor category/value	OR	95% CI
Baseline stroke severity							
IS + HS	39[a]	1197	IN+	84	SSS per 10-pt decrease	1.90	1.70–2.30
	47	141	SD	6	NIHSS[b]	1.74	1.13–2.63
	43	412	SD+	3	mNIHSS	1.16	1.07–1.25
	46	165	IN	36	Orgogozo's score per 1-pt increase	0.97	0.96–0.99
	48[a]	84	SD	3	SSS at week 1 per 10-pt increase[c]	0.31	0.13–0.91
IS	32	525	SD	60	• NIHSS 0–5 (mild)[d]	ref	
					• NIHSS ≥ 14 (severe)	50	20.00–100
					• NIHSS 6–13 (moderate)	3.85	2.08–7.14
	25	256	SD+	3	NIHSS per 1-pt increase	2.31[e]	1.22–4.38
	23	476	SD+	6	mNIHSS per 1-pt increase[f]	1.32	1.19–1.46
	34	1268	SD+	3	NIHSS per 1-pt increase	1.18	1.15–1.22
Urinary continence							
IS + HS	40[a]	222	IN+	3	New impaired awareness UI	27.5	7.00–108.20
	41[a]	234	IN+	12	New impaired awareness UI	13.4	3.40–52.40
	45	752	IN	12	UI at day 7[d]	4.4	2.10–9.60
	37	171	IN	12	UI on admission[b]	3.57	1.18–11.11
IS	32	525	SD	60	UI within 7–10 d[d]	3.32	1.83–6.04
Level of consciousness							
IS + HS	2	11041	IN	3	Fully conscious on admission	0.32	0.27–0.38
HS	36	418	SD+	3	Conscious (GCS ≥ 9)[g]	0.13	0.05–0.29
ADL functioning/disability							
IS + HS	38	103	IN	36	BI on admission 0–15[b]	11.5	2.20–60.30
	40[a]	222	IN+	3	Mobility: walk speed <0.64 m/s	8.2	2.60–26.20
	41[a]	234	IN+	12	BI (without UI item) on admission <9	3.9	1.30–11.80
	45	752	IN	12	BI at day 7 <10[d]	2.3	1.10–4.80
	43	412	SD+	3	mRS	1.44	1.02–2.05
Prestroke ADL functioning/disability							
IS + HS	41	234	IN+	12	Poor instrumental ADL (NEADL <52)	2.6	1.00–6.60
	43	412	SD+	3	mRS	1.36	1.02–1.80
IS	25	256	SD+	3	Presence of any disability (GOS)	4.40[e]	1.34–14.44
Cognitive functioning							
IS + HS	41	234	IN+	12	Cognitive impairment (SINIS <54)	3.9	1.40–10.70
	44	151	IN	6	Impaired orientation (item SSS)[b]	3.09	1.05–9.10
	47	141	SD	6	Better cognitive performance (AMT)[b]	0.68	0.48–0.97
Prestroke cognitive functioning							
IS + HS	46	165	IN	36	Worse cognitive performance (IQCODE per 1-pt increase)	1.03	1.00–1.06
HS	36	418	SD+	3	No previous cognitive impairment[g]	0.23	0.08–0.67
Emotional functioning							
IS	27	340	SD	24	Early depressed mood[d]	3.72	1.29–10.71
				12		2.91	1.07–7.91
				6		2.81	1.13–6.99

[a]References [39,48], Copenhagen Stroke Study; Pettersen et al. [40,41].
[b]Only patients in rehabilitation departments.
[c]Only patients with Scandinavian Stroke Scale <15.
[d]Only first stroke.
[e]Only results for outcome measured with BI are presented.
[f]Only men with anterior circulation stroke.
[g]Only primary intracerebral hemorrhage.
IN, institutionalization; SD, severe disability; +, including death; IS, ischemic stroke; HS, hemorrhagic stroke; OR, odds ratio; CI, confidence interval; SSS, Scandinavian Stroke Scale; (m)NIHSS, (modified) National Institute of Health Stroke Scale; UI, urinary incontinence; GCS, Glasgow Coma Scale; BI, Barthel Index; mRS, modified Rankin Scale; NEADL, Nottingham Extended ADL scale; GOS, Glasgow Outcome Scale; SINIS, Screening Instrument for Neurocognitive Impairments in Stroke; AMT, Abbreviated Mental Test; IQCODE, Informant Questionnaire for Cognitive Decline in the Elderly.

This review does have some limitations. First, publications may have been missed despite a thorough research with the help of a medical information specialist. Second, this review does not define ''levels of evidence'' for the identified prognostic factors based on the risks of bias in the selected studies. Recently, Veerbeek et al. [8] concluded that most prognostic studies in the early post-stroke phase are still of insufficient methodological quality. Rather than simply confirming this conclusion, we wanted to explore the full range of possible prognostic factors for a poor outcome after a stroke. We believe that this exploratory study is valid as crucial aspects of methodological quality were taken into consideration in our selection criteria (such as a follow-up period of sufficient length, reliable and valid outcome measures and the use of multivariable regression analyses), and other potential sources of bias are evaluated in this discussion. Strength of this review is that we also systematically assessed the number of studies that did *not* find a statistically significant effect for a possible prognostic factor. Previous reviews based their evidence on the number and quality of ''positive'' studies, regardless of the number and quality of ''negative'' studies. However, the contributions of positive and negative studies are equally important in assessing the overall evidence.

Based on the ratio of the number of studies that identified a variable as a prognostic factor to those that did not, there are

rather consistent findings that greater age (12:4), a more severe stroke (8:0), the presence of UI (4:0) and a larger stroke volume (3:0) are predictors for a poor stroke outcome. In contrast to our clinical expectations however, there are inconsistent findings regarding the prognostic value of a high degree of dependency in basic ADLs (4:3) and impaired cognition (3:2). Furthermore, prognostic factors in the domains of emotional and communicative functioning rarely feature in studies on predictors of a poor stroke outcome. The major conclusion of this literature review has to be therefore, that the current evidence for prognostic factors for poor outcome is insufficient for the development of a clinical prediction tool that is better than physicians' informal predictions. However, the studies provide much information to guide future research.

Greater age and a more severe stroke are well-known predictors for stroke outcomes (see for example Veerbeek et al. [8]). The results of this review suggest that the effect of these two variables on poor stroke outcome is not linear: studies that included ''very great age'' or ''severe stroke'' as a separate category (as opposed to older patients or a more severe stroke in general) found larger effects. With respect to very great age, this hypothesis is supported by the International Stroke Trial data, which shows a much higher frequency of poor outcomes in people aged over 80 [51].

The presence of UI was identified previously as a predictor for ADL after a stroke in the review by Meijer et al. [5], but not in the review by Veerbeek et al. [8]. When predicting a poor stroke outcome as we defined it, UI seems to play an important role as a marker of considerable brain damage. It seems obvious that it is important to distinguish newly diagnosed UI from premorbid UI, but this is not done consistently in the studies selected [32,37]. A very interesting finding is that of Pettersen et al. [40,41] that only patients with a reduced awareness of bladder needs were at higher risk of a poor outcome, not patients who were aware of and embarrassed about their problem. They found very large effects for this clinical subtype of UI, both at 3 months and at 1 year after a stroke, and even when measures of attention were added in a second statistical model. However, their cohort only contained a small number of patients with a poor outcome, so a larger sample would be necessary to confirm these results.

Stroke volume directly reflects the amount of brain damage, and its predictive value therefore seems obvious. Rather large effects were found in a selected population of IS patients [25] and of (intracerebral) HS patients [36], independent of stroke subtype (lacunar or not in IS [25] and lobar, deep or infratentorial in HS [36]). However, both studies analyzed data retrospectively.

When viewing the inconsistent findings with regard to impaired cognition (3:2), there appears to be a clear distinction in the measurement instruments used. All studies that identified impaired cognition as a prognostic factor for a poor outcome used a measurement instrument other than the widely used Mini-Mental State Examination (MMSE) [52]. In contrast, impaired cognition was not identified as a prognostic factor when the MMSE was used. Although the MMSE is one of the most commonly used brief mental tests, its disadvantage is that it compresses many cognitive functions together. Meanwhile, it does not account for specific cognitive disabilities such as neglect and problems in executive functioning [53]. It seems essential to use a screening instrument that deliver insight in profiles of cognitive functioning, such as The Screening Instrument for Neuropsychological Impairments in Stroke (SINIS) [54] that was used in the study of Pettersen et al. [41].

With regard to the findings regarding ADL functioning/disability, we did not find such a clear distinction in measurement instruments used, although there is growing consensus that the BI is the optimal tool [55]. However, the inconsistent findings could also be explained by differences in timing of assessment. A recent study explored that the most optimal timing for assessment of the BI to predict outcome of ADL at 6 months seems to be at day 5 post-stroke [55].

Prognostic factors in the domain of emotional functioning rarely feature in studies on predictors of a poor stroke outcome. This is remarkable because it has been generally recognized that post-stroke depression predicts poorer physical functioning [56]. In our review, only Willey et al. [27] found an effect of early depressed mood in IS on a poor outcome; this effect increased from 6 months up to 2 years after the stroke. In contrast, Saxena et al. [47] observed that depressive symptoms were only associated with the *rate* of functional recovery. They therefore concluded that depressive symptoms may slow down physical functional recovery but may not influence the level of dependence finally achieved. However, the follow-up period in this study was 6 months, so that an effect of depressive symptoms on stroke outcome in the long term could have been missed.

Furthermore, it is striking that we did not find any study that evaluates prognostic factors in the domain of communicative functioning. Although screening of stroke-related communication disorders is part of the procedure for stroke severity scales, this provides no accurate information on the prognostic value of aphasia and/or dysarthria for poor stroke outcome. It seems that prognostic studies in this field mainly focus on specific outcome measures in the communication domain [57,58]. We suggest that future research should also focus on the predictive value of communication parameters for poor stroke outcome as we defined it. It is our clinical experience that a substantial proportion of stroke patients who are institutionalized and/or severely disabled have aphasia and/or dysarthria. In addition, there are studies beyond our selection criteria that support our notion. For example, a study among rehabilitating stroke patients (with a median onset-admission interval of >1 month) showed that the presence of global aphasia increases the risk of no improvement in ADL nearly five times [59].

Finally, we would like to focus on prognostic factors that have been studied many times. First, there are rather consistent findings that female gender (1:12) and a history of strokes, heart disease and hypertension (0:6 to 0:9) do not predict a poor outcome (see also, Veerbeek et al. [8]). The non-effect of the latter three classical stroke risk factors emphasizes the fact that the factors known to influence stroke *incidence* do not necessarily have to be the same as the factors influencing stroke *outcome.*

Second, there still appears to be uncertainty about which BP component (4:2) gives the best information for prognosis. In general, BP is known to rise within the first 24 h and then gradually fall over the following week [60], but its influence in IS is complicated. Elevated BP may be of benefit in terms of increasing blood flow in the ischemic areas of the brain, but conversely it can also increase the risk of cerebral edema and hemorrhagic transformation of the infarct. It should be noted that all the studies involving BP in our review analyzed data from randomized controlled trial cohorts (except Boreas et al. [19]), which limits the generalization of the results. Given the fluctuations in BP after a stroke, it seems that future research on the prognostic value of BP should focus on repeated measurements to describe the BP trajectory in the first post-stroke week.

A clinical prediction tool should give the best possible prediction of a poor stroke outcome with as few variables as possible, using variables that can easily be determined in clinical practice. The results of this review showed that age (including very great age), stroke severity and the presence of UI (with impaired awareness) are important candidate variables. Furthermore, the combination with brain imaging information

(stroke volume) seems to be very valuable [25], at least in developed countries. However, the prognostic performance of merely these variables in the first month after stroke will not be better than a physician's informal prediction for an individual stroke patient. The results of this review reveal the need for research on optimal screening instruments in multiple domains of functioning. The timing of assessment is hereby a crucial aspect, because clinical functioning in the early post-stroke period is time-dependent and also influenced by medical interventions in the acute stroke care, such as thrombolysis or decompressive hemiocraniectomy.

Although, it is the ultimate goal to develop a clinical prediction tool that could be used for all stroke patients, it is a fact that the stroke population is very heterogeneous. It seems it will be necessary to develop clinical prediction tools for more homogeneous subgroups to enable more accurate prediction for individual patients. One possibility is to stratify the stroke population by stroke subtype. In our review for example, Rost et al. [36] developed a prediction tool for patients with an intracerebral HS, the most devastating and least treatable form of stroke in general. For the group of IS it should also be considered to develop clinical prediction tools for clinically distinguished subtypes. The studies in our review that used a selected group of IS patients tended to identify different prognostic factors for a poor stroke outcome. In a cohort of patients with a first lacunar infarct, De Jong et al. [17] found diabetes mellitus and leukoaraiosis as independent prognostic factors. The remarkable finding of Bang et al. [23] is that, current smoking has a positive effect on stroke outcome applied to atherosclerotic stroke patients. Although, we did not find convincing evidence for a main effect of stroke subtypes according to the OCPS [49] or the TOAST classification [50] on poor stroke outcome, we suggest that future research focuses on the interaction of stroke subtypes with other predictors. If stratified by stroke subtype, clinical prediction tools could enable prognostication for individual stroke patients that is more accurate than physicians' informal predictions.

Conclusion

There are rather consistent findings that greater age (including very great age), a more severe stroke (measured through a clinical evaluation scale), the presence of UI (with impaired awareness) and a larger stroke volume (measured through brain imaging techniques) are predictors in the first month post-stroke for a poor stroke outcome. In contrast to our clinical expectations, the prognostic value of a high degree of dependency in basic ADLs and impaired cognition remains unclear. Furthermore, there are very few studies in the domains of emotional and communicative functioning. This current evidence is insufficient for the development of a clinical prediction tool that is better than physicians' informal predictions. Future research should focus on the selection of optimal screening instruments in multiple domains of functioning, including the timing of assessment. We suggest developing clinical prediction tools stratified by more homogeneous, clinically distinguished stroke subtypes to enable more accurate prognostication in individual stroke patients.

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