General and disease-specific risk factors for depression after ischemic stroke: a two-step Cox regression analysis

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ABSTRACT

Background: Post-stroke depression (PSD) frequently complicates stroke and is associated with an impaired functional outcome, more severe cognitive deficits, a reduced quality of life, and a higher mortality. The aim of this study was to assess whether general risk factors for major depressive disorder (MDD) in the community are also risk factors for PSD, and to identify additional, stroke-related risk factors.

Methods: In a hospital setting, 190 consecutively admitted patients were assessed for MDD 1 month after stroke, and at follow-up after 3, 6, 9 and 12 months. A Cox model was created with four established risk factors for MDD in the community (female sex, prior personal history of depression, positive family history of depression, and somatic comorbidity other than stroke). Five potential disease-related risk factors (disability, cognitive deterioration, inter- and intra-hemispheric lesion location, and generalized vascular damage on computed tomography (CT) scan) were then added individually to this model, to see whether these would improve the significance of the overall model.

Results: The Cox model of four general risk factors for depression in the community was shown to be a valid model to predict depression in stroke patients. Of the disease-specific factors, only incorporation of “disability” in this model improved its significance.

Conclusion: Established risk factors for depression in the community are also predictors of depression in the first year after stroke. Disability is a non-specific...
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disease-related variable that is associated with PSD. The contribution of stroke-specific factors may be less than is generally assumed.

**Keywords:** Disability, cognitive deterioration, lesion location, follow-up stroke, depression, risk factors

**Introduction**

The prevalence of post-stroke depression (PSD) ranges from 13% in community studies to 23% in neurological inpatient and outpatient populations (Chemerinski and Robinson, 2000). PSD is associated with impaired functional outcome, more severe cognitive deficits, reduced quality of life, and higher mortality (Kauhanen et al., 1999; King, 1996; Morris et al., 1993). Knowledge of risk factors for PSD may assist in the identification of patients at risk of depression and thus facilitate targeted interventions.

Several large-scale prospective studies have identified risk factors for depression in the general population, such as female sex, being single, lower level of education, the presence of physical disease, and a personal or family history of depression (Beekman et al., 2001; Lindeman et al., 2000; Schoevers et al., 2000). It may be assumed that these risk factors for depression in the community also constitute risk factors for depression in stroke patients, although no study has yet specifically addressed this issue. If this is indeed the case, the influence of these general risk factors should be controlled for when searching for specific stroke-related risk factors for depression.

The aim of this study was to evaluate whether risk factors for depression in the general population are also risk factors for PSD, and to assess whether there are additional, independent stroke-specific risk factors.

**Participants and methods**

**Participants**

From September 1997 to September 1999, 190 consecutive patients with a first-ever ischemic stroke underwent a standardized assessment. Patients were recruited from the Accident & Emergency Department and the Department of Neurology of Maastricht University Hospital. The diagnosis of stroke was made on the basis of the World Health Organization (WHO) criteria (National Institute of Neurological Disorders and Stroke, 1990). The ischemic nature of the stroke was verified by a computed tomography (CT) scan. In the absence of ischemic changes on the CT scan, differentiation of left-sided and right-sided stroke was made on the basis of the clinical presentation. More details on the selection criteria of the study population are described elsewhere (Aben et al., 2002a).
Assessments
A first assessment took place within 1 month of stroke. All patients underwent the Structured Clinical Interview for DSM-IV depression (SCID-D) to confirm or reject a diagnosis of major depressive disorder (MDD) according to DSM-IVR criteria (American Psychiatric Association, 2000; Spitzer et al., 1987). The severity of depressive symptoms was assessed with the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960). The cognitive status of patients was assessed with the Mini-mental State Examination (MMSE; Folstein et al., 1975). Disability was rated with the Rankin score (Rankin, 1957). Patients were asked to complete three self-rating scales for depression: the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS) and the Symptom Checklist-90 (SCL-90), which includes a “depression” subscale (Arrindell and Ettema, 1986; Beck et al., 1961; Zigmond and Snaith, 1983).

Information on potential risk factors was gathered during a clinical interview. We focused on four established risk factors for depressive disorder in the general population and five potential disease-related risk factors. The general risk factors included sex, prior personal history of depression, positive family history of depression in first- or second-degree relatives, and the presence of comorbid somatic disorders other than stroke, resulting in actual disability or handicap or need for medical attention. Disease-related risk factors for depression were the level of disability and cognitive impairment at 1 month after stroke, the side of stroke, the involvement of frontal brain regions, and the presence of generalized vascular damage on CT scan. Vascular damage was quantified by a neurologist on the basis of a modified Fazekas score, based on the presence of periventricular and deep white matter hyperintensities, and subcortical gray matter lesions.

Follow-up assessments took place after 3, 6, 9 and 12 months. Patients completed the three self-rating scales for depression by mail. If they scored above the cut-off point for depression on one of these scales, they were called in and interviewed with the SCID-D to confirm the diagnosis of MDD. Cut-off points for depression were set at 9/10 for the BDI (meaning that 9 or lower is not considered indicative for depression, and 10 or higher is suspect for depression), and 7/8 for the HADS. On the depression subscale of the SCL-90, the cut-off was set at 22/23 for men, and 27/28 for women (Aben et al., 2002b).

Statistics
Two consecutive Cox regression analyses were performed with MDD as the outcome variable and the potential risk factors as independent predictive variables. In the first analysis a multivariate Cox model was constructed with the four established risk factors for depression in the general population. In the second part of the analysis, the five potential disease-specific risk factors were
individually added to this model to see whether they increased the strength of the predictive model. The level of significance was set at 0.05 (two-tailed). All analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 10.0 (SPSS Inc., Chicago, IL, 1998).

**Results**

Because of missing data, mainly on current somatic comorbidity and on family history of depression, 25 of the 190 screened patients were excluded from the analysis. The excluded group was not different from the included group with respect to age, sex and other parameters, except for a slightly higher Rankin score (Table 1). The remaining patients were 89 men and 76 women, with an average age of 68.1 years (S.D. 11.8). The 1-year cumulative incidence of MDD was 23%. An overview of patient characteristics is given in Table 1.

In the first stage of the regression analysis, a Cox model was created that incorporated the four risk factors for depression in the general population. The bivariate significances of these risk factors are shown in Table 2, along with the significance of the contribution of these risk factors in a multivariate Cox model. Although a family history of depression was the only variable that in itself contributed significantly to the multivariate model, the model as a whole was significant ($\chi^2 = 12.6$, d.f. = 4, $p = 0.01$). In the bivariate approach, both a previous personal history of depression and a family history of depression were significant predictors of depression ($p = 0.05$ and 0.006, respectively), whereas in the multivariate analysis only a family history of depression is a predictor of PSD ($p = 0.03$).

**Table 1.** Patient characteristics of the 165 patients included and the 25 patients excluded from the analysis. The significance ($p$) of the between-group test statistic ($t$ or $\chi^2$) is also tabulated

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>INCLUDED PATIENTS</th>
<th>EXCLUDED PATIENTS</th>
<th>p-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 165$</td>
<td>$n = 25$</td>
<td></td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>46</td>
<td>52</td>
<td>0.58</td>
</tr>
<tr>
<td>Average age (S.D.)</td>
<td>68.1 (11.8)</td>
<td>71.4 (10.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Somatic comorbidity (%)</td>
<td>86</td>
<td>92</td>
<td>0.47</td>
</tr>
<tr>
<td>Personal history of depression (%)</td>
<td>21</td>
<td>29</td>
<td>0.40</td>
</tr>
<tr>
<td>Family history of depression (%)</td>
<td>53</td>
<td>43</td>
<td>0.57</td>
</tr>
<tr>
<td>Average Rankin score (S.D.)</td>
<td>2.3 (1.2)</td>
<td>2.9 (0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Average MMSE score (S.D.)</td>
<td>26 (3.0)</td>
<td>26 (3.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Side of lesion (% left-sided lesion)</td>
<td>47</td>
<td>46</td>
<td>0.90</td>
</tr>
<tr>
<td>Involvement of anterior regions</td>
<td>34</td>
<td>33</td>
<td>0.95</td>
</tr>
<tr>
<td>Vascular damage (% evidence on CT scan)</td>
<td>52</td>
<td>57</td>
<td>0.65</td>
</tr>
</tbody>
</table>

S.D. = standard deviation; MMSE = Mini-mental State Examination; CT = computed tomography.
Table 2. Hazard ratios (HR), 95% confidence intervals (CI), and two-tailed p-values of the four general risk factors for post-stroke depression in the bivariate model and in the four-factor Cox regression model. The significance of the multivariate Cox model was 0.01 ($\chi^2 = 12.6$, d.f. = 4)

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>HR</th>
<th>95% CI</th>
<th>p-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivariate model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1.80</td>
<td>0.93–3.47</td>
<td>0.08</td>
</tr>
<tr>
<td>Somatic comorbidity</td>
<td>2.02</td>
<td>0.62–6.57</td>
<td>0.24</td>
</tr>
<tr>
<td>Personal history of depression</td>
<td>1.98</td>
<td>0.99–3.94</td>
<td>0.05</td>
</tr>
<tr>
<td>Family history of depression</td>
<td>2.51</td>
<td>1.31–4.82</td>
<td>0.006</td>
</tr>
<tr>
<td>Multivariate Cox model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1.63</td>
<td>0.84–3.16</td>
<td>0.15</td>
</tr>
<tr>
<td>Somatic comorbidity</td>
<td>1.54</td>
<td>0.46–5.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Personal history of depression</td>
<td>1.58</td>
<td>0.77–3.21</td>
<td>0.21</td>
</tr>
<tr>
<td>Family history of depression</td>
<td>2.16</td>
<td>1.1–4.25</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 3. Hazard ratios (HR), 95% confidence intervals (CI), and two-tailed p-values of five disease-specific risk factors for depression in stroke patients in the five-factor Cox model. The five disease-specific factors were individually added to the general model. The two-sided p-values of the resulting five-factor models are shown as well.

<table>
<thead>
<tr>
<th>STROKE SPECIFIC RISK FACTOR</th>
<th>HR</th>
<th>95% CI</th>
<th>p-VALUE</th>
<th>FIVE-FACTOR MODEL p-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankin score</td>
<td>1.54</td>
<td>1.11–2.14</td>
<td>0.01</td>
<td>0.002</td>
</tr>
<tr>
<td>MMSE score</td>
<td>0.96</td>
<td>0.86–1.07</td>
<td>0.47</td>
<td>0.02</td>
</tr>
<tr>
<td>Left hemisphere lesion</td>
<td>0.86</td>
<td>0.44–1.62</td>
<td>0.61</td>
<td>0.03</td>
</tr>
<tr>
<td>Frontal involvement</td>
<td>0.89</td>
<td>0.44–1.80</td>
<td>0.85</td>
<td>0.03</td>
</tr>
<tr>
<td>Vascular damage on CT scan</td>
<td>1.51</td>
<td>0.78–2.92</td>
<td>0.22</td>
<td>0.02</td>
</tr>
</tbody>
</table>

MMSE = Mini-mental State Examination; CT = computed tomography.

In the second step of the analysis, potential disease-specific risk factors for depression were added individually to the four-factor Cox model, to see whether this would lead to improvement in the model. Table 3 shows the odds ratios and significance of the resulting five-factor models after inclusion of each of the potential disease-related risk factors. Although the resulting five-factor models were all significant, only the model that incorporated the Rankin score as a predictor was a significant improvement over the model that incorporated the four general risk factors for depression only ($\chi^2 = 6.664$, d.f. = 1, $p = 0.01$).

**Discussion**

In this analysis, we have tried to model risk factors for PSD in a logical and comprehensible approach. First, a multivariate model of general, *a priori* risk factors for PSD was constructed, with the following risk factors included:
factors for depression was calculated in a population of stroke patients. Next, potential stroke-related risk factors were added to this model to see whether these would improve the model’s predictive power. This approach corrects for the confounding influences of general risk factors for depression in the search for stroke-related risk factors.

The 1-year cumulative incidence of PSD in our study is comparable to that in other studies (Aben et al., 2001; Chemerinski and Robinson, 2000). Our model of general risk factors for depression in the community (including sex, previous personal or family history of depression, and somatic comorbidity) was shown to be a good model to predict depression in stroke patients. Interaction between the various risk factors is apparent from the differences in the hazard ratios of these factors in a bivariate approach, when compared to a multivariate approach. In the multivariate model, a positive family history was the only factor that independently increased the risk for PSD. To our knowledge no study has yet looked at family history of depression as a potential predictor for PSD. Other studies have identified previous depression and female sex as non-specific factors associated with an increased risk of PSD, but this could not be confirmed in our analysis (Andersen et al., 1995; Burvill et al., 1997).

A number of prospective studies have addressed potential stroke-specific risk factors for depression. Some have found that increased functional impairment, more severe cognitive impairment, previous stroke, left-sided lesion location, and involvement of anterior cerebral regions constitute risk factors for PSD (Andersen et al., 1995; Beekman et al., 1998; Burvill et al., 1997; Kim and Choi-Kwon, 2000; Narushima et al., 2003; Shimoda and Robinson, 1999), although this has not been confirmed in other studies (Burvill et al., 1997; Carson et al., 2000; Singh et al., 1998; Stewart et al., 2001). However, only a few studies have followed a multivariate approach and corrected for established general risk factors for depression in the community. In our study, potential disease-related factors, such as cognitive impairment, lesion location, and leukoaraiosis on CT, could not improve the four-factor model based on general risk factors.

The only disease-specific factor that improved the statistical strength of the general model was the Rankin score. Several studies confirm an association between disability and PSD (Beekman et al., 1998; Burvill et al., 1997; Chemerinski and Robinson, 2000). The question arises whether disability should be seen as a specific stroke-related factor. Disability is known to be a risk factor for depression in the community, as well as in patients with a variety of diseases such as cardiovascular disease, diabetes, cancer, Alzheimer’s disease and Parkinson’s disease (Cole and Dendukuri 2003; Cole et al., 1996; Katon, 2003). In both Parkinson’s disease and Alzheimer’s disease it has been demonstrated that a model consisting of general risk factors to predict depression was not improved
by introducing disease-specific factors (Leentjens et al., 2002; Van Winkel et al., 2006). Thus, the lack of specific disease-related factors, and especially factors relating to the pathophysiology and location of stroke, to contribute significantly to a multivariate model of risk factors for depression in stroke patients is in agreement with findings in other neuropsychiatric populations. One possible explanation for this finding may be that the shared factor in the etiology of depression related to physical disease is the fact that these diseases, or the resulting disability, may lead to stress responses that alter the function of the hypothalamic–hypopituitary–adrenal axis and thus result in a non-specific disease-related risk of depression (Holsboer, 2000).

There are a number of limitations to our study. First, for pragmatic reasons, only patients scoring above a specified cut-off score on one of the depression ratings scales were called in for further assessment. Although it is theoretically possible that depressed patients may be missed in this approach, this seems unlikely because multiple scales were used and these scales have a high sensitivity and negative predictive value at the specified cut-off scores (Aben et al., 2002b). A second limitation is the choice of variables. Because of the sample size limitations that Cox regression sets, the number of potential risk factors included in the analysis was nine. As a consequence, a selection of potential risk factors had to be made. This implies that some other potential risk factors, such as the level of brain atrophy, negative life events, and premorbid personality traits, have not been incorporated in the model. Moreover, previous personal or family history was based on patient recollection, which may have led to underestimation of this variable. Furthermore, we assessed risk factors throughout the first year following stroke. The identification of some variables, such as lesion location, as a risk factor may depend on the time after stroke (Robinson, 2003). The inclusion of patients who had not showed a lesion on CT scan may have been another confounder in the assessment of lesion location as a risk factor. Finally, with an average age of 68, our population consisted of relatively young patients, and our results may not necessarily apply to older subjects with stroke.

**Conclusion**

A Cox regression model based on four risk factors for depression in the general population was shown to be a valid model to predict depression in the first year after stroke. The level of disability was the only stroke-related factor that could improve this model. Based on the non-specific nature of “disability” as a risk factor, as well as on similar findings in other neurological diseases, it is suggested that non-specific factors related to disease in general may offer a more likely explanation for the high prevalence of PSD than factors that are specifically related to the pathophysiology of stroke. In recognition of the complex nature of
depression, future research of risk factors for PSD should follow a multivariate approach that corrects for general risk factors for depression in the community.

**Conflict of interest**

None.

**Description of authors’ roles**

A.F.G. Leentjens designed and performed the analysis and wrote the manuscript. I. Aben collected the data and contributed to the manuscript. J. Lodder and F.R.J. Verhey designed and supervised the study and contributed to the manuscript.

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**References**


