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MEDICAL ILLNESSES AND RISK OF DELIRIUM IN ACUTE HOSPITALIZED ADULT-OLDER PATIENTS

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Abstract: *Objectives:* The pathogenesis of delirium in hospitalised patients is complex and multi-factorial. Although several medical conditions had been associated with delirium, the real impact of different diseases on delirium onset has not been completely clarified. In this study we provided a comparison of delirium prevalence across various diseases in a large sample of adult/older individuals > 60 years (mean age: 70.5 years) admitted to acute medical wards. *Design:* Observational cross-sectional study. *Setting:* St. Anna University Hospital (Ferrara, Italy). *Population:* Hospital-based population; data from 74.379 consecutive discharge records of subjects ≥ 60 years were analysed. *Measurements:* DRGs, primary/secondary diagnosis (ICD-9-CM code), number of procedures and admissions, length of hospital stay, and possible death were evaluated. ICD-9 codes for delirium included 290.11, 290.3, 290.41, 293.0, and 293.1. *Results:* Overall, 1300 patients received a delirium diagnosis. Compared with controls, they were characterized by higher number of diagnoses, procedures, and comorbidity. The risk of delirium was associated with DRGs related to brain pathologies, major orthopaedic diseases/procedures, and major infections. As regards ICD-9 diagnoses, 13.7% (n.179) of delirium diagnoses could be attributable to cerebral atherosclerosis, 9.3% (n.121) to urinary tract infections, 6.5% (n.85) to Alzheimer's disease, 5.5% to hypertension, 3.6% to diabetes, and 3.5% to atrial fibrillation (total: 42.1%). *Conclusions:* Our data suggest that among hospitalised elderly patients urinary infections might represent the most frequent modifiable risk factor for delirium. Clinicians need to have a high index of suspicion as regards the presence of urinary tract infections in this subjects, especially in those with cognitive impairment, since its early recognition and treatment might contribute to decrease the probability of delirium onset.

Key words: Delirium, medical illness, hospital, older.

Introduction

Delirium is a common clinical manifestation in hospitalized adult/older patients. Its prevalence varies widely depending from clinical setting and diagnostic criteria, ranging from 10% to 60% in general medical inpatients (1, 2), from 15% to 50% in post-operative patients, and reaching 75% in intensive care units (3). The clinical expression of delirium varies from a quiet hypoactive form to severe psychomotor agitation, often shifting from one form to the other. The responsible pathophysiological mechanisms are not fully understood, although it seems that a derangement of cholinergic/dopaminergic neurotransmission and cytokines/hormones levels in response to acute inflammation or stress might explain part of it (4). The rapid onset, transient nature, and presentation of symptoms sometimes make it challenging the diagnosis of delirium, and some Authors suggested that the problem entity might be underestimated (5). Moreover, delirium often implies complications that are far beyond the length of hospital stay (6) and the admission to long-term care facilities (7). As a matter of fact, patients that experience delirium during hospitalization lose cognitive and functional reserve (8) and often have increased death rates (9).

On the whole it appears that the aetiology of delirium is complex and multi-factorial, and it is common clinical experience that the exposure to the same risk factor has different effects in different subjects, probably due to differences in cognitive reserve and individual response. Since delirium has been associated with relevant outcomes from the clinical, social, and economical point of view (10), many efforts have been made in order to identify possible modifiable risk factors. For example, Inouye et al. found a significant association between delirium and older age, visual and hearing impairment, poly-pharmacy, bladder catheter, and social isolation. As

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specifically regards medical illnesses, severe acute diseases like hip fracture and stroke, as well as other medical conditions including cognitive impairment, dehydration, and malnutrition have been associated with delirium (11, 12). Nevertheless, although several acute medical conditions have been consistently related to delirium, it is has not been quantified their real impact on delirium onset in hospitalized older individuals.

The specific aim of this study was to analyse thoroughly the association between the medical illnesses and diagnosis of delirium in a large sample of individuals admitted to acute medical wards of a University Hospital.

Methods

Data from 74.379 discharge records from St. Anna University Hospital of Ferrara were retrospectively analyzed. This hospital serves the entire community of Ferrara, a town of approximately 150.000 residents located in North-East Italy. Discharge records included all the patients aged ≥ 60 years (78% ≥ 65 years) admitted for acute medical illness to the Medicine Department (including 4 Internal Medicine and 1 Geriatrics acute medical wards) or a Neurology Unit, in a 8-years period of time from January 2003 to December 2011.

The variables considered in the analysis included: age, gender, number of admissions to hospital (if a patient was admitted more than once, each discharge contributed to a different observation), length of stay in hospital, disease related group (DRG), principal diagnoses by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), number of diagnoses, number of major procedures during stay in hospital, possible in-hospital death of patient and age at death. DRG is a classification of patients, currently used in Italy, by diagnosis (or surgical procedure) into major diagnostic categories each containing specific diseases, disorders, or procedures; it is based on the concept that treatment of similar medical diagnoses generate similar costs. The ICD-9-CM is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the USA. The ICD-9-CM is used to code and classify mortality data from death certificates in Italy. In this study the codes were assigned by S. Anna Hospital trained professional coders.

From the general data of the patients, the Charlson index (13), the Deyo index (14), and the Elixhauser index (15) were calculated.

In order to identify the diagnosis of delirium in the discharge records we searched for delirium diagnosis defined by the following ICD-9-CM codes: 290.11 (presenile dementia with delirium), 290.3 (senile dementia with delirium), 290.41 (vascular dementia with delirium), 293.0 (delirium due to conditions classified elsewhere), and 293.1 (sub acute delirium). Alcohol withdrawal delirium (291.0) and drug-induced delirium (292.81) were excluded.

No identifying information was available to the Authors for this study in order to protect the anonymity of the patients. The study protocol was approved by the Ethical Committee of St. Anna University Hospital of Ferrara.

Statistical analysis

Continuous variables were expressed as mean (SD) or median (interquartile range) when the distribution was not normal. Mean values were compared by ANOVA. Median values were compared by non-parametric test (Mann-Whitney). Prevalence was compared by the $\chi 2$ test.

In order to evaluate the association between delirium and DRG or ICD-9-CM diagnoses, the likelihood (Odds Ratio, O.R.; 95% Confidence Interval, C.I.) of being affected by delirium in the presence of a specific diagnosis was calculated by means of multivariate logistic regression analysis. The analysis was adjusted by including age, gender, and number of admissions to hospital as covariates. Due to the skewed distribution of values, number of admissions to hospital was log-transformed before entering regression analysis, to approximate normal distribution.

The excess risk fraction (ERF) was calculated as follows: [(O.R. -1.0) / O.R.] x 100 where the O.R. represents the risk of receiving a diagnosis of delirium in patients exposed to a specific ICD-9-CM diagnosis (16). The ERF has been suggested as an alternative to attributable risk when the causality has not firmly established. The formula used to calculate ERF has been previously used in case-control studies in which the incidence was not available, but the O.R. could be used as an estimate of the relative risk (16). SPSS for Windows, version 13.0 (SPSS, Inc, Chicago, IL) statistical packages were used.

Results

The principal characteristics of 74.349 consecutive hospital discharges, according to absence or presence of a diagnosis of delirium, are reported in Table 1. In this sample, 1.300 patients had a diagnostic code corresponding to delirium (alcohol withdrawal and drug-induced excluded), with a prevalence of 1.75%. In this large sample of inpatients aged over 60 years, delirium diagnosis was reported in a similar prevalence across different settings: 1.70% in Neurology, 1.72% in Internal Medicine, and 1.78% in Geriatrics. Compared with controls, patients with delirium were characterized by higher number of diagnoses and procedures, and higher Charlson and Deyo scores. No significant differences emerged as regards gender, mean age,

number of admissions to hospital, length of stay, total in-hospital mortality, and Elixhauser index.

Table 1

Principal characteristics of 74.379 consecutive hospitalised adult/older patients according to absence (controls: n.73.079) or presence (n.1.300) of a diagnosis of delirium (by ICD-9-CM) in discharge records

	Whole sample (n. 74.379)	Controls (n. 73.079)	Delirium (n. 1.300)	p
Age (mean/SD)	70.5±16.4	70.5±16.4	71.5±16.2	0.16
Gender (Females)	52.9%	52.9%	51.4%	0.27
N° of admissions *	2.13±2.47	2.13±2.47	2.13±2.51	0.958
Lenght of stay *	7 (4-12)	7 (4-12)	7 (4-12)	0.50
N° of diagnoses *	3 (2-5)	3 (2-5)	5 (3-6)	0.001
N° of procedures *	2 (0-3)	2 (0-3)	2 (1-4)	0.001
In-hospital mortality	7.5%	7.4%	8.0%	0.49
Mean age at death	78.6±12	78.6±11.9	79±11.9	0.68
Charlson index *	1 (0-3)	1 (0-3)	2 (1-3)	0.001
Deyo index	4.26±2.49	4.25±2.49	4.60±2.28	0.001
Elixhauser index *	2 (1-3)	2 (1-3)	2 (1-3)	0.08

* Median (interquartile range)

Delirium and DRGs

As expected, DRGs were distributed over a wide range. We focused on most frequent DRGs reported in patients with delirium, and compared them with the equivalent DRGs prevalence reported in controls (Table 2). In delirium patients, organic disturbances & mental retardation (DRG 429) was the most frequent diagnosis (18.7%), followed by cerebrovascular disorders (DRG 14-17: 10.4%), acute adjustment reaction & psychological dysfunction (DRG 425: 8.6%), and degenerative nervous system disorders (DRG 12: 7.9%). After these four DRGs, related to delirium itself or to diseases of central nervous system (CNS), the most frequent DRGs were pneumonia & pleurisy (DRG: 89-80: 4.8%), heart failure & shock (DRG: 127: 4.6%), and septicaemia (DRG: 416-576: 3.5%).

The prevalence of the most frequent DRGs was significantly different between patients with delirium and controls. In particular, organic disturbances and mental retardation, cerebrovascular disease, acute adjustment reaction and physical dysfunction, degenerative nervous system disorders, pneumonia and pleurisy, septicaemia, kidney/urinary tract infections (UTI), hip/femur procedures, major joint replacement, and transient ischemia of the brain were more frequent in delirium patients compared with controls. On the

Table 2

Prevalence of most common disease related groups (DRGs) in 1.300 consecutive hospitalized adult/older patients with diagnosis of delirium, and equivalent prevalence in 73.079 hospitalized older controls. The Odds Ratio (O.R. 95%C.I.; age, gender, and number of admissions adjusted) for the diagnosis of delirium in the presence of a specific DRG is also reported

	Controls n. 73079		Delirium n. 1300		χ^2			
Disease Related Group	n.	%	n.	%	p	O.R.	95% C.I.	
429 ORGANIC DISTURBANCES & MENTAL RETARDATION	770	1.1	243	18.7	0.001			
14-17 CEREBROVASCULAR DISORDERS	5551	7.6	135	10.4	0.001	1.41	1.17	1.68
425 ACUTE ADJUSTMENT REACTION & PSYCHOSOCIAL DYSFUNCTION	187	0.3	112	8.6	0.001			
12 DEGENERATIVE NERVOUS SYSTEM DISORDERS	1282	1.8	103	7.9	0.001	4.81	3.91	5.93
89-80 SIMPLE PNEUMONIA & PLEURISY AGE >17 WC/C	2282	3.1	62	4.8	0.001	1.55	1.20	2.01
127 HEART FAILURE & SHOCK	4765	6.5	60	4.6	0.005	0.69	0,53	0.90
416-576 SEPTICEMIA AGE >17	1162	1.6	46	3.5	0.001	2.27	1.68	3.06
316 RENAL FAILURE	2506	3.4	26	2.0	0.005	0.57	0.38	0.84
320-321 KIDNEY & URINARY TRACT INFECTIONS AGE >17 WC/C	637	0.9	24	1.8	0.001	2.13	1.41	3.22
82 RESPIRATORY NEOPLASMS	1512	2.1	20	1.5	0.20	0.74	0.47	1.15
210 HIP & FEMUR PROCEDURES EXCEPT MAJOR JOINT AGE >17 WC	191	0.3	20	1.5	0.001	5.96	3.74	9.48
87 PULMONARY OEDEMA & RESPIRATORY FAILURE	2225	3.0	19	1.5	0,001	0,47	0.30	0.74
544 MAJOR JOINT REPLACEMENT/REATTACHMENT LOWER EXTREMITY	115	0.2	18	1.4	0.001	8,90	5.40	14.68
88 COPD	1097	1.5	17	1.3	0.63	0.86	0.53	1.40
1 CRANIOTOMY AGE >17 WC	358	0.5	16	1.2	0.001	2.53	1.52	4.18
524 TRANSIENT ISCHEMIA OF THE BRAIN	248	0.3	16	1.2	0.001	3.65	2.20	6.08
207 DISORDERS OF THE BILIARY TRACT WC	645	0.9	11	0.8	1.0	0.95	0.52	1.74
148 MAJOR SMALL & LARGE BOWEL PROCEDURES WC	243	0.3	10	0.8	0.01	2.32	1.23	4.38
203 MALIGNANCY OF HEPATOBILIARY SYSTEM OR PANCREAS	1138	1.6	9	0.7	0.01	0.44	0.22	0.85
202 CIRRHOSIS & ALCOHOLIC HEPATITIS	1449	2.0	8	0.6	0.001	0.30	0.15	0.61
78 PULMONARY EMBOLISM	600	0.8	7	0.5	0.34	0.65	0.31	1.38
174 G.I. HEMORRHAGE WC	985	1.3	7	0.5	0.01	0.39	0.18	0.83
182 ESOPHAGITIS, GASTROENT & MISC DIGEST DIS. AGE >17 WC	895	1.2	7	0.5	0.02	0.43	0.20	0.92
296 NUTRITIONAL & MISC METABOLIC DISORDERS AGE >17 WC	292	0.4	7	0.5	0.37	1.34	0.63	2.86
395 RED BLOOD CELL DISORDERS AGE >17	975	1.3	7	0.5	0.01	0.40	0.19	0.84

WC: without complications; C: with complications; COPD: chronic obstructive pulmonary disease.

Table 3

Prevalence of the most common ICD-9-CM diagnoses in 1.300 consecutive hospitalised adult/older patients with diagnosis of delirium, and equivalent prevalence in 73.079 hospitalized older controls

	Controls n. 73079		Delirium n. 1300		
ICD-9-CM DIAGNOSES	**n.**	**%**	**n.**	**%**	**p**
401.1-401.9 Benign Hypertension – Hypertension not specified	16205	22.2	355	27.5	0.001
437.0-437.1 Cerebral atherosclerosis - Other ischemic cerebrovascular disease	6106	8,4	276	21,2	0.001
414.8-414.9 Other specified forms of CHD – CHD, unspecified	11218	15.4	202	15.5	0.44
599.0 Urinary tract infection, site not specified	3332	4,6	178	13,7	0.001
427.31 Atrial fibrillation	7084	9,7	167	12,8	0.36
250.0 Diabetes mellitus without mention of complication	5799	7,9	148	11,4	0.17
331.0-331.2 Alzheimer's disease and Senile degeneration of brain	2524	3,5	128	9,8	0.001
402.90 Hypertensive heart disease, without heart failure	4135	5,7	95	7,3	0.95
428.0-428.9 Congestive heart failure, unspecified - Heart failure, unspecified	3612	4,9	92	7,1	0.001
485 Bronchopneumonia, organism unspecified	2812	3,8	77	5,9	0.11
574.2 Calculus of gallbladder without mention of cholecystitis	2877	3,9	64	4,9	0.91
491.20 Obstructive chronic bronchitis without exacerbation	2747	3,8	63	4,8	0.99
584.9 Acute renal failure, unspecified	2439	3,3	61	4,7	0.49
585 Chronic kidney disease	4393	6,0	60	4,6	0.001
244.9 Unspecified hypothyroidism	2202	3,0	52	4,0	0.83
518.81 Acute respiratory failure	3375	4,6	47	3,6	0.001
491.21 Obstructive chronic bronchitis, with (acute) exacerbation	2497	3,4	44	3,4	0.10
433.30 Multiple and bilateral occlusion and stenosis of precerebral arteries	2183	3,0	42	3,2	0.31
728.2 Muscular wasting and disuse atrophy, not elsewhere classified	1197	1,6	40	3,1	0.02
285.1 Acute posthemorrhagic anemia	1809	2,5	37	2,8	0.57
276.5 Volume depletion	704	1,0	37	2,8	0.001
041.4 Other bacterial infections: Escherichia coli	794	1,1	37	2,8	0.001

Table 4

Odds Ratio (O.R. 95%C.I.; age, gender, and number of admissions adjusted) for the diagnosis of delirium in the presence of a specific ICD-9-CM diagnosis in 74.379 adult/older hospitalize patients. The excess risk fraction (ERF), and the number of delirium cases attributable to a specific ICD-9-CM diagnosis are also reported

ICD-9-CM	**O.R.**	**95%C.I.**		**E.R.F.**	**Delirium attributable to diagnosis**
Urinary tract infection, site not specified	3,518	3,016	4,104	71%	121
Other bacterial infections: Escherichia coli	3,067	2,295	4,099	67%	22
Volume depletion	3,054	2,285	4,081	67%	24
Alzheimer's disease - Senile degeneration of brain	3,052	2,532	3,678	67%	85
Cerebral ATH - Other generalized ischemic CVD	2,960	2,585	3,389	65%	179
Muscular wasting and disuse atrophy, not elsewhere classified	1,999	1,495	2,672	49%	19
Acute renal failure, unspecified	1,694	1,275	2,250	40%	18
Monoclonal paraproteinemia	1,666	1,201	2,312	39%	14
Bronchopneumonia, organism unspecified	1,559	1,249	1,946	35%	28
Congestive heart failure, unspecified - Heart failure, unspecified	1,462	1,180	1,812	31%	29
Acute posthemorrhagic anemia	1,378	1,020	1,862	27%	5
Hypertensive heart disease, without heart failure	1,337	1,110	1,610	24%	22
Benign Hypertension + Hypertension Unspecified	1,31	1,16	1,49	23%	71
Diabetes mellitus, without mention of complication	1,273	1,079	1,503	21%	47
Atrial fibrillation	1,249	1,071	1,458	19%	45
Unspecified hypothyroidism	1,274	,976	1,663		
Calculus of gallbladder without mention of cholecystitis	1,189	,920	1,535		
Obstructive chronic bronchitis, without exacerbation	1,178	,926	1,498		
Other specified forms of CHD + CHD, unspecified	1,014	,812	1,18		
Multiple and bilateral Occlusion and stenosis of precerebral arteries	1,007	,757	1,340		
Obstructive chronic bronchitis, with (acute) exacerbation	,990	,750	1,307		
Chronic kidney disease	,885	,722	1,086		
Acute respiratory failure	,856	,656	1,116		

contrary, heart failure and shock, renal failure, pulmonary oedema, and respiratory failure were more frequent in non-delirium patients.

The risk (O.R.; 95%C.I. - adjusted for age, gender, and number of admissions) of receiving a diagnosis of delirium in the presence of a specific DRG is also reported in Table 2. After excluding DRG 429 and 425 (both containing the diagnosis of delirium), the risk for delirium was strongly associated with the DRGs related to CNS pathologies (14-17, 12, 1, and 524), but also with DRG 210 and 544 (major orthopaedic diseases and procedures), and with DRG 416-576, 320-1, and 89-80 (major infections).

Delirium and ICD-9 diagnoses

Successively, we examined the ICD-9-CM diagnoses reported in the discharge records including primary and secondary diagnosis. In Table 3 are reported (in decreasing order) the most common medical diagnoses coded in patients with delirium and the equivalent prevalence reported in controls. In patients with delirium, hypertension (benign/not specified) was the most frequent diagnosis, followed by cerebral atherosclerosis/cerebrovascular (CVD) disease, coronary heart disease (CHD), atrial fibrillation, diabetes, and Alzheimer's disease. The prevalence of hypertension, cerebral atherosclerosis, UTI, Alzheimer's disease, congestive heart failure, volume depletion, and E. coli infections was higher in delirium patients compared with controls. On the contrary, chronic kidney disease and acute respiratory failure were more common in controls.

The likelihood of being affected by delirium according to the presence of a specific ICD-9-CM diagnosis was also calculated (Table 4). The Odds Ratio (O.R.) was adjusted for of age, gender, and number of admissions, in order to overcome their possible confounding effect. Compared with controls, the risk of delirium was higher (about three times) in the presence of UTI, E. coli infections, volume depletion, Alzheimer's disease, and cerebral atherosclerosis. Moreover, a mild but significant increase in the likelihood (about two times) was observed in the presence of muscular wasting, acute renal failure, and bronchopneumonia. In Table 4 is also reported the excess risk fraction (ERF - %) according to the presence of a specific ICD-9-CM diagnosis. The ERF was high (> 60%) for UTI, E. coli infections, volume depletion, Alzheimer's disease, and cerebral atherosclerosis; nevertheless, the absolute number of attributable diagnoses of delirium was sensibly different despite similar ERF.

As regards in-hospital mortality, the most frequent DRGs in deceased delirium patients were those related to CNS pathologies (including 429, 425, 14-17, 12, and 524: 48%), followed by heart failure and shock (6%), septicaemia (4%), and pneumonia/pleurisy (4%).

In deceased controls, the most frequent DRGs were, again, two DRGs related to CNS diseases (14-17 and 12: 9.9%), followed by heart failure and shock (6.6%), renal failure (3.7%), pneumonia/pleurisy (2.9%), and pulmonary oedema/respiratory failure (2.9%).

Discussion

We investigated the association between medical illnesses and diagnosis of delirium in a large database including over 74.000 older adults admitted to University Hospital acute medical wards over a period of nine years. In general, patients with delirium had a more severe comorbidity compared with controls, as indicated by the higher number of diagnoses and procedures, and by higher scores in Charlson and Deyo indexes. Charslon index is a validated comorbidity index able to predict ten-years mortality, based on more than twenty medical conditions, while the Deyo index is a comorbidity index specifically designed for use with medical records and research relying on ICD-9-CM codes. This data further support the concept that the simultaneous presence of different pathologies, as well as their severity might facilitate, through different mechanism, the onset of delirium in adult/older subjects. Unlike previous studies that evaluated medium/long term survival in delirium patients, we didn't find an increase in total mortality in delirium patient during the course of hospitalization. Nevertheless, it has to be underlined that: 1. we registered only the in-hospital mortality, and 2. the median length of stay in hospital was lower than 7.5 days. Actually, it is possible that also in our subjects with delirium mortality might be higher compared with controls, but this phenomenon might be observed in the weeks or month following the discharge.

Delirium and DRGs

Besides DRG 429 and 425 (including delirium diagnosis), delirium was strongly associated with the DRGs related to CNS pathologies (cerebrovascular diseases, brain transient ischemia, and degenerative nervous system disorders). This was expected since in these medical conditions a direct chronic/acute damage of CNS is observed, with reduction of cognitive reserve and/or alteration of neurotransmission and cytokines levels. Also DRGs associated with major hip and femur/other joints surgical procedures and DRGs related with major infections including septicaemia, UTI, and pneumonia/pleurisy were strongly associated with delirium. In older people, delirium is a common complication after femoral neck fractures, and might have serious impact on outcome (17). It has been associated with a number of perioperative/postoperative conditions and complications such as long waiting time before operation, type of anesthesia, anemia, UTI and urinary retention, wound infections, fever, and feeding problems (2, 3, 7, 9-11, 17). Infections are known to be associated with delirium onset. In sepsis, which can complicate both urinary tract infections and pneumonia, delirium often occurs early, and may be transient or reflect irreversible brain damage (18). The potential mechanisms for delirium in patients with sepsis include vascular damage and activation of endothelial, damage of the blood-brain barrier, metabolic disorders, and brain inflammation (18). Interestingly, it can be noted that among DRGs related to lung diseases, only pneumonia/pleurisy was significantly associated with delirium, while other conditions such as lung cancer, pulmonary embolism,

acute COPD, and respiratory insufficiency were not. This observation seems to indirectly suggest that the pathogenesis of delirium in these patients might be related to the infective process (via cytokines or hormones dysregulation) rather than to the presence of alteration of gas exchange including hypoxia.

Delirium and ICD-9 diagnoses

We also focused on the possible association between most common ICD-9 CM diagnoses and delirium. The likelihood of receiving a diagnosis of delirium was high (O.R. about 3) in case of UTI and E. coli infections, volume depletion, Alzheimer's disease, and cerebral atherosclerosis. More interestingly, we calculated the excess risk fraction (ERF) for each ICD-9-CM diagnosis. Among all subjects bearing a specific diagnosis in the sample, the ERF refers to the risk of developing delirium specifically attributable to that precise disease. Again, the ERF was high (> 60%) for UTI, E. coli infections, volume depletion, Alzheimer's disease, and cerebral atherosclerosis. Nevertheless, the absolute number of attributable delirium diagnoses was sensibly different despite similar ERF, depending on the absolute prevalence of the disease. For example, although the likelihood of having a diagnosis of delirium was identical (O.R. 3.05), the number of attributable cases was absolutely different in the presence of Alzheimer's disease (n.85) compared with volume depletion (n.24), due to the different prevalence of these two conditions among delirium patients (9.8% vs 2.8%). On the whole, 179 diagnoses of delirium (13.7%) could be attributable to cerebral atherosclerosis/ other ischemic CVD, 121 (9.3%) to UTI, 85 (6.5%) to Alzheimer's disease, 71 (5.5%) to hypertension, 47 (3.6%) to diabetes, and 45 (3.5%) to atrial fibrillation. All together, these ICD-9-CM diagnoses explained 42.1% of attributable risk of developing delirium, while all the ICD-9-CM diagnoses considered in Table 4 explained 56% of the risk.

In term of attributable diagnoses, cerebral atherosclerosis and generalized ischemic CVD disease together with Alzheimer's disease had the major impact on the diagnosis of delirium with 264 cases (20.2%). Nevertheless, it is interesting to note as 121 diagnoses (9.3%) were attributable to UTI, suggesting that this specific type of infection was the strongest determinant of delirium in our sample, after the pathologies of the brain.

The reason why UTI might cause delirium is not completely understood. It has been speculated that the inflammatory response causes a release of cytokines which in turn induce a dissociation in neurotransmitters; however, this does not explain why urinary tract, and not infections in other sites, might be so strongly associated with delirium. Fluid and electrolyte abnormalities are frequent in delirium; dehydration coupled with electrolyte and/or glucose imbalance might be specifically associated with UTI (and not with other types of infections) driving the process underlying delirium. Being recognized late, severe UTI might be more frequent in patients with dementia, and this might contribute to delirium onset. Additionally, UTI may affect kidneys becoming pyelonephritis; this may complicate with high fever and sepsis, which in turn may both affect brain functions causing delirium.

Diabetes, hypertension, and atrial fibrillation were also significantly associated with delirium, with a global ERF of 12.6% (163 cases). These three medical conditions are known risk factors for cerebrovascular disease, and have been consistently associated with dementia (19, 20); they might contribute, through different mechanisms, to reduce cognitive reserve in older individuals by affecting central nervous system (CNS).

Finally, we have to acknowledge some important limitations of the study.

Delirium was coded in 1.75% of discharge records; this prevalence is low when compared with those reported in other samples of hospitalized older patients (1-3). The mean age of our sample (70.5 years) was sensibly lower compared with other studies on delirium (2), and might have contributed to reduce delirium prevalence, since age is exponentially associated with delirium onset (11, 12). Moreover, our results derive from a database containing over 74.000 discharge records; unfortunately, the underestimation of prevalence is common in administrative database reports (21, 22), particularly when the diagnosis of interest is not the admitting or the principal one. It has been suggested that databases may be more reliable in case of symptomatic conditions (23); moreover, medical conditions with fluctuating nature and/or varied presentation (like delirium) may be undercoded. For example, by utilizing ICD-9 codes, Kales et al. found a prevalence of delirium of 4% in a nationwide Veteran's hospital among older patients (24). More recently, by analysing ten years acute care hospitalizations from a large administrative New York state database, Lin et al. found a much lower prevalence (0.8%) (25). Unlike the study of Kales, but similarly to our study, they did not consider ethanol related delirium. It is probable that in our study several cases of delirium might have been incorrectly included in the control group; nevertheless, this phenomenon might represents a "conservative" error and, in case, it would reinforce the results of the study.

Conclusion

In adult-older acute medical ward in-patients, delirium was associated with higher levels of comorbidity and with DRGs related to CNS pathologies, orthopaedic procedures, and major infections. The low prevalence of delirium reported in this sample suggests that practitioners probably need more education on

diagnosing and coding delirium.

Among ICD-9 diagnoses, an important excess risk for delirium was found in CNS pathologies, cerebrovascular risk factors, and UTI. Since UTI might represent the most frequent modifiable risk factor for delirium in hospitalized individuals, their prevention and early diagnosis/treatment might contribute to reduce delirium incidence. Clinicians need to have a high index of suspicion relative to the presence of UTI in elderly patients, especially in those with cognitive impairment, since its early recognition and treatment might contribute to decrease the probability of delirium onset.

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