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Delirium, dementia and in-hospital mortality: the results from the Italian Delirium Day 2016, a national multicenter study.

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Abstract (307)

Background: There is little evidence about the prevalence of cognitive impairment, dementia and delirium and their effect on in-hospital older mortality in large multicenter studies. The aims of the 2016th edition of the “Delirium Day”, a single-day multicenter study that is carried out yearly in Italy were to assess: 1) the point-prevalence of four cognitive disorders (i.e., cognitive impairment/no dementia, dementia, delirium and delirium superimposed on dementia, DSD) in older patients admitted to acute hospital wards and 2) the effect of these conditions on in-hospital mortality.

Methods: This study included 2037 older patients (aged ≥ 65 years) across 205 acute hospitals. The main variables included cognitive impairment (4AT score ranging between 1 and 3), delirium (4AT scored ≥ 4), dementia (as reported on clinical charts), DSD (pre-existing diagnosis of dementia and 4AT ≥ 4), functional status (Activities of Daily Living), comorbidity (Charlson Index), medications, feeding tubes, peripheral venous and urinary catheters and physical restraints. The group without cognitive impairment was defined as the reference category for comparisons with the other four groups (cognitive impairment/no dementia, dementia, delirium, and DSD), and multivariate analyses were performed using logistic regressions adjusted for covariates.

Results: The mean age was 81.17 ± 7.7 years (53.1% female). Overall, 893 patients (43.8%) had neither delirium, nor dementia nor cognitive impairment, 483 (23.7%) had cognitive impairment/no dementia, 230 (11.3%) dementia alone, 187 (9.2%) delirium alone and 244 (12.0%) DSD. Overall, 99 (4.8%) patients died. In the multivariable logistic regression analysis, participants with delirium alone (Odds Ratio, O.R. 2.56, 95% Confidence interval, C.I. 1.29–5.09) and those with DSD (OR. 2.60, 95% C.I. 1.39–4.85) had higher mortality risk compared to reference group.

Conclusions: Delirium and DSD were highly prevalent among hospitalized patients and significantly increased in-hospital mortality. Clinicians should systematically assess these conditions in older hospitalized patients and recognize them as markers of critical conditions and predictors of imminent death.

69 **Key words:** delirium, dementia, prevalence, “in-hospital mortality”, “delirium day”

Introduction

Delirium is a neuropsychiatric disorder, characterized by an acute change and fluctuation of cognitive functions, inattention and impaired awareness, often associated with disturbed behavior, perception disturbances and altered sleep cycle.¹ It occurs on average on one out of 5 hospitalized older patients². The development of delirium is generally triggered by different factors, including infection, dehydration, specific organ failures, metabolic disorders, pain, substance intoxication or withdrawal and sleep deprivation.^{1,3} Delirium is a costly condition⁴, with several prognostic implications, including worsening of cognitive status and progression to dementia, worsening of functional status^{5,6}, increasing patients' and caregivers' burden^{7,8} and elevated mortality in the middle-long term^{9,10}. A robust association is well appreciated between delirium and in-hospital mortality in the Intensive Care Units (ICU)^{9,11,12}, whereas few studies have assessed the association of delirium with in-hospital death in medical and surgical wards^{13,14}.

Preexisting dementia is a major predisposing risk factor for delirium, implying that many patients with dementia are at risk of developing a condition which is labeled as delirium superimposed on dementia (DSD)¹⁵. The prevalence of DSD in hospital populations ranges from 22% to 89%¹⁶. According to several studies, DSD is associated with higher health care costs and worse functional outcomes compared with patients with dementia alone^{6,16,17}. As well as for delirium alone, few studies have assessed the association of DSD with in-hospital mortality¹³.

In 2015, a researchers working group endorsed by four Italian scientific associations conducted a multicenter point-prevalence study entitled "Delirium Day", with the aim of detecting the prevalence of delirium over a single day in acute hospital and rehabilitation wards across Italy². Overall, among a total of 1867 patients aged 65 years and older, the study found a delirium prevalence of 22.9%, with more than half of delirious patients having a pre-existing dementia. Major limitations of the 2015 "Italian Delirium Day" were that most patients were enrolled in acute geriatric wards and the lack of delirium outcomes assessment.

In 2016, a new edition of the "Italian Delirium Day" was carried out, promoted by ten scientific Italian associations, with the following aims: i) to provide a real-world picture of the prevalence of four cognitive disorders (i.e., cognitive impairment/no dementia, dementia, delirium and DSD) in a large population of older patients across acute hospital wards in Italy, and: ii) to assess the impact of these conditions on in-hospital mortality.

Methods

The "Delirium Day" is a national multicenter point-prevalence study held every year in Italy since 2015 to disseminate the culture and awareness of delirium among hospital and extra-hospital

healthcare staff. Data are collected on an index day, involving acute hospital wards, rehabilitation and long-term care units, nursing homes and hospices. For the 2016 “Delirium Day” edition, the physicians associated with 10 Italian Scientific Associations (i.e., the Italian Association of Psychogeriatrics, AIP; Italian Society of Gerontology and Geriatrics, SIGG; Italian Society of Geriatrics Hospital and Territory, SIGOT; Extra-hospital Geriatric Association, AGE; Italian Society of Internal Medicine, SIMI; Federazione Associazioni Dirigenti Ospedalieri Internisti, FADOI; Italian Society of Neurology, SIN; Italian Society of Neurology for the Dementia, SINDeM; Italian Society of Surgery, SIC; Italian Society of Palliative Care, SICP) were invited by email to participate in the study. No incentives were offered to participants and Scientific Associations.

Subjects and study protocol.

September 28th, 2016 was the index day. All patients admitted to the participating centres from 00:00 to 23:59 of the index day were potentially eligible if they were aged 65 years and over, were able to speak Italian language and provided a written informed consent by themselves or by proxies (when patients were not capable because of severe cognitive impairment or delirium). Exclusion criteria were: coma, aphasia, blindness, deafness and end of life status, as defined by clinical judgment. Those who declined to participate in the study were also excluded. The Ethical Committee of the Monza Brianza Province approved the study protocol.

All patients eligible for the study were evaluated over a 24-hour period according to this protocol:

- a. *Detection of delirium and cognitive impairment:* the presence of delirium and cognitive impairment were assessed with the 4AT ¹⁸. The 4AT is a recently validated instrument, which has demonstrated good sensitivity and specificity in elderly patients for the diagnosis of delirium. A score of 0 indicates absence of dementia or delirium, a score between 1 and 3 suggests of possible cognitive impairment but not delirium, while a score ≥ 4 is strongly suggestive of delirium, including DSD.
- b. *Clinical assessment.* For all patients, a comprehensive clinical assessment was collected, including age, gender and date of hospital admission. Functional status prior to admission was assessed using the Activities of Daily Living (ADL)¹⁹. Comorbidities were assessed using the Charlson Index ²⁰, excluding dementia from the total score. Dementia was defined as the presence of a documented diagnosis in the medical records and/or prescription of Acetylcholinesterase inhibitors (AChE-I) or memantine prior to admission. The use of specific pharmacological classes (i.e., anti-hypertensives,

antiplatelets, antiarrhythmics, statins/lipid lowering drugs, antidiabetics, antiulcers, antibiotics, benzodiazepines, antipsychotics, antidepressants, antiepileptics and AChE-I/memantine) taken by each patient on the index day was also recorded, together with the use of feeding tubes [i.e., nasogastric tube (NT) or percutaneous endoscopic gastrostomy (PEG)], peripheral venous catheters, urinary catheters and physical restraints (vests, wrists, inguinal restraints and bedrails). The reason for using physical restraints was also collected.

Variables of exposure and outcome measure

The exposure variable was the combination of delirium and dementia/cognitive impairment diagnosis. We examined the overlap between these conditions, by categorizing the cases into five groups: no cognitive impairment, cognitive impairment/no dementia, dementia alone, delirium alone, DSD. The group “no cognitive impairment” was composed by patients with 4 AT score =0 and no pre-existing diagnosis of dementia. The group “cognitive impairment/no dementia” included patients without pre-existing diagnosis of dementia who obtained a 4AT score ranging from 1 to 3. The group “dementia alone” included patients with a pre-existing diagnosis of dementia and obtaining a 4AT score $\leq 3/12$. The group “delirium alone” included patients with a 4AT score $\geq 4/12$ and no history of dementia and the group “DSD” included those with a 4AT score $\geq 4/12$ and history of dementia.

The outcome measure of this study was in hospital mortality, as reported by the researchers involved in the study in each center.

Data collection and Ethical procedures

The data were recorded using a web-based electronic case report form (e-CRF). Each participating center received a username and password that allowed researcher to access the e-CRF. After accessing the e-CRF, each clinician was asked to indicate the number of eligible patients and of those who accepted to participate. Then, an automatic message allowed the clinician to complete the data collection in the e-CRF. It was not possible to submit the data-form without the mandatory clinical data. The data were completely anonymous and it was not possible to trace the identifying characteristics of any individual patient.

Statistical analyses

We analyzed the cohort characteristics according to the cognitive status in five groups (no cognitive impairment; cognitive impairment/no dementia; dementia alone; delirium alone; DSD)

using mean and standard deviations (or median and interquartile ranges) if the variable was distributed in a continuous way, or using frequencies and percentages if the variables were categorical. Comparison between patient groups was performed using the one-way ANOVA, or the Kruskal-Wallis test, where required for continuous variable. The categorical variables were compared between groups using the chi-square test, or Fisher exact test, where required.

The effect of group membership on in-hospital mortality was assessed using a multivariate logistic regression model, adjusted for covariates. A stepwise selection procedure was used to select the final model (we included all variables reported in Table 1 with the exception of feeding tube and AChE-i/memantine due the low percentage of patients exposed). The variables relative to group's membership were forced in the model, with a significance level of 0.20 for entering an effect into the model and a significance level of 0.10 for an effect to stay in the model.

A sensitivity analysis was conducted to check whether the results of the stepwise selection procedure may have changed by using a different approach to select the covariates. We used the branch-and-bound algorithm by Furnival and Wilson²¹, a method that can be used to find the best subset of regression variables without examining all possible subsets and computing all possible regressions. The result is a reduction of several orders of magnitude in the number of operations required to find the best subsets. The algorithm finds a pre-ordered number of models with the highest likelihood score (chi-square) statistic for all possible regressions. Specifically, we considered only the best models with a number of covariates varying from 5 to 13.

All tests were two-sided and a level of significance was established as 95 % ($p < 0.05$). All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Overall, 205 acute hospital wards, 29 rehabilitation facilities, 32 nursing homes and 10 hospices collected the study data on the index day. Figure 1 shows the flow chart of the study. Among 4810 patients enrolled, 1778 were residents in nursing home, admitted to hospice and palliative care or to long-term care/extra-hospital rehabilitation and 515 were admitted to intensive-care units, in-hospital rehabilitation or emergency departments. Of the 2517 patients admitted to acute hospital wards, 457 were excluded because of missing notes on discharge or on vital status and 23 because of incorrect data reporting on the e-CRF. Overall, 2037 patients were included in the current study, of whom 945 (46.4%) from Geriatrics, 693 (34.0%) from Internal Medicine, 144 (7.1%) from Neurology, 104 (5.1) from Orthopedics, 83 (4.1) from General Surgery, and 69 (3.3%) from Cardiology, Neurosurgery or Infectious disease wards. The baseline clinical characteristics of patients with missing data on follow-up were not significantly different from those patients with full

data, except for the prevalence of delirium and DSD which was lower among the latter and the functional status, which was better in patients with full data, and the use of urinary catheter which was more frequent in those with missing data (Appendix).

The mean age of the sample was 81.17 (SD 7.75) and over half were females (53.2%). Eight hundred ninety-three patients (43.8%) had neither delirium, nor dementia nor cognitive impairment, 483 (23.7%) had cognitive impairment/no dementia, 230 (11.3%) dementia alone, 187 (9.2%) delirium alone and 244 (12.0%) DSD. Table 1 shows the cohort characteristics of the patients in the five groups. Those in the DSD group were older and more disabled in comparison to the others. Furthermore, they were more frequently prescribed with antibiotics, antipsychotics, antidepressants and AChE-I/memantine and they had more frequently physical restraints. Along with patients in the delirium group they had also more frequently NTs/PEG tubes and peripheral venous catheters. In comparison to others, patients with delirium alone were more frequently prescribed antiarrhythmic and antiepileptic medications whereas in those with neither delirium nor dementia and those with cognitive impairment/no dementia there was a higher prevalence of statins/ lipid-lowering drugs. Both patients with delirium alone and DSD had significantly higher use of urinary catheters than others. At discharge, the length of hospital stay was significantly longer and the in-hospital mortality rate higher in patients with delirium alone and in those with DSD in comparison to their counterparts.

In figure 2 the prevalence of cognitive disorders is reported for each hospital ward. Neurology had the highest prevalence of delirium alone, Geriatrics the highest prevalence of DSD and dementia alone, whereas the prevalence of cognitive impairment/no dementia was highest in Orthopaedics.

In the multivariable logistic regression analysis (Figure 3), participants with delirium alone (Odds Ratio, O.R. 2.56, 95% Confidence interval, C.I. 1.29–5.09) and those with DSD (O.R. 2.60, 95% C.I. 1.39–4.85) had a higher mortality risk compared to participants with no cognitive symptoms. Patients with dementia alone and those with cognitive impairment alone did not show a significant increased risk with respect to patients without cognitive symptoms. The following variables were also significantly associated with in-hospital death: Charlson Index score (O.R. 1.10, 95% C.I. 1.02–1.17), urinary catheter (O.R. 1.78, 95% C.I. 1.15–2.76), number of drugs (O.R. 1.15, 95% C.I. 1.02–1.30), and, with a protective effect, the use of statin/lipid-lowering drugs (O.R. 0.21, 95% C.I. 0.09–0.50) and use of antiplatelet drugs (O.R. 0.50, 95% C.I. 0.31–0.80).

The sensitivity analysis, which was performed by changing the algorithm for the selection of covariates included in the stepwise regression, showed negligible improvement in the likelihood score statistic when adding a further covariate to those selected by the stepwise algorithm.

Discussion

This multicenter nationwide study examined the point-prevalence of four cognitive disorders (i.e., cognitive impairment/no dementia, dementia alone, delirium alone, DSD), and their related risk of mortality in a large cohort of medical and surgical older inpatients from 205 acute hospital wards in Italy. The results show that delirium and DSD were highly prevalent and that both conditions were significantly associated with an increased risk of in-hospital death. Furthermore, an additional 11.2% of patients had dementia alone and 23.7% cognitive impairment; none of these two conditions were independently associated with in-hospital mortality.

The global prevalence of delirium is 21.2%, a figure which is very similar to the findings of 2015 “Delirium Day” edition and other studies ^{2, 22}. Overall, delirium alone was present in nearly one in ten patients and DSD in one in eight patients. The mean prevalence of DSD is within the expected range for this condition among hospitalized patients in different acute hospital wards, although recent studies found even higher proportion ^{13, 23}. Neurology and Geriatrics wards had the highest prevalence of delirium, with delirium alone more common in Neurology and DSD in Geriatrics ward, consistently with the highest prevalence of dementia in the latter setting. Delirium prevalence was only slightly lower in Internal Medicine and Orthopedics wards. However, we cannot exclude that data from Neurology and Orthopedic wards might be biased by the low number of patients assessed.

The prevalence of cognitive impairment/no dementia and dementia alone are in agreement with other studies conducted among older patients in acute medical wards ^{24 25}. The real nature of cognitive impairment/no dementia should only be hypothesized. It might be possible that this disorder may reflect a condition of undiagnosed and initial dementia, as it is well-known that dementia is frequently under-recognized in acute hospital wards ¹⁷. This disorder may also reflect a condition of attenuated delirium ¹ or even the combination of frailty and physical illnesses that, interacting with hospital environment, may impact cognition. Future studies are needed to clarify this point.

Current evidence of the association between delirium and in-hospital death in medical and surgical ward is not univocal. In our cohort, we found a significant increase in the risk of in-hospital mortality in patients with delirium and DSD. Conversely, Inouye ²⁶, and Adamis ²⁷ found no association between delirium and in-hospital mortality in acute medical inpatients. Similar results were found in cohorts of patients who underwent surgery for hip fracture ^{28, 29}. Other studies found a significant association between delirium and in-hospital mortality but did not control for covariates ^{30, 31}. More recently, Hamilton conducted a systematic review and meta-analysis of 34

studies on post-operative delirium. Of the 11 studies that assessed the relationship between delirium and in-hospital mortality, 7 did not find a significant association between the two conditions ³². Other studies indicate that delirium and DSD are directly harmful to older patients. Pendlebury, in a cohort of 503 consecutive patients admitted to acute hospital general medicine, found that delirium affected one fifth of all acute medical admissions (a third of those aged ≥ 75 years), and was associated with increased mortality after adjustment for age ²². Dharmarajan, in 469 older patients admitted to a large academic hospital, found that incident delirium occurred in 15% of patients and that delirium increased mortality at 90 days ¹⁴. Importantly, delirium affected mortality not only with a direct proper effect, but also by acting in combination with other noxious insults (i.e., use restraining devices and development of hospital acquired conditions), which may occur during hospitalization ¹⁴. Recently, in a single center cohort of 1409 patients aged 80 years or more admitted to a geriatric ward, Avelino-Silva reported that both delirium and DSD were associated with in-hospital mortality, after controlling for many potential confounders. ¹³ Our work is thus in agreement with these latter studies, supporting an independent harmful effect of delirium and DSD on in-hospital mortality. Importantly, we found that delirium and DSD had similar odd of mortality, suggesting that the excess of mortality seen in our patients was actually related to delirium rather than by the additional effect of delirium on a pre-existing dementia. This finding is in agreement with some studies ^{13, 33} and in disagreement with others showing an excess of mortality in DSD patients compared to patients with delirium without dementia ^{6, 34}.

This study also found that other factors (i.e, comorbidity, polypharmacy, use of urinary catheter, antiplatelet and of statins/ lipid-lowering drugs) had an independent association with in-hospital mortality. The negative effect of comorbidity on in-hospital death has been already found by others ³⁵, and thus is not surprising. Conversely, the relationship of medication regimen complexity with in-hospital mortality is not clarified yet ³⁶. There are studies finding a positive association between polypharmacy and mortality³⁷ while others do not confirm it³⁸. We can therefore speculate that, in our study, the number of drugs can be a proxy of disease severity potentially driving the association with mortality or there might be a direct effect of polypharmacy-related adverse drug events in frail patients. The excess of in-hospital mortality due to urinary catheter may be explained by the increased risk of infections associated with its use ³⁹. However, it cannot be ruled out that urinary catheter might be a proxy of clinical instability, such as for patients with acute decompensation of heart failure ⁴⁰. The protective effect of statin/ lipid-lowering and antiplatelet drugs on in-hospital mortality should also be explained. Studies support the notion that statins can improve in-hospital mortality in patients with acute myocardial infarction ⁴¹. Accordingly, one could argue that patients taking statin/ lipid-lowering drugs in our study may have

been protected by adverse cardiovascular events. The same might be hypothesized for antiplatelet medications, which are known to exert a protective effect on mortality in patients with cardiovascular⁴² and other diseases⁴³. Additional explanations might be related to the direct effect of statins on delirium reduction especially in septic patients⁴⁴. However, the most suitable explanation, provided that our study was not designed to identify a causal relationship between drug exposure and patients' mortality, is that prescription of cardiovascular medications in our patients reflected better global health care, resulting in lower mortality, as previously suggested in studies on older subjects with previous myocardial infarction⁴⁵ and sepsis⁴⁶.

We did not observe a statistically significant association between cognitive impairment/no dementia - dementia alone and in-hospital mortality. This is in agreement with two studies by Avelino-Silva et al¹³ and by Zekry et al⁴⁷ but not with a study by Sampson et al¹⁷. However, in the study by Sampson et al, the adjusted multivariate model to assess the effect of cognitive impairment and dementia on in-hospital mortality included only few variables (namely age and APACHE score) as confounders¹⁷. This may have influenced the results of the study. Indeed, in a subsequent prospective cohort study, the same authors found that dementia was not an independent predictor of in-hospital mortality when adjusted for a larger group of variables, including a score of frailty⁴⁸. It might also be possible that dementia requires longer period of time to exert its negative effect after hospitalization, as shown by a previous study⁴⁸. Future studies are required to further evaluate this aim.

Some strengths of the study need to be highlighted. First, this is a real-world study including a large cohort of patients from various medical and surgical hospital wards and the largest multicenter study that assessed the point-prevalence and the effect of delirium and DSD on in-hospital mortality. Second, the diagnosis of delirium was obtained using a tool (i.e., the 4AT), which is simple to administer and does not require specific training. This peculiarity makes our study unique, because a similar sample size and such a large number of acute medical and surgical wards involved in a study are probably not achievable by using tools to detect delirium and DSD that require specific training and education. This study may therefore be regarded as a paradigm of the real-world impact of delirium on in-hospital mortality of older patients.

However, our study has several limitations. First, participation in our study was on a voluntary basis, which means that centers involved may be not fully representative of the world of the acute hospitals in Italy. Second, we did not collect data regarding the main reason of hospital admission nor the causes of death, preventing us from assessing the role of precipitating factors of delirium, such as acute diseases. Third, we did not assess the duration of delirium, which may have influenced the outcome at discharge, as demonstrated in previous study⁴⁹. Fourth, the diagnosis of

cognitive impairment/no dementia was based on the results of a tool (i.e., the 4AT), which has not been validated for this aim. However, prevalence of cognitive impairment/no dementia in this study was similar to previous studies²⁵ indirectly suggesting that our approach was reliable. Fifth, there was a relatively high rate of missing data for the outcome, rising the potential for a selection bias. However, the comparison of baseline clinical characteristics between patients with full and missing data suggests that, if all data on participants would have been collected, we would probably have observed an even greater effect of DSD on in-hospital mortality, since the proportion of these patients was significantly higher among those with missing data. Sixth, some hospital wards had no death events, so we did not include the hospital ward as covariate in the model. We believe this might not create a bias since it is likely that patient's characteristics and not the hospital ward should be associated with death. In fact, an analysis performed by restricting the patients' cohort only to the ward types in which there were at least 5 deaths showed results similar to those obtained in the study analyses. Indeed, the best model selected by the stepwise approach is unchanged with an O.R. of 2.22 (95% C.I.: 1.08-4.55) for delirium alone and an O.R. of 2.15 (95% C.I.:1.14-4.06) for DSD.

In conclusion, in this large multicenter nationwide point prevalence study, delirium and DSD were highly prevalent among hospitalized patients and significantly affected in-hospital mortality. Clinicians should systematically assess delirium in older hospitalized patients because it is a marker of critical conditions. The "Delirium Day" study may represent a pragmatic model to investigate delirium and DSD prevalence and outcomes-related in hospitalized persons. A future objective of this project is to become a National platform to assess the quality of the assistance provided to older subjects in different settings of care.

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