Adverse Clinical Events and Mortality During Hospitalization and 3 Months After Discharge in Cognitively Impaired Elderly Patients

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Background. Controversial findings are reported on hospital outcome in cognitively impaired patients. The aim of this study was to explore mortality risk according to cognitive status during hospitalization and after 3 months in elderly patients.

Methods. Sixty-six internal medicine and geriatric wards in Italy participated in the “Registry Politerapie SIMI (REPOSI)” during 2010. Of the 1,380 in-patients, aged 65 and older enrolled, 1,201 were included. Cognition was evaluated with the Short Blessed Test (SBT). Logistic regression was used to evaluate the association of questionable and impaired cognition (according to SBT cutoff points) with mortality during hospitalization and at follow-up. Morbidity, function, and adverse events during hospitalization were covariates.

Results. Four hundred and twenty-one participants were classified as normal, 219 questionable, and 561 cognitively impaired. Forty-nine patients died during hospitalization and 70 during follow-up. Sixty-seven point three percent versus 32.7% (p < .001) of patients who died during hospitalization and 54.3% versus 45.7% (p < .001) during follow-up had at least one adverse event. After multiajustment, impaired cognition was associated with in-hospital mortality (odds ratio [OR] = 3.1; 95% confidence interval [CI] = 1.1–8.6) but not with mortality at follow-up. Increase severity of cognitive impairment was associated with higher odds of mortality (from 2.7 in those with moderate impairment to 4.2 in those with severe impairment). After stratification for adverse clinical events, impaired cognition resulted associated with mortality only in patients having at least one event.

Conclusion. Elderly patients with cognitive impairment are more likely to die during hospitalization with a severity-dependent association. Adverse events may represent an important target of prevention due to their high association with mortality and cognitive impairment.

Key Words: Older patients—Cognitive impairment—Acute illnesses—Hospitalization—Adverse events—Mortality.

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Due to the well-known demographic and epidemiological transitions, an increasing number of old people will be hospitalized while suffering not only from the acute disease leading to admission but also due to several coexisting chronic diseases and syndromes, such as cognitive impairment. Several studies have shown that patients with dementia or cognitive impairment are likely to have such adverse outcomes as high risk of institutionalization after discharge (1,2), longer length of hospital stay (3), and functional status decline prior and after hospitalization (4,5). Moreover, a few studies showed that dementia is associated with long- and short-term mortality after hospital admission (6). Morrison and colleagues (7) found that the admission to hospital of a person with dementia and acute medical illness is a critical event associated with high 6-month mortality rates. Recently, Sampson and colleagues (8) showed that dementia is...
associated with markedly high mortality during hospital stay, especially those patients with severe cognitive impairment. In the first wave of the Registry Politerapia SIMI (Italian Internal Medicine Society), REPOSI, held in 2008, we found that patients with a diagnosis of dementia were more likely to die during hospital stay compared with their cognitively intact peers despite similar comorbidities (9). Finally, a frequent event in patients with dementia, that is, the onset of delirium during hospital stay (10), has been found as a risk factor for both short- and long-term mortality (11,12). For this reason, the onset of delirium after admission was recorded as an adverse clinical event in this population sample.

The aim of this study was to explore if older persons admitted to acute hospital wards with questionable or impaired cognition have a higher risk of in-hospital and 3-month mortality compared with their cognitively intact peers, after controlling for other key factors, including physical illnesses, functional disability, and adverse clinical events during hospitalization. Data were obtained from the REPOSI during 2010 in 66 internal medicine and geriatric wards in Italy.

**Methods**

**Data Collection**

This study was conducted between January 2010 and December 2010 in 66 hospitals wards located in different regions of Italy, all participating in the REPOSI, a collaborative and independent joint effort of the Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute of Pharmacological Research. The design of REPOSI was previously described in details (13). Briefly, the registry was designed with the purpose to create a network of internal medicine and geriatric wards in order to evaluate patients affected by multiple diseases and prescribed with polytherapy. The specific aims of REPOSI were as follows: to describe prevalence of co-occurring multiple diseases and treatments in hospitalized elderly patients; to correlate clinical characteristics of the patients with type and number of diseases and treatments; and to evaluate the main clinical outcomes at hospital discharge and to compare drug prescriptions at admission, discharge, and follow-up. All the patients admitted to the participating wards were consecutively recruited if they were aged 65 years and older. Participation was voluntary and an informed consent was signed by all patients. A sample of at least 20 patients consecutively admitted to each participating hospital during a period of 4 weeks, 3 months apart each from the other (one in February, one in June, one in September, and one in December 2010) was enrolled in the study. A standardized web-based case report form was filled in by the attending physicians, including sociodemographic factors, clinical parameters, diagnoses, and medications prescribed at both hospital admission and discharge and clinical events during hospitalization. Telephone follow-up was performed 3 months after hospital discharge collecting data on mortality. All the data recorded in the net were collected and checked by a central monitoring institution (the Mario Negri Institute for Pharmacological Research, Milan).

The study was approved by the Ethical Committee of the IRCCS Ca Granda Maggiore Policlinico Hospital Foundation, Milan.

**Assessment of Cognitive Status**

The Short Blessed Test (SBT) was performed within 2 days of hospital admission. SBT is a 6-item Orientation-Memory-Concentration-Test validated as a measure of cognitive impairment (14). Based on findings from the Memory and Aging Project (15), the following cutoff points were considered normal cognition (score of 0–4), questionable impairment (score of 5–9), and impairment consistent with dementia (score of 10–28). In the final analysis, impaired patients were also divided in those with moderate impairment (score of 10–19) and severe impairment (score ≥ 20).

**Assessment of Performance in Basic Activities of Daily Living**

The Barthel Index is a scale used for the assessment of performance in basic activities of daily living (16) that considers 10 basic functions and yields a score of 0–100. A higher score is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital. The Barthel Index was categorized according to four cutoff points, which are as follows: 75–100 as reference (no-mild disability), 50–74 (moderate disability), 25–49 (severe disability), and 0–24 (completely dependent).

**Assessment of Diseases**

Diseases examined in this study were diagnosed on the basis of physical examination, clinical history, and laboratory and instrumental data collected by the attending physicians. The International Classification of Diseases—Ninth Revision (17) was used for classifying diseases. The Cumulative Illness Rating Scale was adopted in order to evaluate the global health status of participants (18). Clinicians evaluate in each patient the disease and impairment of major organ systems, which are rated from 1 (no impairment to that organ/system) to 5 (impairment is life threatening). A severity index and a comorbidity index can be derived. The comorbidity index is calculated according to the number of organ systems affected by a severity of at least 3. In this study, the Cumulative Illness Rating Scale comorbidity index was used for descriptive purpose only but was not included in the multivariate models. Instead, single diseases potentially related to death were included because they were thought to be more informative than the index alone.
Adverse Clinical Events

Adverse clinical events were defined as any acute clinical problem that newly occurred during hospitalization (and was not present at admission [19]). The participating centers were not provided with an encoded list of possible adverse events. The judgment was clinical and the final data on adverse events were checked by a senior physician from the central monitor group. The final list of adverse events in alphabetical order was the following: acute renal failure, acute pulmonary embolism, acute heart failure, acute coronary heart disease, acute respiratory failure, allergy, arrhythmias, bedsores, behavioral disturbances, delirium, electrolyte disorders, epilepsy, falls, fever, fractures, hemorrhagic events, hypertensive crisis, infections (intestinal, skin, bronchitis, sepsis, pancreatitis, urinary, herpes zoster), pneumonia, stroke, syncope, thrombosis, uncontrolled diabetes, and vertigo.

Mortality

Information on survival status of the patients was collected during hospitalization and assessed 3 months after discharge by telephone interview to patients or relatives. Follow-up data were available for 900 participants out of the 1,380 enrolled (65%) and for 850 out of those included in this study (n = 1,201; 71%). In fact, the initial registry sample included 1,380 participants. For 32 of them, information on survival status at discharge was missing, 120 were transferred to other hospital units, and 27 had missing data on the SBT. Thus, 1,201 patients were included in this study.

Statistical Analysis

Sociodemographic and clinical characteristics of the sample according to cognitive status were described using univariate analysis (mean or percentage). Ninety-five percent confidence intervals (CIs) were calculated for means and proportions. Logistic regression models were run to analyze the association between cognitive impairment and mortality during hospitalization and after 3-month follow-up. Covariates were dichotomized according to clinical judgment or mean values. The adjustment included age (years), dichotomized 80+ vs <80 in order to highlight the effect of the oldest old), gender (males vs females), education (years of schooling), functional status (the Barthel Index was categorized according to four cutoff points; 75–100 as reference [no-mild disability], 50–74 [moderate disability], 25–49 [severe disability], and 0–24 [completely dependent]), adverse clinical events during hospitalization (1+ vs 0 events), and diseases potentially related to death (malignancy, cerebrovascular diseases, chronic obstructive pulmonary disease, heart failure, coronary heart disease, and chronic renal failure). In order to evaluate if the severity of cognitive impairment was associated with a different risk of death, the SBT scale score was further categorized according to four cutoff points; 0–4 (normal), 5–9 (questionable), 10–19 (moderate impairment), and 20+ (severe impairment). Finally, stratification was employed in order to evaluate a possible interaction between adverse clinical events and having questionable or impaired cognition versus being normal.

All the statistical calculations were performed with the software STATA 12th version (College Station, Texas, USA).

Results

Of the 1,201 patients included in this study, 48.3% were men. The mean age of the patients was 79 years. Thirty-four percent of them had at least one adverse clinical event during the hospital stay (ranging from 0 to 6 events). Concerning cognitive status, 421 patients were classified as normal, 219 questionable, and 561 cognitively impaired according to SBT cutoff points. Forty-nine patients (4.0%) died during hospitalization and 70 (8.2%) during the 3-month follow-up. Patients who underwent or not the follow-up did not differ according to age (mean 78.8 vs 79.2 years, p = .475), gender (49.3 vs 49.9% males, p = .827), SBT (mean 9.6 vs 10.2, p = .205), and adverse events (mean 1.5 vs 1.6, p = .475). Patients without follow-up were slightly more functionally impaired (mean Barthel Index 71.4 vs 79.5, p < .001). The main causes of in-hospital death were pneumonia or respiratory failure, cardiovascular diseases, and sepsis, whereas the main causes of 3-month mortality were pneumonia or respiratory failure, malignancy, and cardiovascular diseases. Sixty-seven point three percent versus 32.7%, p < .001, of patients who died during hospitalization and 54.3% versus 45.7%, p < .001, who died during follow-up had at least one adverse event compared with survivors.

Table 1 shows sociodemographic and clinical characteristics in the whole patient sample and according to cognitive status. Patients with questionable or impaired cognition were more likely to be older, less educated, and more functionally impaired; a higher proportion of them had at least one adverse clinical event during hospital stay and died during hospitalization or follow-up (Table 1). They were also more likely to die because of pneumonia or respiratory failure and sepsis during hospitalization and because of pneumonia or respiratory failure, sepsis, malignancy, and cardiovascular diseases at follow-up than those cognitively intact.

The most frequent adverse clinical events are described in Figure 1 according to cognitive status. They were urinary infection, pneumonia, acute renal failure or electrolyte disorders, respiratory failure, delirium, and Clostridium difficile infection.

The crude effects of questionable and impaired cognition in in-hospital and 3-month mortality (being normal
cognition the reference group) were as follows: for questionable cognition OR = 2.3 (95% CI = 0.7–7.7) and OR = 2.1 (95% CI = 1.0–4.4) and for impaired cognition OR = 6.0 (95% CI = 2.3–15.4) and OR = 1.9 (95% CI = 1.07–3.6), respectively. Due to the high correlation between the SBT score and the Barthel Index score (Pearson correlation: −0.526, p < .001), we also analysed the crude effects of functional impairment on in-hospital and 3-month mortality (being normal-mild disability, the reference group) that were as follows: for moderate impairment OR = 0.6 (95% CI = 0.1–2.6) and OR = 2.2 (95% CI = 1.0–4.9), for severe impairment OR = 3.0 (95% CI = 1.2–7.4) and OR = 4.7 (95% CI = 2.1–10.4), and for complete disability OR = 5.6 (95% CI = 2.7–11.3) and OR = 6.8 (95% CI = 3.4–13.6), respectively. Multivariate logistic regression models meant to identify whether there was an independent association between cognitive impairment and in-hospital (Model 1 and 2) and 3-month mortality (Model 3 and 4). Model 1 and 3 were adjusted only for age and gender, whereas Model 2 and 4 also for education, functional status, adverse clinical events, and diseases. Cognitively impaired patients were more likely to die during hospitalization, whereas questionable impaired patients showed no association with in-hospital mortality. On the other hand, both questionable and cognitively impaired patients did not show an independent effect on mortality at follow-up compared with those classified as cognitively normal. Adverse clinical events were also independently associated with in-hospital and follow-up mortality (Table 2; Model 2 and 4). The other variables significantly associated with mortality were older age, male gender, and being affected by malignancy and chronic renal failure (Table 2).

In order to better evaluate whether an increasing severity of cognitive impairment was associated with an increased risk of death, the SBT scale score was categorized according to four cutoff points: 0–4 (normal, reference group), 5–9 (questionable), 10–19 (moderate impairment), and 20+ (severe impairment). After multiajustment, the ORs for in-hospital mortality were as follows: for questionable impairment, OR = 2.2 and 95% CI = 0.66–7.71; for moderate impairment, OR = 2.7 and 95% CI = 1.00–7.96; and for severe impairment, OR = 4.2 and 95% CI = 1.29–13.78. The association with 3-month mortality was not significant.

Finally, the models testing mortality were stratified according to adverse events. Being cognitively impaired was highly associated with mortality during hospital stay only in patients who had at least one adverse event during hospitalization (Table 3).
DISCUSSION

These findings obtained in the frame of the REPOSI registry confirmed previous results on the independent association between in-hospital mortality and cognitive impairment (9), and added novel information on patients with different severity of cognitive impairment and on mortality at 3 months after discharge. The association between cognitive impairment and in-hospital mortality remained statistically significant after adjustment for several covariates, including morbidity, functional status, and adverse clinical events, whereas the one with 3-month mortality was annulled by the inclusion in the models of functional status. Moreover, increasing severity of cognitive impairment was associated with an increasing probability to die during hospitalization. Adverse clinical events were especially frequent in patients with cognitive impairment and were independently associated with mortality both during hospital stay and at follow-up. After stratification for adverse clinical events, impaired cognition resulted highly associated with in-hospital mortality only in patients having at least one event.

One of the major consequences of the ongoing demographic changes and population aging is the increase in the occurrence of mental diseases (20) that will result in an increasing number of patients with cognitive impairment being hospitalized in an acute care unit, such as geriatric

<table>
<thead>
<tr>
<th>Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for In-Hospital (Model 1 and 2) and 3-Month Mortality (Model 3 and 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-Hospital Mortality</strong></td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
</tr>
<tr>
<td>SBT</td>
</tr>
<tr>
<td>Normal</td>
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<tr>
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<tr>
<td>Impaired</td>
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<tr>
<td>Barthel Index</td>
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<td>No-mild disability</td>
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<td>Moderate disability</td>
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<td>Complete disability</td>
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<td>Age, y (80+ vs &lt;80)</td>
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<tr>
<td>Male vs female</td>
</tr>
<tr>
<td>Adverse events (1+ vs 0)</td>
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<td>Malignancy</td>
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<td>CRF</td>
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Notes: Model 2 and 4 were adjusted also for education, CHD, AF, COPD, CVD, and HF, which are not reported in the table because not significant. AF = atrial fibration; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVD = cerebrovascular disease; HF = heart failure; SBT = Short Blessed Test.

Table 3. Odds Ratio (OR) and 95% Confidence Intervals (CI) for In-Hospital and 3-Month Mortality After Stratification for the Presence of At Least One Adverse Clinical Event

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<tr>
<th>At Least One Adverse Clinical Event</th>
<th>No Adverse Clinical Event</th>
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<tbody>
<tr>
<td>In-hospital mortality</td>
<td>Three-month mortality</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td><strong>95% CI</strong></td>
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<td>SBT</td>
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<tr>
<td>Normal</td>
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<td>Questionable</td>
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<tr>
<td>Impaired</td>
<td>13.2</td>
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<tr>
<td>Barthel Index</td>
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<tr>
<td>No-mild disability</td>
<td>R</td>
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<tr>
<td>Moderate disability</td>
<td>0.6</td>
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<tr>
<td>Severe disability</td>
<td>1.7</td>
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<tr>
<td>Complete disability</td>
<td>3.5</td>
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<tr>
<td>Age, y (80+ vs &lt;80)</td>
<td>1.2</td>
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<tr>
<td>Male vs female</td>
<td>1.8</td>
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<tr>
<td>Malignancy</td>
<td>1.2</td>
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<tr>
<td>CRF</td>
<td>2.8</td>
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Notes: Models were adjusted also for education, CHD, AF, COPD, CVD, and HF, which are not reported in the table because not significant. AF = atrial fibrillation; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVD = cerebrovascular disease; HF = heart failure.

*Predicts failure perfectly (no one in this group died during hospitalization).
and internal medicine wards. Previous studies on the effect of dementia on hospital outcomes gave controversial results. Zekry and colleagues (1) investigated geriatric patients from acute and rehabilitation hospitals and found that dementia was not predictive of in-hospital death, but only of discharge to a nursing home. In an additional study from the same group, dementia was confirmed not to be predictive of short- or long-term mortality if comorbidities were included in the model (21). On the other hand, Dinkel and Lebok (22) compared hospital outcomes in German patients with and without dementia and found that in-patients with dementia had a twofold likelihood to die during hospitalization than those without dementia of the same age. These results were explained by a higher number of comorbid conditions in patients with dementia compared with those who were cognitively intact (22). A greater load of comorbidity and geriatric syndromes was observed also in patients with dementia admitted to an Italian hospital, who showed a higher mortality risk than in their cognitively intact pairs (23). We found similar results regarding the association of dementia with mortality during acute hospitalization in the first wave of the REPOSI, but—in that study—patients with dementia had a similar number of comorbid conditions than those without dementia (9). In this second wave of the registry, not only more information on possible confounders, such as functional status, was collected compared with the first wave, but also the severity of cognitive impairment was tested by using the SBT scale. Increasing severity of cognitive impairment resulted in an increasing probability to die during hospitalization, ranging from an OR of 2.7 in those with moderate impairment to 4.2 in those with severe impairment.

The reasons why patients affected by cognitive impairment may be at high risk to die during acute diseases are still not unclear. Some studies have shown that the acute care of patients affected by dementia tends to be suboptimal (6,24), whereas other studies found that patients with dementia receive the same procedures and good care of those without such diagnosis (7). The assumption of an underestimation of comorbidities in patients with dementia is unlikely to be real in an acute hospital setting, where regular diagnostic procedures are offered to all admitted patients, especially in internal medicine and geriatric wards. Our hypothesis is that the interaction with the acute hospital environment may be particularly challenging for people with cognitive impairment. It is possible that persons with dementia have more difficulties to cope with the acute stressors related to hospitalization compared with those without such diagnosis. The high frequency of adverse clinical events found in the frame of this study in these patients is consistent with this hypothesis. In our previous study (9), an additive effect was found for dementia and adverse events on in-hospital mortality. In this study, besides confirming the independent association of adverse events on mortality during hospital stay, this association was also present at follow-up. Moreover, the presence of an association between adverse events and cognitive impairment on mortality was established; in fact, the effect of impaired cognition on mortality was significant and strong only in patients who had at least one adverse event during hospital stay. One of the collected adverse events was delirium, a frequent occurrence in acutely hospitalized patients with cognitive impairment. Delirium was recorded as an adverse event only if definitely not already present at admission; in fact, in this study, prevalence of delirium was much lower than in others (10). This decision was adopted in order to avoid an overlap between cognitive impairment diagnosis established with the SBT and delirium already present at admission and captured by some items of the same scale.

Cognitive impairment and functional decline are often associated in geriatric patients, and, in the majority of cases, disability is a consequence of cognitive impairment. Nevertheless, in this study, cognitive impairment was still independently associated with in-hospital mortality after the inclusion in the analysis of functional status. On the other hand, functional disability was strongly associated with 3-month mortality annulling the effect of cognition. This finding could be explained by considering that disability may be a measure of severity of diseases other than cognitive impairment. Indeed, the analyses were adjusted for specific diseases, but not for the severity of each clinical conditions (information not available in the REPOSI registry), and disability has been already shown to be a good indicator of disease severity when evaluating mortality in elderly people (25,26). This hypothesis underlines the fact that moderate and severe cognitive impairment increase the risk of in-hospital mortality independently also from the severity of their comorbidities.

Major strengths of this REPOSI study are the multicentre design that involved 66 internal medicine and geriatric wards throughout Italy, resulting in a sample representative of the hospitalized elderly population in the country; and the inclusion of the patients during a period of 4 weeks (one per season), in order to balance the effect of seasons on acute diseases leading to hospitalization. However, a few limitations need to be mentioned. First, problems can arise by using hospital data for research purposes because hospital records are not designed for research purposes but rather for patient care, and their diagnostic quality may vary depending on different hospitals, physicians, and clinical units. Moreover, hospital admissions are often selective on the basis of ward characteristics, severity of disease, associated medical conditions, and admissions policies that may vary from hospital to hospital. Second, information after 3 months was collected by phone calls and, thus, we cannot completely rule out recall biases as well as missing data of people who died during the follow-up. Finally, cognitive impairment and dementia in medical in-patients can be missed by physicians (27), however, a simple screening tool such as the SBT used in this study may help to identify patients with cognitive impairment even if a diagnosis of dementia is not reported.
In conclusion, these findings provide evidence that impaired cognition is an independent risk factor for mortality during acute hospital stay. Moreover, there is a correlation between the severity of cognitive impairment and mortality. Adverse clinical events during hospital stay may represent a target of prevention due to their high correlation with mortality and cognitive impairment.

Supplementary Material
Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

References