

# Depressive Symptoms and 3-Year Mortality in Older Hospitalized Medical Patients

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**Background:** Depressive symptoms are common in hospitalized older persons. However, their relation to long-term mortality is unclear because few studies have rigorously considered potential confounders of the relation between depression and mortality, such as comorbid illness, functional impairment, and cognitive impairment.

**Objective:** To measure the association between depressive symptoms and long-term mortality in hospitalized older persons.

**Design:** Prospective cohort study.

**Setting:** General medical service of a teaching hospital.

**Patients:** 573 patients 70 years of age or older.

**Measurements:** Depressive symptoms (Geriatric Depression Scale score), severity of acute illness (Acute Physiology and Chronic Health Evaluation II score), burden of comorbid illness (Charlson comorbidity index score), physical function (a nurse assessed dependence in six activities of daily living), and cognitive function (modified Mini-Mental State Examination) were measured at hospital admission. Mortality over the 3 years after admission was determined from the National Death Index. Mortality rates among patients with six or more depressive symptoms were compared with those among patients with five or fewer symptoms.

**Results:** The mean age of the patients was 80 years; 68% of patients were women. Patients with six or more depressive symptoms had greater comorbid illness, functional impairment, and cognitive impairment at admission than patients with fewer depressive symptoms. Three-year mortality was higher in patients with six or more depressive symptoms (56% compared with 40%; hazard ratio, 1.56 [95% CI, 1.22 to 2.00];  $P < 0.001$ ). After adjustment for age, acute illness severity, comorbid illness, functional impairment, and cognitive impairment at the time of admission, patients with six or more depressive symptoms continued to have a higher mortality rate during the 3 years after admission (hazard ratio, 1.34 [CI, 1.03 to 1.73]). Although depressive symptoms contributed less to the mortality rate than did the total burden of comorbid medical illnesses, the excess mortality rate associated with depressive symptoms was greater than that conferred by one additional comorbid medical condition.

**Conclusions:** Depressive symptoms are associated with long-term mortality in older patients hospitalized with medical illnesses. This association is not fully explained by greater levels of comorbid illness, functional impairment, and cognitive impairment in patients with more depressive symptoms.

Hospitalization is associated with a long-term increased risk for death, especially in older persons (1–4). Although the mediators for this increased risk have not been fully elucidated, depression may play an important role. Because depression is common in hospitalized older patients, an association between depression and mortality in this population would be of significant clinical importance (5–13). The hypothesis that depression may be a mediator of death in hospitalized patients is supported by studies demonstrating that depressive symptoms are associated with increased mortality in community-dwelling patients and in highly selected groups of hospitalized older patients, such as those with acute myocardial infarction (14–18). These studies have often been limited by inadequate accounting for the complex interrelations between depressive symptoms and other predictors of death, such as acute physiologic impairment, chronic comorbid illness, functional impairment, and cognitive impairment. Because depressive symptoms are clearly correlated with and may partly be the result of these other factors (5, 19–20), improving our understanding of the relation between depression and death requires use of standardized methods to measure and adjust for confounders.

We tested the hypothesis that depressive symptoms are associated with long-term mortality in hospitalized older patients. We demonstrated previously that depressive symptoms are strongly associated with adverse health status outcomes in hospitalized medical patients through 90 days after admission (21). However, our initial study found no association between depressive symptoms and mortality during the first 90 days after admission (21). In this report, we extend mortality follow-up to 3 years by merging our data with a national mortality database. Furthermore, we adjusted for standard measures of physiologic impairment, comorbid illness, and functional impairment at hospital admission to control for the possibility that higher levels of these confounders in patients with more depressive symptoms affect the association between depressive symptoms and death.

## Methods

### Patients

Patients were drawn from serial, prospective longitudinal studies of functional change in older hos-

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pitalized patients on the general medical service of University Hospitals of Cleveland. The inclusion and exclusion criteria for these studies are described elsewhere (3, 21, 22). The first study enrolled 206 patients 75 years of age or older who were admitted between March 1990 and July 1990. The second study, a controlled trial of an intervention to improve functional outcomes, enrolled 651 patients 70 years of age or older who were admitted between November 1990 and March 1992. The first study, which was a pilot study for the second study, enrolled consecutive patients. The second study randomly assigned patients to an intervention designed to improve functional outcomes in older persons or to usual care (22). In each study, patients admitted to the intensive care unit, telemetry service, or oncology service were excluded. Data collection procedures in both studies were almost identical. Other than a slightly higher mean patient age in the first study cohort, the demographic, clinical, and functional characteristics of patients in the first study, the control group of the second study, and the intervention group of the second study were similar. Additional analyses that adjusted for whether patients were in the first study cohort or the control group compared with the intervention group of the second study cohort yielded results that were almost identical to the results reported here.

Of 857 older patients enrolled in the two studies, 284 were excluded from the current study because they were too ill or confused to be interviewed about depressive symptoms at the time of admission ( $n = 164$ ), were admitted from nursing homes ( $n = 38$ ), were not available for interview ( $n = 37$ ), declined interview ( $n = 27$ ), or died before being approached ( $n = 18$ ). We excluded patients admitted from nursing homes because interview data were less consistently obtained from these patients. Thus, the analytic sample for this study comprised 573 patients.

### Assessment of Depressive Symptoms

Within 48 hours of admission, patients were interviewed by using the 15-item Geriatric Depression

Scale to assess depressive symptoms over the past week (23, 24). The Geriatric Depression Scale is well suited for use in acutely ill older persons because it focuses on symptoms of depression that are less likely to be directly influenced by somatic illness. Examples of items on this scale include feeling bored, dropping activities and interests, feeling helpless, feeling worthless, feeling that life is empty, feeling that others are better off, preferring to stay at home instead of doing new things, and feeling hopeless. We divided patients into those reporting five or fewer symptoms and those reporting six or more symptoms; these are commonly recommended cutoffs on the 15-item Geriatric Depression Scale (24–26).

### Measurement of Mortality

We determined mortality and date of death during the 3 years after hospitalization by merging our files with the National Death Index, a database of all deaths in the United States generated from state death certificates. Its sensitivity and specificity have been reported to be 98% and 100%, respectively (27).

### Measurement of Potential Confounders

Shortly after admission, we surveyed each patient's primary nurse about the patient's independence in six activities of daily living (dressing, bathing, grooming, toileting, transferring, and eating) based on the scale of Katz (28). Within 48 hours of admission, we administered to patients the first 21 items of the 30-item Folstein Mini-Mental State Examination (29). To minimize respondent burden, we used only the first 21 items. Scores on the 21-item instrument have previously been shown to correlate highly ( $r = 0.9$ ) with scores on the 30-item instrument and to have construct validity on the basis of their strong association with functional outcomes (30). Data gathered from medical records included the reason for admission, the components of the Acute Physiology and Chronic Health Evaluation (APACHE) II score (31), and the components of the weighted Charlson comorbidity index of illness (32). The APACHE II score is a commonly used measure of physiologic severity, and the Charlson score is often used as a measure of the burden of comorbid illness.

### Statistical Analysis

For our primary set of analyses, we compared patients who had six or more depressive symptoms (depressed patients) with patients who had five or fewer symptoms (nondepressed patients). We used the chi-square test or *t*-test to compare the characteristics of patients in each category at hospital admission. Survival curves describing mortality in the 3

**Table 1. Most Common Reasons for Hospital Admission ( $n = 573$ )**

Reason for Admission	Patients, $n$ (%)
Chronic obstructive pulmonary disease or asthma	64 (11.1)
Chest pain	52 (9.1)
Gastrointestinal bleeding	49 (8.6)
Pneumonia	46 (8.0)
Congestive heart failure	45 (7.9)
Abdominal pain	39 (6.8)
Dehydration or metabolic derangement	30 (5.2)
Fever (rule out sepsis)	28 (4.9)
Syncope, falls, or dizziness	24 (4.2)
Stroke or transient ischemic attack	17 (3.0)

years after hospitalization in each group were prepared by using the method of Kaplan and Meier.

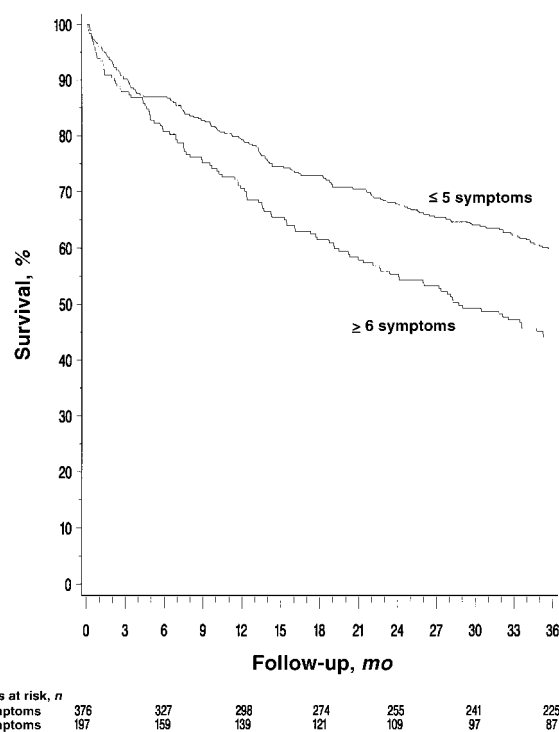
We used Cox regression to determine whether depressive symptoms were independently associated with mortality over 3 years. In the first model, we measured the unadjusted association between depressive symptoms and mortality. In the next four models, we determined the association between depressive symptoms and mortality after controlling for APACHE II scores, Charlson comorbidity index scores, dependence in activities of daily living, or cognitive function. In the sixth model, we controlled for all of these potential confounders as well as age, sex, ethnicity, and whether the patient lived alone.

We did two secondary analyses. First, we modeled depression scores as the number of depressive symptoms on admission. We also determined the hazard ratio associated with multiple cut-points on the Geriatric Depression Scale.

## Results

The mean age of the 573 patients was 79.9 years; 67.8% of patients were women and 39.4% were African-American. About half were independent in all activities of daily living at hospital admission. **Table 1** lists the 10 most common reasons for hospital admission, classified by using the method of Charlson (33). The mean number of depressive symptoms at hospital admission was 4.5, and 34% of patients reported six or more symptoms. At admission, patients with six or more depressive symptoms had higher comorbidity scores, were more likely to have congestive heart failure or chronic obstructive pulmonary disease, had lower cognitive function scores, and were dependent in more activities of daily living (**Table 2**).

Three years after admission (**Figure**), the mortality rate was higher among patients with six or more depressive symptoms than among patients with five or fewer depressive symptoms (56% compared with 40%;  $P < 0.001$ ). Of the 376 patients with five or fewer depressive symptoms at admission, 78 (21%) died during the first year of follow-up, 121 (32%) died during the first 2 years, and 151 (40%) died during the 3 years. Of the 197 patients with six or more depressive symptoms on admission, 58 (29%) died in the first year, 88 (45%) died during the first 2 years, and 110 (56%) died during the 3 years. The unadjusted hazard ratio over 3 years of follow-up for patients with six or more depressive symptoms was 1.56 (95% CI, 1.22 to 2.00). Patients with six or more depressive symptoms were also slightly more likely than patients with five or fewer symptoms to be discharged to a nursing home (8.3% compared with 4.9%;  $P = 0.11$ ).



**Figure.** Mortality over 3 years (1095 days) in patients who had six or more depressive symptoms compared with patients who had five or fewer symptoms.

Although adjustment for physiologic severity, comorbid illness, dependence in activities of daily living, and cognitive function each reduced the strength of the association between depressive symptoms and mortality, in each case this association remained statistically significant (**Table 3**; models 2 to 5). After adjustment for all of these potential confounders, as well as age, ethnicity, sex, and living alone (**Table 3**; model 6), the mortality rate continued to be higher among patients with six or more depressive symptoms (hazard ratio, 1.34 [CI, 1.03 to 1.73]). The mortality rate associated with significant depressive symptoms exceeded that of 5 additional APACHE points, 1 additional comorbid condition, 3 additional dependencies in activities of daily living, or 7 additional errors on the Mini-Mental State Examination.

In a secondary analysis, we measured the association of depressive symptoms and mortality, treating depressive symptoms as a linear variable. After adjustment for the same potential confounders considered in the above analyses, each additional depressive symptom was associated with a 3.5% (CI, -0.4% to 7.5%) increase in the relative mortality rate ( $P = 0.07$ ). In a final analysis, we divided patients into the following categories on the basis of number of depressive symptoms: 0 or 1, 2 or 3, 4 or 5, 6 or 7, 8 or 9, or 10 or more symptoms. The respective hazard ratios for each of these categories were 1.0 (reference), 0.96, 1.09, 1.31, 1.34, and 1.41 ( $P$  for trend = 0.03).

**Table 2. Characteristics of Patients at Hospital Admission\***

Characteristic	Patients with $\leq 5$ Depressive Symptoms ( <i>n</i> = 376) <sup>†</sup>	Patients with $\geq 6$ Depressive Symptoms ( <i>n</i> = 197) <sup>†</sup>	<i>P</i> Value
Median age (interquartile range), <i>y</i>	79.2 (75.4–83.8)	78.7 (74.8–83.0)	>0.2
Women, %	66	71	>0.2
Nonwhite ethnicity, %	40	38	>0.2
Living alone, %	43	44	>0.2
Median Charlson Comorbidity Index score (interquartile range)	2 (1–3)	2 (1–3)	<0.001
Mean Charlson Comorbidity Index score $\pm$ SD	2.0 $\pm$ 2.1	2.6 $\pm$ 2.3	0.004
Comorbid conditions, %			
Previous myocardial infarction	19	20	>0.2
Congestive heart failure	20	37	<0.001
Chronic obstructive pulmonary disease	14	26	<0.001
Diabetes	17	19	>0.2
Cancer	20	20	>0.2
Median APACHE II score (interquartile range)	12 (9–15)	12 (10–15)	>0.2
Median cognitive function score (interquartile range) <sup>‡</sup>	19 (15–20)	18 (14–20)	0.15
Median dependent activities of daily living (interquartile range), <i>n</i>	1 (0–4)	3 (0–5)	<0.001

\* APACHE = Acute Physiology and Chronic Health Evaluation.

<sup>†</sup> Depressive symptoms were measured with the 15-item Geriatric Depression Scale.

<sup>‡</sup> Measured with the first 21 items of the Folstein Mini-Mental State Examination.

## Discussion

Although depressive symptoms are common in hospitalized patients (5–10), the relation of depressive symptoms to long-term mortality is not well understood. We therefore studied the relation between depressive symptoms and 3-year mortality in a diverse group of hospitalized medical patients. We found that the rate of death was 56% higher (CI, 22% to 100%) in patients with six or more depressive symptoms than in patients with fewer depressive symptoms. Patients with more depressive symptoms on admission had significantly more comorbid illness, functional impairment, and cognitive impairment at hospital admission. Although adjustment for these factors explained part of the association between depressive symptoms and mortality, patients with six or more depressive symptoms continued to have a 34% higher (CI, 3% to 73%) mortality rate after adjustment for each of these factors. Although depressive symptoms contribute less to the mortality rate than does the total burden of comorbid medical illness, the excess rate of death associated with depressive symptoms was greater than that conferred by one additional comorbid medical condition.

Our results are consistent with epidemiologic studies in community patients that showed an association between depressive symptoms and mortality (14, 15). Many of these studies, however, did not use validated methods of adjusting for comorbid illness and often did not control for baseline functional status, leaving it unclear whether depression may have simply been a marker for unmeasured illness severity and poor baseline health status. Of note, in one of the few community-based studies that adequately adjusted for comorbidity and functional status, the relation between depressive symp-

toms and long-term mortality was similar to the relation that we observed in acutely ill older patients: The report by Whooley and Browner (16) from the Study of Osteoporotic Fractures indicated that although much of the association between depressive symptoms and mortality is explained by greater comorbid illness and functional impairment in women with depressive symptoms, the mortality rate was still 31% higher among women with depressive symptoms after adjustment for these factors.

Most previous studies measuring the association between depression and mortality in patients with medical illnesses have considered only highly selected groups of patients. For example, Rovner and colleagues (17) found a similarly elevated risk for death in nursing home patients, and Roach and coworkers (34) showed an association between depression and mortality in critically ill adults, mostly with terminal illness. In a study limited to patients hospitalized with myocardial infarction, Frasure-Smith and associates (18) reported that patients with major depression were more than three times more likely to die over the subsequent 6 months than patients without depression. This large risk, which is considerably greater than the risk we report, may be explained in part by unmeasured confounders, given that differences between depressed and nondepressed patients in terms of comorbid illness, functional status, and cognitive status were not considered.

Only a few previous investigations have dealt with diverse groups of hospitalized general medical patients. For example, Koenig and colleagues (35) showed an association between depression and in-hospital mortality, and Ganzini and associates (36) found an association between depression and 30-month mortality in hospitalized veterans. Both of these studies had relatively small samples and were

limited almost entirely to men. In one of the few larger studies of general medical patients, Inouye and coworkers (4) recently showed that a functional status index that included depressive symptoms improved mortality predictions based on commonly used prognostic indices. Our results extend these studies by providing additional evidence of an association between depressive symptoms and mortality in a diverse group of general medical patients with multiple diagnoses. Furthermore, our results show that although greater levels of illness severity, comorbid illness, and functional dependence explain part of the previously described association, depressive symptoms remain a predictor of mortality after adjustment for these confounders.

Depressive symptoms in late life may be manifested in different ways, each of which suggest potential mechanisms for the relation between depression and mortality (37). For example, depressive symptoms can result in cognitive symptoms, such as disturbances in thinking, problem solving, and self-efficacy. Such deficits may be accompanied by diminished adaptive skills in the face of illness, including the inability to seek expert advice or adhere to necessary treatment regimens. For example, Ladwig and associates (38) reported that patients with depression after myocardial infarction are more likely to continue smoking than patients without depression. Affective symptoms, such as feelings of hopelessness, low self-esteem, and sadness, may discourage friends and families from providing needed assistance by resulting in behaviors that diminish the ability of older persons to marshal social support, such as discouraging friends and family from providing needed assistance. Psychomotor symptoms, such as decreased activity caused by psychomotor retardation, inertia, and increased passivity, may contribute to functional loss through lack of activity and exercise. Taken together, these processes may accelerate functional decline and prevent functional recovery in older persons with chronic illnesses (3, 39). We previously demonstrated in this group of

patients that those with the most depressive symptoms were both more likely to experience a decline in function and less likely to improve than patients with fewer depressive symptoms between admission and 3 months after admission (3).

Depressive symptoms may also increase the risk for death and poor outcomes through biological mechanisms. For example, it has been reported that wound healing is impaired in patients experiencing psychological stress (40). Another study (41) showed higher rates of ischemia during periods of psychological distress among patients with coronary artery disease.

One possible explanation of an association between depressive symptoms and mortality may be that rates of depression are higher in patients who believe that they are at risk for imminent death. However, if these beliefs resulted in depressive symptoms, one would expect the association between depression and mortality to be greatest during the early days of follow-up and to rapidly diminish with time. The survival pattern that we observed in our patients indicates that the association between depressive symptoms and mortality is not greater in the early days of follow-up.

An important strength of our study was the ability to control for other prognostic factors, such as comorbid illness, functional status, and cognitive status, that are associated with both depression and mortality. We previously demonstrated the utility of prognostic adjustment methods that combine physiologic instability, comorbid illness, and functional dependence in hospitalized older patients (3). Nonetheless, the relation among comorbid illness, cognitive function, and physical function in older people is complex, and complete risk adjustment may not be possible. It is also possible that depressive symptoms may be markers for other conditions associated with higher mortality that we did not measure, such as poor social support, malnutrition, and tobacco smoking (42–44).

On the other hand, our prognostic adjustment

**Table 3. Association between Depressive Symptoms and 3-Year Mortality**

Variable in Model	Hazard Ratio (95% CI)					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6*
≥6 depressive symptoms†	1.56 (1.22–2.00)	1.53 (1.20–1.96)	1.38 (1.07–1.76)	1.47 (1.14–1.88)	1.49 (1.16–1.91)	1.34 (1.03–1.73)
Physiologic severity (per point)‡	–	1.08 (1.05–1.11)	–	–	–	1.05 (1.02–1.08)
Comorbid illness (per point)§	–	–	1.23 (1.17–1.28)	–	–	1.21 (1.15–1.26)
Dependence in activities of daily living (per dependency)	–	–	–	1.11 (1.05–1.17)	–	1.07 (1.01–1.14)
Cognitive function (per error)¶	–	–	–	–	1.05 (1.02–1.09)	1.04 (1.00–1.07)

\* Model also adjusts for age, ethnicity, sex, and living alone.

† Compared with patients who had five or fewer depressive symptoms. Depressive symptoms were measured by using the 15-item Geriatric Depression Scale.

‡ Measured by using the Acute Physiologic and Chronic Health Evaluation II score.

§ Measured by using the Charlson Comorbidity Index score.

|| Measured by using the Katz scale.

¶ Measured by using the first 21 items of the Folstein Mini-Mental State Examination.

methods may have caused us to underestimate the association between depression and mortality. This is because the depressive symptoms that we measured at the time of admission had probably been present for an unknown length of time before hospitalization. If these depressive symptoms resulted in functional or cognitive impairment before hospitalization, adjusting for functional or cognitive impairment at the time of the hospitalization may have adjusted for part of the causal mechanism by which depression resulted in higher mortality rates.

Our study had several limitations. First, we excluded patients who could not be interviewed at admission, such as those with delirium or severe dementia, and those who were admitted to intensive care units and subspecialty medical services. Because patients excluded from our study may have different clinical characteristics than enrolled patients, it is not clear whether our results can be generalized to excluded patients.

Second, our measure of depression was depressive symptoms, not major depression, and we do not know how many patients in this study had major depression. Therefore, we cannot describe the relation between a clinical diagnosis of depression (based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition) and mortality (45). Nonetheless, our results clearly establish the prognostic importance of a simple, easy-to-administer inventory of depressive symptoms, given that reporting many of these symptoms is an independent predictor of long-term mortality. Furthermore, previous work suggests that depressive symptoms are clinically important regardless of whether patients qualify for a diagnosis of major depression (46, 47). This is because patients with subsyndromal depression represent much of the morbidity associated with depression in community-wide studies (46) and because the diagnostic criteria for major depression may not account for the possibility that depression may present differently in older patients than in younger patients (47).

Third, we do not know how many of our patients were being treated for depression; thus, we cannot determine the effects of treatment for depression on survival. However, to the extent that treatment of depression may mitigate adverse outcomes, treatment of depressed patients would have biased our results toward finding a lack of association between depressive symptoms and mortality. Similarly, because we do not know how many of our patients had a clinical diagnosis of depression, we are unable to determine the relation between clinically diagnosed depression and mortality.

Fourth, although our study represents one of the most comprehensive efforts to date to understand how the relation among depressive symptoms, co-

morbid illness, functional status, and cognitive status influences the association between depressive symptoms and mortality, we have measures of these variables at only one point in time. Further efforts to extend this understanding will require serial measures of each of these factors over time.

Fifth, our sample was not large enough to determine whether the relation between depressive symptoms and mortality varied in different subgroups. Finally, we did not have information on cause of death. This information, however, is of limited utility in older patients, in whom the cause of death is usually multifactorial (48, 49).

Although depressive symptoms are common in hospitalized older patients, they are usually not recognized or treated by clinicians (8, 13). This may reflect an emphasis on treatment of acute illnesses in the inpatient setting; however, depression is also under-recognized in primary care settings (50). The failure to recognize depressive symptoms may partly reflect a bias of clinicians toward recognition of problems that fit better within traditional biomedical paradigms over problems of a more psychosocial nature (51). This bias is implicitly supported by societal and public policy, which systematically discourages treatment of mental health concerns by placing greater restrictions on mental health care than on care for traditional medical concerns (52).

In conclusion, our results show that measurement of depressive symptoms in hospitalized older patients identifies a group at high risk for long-term mortality. Clinicians should not ascribe this high risk entirely to greater severity of illness in patients with more depressive symptoms, because the poor outcomes of depressed patients are not entirely accounted for by measurable differences in illness severity. Depression may have important interactions with medical illnesses that promote poorer outcomes. Future research should address whether treatment of depressive symptoms improves outcomes in these patients.

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