The Effect of Gender and Age at Onset of Depression on Mortality

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Background: Depression has a marked negative impact on geriatric patient mortality and morbidity. The risk factors and exact reasons for these effects are not well understood.

Method: Seeking to better define the factors, we retrospectively analyzed the effects of gender and age at onset of affective disorder in a naturalistic study of 192 geriatric patients consecutively admitted to a large midwestern tertiary care center between 1980 and 1987 for the treatment of unipolar depression.

Results: After controlling for age at index admission, patients with an onset of depression before age 40 suffered significantly ($p < .05$) less mortality in follow-up than those with onset after age 40. When effects of gender are examined, the effects of age at onset are most profound in women, with a threefold increase in the rate of death in the cohort with age at onset of depression after 70 years when compared to those with onset before age 40.

Conclusion: These results and those of others suggest that depressed elderly women with no previous history of affective disorder are at a markedly increased risk compared with elderly women with a history of affective illness for morbidity and mortality and that a significant proportion of elderly depressed patients are admitted to a psychiatric hospital for a depression that is secondary to serious medical illness.

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The effect of depression on the survival of older adults has come under increasing scrutiny. Evidence has emerged confirming the long held clinical notion that medically ill patients with coexistent affective symptoms have a poorer prognosis than those without affective symptoms.[1–3] Unfortunately, the exact causal nature and the extent of the types of affective and somatic illnesses involved in this association remain unclear. Part of the confusion stems from our lack of understanding of the etiology combined with our inability to confidently assess the causative factors in individual cases of geriatric depression.

Prior research has demonstrated that depressed elderly patients have more concomitant medical diagnoses and less family history of affective disorder[4] than younger patients. These factors suggest that the genetic contribution to depression between the two groups may be quantitatively or qualitatively different and that a greater proportion of the elderly admissions may be for depression that is associated with and perhaps secondary to serious medical illness (secondary depression). If this is so, since comorbid medical conditions should decrease overall survival, the initial clinical presentation and the overall prognosis should differ between elderly patients with a long history of affective illness admitted for an episode of recurrent unipolar depression and those admitted for first-episode, late-onset "unipolar depression" that is secondary depression. To test the hypothesis that many elderly patients presenting with unipolar depression may have secondary depression, we reviewed the charts of 192 elderly patients admitted for unipolar depression, separated the patients into groups based on their age at onset of depression, and analyzed their initial presentations with respect to survival.

METHOD

Patients

A computerized search of the database of The University of Iowa Hospitals and Clinics was performed to identify patients 65 years and older entered into the hospital database with the admitting diagnosis of any type of depression between January 1, 1980, and December 31, 1987. A total of 279 patients, representing 361 separate

admissions, were identified by the computer. The mean admission date was September 3, 1984 (range, February 2, 1980–December 17, 1987). Only the first admission (index) of each patient was used in the study. All available patient records were then reviewed. One hundred ninety-two patients had been admitted with an initial diagnosis of unipolar major depression by DSM-III criteria,[5] which was confirmed by the staff physician at the formal ward clinical evaluation after admission. Patients not meeting depression criteria, not staying for formal evaluation, or not diagnosed as suffering from unipolar depression by the staff physician were excluded from the study. This study met all institutional guidelines for retrospective research activities.

Variables

A subject was defined as having psychomotor retardation or agitation at the time of admission if he/she was specifically described as being "retarded" or "agitated" in the admission note or described as suffering from psychomotor disturbance per the three-factor "non-interactiveness with retardation or agitation" definition of Parker et al.[6] Hallucinations and delusions were counted as present if they were recorded in admission notes or in the initial mental status examinations. Comorbid illness was noted if it was recorded at the time of admission and appropriately documented or diagnosed by the time of discharge from the hospital. *Myocardial infarction* excluded all episodes where the only evidence of occurrence was an incidental electrocardiogram (ECG) with a diagnosis of myocardial infarction by ECG criteria. *Arrhythmia* was specifically defined as the presence of an abnormal ECG. *Organic brain disease* included Parkinson's disease, cerebrovascular disease, chorea, epilepsy, and any type of dementia. *Cancer* was defined as any active cancer or sarcoma with the exception of basal and squamous cell dermal carcinomas. *Length of stay* was defined as the number of days from admission to discharge from the Psychiatry Service. Clinical outcome, based on the global assessment of the patient by the discharging physician, was assessed per the method of Avery and Winokur.[7] Mortality data were ascertained through computer searches of the states of Iowa and Illinois death indexes. MedisGroup ASG (Admission Severity Group) scores[8] were provided by the University of Iowa Department of Medical Records. In this system, a wide variety of key clinical findings, including pathologic, radiologic, and laboratory abnormalities, are used to generate a severity of illness score of 0 to 4. An admission score of 4 is associated with a 60% in-hospital mortality rate, while fewer than 1% of patients with a score of 0 or 1 die during their hospitalization.

Data Analysis

To facilitate survival analysis, patients were divided into four roughly equivalent groups on the basis of age at onset of depression (< 40, 40–59, 60–69, 70+). Comparison of clinical characteristics used Student's t test and linear models (ANOVA and regression analysis with correction for multiple comparisons [Statview 4.1, Abacus, Berkeley, Calif.] for continuous dependent variables). Chi-square analysis was used for comparisons between categorical variables. Kaplan-Meier product limit survival curves[9] and Mantel-Cox proportional hazards linear rank statistical analyses[10] were performed using BMDP statistical software (BMDP Statistical Software, Inc., Los Angeles, Calif.). Since the 70+ group was significantly older than the three other groups, analyses were conducted with and without data from this late-onset group. These recalculations, using only the patients in the first three groups, where appropriate, are placed in brackets and immediately follow the p values calculated when using all available data.

Table 1. Demographic and Clinical Characteristics*

	Age (y) of Subjects When First Episode of Depression Occurred			
Onset	< 40	40–59	60–69	70+
N	42	47	53	50
Age, mean ± SD y	69.9 ± 5.4	71.6 ± 5.6	70.1 ± 5.0	75.6 ± 3.6[a]
Sex[b] Male/female	4/38	12/35	16/37	28/22
Alive at follow-up,[c] N(%)	32 (76)	25 (53)	30 (57)	26 (52)
Previous admissions,[d] mean ± SD	4.4 ± 4.3	3.3 ± 2.5	1.6 ± 2.3	0.8 ± 1.2
Previous episodes,[d] mean ± SD	5.4 ± 3.3	4.0 ± 2.7	1.8 ± 2.4	1.0 ± 1.4
Psychomotor activity[c]				
Retarded	18	21	23	23
Agitated	12	11	14	8
Hallucinations[c]				
Auditory	2	4	3	0
Visual	3	0	2	0
Tactile	0	0	0	0
Delusions	9	10	10	8

*Statistical analysis was by ANOVA, regression, or chi-square analysis unless otherwise stated.
[a]Different from other cohorts at .05 level via Student's t test.
[b]$p \leq .01$.
[c]Comparisons are not statistically significant by regression, chi-square, or ANOVA analysis.
[d]$p \leq .0001$.

RESULTS

The demographic and clinical characteristics of the treatment groups at the time of admission are given in Table 1. As one might expect, the 70+ group differed significantly ($p < .05$) from the three other groups with respect to age at current admission for depression. Earlier onset of the initial episode of depression was also associated with female gender (ANOVA, $p < .0001$ [$p < .006$]), prior admissions for depression (regression analysis, $p < .0001$ [$p < .0001$]), and prior episodes of depression

Figure 1. Kaplan-Meier Survival Plot of Age-at-Onset Groups for Both Men and Women

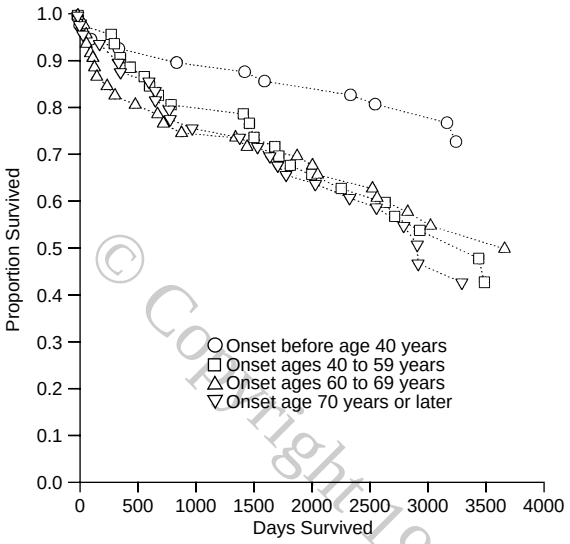
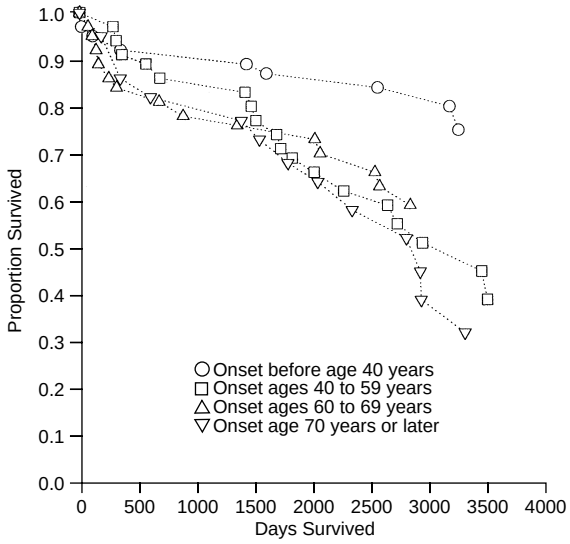


Figure 2. Kaplan-Meier Survival Plot of Age-at-Onset Groups for Women Only



(regression analysis, $p < .0001$ [$p < .0001$]). Clinical phenomenology such as psychomotor activity and psychosis did not correlate with age at onset.

Earlier onset of illness was strongly associated with increased survival. Patients who experienced their first episode of depression before age 40 experienced only half the mortality of patients from the later onset group. As a whole, patients from the < 40 group demonstrated significantly greater survival than patients from each of the three other groups (Figure 1; Mantel-Cox proportional hazards, $p < .05$ [$p < .05$]). Despite the fact that the 70^+ group tended to be significantly ($p < .05$) older than the other groups, the survival curves of the three later onset groups (40–59, 60–69, and 70^+) were not significantly different from one another. Yet all three later onset groups had significantly different ($p < .05$) survival curves than the youngest group (< 40).

Since men have a shorter life expectancy and since the proportion of males was significantly higher in the later onset groups than in the earlier groups, the datapoints corresponding to male patients were removed and the survival curves recalculated using data from only female subjects (Figure 2). Once again, the < 40 group had a significantly higher rate of survival (Mantel-Cox proportional hazards, $p < .05$ [$p < .05$]) than each of the three later onset groups. Survival of the three later onset groups did not significantly differ from one another despite the observation that the 70^+ group was significantly ($p < .05$) older than the two other later onset groups (40–59 and 60–69) (Mantel-Cox proportional hazards, $p < .05$). The overall mortality rate of women in the 70^+ group during the observation period was more than $2^1/_2$ times that of women in the < 40 group (0.68 vs. 0.25, respectively).

Later age at onset of depression was associated with an increased prevalence of certain comorbid medical illnesses at the time of index presentation to our clinical center (Table 2). Patients experiencing depression after the age of 40 were significantly more likely to present with clinically evident congestive heart failure (CHF; ANOVA, $p < .01$ [$p < .02$]) and chronic obstructive pulmonary disease (COPD; ANOVA, $p < .01$ [$p < .05$]) than patients with an early onset of depression. Although the 70^+ group had a higher number of prior myocardial infarction than the other groups, univariate analysis demonstrated only a mild, statistically nonsignificant association (ANOVA, $p \cong .09$ [$p \cong .99$]) between ischemic heart disease and age at onset of the initial episode of depression. The other conditions listed in Table 2 did not significantly correlate with age at onset.

The presence or absence of a particular diagnosis is not always the best predictor of future mortality. Therefore, MedisGroup scoring (ASG), a robust prognosticator of future morbidity and mortality, was performed in a random sampling of half the patients enrolled in the study. In this system, patients are assigned a severity of illness score from 0 to 4 on the basis of a wide variety of key initial laboratory, radiologic, and clinical findings. An admission score of 4 is associated with a 60% in-hospital mortality, while less than 1% of the patients assigned a score of 0 or 1 die during their hospitalization. As shown in Table 2, univariate (ANOVA) analysis using these scores demonstrated that severity of medical illness strongly correlated with age at onset of depression ($p < .02$ [$p < .27$]) only when the 70^+ group was included. Since this suggested that the older patients from the 70^+ group may have biased the calculation, post hoc testing

was performed. Consistent with that hypothesis, a t test showed that the 70+ group was significantly more ill than the pooled earlier onset groups (first three groups ASG 0.41 ± 0.49; 70+ ASG 0.93 ± 0.61, $p < .001$). Surprisingly, although the patients with onset after age 40 were objectively more physically ill, their length of stay in the hospital was slightly, though not statistically significantly, lower than that for the patients with onset before age 40. Likewise, the patients with onset after age 40 were not more likely to be admitted to the more medically intensive medical psychiatry unit than those from younger groups.

Age at onset also was not associated with subsequent clinical improvement of the depression by the time of discharge. Although the rate of complete improvement was slightly numerically lower in the < 40 group, the rate of improvement of depression did not differ significantly between the four groups.

CONCLUSION

The findings demonstrate a clear association between a later onset of depression and (1) the presence of certain concomitant physical illness and (2) higher clinical mortality. Before accepting these results, a few caveats concerning the methodology should be considered. First, the study design is naturalistic. Thus, the information gathered from the charts is subject to the precision and biases of the reviewers and the recall ability of the patients. The treatment of the patients is subject to the biases of the individual treating physicians and the medico-social context in which the patient was seen. This point is perhaps very important, since the signs and symptoms of geriatric depression are often overlooked and undertreated in the physically ill geriatric population.[11] Second, since the main endpoint of the study, death, is ascertained through a regional system of death indexes, the study assumes that there are no overall differences in the state of residence between the groups in the period after discharge.

Overall, the composition of the various groups is clearly gender-biased: the < 40 group comprises more than 75% females, while the later onset groups are closer to a 50:50 representation of both genders, which is consistent with previous findings.[12] The greater proportion of females in the < 40 group is in keeping with previous studies showing a 2:1 female-to-male ratio in the incidence of major depressive disorder (MDD) in the general population.[13] The change in this ratio in the later onset groups both complicates the interpretation of survival analysis in this study and suggests that the etiology of MDD may differ between the earlier and the later onset groups. This point is particularly significant for investigators conducting studies of the genetic causes of MDD. It suggests that the methodologies of their studies include an age cutoff point in the process of determining whether a patient is affected.

Table 2. Medical Comorbidity and Clinical Outcome

Onset	< 40	40–59	60–69	70+
N	42	47	53	50
Disease				
Congestive heart failure[a]	0	1	5	7
Arrhythmia[b]	29	32	33	35
Myocardial infarction[b]	4	1	5	11
Valvular[b]	0	2	2	4
Other heart[b]	1	1	2	1
Chronic obstructive pulmonary disease[a]	0	2	3	9
Emphysema[b]	1	0	0	0
Other lung[b]	0	2	0	0
Hypertension[b]	18	15	15	17
Diabetes[b]	3	7	6	5
Organic brain[b]	8	7	13	6
Cancer[b]	2	4	3	3
Ward[b]				
Psychiatry	42	44	52	47
Medical-Psychiatric	0	3	1	3
MedisGroup severity, mean ± SD	0.25 ± 0.44	0.60 ± 0.49	0.46 ± 0.49	0.93 ± 0.61[c]
Length of stay,[b] mean ± SD d	39 ± 21	35 ± 23	38 ± 20	35 ± 21
Improvement[b]				
Complete	8	18	17	16
Improved	29	22	34	31
Not improved	5	7	2	3

[a] $p \leq .01$ by ANOVA.
[b] Comparisons are not statistically significant by ANOVA, chi-square, or regression analysis.
[c] Different from other cohorts at .05 level via Student's t test.

Survival analysis demonstrates clear differences ($p < .05$) in survival rates between the groups (Figure 1). This difference persists even if the latest onset group is omitted from the analysis. Conceivably, given the shorter life expectancy of men, this difference may have arisen from the steady increase in the percentage of males from the early onset to the later onset groups. However, after removal of the male patients from the analysis, the relationship between later initial onset of depression and increased mortality is still significant ($p < .05$) (Figure 2). This suggests that the differences observed in the initial analysis may be secondary to excessive female mortality and not simply due to the disproportionate number of males in the later onset groups. It would be interesting to see if the survival curves for men parallel the survival curves for women in the same group. Unfortunately, the paucity of males in the earlier onset groups precludes this analysis. The interpretation of these survival analyses is also complicated by the fact that on average, patients in the 70+ group are older than patients in the < 40 group. However, the significance of the relationship between later age at onset and increased rates of mortality holds whether or not the 70+ group is included in the analysis, suggesting that causal factors may underlie these differences.

The findings shown in Table 2 may account for some differing rates of mortality between groups. Cardiopulmonary disease (COPD and CHF) seems to be correlated with late onset of depression, whether or not the 70+ group is included in the analysis. Perhaps this correlation is not surprising since both syndromes share the symptoms of easy fatigability and disturbed rest that are common with MDD. Unlike the current study, prior studies have demonstrated an association of MDD or depressive syndromes with an increased risk of subsequent myocardial infarction or poor outcome after myocardial infarction.[2,14–16] This association may be secondary to the small number of patients who had infarcts in our study and suggests that a larger number of subjects may be necessary before a clear correlation can be demonstrated between the onset of depression late in life and increased risk for myocardial infarction.

Previous studies have reported that depressive symptoms often accompany hypertension,[17] diabetes,[18] and organic brain disease,[19] which includes strokes and dementia in this context. In our study, these diseases were not significantly associated with a later onset of depression. However, it should be noted that in our study, only associations between later onset, not overall incidence, of depression and comorbid illness were examined and that the definitions of these diagnoses used in assigning the retrospective illness were fairly broad. Furthermore, greater numbers and more severe presentations may be needed before a clear association between these conditions and MDD can be demonstrated.

Although the relationship between later onset of depression and both CHF and COPD is highly significant, it may be that the exact nature of the illness is not as important as its severity. To test that hypothesis, we used the MedisGroup severity score (ASG), a well-proven predictor of future morbidity and mortality independent of clinical diagnosis,[8] to assess the relationship between overall severity of illness and age at onset of depression. The initial analysis of the database using all 192 patients demonstrated a significant correlation between age at onset of depression and severity of medical illness (ASG) ($p < .001$). However, once the 70+ group, which was significantly older than the other three groups, was omitted from analysis, the significance of the relationship between age at onset and severity of medical illness disappeared. Furthermore, post hoc testing demonstrated that high mean ASG of the 70+ group was significantly different from that of the pooled ASG of the first three groups, which do not differ significantly in age. Taken together, these results tend to refute the hypothesis that the later onset is secondary to overall medical illness and suggests that the relationship between later onset of depression and cardiopulmonary illness bears further investigation.

Is there a direct relationship between the onset of medical illness and the onset of depression in this population? Given the plethora of positive studies demonstrating the association of various medical illnesses with the onset of depression, the answer is probably yes. But, unfortunately, studies such as this one cannot demonstrate causal relationships between variables, nor is it plausible or ethical to design studies to test this hypothesis. Still, this study extends the findings of previous studies that demonstrated excessive mortality in depressed medically ill patients[1–3,20,21] by identifying a subset of the depressed elderly, those with cardiopulmonary disease but with no long history of prior depression, as being at increased risk for subsequent mortality. This finding suggests that in the increasingly cost-conscious climate in the health care industry, depressed medically ill patients may be the best candidates for medical intervention aimed at reducing overall mortality. Additionally, for investigators searching for genetic causes of depression, these findings suggest that the genetic factors involved in the etiology of the syndrome of late-onset depression may differ from those involved in the onset of depression early in life.

In summary, this study demonstrates that in geriatric populations, hospitalized for the treatment of depression, those patients who have an initial hospitalization for depression late in life have a significantly greater risk of cardiopulmonary comorbidity and mortality than those who had their initial hospitalization for depression before age 40. Thus, on the basis of our findings, we suggest that clinicians be particularly mindful of possible medical comorbidity in depressed geriatric patients presenting with a late initial onset of depression.

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