

Does Delirium Predict Mortality Among Hospitalized Non Demented Elderly? A 3 Months Follow Up Study

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Abstract: In order to study the association between mortality and delirium, a prospective, observational study on 114 elderly 60 years or older medical inpatients, admitted to El-Demerdash hospital Ain Shams University, Cairo, Egypt (Geriatric and Gerontology department), divided into 2 cohorts: 52 patients had prevalent delirium, and 62 controls had no delirium as assessed by the confusion assessment method (CAM) and went through; a) comprehensive geriatric assessment including assessment of cognitive function by the mini mental state examination (MMSE) b) Assessment for pre-hospital cognitive function to the delirious group. c) 3 months follow up by telephone contact to detect mortality. The results was as the following: mortality was significantly ($P = <0.001$) higher in the delirious group 68.8% versus 13.6% in the non delirious group also the median survival duration was significantly shorter in cases than control, with the highest mortality during the first month of follow up (58.3% of cases). Hypoactive delirium was the most prevalent type (69.4% of cases), and it was found to be an independent risk factor in cases mortality. Delirium increases mortality in elderly non demented patients, even after control for confounding variables, mortality is highest during the 1st month of follow up. Hypoactive delirium is an independent risk factor for cases mortality.

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1-Introduction;

Delirium is a clinical syndrome characterized by an acute decline in attention and cognition, it is common in hospitalized and post acute care patients (Kiely *et al.*, 2004). It has been found to be related to several adverse outcomes, including a longer mean length of hospital stay, poor functional status, need for institutional care and mortality (Cole & Primeau, 1993).

With respect to mortality, previous studies have reported association between delirium and mortality, although findings have been not consistent (Rabins & Folstein, 1982) some studies have reported higher inpatient mortality (Siddiqi *et al.*, 2006; Adamis *et al.*, 2006), others not as Inouye *et al.*, 1998, some have reported higher subsequent mortality risk after delirium with various periods of follow up (Rockwood *et al.*, 1999; McCusker *et al.*, 2002) but others not (Francis & Kapoor, 1992, Inouye *et al.*, 1998; Several studies with up to 2 years of follow up reported no significant increase in post discharge mortality (Francis *et al.*, 1990, Pompei *et al.*, 1994). A meta- analysis of eight studies (Cole & Primeau, 1993) estimated a mortality rate of 14.2% for delirious patients at 1 month and 22.2% at 6 months and concluded that the presence of dementia or the severity of illness or both, have influenced the high rate.

Delirium superimposed on dementia (DSD) is highly prevalent and associated with high mortality among elderly patients, demented patients who experienced delirium during hospitalization had a more

than twofold increased risk of mortality in a 12 months follow up study than did patients with dementia alone, with delirium alone, or with neither dementia nor delirium. (Bellelli *et al.*, 2007)

Nevertheless, studies that assess effect of delirium on mortality have a number of methodological limitations, including limited follow-up, and inadequate control of confounding factors such as dementia, comorbidity, and severity of illness. For these reasons this study was conducted, excluding patients with dementia and terminally ill patients, and with matching between cases and control as regarding; sex, educational level and co morbid diseases to decrease some important confounding variables, in order to detect effect of delirium on 3 months mortality among hospitalized non demented elderly patients, compared to matched control. The duration of 3 months follow up was established on the basis of previous studies (McCusker *et al.*, 2002; Gonzalez *et al.*, 2009) that found the survival curve for delirious patients decreased rapidly during the first month after enrollment.

2-Material and methods:

This prospective, observational, cohort study was conducted on elderly patients admitted to El-Demerdash hospital Ain Shams University, Cairo, Egypt (geriatric and gerontology department) during the period from 21\6\2009 to 2\2\2010.

We compared 3 months mortality outcome in 2 cohorts, a delirium cohort detected during the first 48 hours of hospitalization by CAM and a control cohort without delirium.

Participation was based on informed consent from those with capacity to give this, or on agreement from caregiver for those without this capacity, and the study was approved by the scientific board of Geriatrics and Gerontology department, faculty of medicine Ain Shams University. Cairo, Egypt.

Subjects; Inclusion criteria; Only elderly patients (60 years and above) males or females who accepted to participate in the study.

Exclusion criteria; a) Patients with history of dementia. b) Terminally ill patients c) Patients with communication difficulties (sever deafness and aphasia).

Diagnosis of delirium was done during the first 48 hours of admission using the CAM. Delirious patients were 52 cases, controls were selected from patients who were screened for delirium and found not to have it, and controls were 62 patients.

Procedures:

All assessments were done by an experienced geriatrician and each participant underwent;

- A- Geriatric assessment in the form of detailed history taking and physical examination
- B- Assessment of delirium within 48 hours after admission using the confusion assessment method (CAM) to differentiate between cases and control. The confusion assessment method is a structured interview that assesses 9 symptom domain of delirium specified in the Diagnostic and Statistical Manual of Mental Disorders Revised Third Edition. The validity of the CAM algorithm has been demonstrated to have 95% sensitivity and specificity even in a population with a high prevalence of dementia (Inouye *et al.*, 1990).
- C- Exclusion of demented patients was by the MMSE (Mini Mental State Examination), it is the most widely used screening instrument for detection of cognitive impairment in the elderly (Folstein *et al.*, 1975). Many studies have shown that the MMSE has got a high construct validity and test-retest reliability (Tombaugh & McIntyre, 1992). We used the Arabic version (El Okl, 2002) results were correlated with the age and educational level of the participants (Crum *et al.*, 1993), the MMSE was applied to the 2 groups, the non delirious and the delirious patients.
- D- Assessment for pre-hospital cognitive function (Fick, & Mion, 2007) was done to the delirious group through; 1) Reviewing of the patient's medical record for indications of pre-existing dementia and/or functional difficulties. 2) Asking the patient's relatives and caregivers living with the

patients, whether the patient had a diagnosis of dementia or signs and symptoms of possible dementia. Ask about mental status in past 6 months to one year. 3) If a patient was admitted from an assisted living or long term care facility, question the staff about the patient's baseline mental and functional status. 4) Complete a tool, such as the Family Questionnaire, to help assess pre-hospital cognitive and functional abilities, but this 4th point was omitted, due to the high illiteracy level of the participants.

For patients with delirium, the combination of both the MMSE and the pre-hospital cognitive function assessment were used to exclude patients with dementia.

E- Follow up of patients to detect mortality outcome after 3 months was done using telephone interview.(telephone contact was done first after hospital discharge, then every 2 weeks)

3- Statistical analysis and results

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, unpaired student t-test, chi-square, spearman rho test, stepwise logistic regression by SPSS V17.

The study included 114 patients, 52 cases and 62 controls, recruited from geriatric and gerontology department Ain Shams University Hospital, Cairo, Egypt.

The mean age of cases was 71.4 ± 7.6 years and mean age of control 68 ± 6.3 years, and this was statistically significant as shown in table (1), 4 patients were lost to follow up in the delirious group versus 3 patients in the non-delirious group representing 6% of the initial sample and there was no statistically significant differences found between these patients and those who completed the study with respect to baseline variables.

No significant difference between cases and control as regards past medical history, also no significant difference between cases and control as regards causes of admission (primary medical diagnosis at admission), indicating matching between the 2 cohorts regarding co-morbid diseases as shown in table (1). Number of co-morbidities was significantly higher in cases than control, as shown in table (1).

The estimated 3 months mortality in the delirium cohort was 68.8% and for the control cohort 13.6% and this was of statistical significance, as shown in table (2).

The mortality was higher in the first month after enrollment, as 58.3% of cases died during 1st month and median survival duration significantly shorter in cases than control, as shown in table (2)

In the delirium cohort the unadjusted Kaplan-Meier mortality curves showed that mortality increased

rapidly during the 1st month after enrollment and then continued to increase but more slowly, while the mortality curve in the control cohort increased more slowly, figure (1).

Presence of 2 or more co-morbidities and primary medical diagnosis at admission (cause of admission) showed that there was no statistically significant difference between alive and died cases, as shown in table (3).

In the delirium cohort, the most prevalent type of delirium was the hypoactive type as it represented 69.2% of cases, as shown in table (3).

Hypoactive delirium was found to be an independent risk factor for cases mortality by logistic regression model as shown in table (4).

Comparison between cases and control with one comorbidity as regards outcome showed that death was significantly higher in cases than control with Relative risk=4.47, Case had a probability to die 4.47 times like control as shown in table (5), also comparison between cases and control with ≥ 2 comorbidity as regards outcome showed that Death was significantly higher in cases than control with Relative risk=2.16, Case had a probability to die 2.16 times like control as shown in table (5).

Table (1): Comparison between cases and control as regards demographic data, co-morbid diseases and cause of admission;

	Case (N=52)	Control (N=62)	χ^2/t value	P value
Age (Yr; Mean \pm SD)	71.4 \pm 7.6	68 \pm 6.3	2.636 [#]	0.010*
Sex (n,%)				
• Male	14 (26.9%)	27 (43.5%)	3.394 ^{&}	0.065
• Female	38 (73.1%)	35 (56.5%)		
Occupation (n,%)				
• Retired	14 (26.9%)	24 (38.7%)	2.832 ^{&}	0.243
• Manual	1 (1.9%)	3 (4.8%)		
• Others	37 (71.2%)	35 (56.5%)		
Marital status (n,%)				
• With spouse	24 (46.2%)	43 (69.4%)	6.283 ^{&}	0.012*
• Without spouse	28 (63.8%)	19 (30.6%)		
Living with (n,%)				
• Alone	5 (9.6%)	8 (12.9%)	10.778 ^{&}	0.013*
• With spouse	16 (30.8%)	33 (53.2%)		
• With children	21 (40.4%)	9 (14.5%)		
• With both	10 (19.2%)	12 (19.4%)		
Smoking (n,%)				
• Smker	18 (35.3%)	28 (45.2%)	1.129 ^{&}	0.228
• Non/Ex-smoker	33 (64.7%)	34 (54.8%)		
DM (n, %)				
• Absent	22 (42.3%)	22(35.5%)	0.556	0.757
• Controlled	9 (17.3%)	12(19.4%)		
• Uncontrolled	21 (40.4%)	28(45.2%)		
HTN (n, %)				
• Absent	14 (26.9%)	16(25.8%)	0.076	0.963
• Controlled	18 (34.6%)	23(37.1%)		
• Uncontrolled	20 (38.5%)	23(37.1%)		
IHD (n, %)	12 (23.0%)	20(32.3%)	1.050	0.305
AF (n,%)	7 (13.5%)	8 (12.9%)	0.008	0.930
COPD (n, %)	10 (19.2%)	22(35.5%)	3.700	0.054
RI (n, %)	2 (3.8%)	3 (4.8%)	0.066	0.797
Old CVS (n, %)	19 (36.5%)	22(35.5%)	0.014	0.907
Recurrent CVS (n, %)	4 (7.7%)	2 (3.2%)	1.132	0.287
TIA (n, %)	3 (5.8%)	5 (8.1%)	0.251	0.616
Cause of admission				
• Vascular	29 (55.8%)	28 (45.2%)	3.254	0.196
• Uncontrolled DM	7 (13.5%)	5 (8.1%)		
• Infections	16 (30.8%)	29 (46.8%)		
No. of comorbidities				
• One	20 (38.5%)	49 (79.0%)	19.483	<0.001*
• \geq Two	32 (61.5%)	13 (21.0%)		

DM = diabetes mellitus, HTN= hypertension, IHD= ischemic heart disease, AF= atrial fibrillation, COPD= chronic obstructive pulmonary disease, RI= renal impairment, CVS= cerebrovascular disease, TIA= transient ischemic disease.

Table (2): Comparison between cases and control as regards mortality outcome:

	Case (N=48)	Control (N=59)	$\chi^2/z^\#$ value	P value
Outcome Ω				
• Alive	15 (31.3%)	51 (86.4%)	34.111 ^{&}	<0.001*
• Died	33 (68.8%)	8 (13.6%)		
Survival duration in days (Median, IQR)	26 (11-90)	90 (90-90)	-5.829 [#]	<0.001*

Ω 4 cases and 3 controls were failed to know their outcome
& Chi square test # Mann Whitney test *Significant

Unadjusted Kaplan-Meier mortality curves showed that mortality increased rapidly during the 1st month after enrollment.

Table (3): Comparison between alive and died cases as regards causes of admission, No. of comorbidities and type of delirium;

	Live (N=15)	Died (N=33)	χ^2 value ^{&}	P value
Cause of admission				
• Vascular	8 (53.3%)	20(60.6%)	0.432	0.806
• Uncontrolled DM	2 (13.3%)	5 (15.2%)		
• Infections	5 (33.3%)	8 (24.2%)		
No. of comorbidities				
• One	7 (46.7%)	12(36.4%)	0.458	0.499
• \geq Two	8 (53.3%)	21(63.6%)		
• Hypoactive	8 (53.3%)	26(78.8%)	3.728	0.155
• Hyperactive	6 (40.0%)	5 (15.2%)		
• Mixed	1 (6.7%)	2 (6.1%)		

DM= diabetes mellitus.

Table (4): Logistic regression model for independent risk factors of cases mortality:

	B	S.E.	P value	Odd ratio	
				value	95% C.I.
Hypoactive	1.689	0.794	0.034	5.412	1.014-25.68

Beginning with different risk factors in a logistic regression model; Hypoactive type was found to be independent risk factor in cases mortality.

Table (5): Comparison between cases and control (with one pathology) as regards outcome

	Case with one comorbidity (N=10)	Control with one comorbidity (N=46)	χ^2 & z [#] value	P value
Outcome				
• Died	12 (63.2%)	6 (13.0%)	16.865 ^{&}	<0.001*
• Alive	7 (36.8%)	40 (87.0%)		
	Case with ≥ 2 comorbidity (N=29)	Control with ≥ 2 comorbidity (N=13)	χ^2 & z [#] value	P value
Outcome Ω				
• Died	21 (72.4%)	2 (15.4%)	11.784 ^{&}	<0.001*
• Alive	8 (27.6%)	11 (84.6%)		

& Chi square test *Significant

Death was significantly higher in cases than control **with one comorbidity** Relative risk=4.47, Case had a probability to die 4.47 times like control. Death was significantly higher in cases than control **with ≥ 2 comorbidity** Relative risk=2.16, Case had a probability to die 2.16 times like control

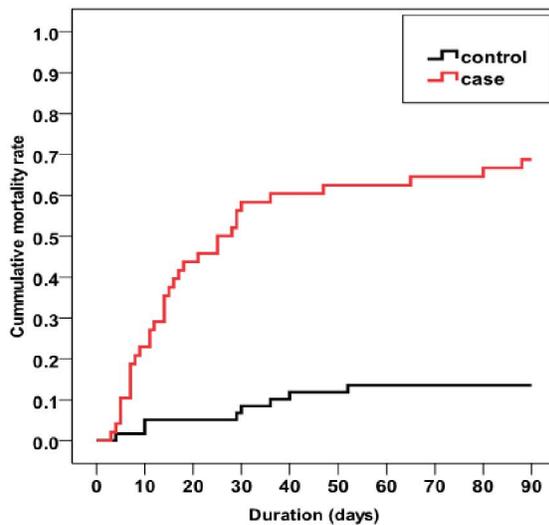


Figure (1) mortality rate of studied cases and control

4-Discussion

The results of this study indicate that the association between 3 months mortality and delirium is significant, as mortality rate in the 48 delirious patients who completed the 3 months follow up was 68.8% (33 patients) versus 13.6% (8 patients) in the 59 non delirious patients, and this was statistically significant, also median survival duration was significantly shorter in cases than control, even after adjustment for most confounding variables, as sex, cognitive function, as demented cases were excluded, and co-morbid diseases as terminally ill patients were also excluded, cause of admission (primary medical diagnosis at admission) was not significantly different between the two groups, our results showed that one or more co-morbid diseases is a risk factor for delirium as shown in table (1), but this significant difference between cases and control regarding number of co-morbid diseases is not found between the died and alive cases as shown in table (3), results also found that comparison between cases and control with one comorbidity and between cases and control with two or more comorbidities showed that death was significantly higher in cases than control, from this we can conclude that number of co-morbidities is not a direct cause of death. So we can say that delirium per say is a predictor for mortality after controlling for most confounding variables.

Previous researches discussing this topic showed conflicting results. Some studies didn't find this relation as, Adamis *et al.* (2007). Didn't find delirium to be an independent predictor of mortality six months after hospital discharge, nor did Inouye *et al.* (1998) in a study that examined patients three months after discharge.

Gonzalez *et al.* (2009), detected the 3 months mortality rate as 25.9% in delirious patients versus 5.8% in non delirious, they concluded that delirium was independently associated with mortality, this difference in death rates could be due to larger sample size (192 delirious patients), also they included incident delirium only.

In a 12 months follow up study (McCusker *et al.*, 2002), they introduced a more control of confounding factors and detected that delirium was an independent marker for mortality, the estimated 12 months mortality rate was 63.3% for the delirium cohort and 17.4% for the control, this high mortality rate could be explained by the longer duration of follow up, the larger sample size (361) and the older age group of the cases as 47.3% of the delirium cohort were above 85 years.

While other studies that detected association between delirium and mortality as an outcome showed a wide range of death rates from 6.1% to 62% (Siddiqi *et al.*, 2006).

The lowest values (6.1%) were obtained from one study (Villalpando-Berumen, 2003) that included only incident delirium cases.

Two studies (Inouye *et al.*, 1998, Navinés *et al.*, 2001) reported that delirium is associated with mortality rate 9% and 23.9% respectively in hospitalized patients, and this is lower than our study as they detected inpatient mortality only.

This high mortality rates found in our study, 68.8% of the delirious group died within 3 months of follow up versus 13.6% in the control group, could be explained by the high illiteracy level of the participants which can delay the admission to hospital and also will affect post hospital care after discharge, from this we can recommend that health care professionals in our community and in similar communities should increase the awareness of elderly and their care givers about the causes, clinical picture, complications, prevention and management of delirium.

Prevalent delirium seems to be a strong marker of high risk of mortality for up to 3 months after delirium in non demented elderly patients, even after controlling most confounding variables, but the highest mortality was in the 1st month, as detected by the unadjusted Kaplan-Meier mortality curves that showed that mortality increased rapidly during the 1st month after enrollment, and this agreed with most of the researches assessing delirium and mortality ((McCusker *et al.*, 2002; Gonzalez *et al.*, 2009). From this we can say that there should be great care for delirious patients especially during 1st month of follow up.

Furthermore, among non demented patients with delirium, hypoactive delirium was the most prevalent and by logistic regression model for independent risk factor for case mortality we found that hypoactive

delirium is an independent risk factor for case mortality as shown in table (4).

These findings agreed with Kiley *et al.* (2007) they found that hypoactive patients were 1.6 times more likely to die during the 1-year follow up period than patients with hyperactive or mixed type. On the other hand, Sagawa, Akechi *et al.* (2009) detected that hyperactive delirium was the commonest type, this might be due to specific etiologies in the cancer patients as this study was on cancer patients only.

The limitations of the current study were directed toward the small sample size, which is mainly related to the lack of cooperation of elderly individuals as the concept of doing scientific research is still not widespread among our community, also the need to assess this relation between mortality and delirium in non demented elderly with more control of confounding variables as age. So, further studies are recommended among more participants using different types of tests to support our results.

5-Conclusion

Delirium increases mortality in elderly non demented patients, mortality is highest during the 1st month of follow up. Hypoactive delirium is an independent risk factor for cases mortality. So delirium, even in non demented elderly, should be considered a significant serious problem and a marker for mortality, detection of delirium should promote efforts to identify and treat underlying medical problems and identify potentially modifiable factors leading to delirium and subsequently death, also post discharge interventions are important as mortality is sustained beyond hospital discharge.

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