The attributable mortality of delirium in critically ill patients: prospective cohort study

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STUDY QUESTION

What is the mortality due to delirium in critically ill patients?

SUMMARY ANSWER

Delirium prolongs stay on an intensive care unit but does not cause death in critically ill patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous observational studies have suggested that delirium increases the risk of death in critically ill patients by up to threefold but failed to adjust for confounding caused by time varying disease severity and for competing events that occur during intensive care unit admissions. Our study suggests that delirium does not cause short term mortality in critically ill patients after correction for time dependent sources of confounding.

Participants and setting

Consecutive adults admitted to a 32 bed mixed intensive care unit in the Netherlands for a minimum of 24 hours.

Design, size, and duration

Prospective cohort study of 1112 patients admitted between January 2011 and July 2013. Trained observers evaluated delirium daily using a validated protocol, which included a confusion assessment method for evaluation on the intensive care unit. The primary outcome of interest was mortality during admission to an intensive care unit. We used logistic regression and competing risks survival analyses to adjust for baseline variables, treating discharge from the intensive care unit as a competing risk for mortality. In addition, to adjust for confounding by evolution of disease severity before the onset of delirium, we performed a marginal structural model analysis.

Main results and the role of chance

Delirium was significantly associated with mortality in the multivariable logistic regression analysis (odds ratio 1.77, 95% confidence interval 1.15 to 2.72) and survival analysis (subdistribution hazard ratio 2.08, 95% confidence interval 1.40 to 3.09). However, the association disappeared after adjustment for time varying confounders in the marginal structural model (subdistribution hazard ratio 1.19, 95% confidence interval 0.75 to 1.89). Using this approach, only 7.2% (95% confidence interval −7.5% to 19.5%) of deaths in the intensive care unit were attributable to delirium, with an absolute mortality excess in patients with delirium of 0.9% (95% confidence interval −0.9% to 2.3%) by day 30. In post hoc analyses, however, delirium that persisted for two days or more remained

Cumulative incidence of observed and estimated mortality during stay on intensive care unit (ICU)
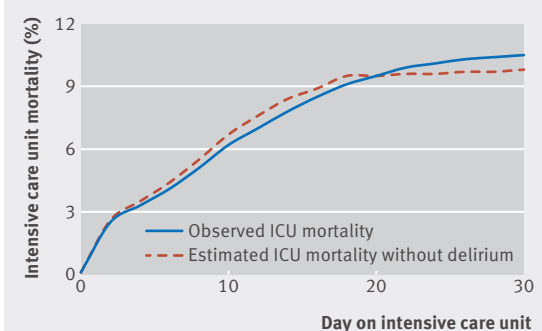
associated with a 2.0% (95% confidence interval 1.2% to 2.8%) absolute mortality increase. Furthermore, competing risk analysis showed that delirium of any duration was associated with a significantly reduced rate of discharge from the intensive care unit (cause specific hazard ratio 0.65, 95% confidence interval 0.55 to 0.76).

Bias, confounding, and other reasons for caution

Since this is an observational study we cannot rule out residual confounding, even after accounting for a relatively large number of covariables. Furthermore, because the assessment of delirium in unresponsive patients is impossible and the statistical models that we used required a dichotomous classification of participants, we chose to recategorise patients who were comatose as delirious and patients who were sedated as non-delirious. In doing this, we cannot rule out the possibility of misclassification being introduced. Finally, delirium can be the first symptom of an impending complication, such as sepsis acquired in the intensive care unit. When this happens, any mortality due to this sepsis event may be falsely attributed to delirium. The true association between delirium and mortality may then be weaker than we report.

Generalisability to other populations

The results are generalisable to other critically ill patients, although the association between delirium and death may vary among centres using different strategies from ours for the prevention or treatment of delirium.

Study funding/potential competing interests

Mediterranean diet and telomere length in Nurses' Health Study: population based cohort study

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STUDY QUESTION
What is the association between adherence to the Mediterranean diet and leukocyte telomere length?

SUMMARY ANSWER
Greater adherence to the Mediterranean diet is significantly associated with longer telomeres, even after adjustment for potential confounders.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Telomere length variability may be partially explained by lifestyle practices, but no study has examined whether adherence to the Mediterranean diet is associated with longer telomere length, a biomarker of aging. Greater adherence to the Mediterranean diet was associated with longer telomeres, further supporting the benefits of adherence to the Mediterranean diet for promoting health and longevity.

Design
The Nurses' Health Study is an ongoing prospective cohort study of 121 700 nurses enrolled in 1976. In 1989-90 a subset of 32 825 women provided blood samples.

Participants and setting
Nested case-control studies of telomere length and incident chronic disease were conducted within the blood sub-cohort of the Nurses' Health Study. We included in this analysis 4676 disease-free women from this sub-cohort with telomere length measured who had also completed food frequency questionnaires.

Primary outcome(s)
The main outcome was relative telomere lengths in peripheral blood leukocytes measured by quantitative real time polymerase chain reaction.

Main results and the role of chance
No differences existed in the distributions of main lifestyle factors between the study participants (n=4676) and the rest of the Nurses' Health Study blood sub-cohort (n=32 825) after age standardization. In this large cross sectional study of healthy middle aged and older women from the well characterized Nurses' Health Study, greater adherence to the Mediterranean diet was significantly associated with longer leukocyte telomere length (P for trend=0.016), even after adjustment for multiple confounders (P for trend=0.004). Notably, whereas higher adherence to the Mediterranean diet was significantly associated with longer leukocyte telomere length, none of the individual components showed an association with leukocyte telomere length.

Bias, confounding, and other reasons for caution
The cross sectional design precludes us from establishing a temporal association between dietary habits and telomere length. Leukocyte telomere length was assessed using a single measure, so we cannot estimate rates of attrition; this would require a prospective study with repeated measurements of leukocyte telomere length. Although all analyses were adjusted for multiple covariates, unmeasured or residual confounding cannot be ruled out. Variables potentially associated with telomere length, such as self reported diabetes, hypertension, and obesity, have been validated.

Generalizability to other populations
The women in the Nurses' Health Study are predominantly of European ancestry, and telomere dynamics may differ among other ethnicities; therefore, results may not be generalizable. However, the homogeneity among Nurses' Health Study participants strengthens the internal validity of these findings by maximizing the quality of reported data.

Study funding/potential competing interests
The Nurses' Health Study is supported by the National Cancer Institute and the National Institutes of Health. MC-B is also supported by a Sara Borrell postdoctoral fellowship from the Spanish Ministry of Health, Carlos III Health Institute. MD is supported by a grant from the National Cancer Institute. QS is supported by an NHLBI sponsored career development award.

Estimated least squares mean telomere length z scores (and standard errors) by Mediterranean diet score categories						
	Alternate Mediterranean diet score					
Analysis	≤2 (n=891)	3 (n=795)	4 (n=909)	5 (n=880)	≥6 (n=1201)	P for trend
Age adjusted	−0.028 (0.033)	−0.039 (0.035)	−0.011 (0.033)	0.029 (0.033)	0.054 (0.029)	0.016
Multivariable adjusted*	−0.038 (0.035)	−0.049 (0.036)	−0.010 (0.033)	0.039 (0.034)	0.072 (0.030)	0.004

*Adjusted for age, body mass index, pack years of smoking, physical activity, and total caloric intake.

Angiotensin receptor blocker in patients with ST segment elevation myocardial infarction with preserved left ventricular systolic function: prospective cohort study

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STUDY QUESTION

Does treatment with angiotensin receptor blocker reduces the risk of cardiac death or myocardial infarction in patients with ST segment elevation myocardial infarction (STEMI) and preserved left ventricular systolic function after primary percutaneous coronary intervention?

SUMMARY ANSWER

Treatment with angiotensin receptor blockers showed beneficial effects comparable with angiotensin converting enzyme (ACE) inhibitors in STEMI patients with preserved left ventricular systolic function.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Current guidelines do not cover the use of angiotensin receptor blockers in low risk patients with STEMI, although they are recommended as an alternative to ACE inhibitors in STEMI patients with heart failure or left ventricular systolic dysfunction. The present study showed that treatment with angiotensin receptor blockers is associated with a similar risk of cardiac death or myocardial infarction compared with the ACE inhibitor group and a lower risk compared with no treatment with a renin angiotensin system blocker.

Participants and setting

Between November 2005 and September 2010, we studied 6698 STEMI patients who underwent primary percutaneous coronary intervention and had a left ventricular ejection fraction ≥40%. We used a nationwide prospective multicentre registry of patients presenting with acute myocardial infarction from 53 centres in Korea.

Design, size, and duration

This was a prospective cohort study using data from a large scale registry; 6698 patients were ultimately included in this analysis. Patients were divided into the angiotensin receptor blocker group, ACE inhibitor group, and no renin angiotensin system blocker group according to the use of angiotensin receptor blocker or ACE inhibitors at discharge. We compared the incidence of cardiac death or myocardial infarction among the three groups with a median follow-up of 12 months.

Main results and the role of chance

Cardiac death or myocardial infarction occurred in 21 patients (1.8%) in the angiotensin receptor blocker group, 77 patients (1.7%) in the ACE inhibitor group, and 33 patients (3.5%) in the no blocker group. After propensity score matching (1175 pairs), there was no significant difference in the rate of cardiac death or myocardial infarction between the angiotensin receptor blocker group and the ACE inhibitor group (21 (1.8%) v 23 (2.0%); adjusted hazard ratio 0.65, 95% confidence interval 0.30 to 1.38; P=0.65). The angiotensin receptor blocker group had a lower rate of cardiac death or myocardial infarction than the no blocker group in matched populations (803 pairs) (14 (1.7%) v 25 (3.1%); 0.35, 0.14 to 0.90; P=0.03).

Bias, confounding, and other reasons for caution

The non-randomised nature of the registry data could have resulted in selection bias, and, although we performed a propensity score matched analysis to adjust for these potential confounding factors, we could not correct for unmeasured variables.

Generalisability to other populations

The results are generalisable to countries where rates of primary percutaneous coronary intervention as reperfusion therapy are high in STEMI patients.

Study funding/potential competing interests

Clinical outcomes in patients with ST segment elevation myocardial infarction with preserved left ventricular systolic function according to treatment at discharge during follow-up in propensity matched population				
Propensity matched population	ARB (n=1175)	ACEI (n=1175)	Adjusted hazard ratio (95% CI)	P value
Cardiac death or MI	21 (1.8)	23 (2.0)	0.65 (0.30 to 1.38)	0.65
All cause death	32 (2.7)	18 (1.5)	1.23 (0.59 to 2.56)	0.58
Cardiac death	15 (1.3)	11 (0.9)	1.14 (0.41 to 3.15)	0.80
Myocardial infarction	7 (0.6)	12 (1.0)	0.30 (0.08 to 1.09)	0.07

ARB=angiotensin receptor blocker; ACEI=angiotensin converting enzyme inhibitor; MI=myocardial infarction.