Does Depression in Older Medical Inpatients Predict Mortality?

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Background. Previous studies of the effect of depression on mortality among older medical inpatients have yielded inconsistent results. We examined the effects on mortality of both a diagnosis of depression at hospital admission and a history of previous depression, taking into account potential sources of bias (sample selection and confounding).

Methods. Medical inpatients aged 65+ with at most mild cognitive impairment were recruited at two Montreal hospitals and were screened for depression. All those with a diagnosis of major or minor depression (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria) and a random sample of nondepressed patients were invited to participate. Baseline data included: history of previous depression, severity of physical illness, comorbidity, and health services utilization. Cox proportional hazards methods were used to analyze survival during the 16- to 52-month follow-up period.

Results. Five hundred patients were enrolled; 116 (23.2%) had a history of previous depression. After adjustment for demographic factors, physical illness, cognitive impairment, and prior service utilization, the only depression group with significantly different mortality was patients with both current major depression and a history of depression, who had lower mortality than all other patient groups (hazard ratio 0.42; 95% confidence interval: 0.25, 0.70).

Conclusions. Among patients with no history of depression, a diagnosis of depression was not associated with mortality after adjustment for confounding by physical illness and other factors. Coincident major depression and history of depression was associated with decreased mortality.

Depression (either symptoms or diagnosis) appears to be a risk factor for mortality among older populations in most large, community-based longitudinal studies, even after adjustment for other risk factors [e.g., age, comorbidity, and disability (1,2)]. Older depressed medical inpatients experience high mortality rates (3); however, an independent effect of current depression on mortality has been reported in some studies [in-hospital (4–6) and after discharge (7,8)] but not in others (9,10). In addition to current depression, a history of previous depression has been reported to be a risk factor for inhospital mortality in one of these studies (6).

There are at least four potential explanations for the inconsistencies in these results. First, selection bias may arise from different hospitalization rates between depressed and nondepressed people (9–11). If patients with prior depression are more likely to be hospitalized at lower levels of severity of physical illness, lower severity could offset the effect of depression on mortality. Second, selection bias may also be due to differential rates of study participation in patient subgroups with different risks of mortality (e.g., lower participation among patients with both depression and especially severe physical illness). Third, there may be residual confounding due to inadequate adjustment for other risk factors for mortality [particularly the severity of the primary medical illness, comorbid medical conditions, physical disability, and cognitive impairment (12)]. Fourth, depression is measured differently in different studies, e.g., using standardized diagnostic criteria versus a symptom rating scale.

We undertook this study in an older hospitalized cohort to examine the effects on mortality of both a diagnosis of depression at hospital admission and a history of previous depression, taking into account potential sources of bias (sample selection and confounding).

Methods

Study Sample

Methods of recruitment of the study sample have been described in detail previously (13). The study sample was enrolled at two university-affiliated general acute care Montreal hospitals between October 1999 and November 2002. Patients were selected using random sampling from lists of nonelective consecutive admissions of patients aged 65 or older to the medical services. The following patients were excluded: admissions to palliative care, those who did not speak or understand English or French or were unable to communicate, and those who lived off the island of Montreal (because of greater difficulty in follow-up).
Patients admitted to the intensive care or cardiac monitoring units were screened after transfer to a medical ward. Eligible patients were screened using the Short Portable Mental Status Questionnaire (14); those with 5 or more errors [indicating moderate-severe cognitive impairment (15)] were excluded because the presence of cognitive impairment complicates diagnosis and measurement of depression (16). Patients were then screened for depression (major and minor) using the Diagnostic Interview Schedule (DIS) (Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria; see below) (17).

All depressed patients and a systematic (random) sample of nondepressed patients were invited to participate in the longitudinal component of the study, and a baseline research interview was scheduled to collect more detailed information, including the Hamilton Depression Rating Scale (18). At one hospital, patients with major depression were invited to participate in a concurrent randomized controlled trial that compared systematic detection and multidisciplinary management with usual care (19). The intervention did not affect mortality; patients who participated in the randomized controlled trial have been included in this analysis.

Information collected at the time of enrollment included history of depression, clinical severity of physical illness, and demographic information (see below). Other data sources included: (a) review of patient medical charts at the two hospitals (by a research assistant who was blind to study group); (b) abstraction of administrative databases at the two hospitals; and (c) provincial hospital discharge, physician billing, and prescription databases (all patients are covered by government health insurance for these services). Mortality data were extracted from the provincial database in March 2004 (follow-up ranged from 16 to 52 months). Dates of death were checked against those found in the medical chart. Two deaths were missed in the database: The dates of these deaths were verified in other hospital databases and were included in the analysis.

The study protocol was approved by the research ethics committees of both hospitals. We were not, however, permitted to obtain information on: (a) characteristics (demographics, depression) or mortality of patients who were not eligible for the study or who refused the depression screening; and (b) mortality data for patients who were screened for depression but refused study participation. Patients with severe depression (clinical criteria) were referred to a geriatric psychiatrist (MC) or a geriatrician (SW).

Measures

Depression.—The depressive disorders section of the DIS assesses nine symptoms of depression: two core symptoms (depressed mood, lack of interest or pleasure) and seven others (sleep, appetite, fatigue, psychomotor, concentration, worthlessness, suicidality). Patients were classified as having current (at least two weeks’ duration of symptoms) major, minor, or no depression with DSM-IV criteria; symptoms were counted towards the diagnosis regardless of their presumed origins, whether physical illness or depression (a sensitive and reliable approach for predicting the persistence of symptoms) (20). The inter-rater reliability of the DIS was assessed in a convenience sample of 28 patients at intervals throughout the study period, using independent simultaneous ratings by two or more raters, including the study psychiatrist (MC). Values of the kappa coefficient were 0.78 (95% confidence interval [CI]: 0.52, 1.00) for a diagnosis of major depression versus minor or no depression, and 0.61 (95% CI: 0.35, 0.87) for a diagnosis of either major or minor versus no depression.

History of previous depression.—Patients were considered to have a history of depression at enrollment if either they reported (in response to a direct question) that they had ever been told by a doctor that they were depressed or there was a diagnosis of depression in the hospital chart at a previous admission during the past 2 years.

Treatment.—Antidepressant medication prescriptions during the 12 months before admission were abstracted from the prescription database.

Physical illness at enrollment.—Five measures of physical illness were used. First, the Charlson Comorbidity Index was derived from chart review of diagnoses during the 2 years before enrollment (21). Second, clinical severity of the medical illness was assessed at enrollment based on a global clinical impression with a scale ranging from 1 (not ill) to 9 (moribund) (22). Third, the Acute Physiology Score (APS), derived from laboratory test results and vital signs from the Acute Physiology and Chronic Health Evaluation (APACHE II) was coded from the computerized laboratory test results and hospital chart data (23). Fourth, the primary discharge diagnosis from the hospital administrative database was classified into 5 categories: circulatory, respiratory, neoplasm, symptoms or signs only, or other. Fifth, the Chronic Disease Score based on medication prescriptions during the previous 12 months was computed from the prescription database (24).

Cognitive impairment.—Because patients with a Short Portable Mental Status Questionnaire (SPMSQ) score 5 or more were excluded, level of cognitive impairment was defined as the number of errors on the SPMSQ score, from 0 to 4.

Sociodemographic and other variables.—Age, sex, marital status, living arrangements (alone or with others), language of interview (English or French), and hospital of admission were measured at enrollment.

Health services utilization.—The following measures of health services utilization during the 12 months before admission were abstracted from provincial databases: number of hospital days, number of physician visits, and number of emergency department visits (excluding those at which the patient was admitted). Use of home care services was obtained by self-report.

Objective 1.—To determine whether the severity of physical illness and previous health services utilization...
differed by current depression and a history of depression, we used chi-square tests and analysis of variance (ANOVA) to compare the patient groups at baseline. We also used Poisson regression for variables that were not normally distributed; the results were similar, so they are not reported. We tested the following nine comparisons (using a Bonferroni correction): Within each diagnostic group (major, minor, no depression), we compared patients with and without a previous history, and we compared the three diagnostic groups separately for patients with and without a previous history.

Objective 2.—We used Cox proportional hazards analysis to determine the effects of current depression and a history of depression on mortality with and without adjustment for covariates (severity of physical illness, previous health services utilization, cognitive impairment, and sociodemographic variables). Time zero was defined as the date of study enrollment, and participants were censored at the time of loss to follow-up in the administrative database.

RESULTS
Among 1718 eligible patients, 1686 received a screening DIS; the prevalence of depression (major or minor) was 27.9% (471/1686) (Figure 1). Consent rates to study participation were 71.5% (328/459) among patients with a depression diagnosis and 67.2% (172/256) in the sample of nondepressed patients. The crude proportions of participants who died during the follow-up period were 47.0% in both the depressed and nondepressed cohorts (154/328 and 81/172).

Table 1 shows the characteristics of the patients by current depression diagnosis and history of depression.
Among patients with current major depression, those with a history of previous depression were younger and more likely to have been prescribed an antidepressant medication during the previous 12 months; after the Bonferroni correction, these differences were no longer significant after the Bonferroni adjustment. Antidepressant prescriptions were also associated with a history of depression among patients with current major depression. Among patients without a history of depression, those with current major depression had significantly lower mortality (HR = 0.60) whereas those with major depression and no history had significantly higher mortality (HR = 1.41). After adjustment for all the covariates in the table (column 2), the effect for the first group (major depression with a history) became stronger (HR = 0.42) whereas the effect for the second group (major depression with no history) disappeared (HR = 0.96). Other significant predictors of mortality in the multivariate model included three measures of more severe physical illness

### Table 1. Baseline Characteristics of Study Sample by Depression (Current Diagnosis and Prior History)

<table>
<thead>
<tr>
<th>Variables</th>
<th>History of Depression</th>
<th>No History of Depression</th>
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<tbody>
<tr>
<td></td>
<td>Major (N = 82)</td>
<td>Minor (N = 27)</td>
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<tr>
<td>Sociodemographic</td>
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<td></td>
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<tr>
<td>Age, mean (SD)*</td>
<td>76.6 (6.5)</td>
<td>78.2 (7.4)</td>
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<td>Male sex (%)</td>
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<td>Lives alone (%)</td>
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<td>50</td>
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<td>(1)</td>
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<tr>
<td>English language (%)</td>
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<td>81.5</td>
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<tr>
<td>Physical illness</td>
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<td></td>
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<td>Comorbidity, mean (SD)*</td>
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<td>1.5 (1.5)</td>
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<td>(0)</td>
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<tr>
<td>Clinical severity, mean (SD)*</td>
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<td>3.6 (0.8)</td>
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<td>(Missing)</td>
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<td>(1)</td>
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<td>Chronic disease score, mean (SD)</td>
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<td>(0)</td>
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<td>Discharge diagnosis (%)</td>
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<td>Circulatory</td>
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<td>Symptoms/signs</td>
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<tr>
<td>(Missing)</td>
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<td>(0)</td>
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<tr>
<td>Cognitive impairment, mean (SD)*</td>
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<tr>
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<td>(0)</td>
</tr>
<tr>
<td>Antidepressant medication (%)*</td>
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<tr>
<td>Health services utilization</td>
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<tr>
<td>Hospital days/12 mo, mean (SD)*</td>
<td>14.1 (23.3)</td>
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</table>

Notes: *Significant between-groups contrasts (p < .006): Age: 1 vs 4; Comorbidity: 4 vs 5; Clinical severity: 4 vs 5, 4 vs 6; Cognitive impairment: 4 vs 6; Antidepressant medication: 1 vs 4, 2 vs 5, 4 vs 6, 5 vs 6; Hospital days: 4 vs 5. 
SD = standard deviation; ED = emergency department.
DISCUSSION

We undertook this study in older medical inpatients to determine whether a diagnosis of depression at admission

(clinical severity, Charlson Comorbidity Index score, discharge diagnosis of neoplasm), two of higher prior utilization of services (hospital days, physician visits), and one of greater cognitive impairment (SPMSQ score).

We added a variable to the final multivariate model in Table 2 indicating whether the baseline interview had been completed; this variable did not significantly affect mortality, and its inclusion had a minimal effect on the odds ratios for other variables in the model or their CI values (data not shown). Furthermore, we fitted the model for only patients having the baseline interview; again, results were virtually unchanged (Table 2, third column). In this latter model, patients with current minor depression but no prior history also had better survival than the reference group had. A similar result was seen in the main model (second column), although the HR included unity.

In the sample of 500 patients, 92 self-reported a history of depression and 53 had a prior chart diagnosis of depression (29 had both). Only 3 patients had no prior chart; all 3 self-reported no history of depression. We conducted sensitivity analyses considering three different definitions of a history of depression: (i) based only on self-report, (ii) based only on chart diagnosis, and (iii) considering patients with previous antidepressant medications to have a history of depression (in addition to the two other criteria). These analyses yielded similar results (data not shown).

To explore whether the duration or severity of the current episode of major depression differed among patients with and without a history of depression, we compared the duration of the core symptoms (depressed mood, lack of interest or pleasure), the total number of depressive symptoms, and the Hamilton Depression Rating Scale scores (among patients who completed the baseline research interview). There were no significant differences in these variables (Table 3).

We added the following variables to the final multivariate model: (i) based only on self-report, (ii) based only on chart diagnosis, and (iii) considering patients with previous antidepressant medications to have a history of depression (in addition to the two other criteria). These analyses yielded similar results (data not shown).

Notes: *p < 0.05.
1* p < 0.01.
224 patients with minor depression, 6 with no depression.
30.05 < p < 0.10.
4Increase in one unit.

HR = hazard ratio; CI = confidence interval; SPMSQ = Short Portable Mental Status Questionnaire; ED = emergency department.
and a history of previous depression predict future mortality. We considered three methodological explanations for discrepant results on the relationship between depression and mortality reported in previous studies: (i) selection bias due to differential rates of hospitalization, (ii) selection bias due to differential rates of study participation, and (iii) confounding due to differences between depressed and nondepressed patients in other risk factors for mortality. The first explanation, differential rates of hospitalization among depressed and nondepressed people, was partially supported by the results. We found that patients with major depression and a history of previous depression tended to be younger, but had a higher rate of previous emergency department utilization (without admission). This group of patients also experienced significantly lower mortality than all other groups of depressed and nondepressed patients, even after adjustment for covariates (severity of physical illness, mild cognitive impairment, prior health services utilization, and sociodemographic variables). This effect was not apparently due to a greater severity of depression among those patients with a history.

The second explanation, selection bias due to different rates of study participation, was not supported by our results. The effects of depression on mortality among patients who participated in the in-depth baseline study interview (n = 362) were similar to those among the entire sample (n = 456). However, we were unable to assess other sources of selection bias (e.g., at participation in depression screening or at consent to study participation) because we were not given access to the necessary data by our research ethics board. Nevertheless, among patients screened for depression, consent to study participation did not differ by depression diagnosis (Figure 1).

The third explanation, confounding by other risk factors for mortality, was supported by our results. In particular, the increased mortality among patients with major depression without a previous history found in univariate analyses disappeared after adjustment for other risk factors for mortality, as has been reported in a community sample (25). It may be that, among patients with no previous history, more severe physical illness may trigger an episode of depression. In contrast, among patients with a previous history of depression, adjustment for other risk factors for mortality increased the protective effect on mortality of a current diagnosis of major depression, further supporting the existence of a selection bias due to differential rates of admission. Notably, we found that multiple factors independently predicted mortality in our sample (clinical severity of physical illness, comorbidity, mild cognitive impairment, prior physician visits); failure to measure and adjust for all these factors would have introduced residual confounding.

Notable strengths of this study include the use of a standardized diagnostic assessment rather than a depression self-rating scale, and the relatively large sample size and long follow-up, which provided adequate power to detect clinically significant effects of major depression on mortality. At the same time, seven potential study limitations should be noted. First, we did not use diagnostic criteria for a history of depression, but relied on diagnoses either reported by the patients or documented in the chart. Second, we lacked detailed information on history of depression (e.g., age at onset, prior number of episodes). Third, the relatively small number of patients with either minor or no depression among those with a history of previous depression limited our ability to examine whether a history of depression also affected mortality in these groups. Fourth, we had no mortality data for patients who refused to participate in the study. Fifth, the study was limited to patients with at most mild cognitive impairment. Sixth, we excluded the most severely ill patients from the study (i.e., those admitted to intensive care). Seventh, we did not measure other potential risk factors for mortality (e.g., smoking and exercise).

The finding of a “protective” effect of a history of depression among patients with major depression at admission was unexpected. Two other studies in medical inpatients have reported that a history of depression increases mortality. The first was limited to in-hospital mortality (6), and the second (which included younger adults) was limited to patients with acute myocardial infarction (26). At least three explanations may be considered for the protective association between a history of depression and mortality. First, a history of depression as measured in our study implied awareness by a physician that the patient was depressed. This awareness may have improved the treatment of the depression, although it is perhaps unlikely that such improvement in treatment would translate quickly into a difference in mortality. Second, patients with a history of depression may have a less severe course of depression. Unpublished data from the same cohort indicate that a history of depression predicts recovery among patients with major depression. Third, there may be selective admission of patients with both prior and current depression, perhaps because of perceived greater distress on the part of the patient, family members, or admitting physician.
Our results also suggested a protective effect of minor depression among patients without a prior history, although this was statistically significant only in analyses in the sample with a baseline research interview. Prior research in a community sample of older adults has also reported a protective effect of subthreshold depression on mortality among older women (27). This finding is unexplained.

Conclusion

Studies of mortality in older depressed medical inpatients must be interpreted carefully, taking into account the selection biases involved in admission and study participation and residual confounding due to multiple risk factors for mortality. The possibility that patients with a history of previous depression as well as current major depression have a lower threshold for hospitalization merits further investigation. If this hypothesis were confirmed, more clearly defined hospital admission criteria, combined with more effective screening and treatment of depression, could be warranted.

ACKNOWLEDGMENTS

This work was funded by Canadian Institutes for Health Research Grants MOP92494 and MCT-15476.

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Received September 21, 2005 Accepted February 7, 2006
Decision Editor: Luigi Ferrucci, MD, PhD