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Markers of inflammation as risk predictors of lethal outcome in patients diagnosed with delirium

Markeri zapaljenja kao prediktori smrtnog ishoda kod bolesnika sa dijagnozom delirijuma

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Abstract

Background/Aim. Delirium is an acute or subacute, and most frequently reversible syndrome of higher cortical functions disturbances that is manifested as generalized disorder. If not prevented, it is associated with various adverse outcomes. The aim of this study was to determine the connection between the markers of inflammation and lethal outcome in patients diagnosed with delirium, hospitalized in the psychiatric intensive care unit. **Methods.** This retrospective study included 120 patients hospitalized in the psychiatric intensive care unit in whom examination of differences in inflammation markers was done. The examinees have been divided into two groups: the case group of 40 patients who died during the hospitalization, and the control group of 80 examinees who were discharged with the diagnosis *Post delirium status*. The following variables were taken into account: age, gender, clinical diagnosis of infection (pneumonia and urinary tract infection), laboratory parameters (total of white blood cells, granulocytes, monocytes, C-reactive protein − CRP) and type of delirium (withdrawal or organic). **Results.** The average age of the patients was 50.3 ± 13.1 years. The patients who survived delirium, were on the average 10.5 years younger than the deceased ($p < 0.001$). More than half (57.5%) of the deceased had pneumonia. There was a statistically significant correlation between pneumonia and lethal outcome in the patients with delirium ($p < 0.001$). The examinees with lethal outcome had significantly higher median CRP levels than the group of examinees who survived (75.6% ± 54.0 *vs* 30.3 ± 42.5 ng/L, $p < 0.001$). **Conclusion.** Aiming to better and more precise diagnostics of this complicated and still unclear neuropsychiatric syndrome it would be useful to consider introduction of more precise diagnostic algorithms in every unit of intensive care. That would significantly reduce the number of delirium diagnosis overlook, decrease complication of clinical features and would also reduce the unfavorable outcome rate, therefore the total cost of treatment.

Key words:
delirium; intensive care units; inflammation; biological markers; c-reactive protein; prognosis.

Apstrakt

Uvod/Cilj. Delirijum je akutni ili subakutni, najčešće reverzibilni sindrom oštećenja viših kortikalnih funkcija, koji se ispoljava kao generalizovani poremećaj. Ako se ne spreči, povezan je sa mnogostrukim i brzim lošim ishodima. Cilj ovog istraživanja bio je da se ispita povezanost markera zapaljenja i smrtnog ishoda kod bolesnika sa dijagnozom delirijuma, hospitalizovanih u jedinici intenzivne psihijatrijske nege. **Metode.** Retrospektivnom studijom obuhvaćeno je 120 bolesnika lečenih u jedinici intenzivne psihijatrijske nege pod dijagnozom delirijuma kod kojih je sprovedeno istraživanje razlika markera inflamacije. Ispitanici su bili podeljeni u dve grupe: grupu koju je činilo 40 bolesnika umrlih za vreme bolničkog lečenja, i kontrolnu grupu od 80 preživelih ispitanika koji su otpušteni pod dijagnozom „stanje posle delirijuma". Praćene su sledeće varijable: starost, pol, klinička dijagnoza infekcije (pneumonija i urinarna infekcija), laboratorijski parametri (ukupni leukociti, granulociti, monociti, C-reaktivni protein − CRP) i tip delirijuma (apstinencijalni ili organski). **Rezultati.** Prosečna starost ispitanika iznosila je 50,3 ± 13,1 godina. Bolesnici koji su preživeli delirijum bili su prosečno 10,5 godina mlađi od umrlih ($p < 0,001$). Više od polovine umrlih bolesnika (57,5%) imalo je pneumoniju. Utvrđena je statistički značajna povezanost pneumonije i smrtnog ishoda kod bolesnika sa deliri-

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jumom ($p < 0,001$). U grupi umrlih bolesnika, srednja vrednosti CRP-a bila je statistički značajno veća od vrednosti CRP u grupi preživelih (75,6 ± 54,0 *vs* 30,3 ± 42,5 ng/L, $p < 0,001$). **Zaključak.** U cilju bolje i preciznije dijagnostike ovog komplikovanog i još uvek nejasnog neuropsihijatrijskog sindroma, bilo bi korisno razmotriti uvođenje jasnog dijagnostičkog algoritma u svim jedinicama intenzivne nege. To bi moglo znatno smanjiti broj previda delirijuma, odnosno komplikovanje kliničke slike, stopu loših ishoda, a samim tim i ukupne troškove lečenja.

Ključne reči:
delirijum; intenzivna nega, odeljenja; zapaljenje; biološki pokazatelji; c-reaktivni protein; prognoza.

Introduction

Delirium is an acute or subacute, and usually reversible syndrome of higher cortical functions disturbances, manifested as generalized disorder [1]. Its cardinal symptom is attention disorder (includes distractibility, reduced vigilance and tenacity) as well as disturbances of consciousness, predominantly of space orientation. Additional symptoms – disorders of thought, sleep-wake cycle, perception, affect and motor behavior, amend this complex neuropsychiatric syndrome of acute onset and fluctuating course. If not prevented, delirium is associated with multiple and rapid unfavorable outcomes, including the higher risk of institutionalization, as well as of functional deterioration, dementia and death [2]. Contemporary scientific knowledge explains the pathogenesis of delirium by the neurotransmitter imbalance (dopamine, norepinephrine, acetylcholine, serotonin) at the central level, as well as by amino acids level changes, oxidative stress and inflammation [3].

Current studies show a connection between the increase of C-reactive protein (CRP) and interleukin 6 (IL-6) levels on the one hand, and the delirium incidence in postoperative course of surgical patients, on the other hand. These biomarkers could be general indicators of the complex inflammation process that causes delirium. CRP could stimulate series of reactions that lead to the increase of permeability of blood-brain barrier which results in neuronal dysfunction that can be manifested with delirium [3].

A number of meta-analysis find that the prolonged increase of CRP is associated with the increase of mortality rate. Patients in intensive care with high CRP levels have more serious organic dysfunction, longer hospitalization in intensive care unit, and higher mortality rate than patients in intensive care unit with normal CRP blood levels [4, 5]. However, association between CRP and delirium was not yet been proven. Only a few pilot studies have addressed this relation, so far [6]. The first study published in 2007, investigating the relation of CRP level and delirium, found high levels of CRP as a predictor of delirium [7]. Similar results were published in the following years, concluding that control of the blood CRP level can be very effective in prevention and reduction of cost of delirium in the intensive care unit [6, 8].

Considering the exceptional expansion of studies with delirium as a topic in the last ten years, it is expected that soon very complex and heterogeneous pathogenesis of this syndrome will be additionally clarified. The answer to intriguing question on relationship between infection and inflammation syndrome in a seriously ill patient with rapid onset of delirium, its complicated course and general neuronal dysfunction (which today is still described as delirium), could contribute a lot in the field of unfavorable outcome prevention.

The aim of this study was to examine the relation between the markers of inflammation and lethal outcome in patients diagnosed with delirium and hospitalized in the intensive psychiatric care unit.

Methods

In this clinical observational case-control study, the examined group comprised of all inpatients diagnosed with delirium in the period from January 1st 2010 to June 30th 2013 at the Clinic for Psychiatric Disorders "Dr Laza Lazarević", Belgrade, treated in the psychiatric intensive care unit of the Department for Urgent Psychiatry. The examinees were recruited by the consecutive sampling method. The sample was divided into two groups: the case group of the deceased, and the control group of examinees, discharged with the diagnosis "post delirium status".

Delirium was diagnosed according to the criteria of the currently valid International Classification of Diseases (ICD10) and included diagnostic categories F05, F10.4 and F19.4. The sample included adult patients previously examined or treated in other institutions, or previously treated in other departments, as well as the patients first examined in the Clinic for Psychiatric Disorders "Dr Laza Lazarević". The day of admission in the intensive care unit was considered as the first hospital day, disregarding if the patient was previously hospitalized in another institution and diagnosed with other psychiatric disorder.

Patients diagnosed with cancer or other forms of malignity, and those in a postoperative course during the observed period, were excluded from the study.

The group of the deceased was compared with the group of the survived. The following variables were compared: age, gender, clinical diagnosis of infection (pneumonia and urinary tract infection), laboratory parameters (total of white blood cells, granulocytes, monocytes, CRP, erythrocyte sedimentation rate) and the type of delirium (withdrawal or organic delirium). Laboratory parameters taken into consideration were the result of laboratory analysis taken at time when the diagnosis of delirium was suspected.

The data were obtained from the electronic medical records (patients' history, mental status, course of the disease, laboratory analyses). For statistical analysis of the data SPSS (Statistical package for the social sciences) version 22 was used. The data were presented by classical methods of descriptive statistics (arithmetic mean and standard deviation, median and interquartile range, absolute and relative frequencies), and were analyzed using parametric (Student *t*-

test), or nonparametric methods of inferential statistics (Mann-Whitney U-test, Pearson χ^2-test), depending on the nature and distribution of observed characteristics. The normality of distribution of continuous numerical characteristics was examined by inspection of histograms, quintile diagrams and was formally tested by Kolmogorov – Smirnov test. The logistic regression method was used for analysis of relation of binary outcomes and potential predictors.

Results

The study included 120 patients, the average age of 50.3 ± 13.1 years. Men were predominant (80.8%). Those who survived delirium were 10.5 years younger on the average (confidence interval − CI 95% 5.8 to 15.2) than patients with lethal outcome. This difference was statistically significant ($t = 4.462$, df = 118, $p < 0.001$). Frequency of lethal outcomes did not differ significantly between the genders ($\chi^2 = 2.689$, df = 1, $p = 0.101$) (Table 1).

In the group of the survived 16.3% developed pneumonia, in comparison to 57.5% in the group of patients with lethal outcome. There was a statistically significant relation between pneumonia and lethal outcome in the patients diagnosed with delirium ($\chi^2 = 21.607$, df = 1, $p < 0.001$). The patients with urinary tract infection had similar mortality rate (35% patients who survived and 37.5% who died had urinary infection, $\chi^2 = 0.072$, df = 1, $p = 0.788$).

In the group of patients with delirium as part of the withdrawal syndrome 20.2% died, whereas in the group with delirium caused by other reasons 63.9% of the examinees died. In the group of the survived 83.75% had withdrawal syndrome, in comparison to 42.5% in the group of those with lethal outcome. There was a statistically significant correlation between etiology of delirium and lethal outcome ($\chi^2 = 21.607$, df = 1, $p < 0.001$).

The mean of total leukocyte count in the group of the survived was 9.7×10^9/L ± 4.3×10^9/L, while the leukocyte mean level in the group who did not survive was 11.9×10^9/L ± 5.6×10^9/L. The examinees with lethal outcome had a significantly higher number of white blood cells ($Z_U = -2.45$, $p = 0.014$) and granulocytes ($t = 4.976$; $p < 0.001$), but significantly lower values of monocytes ($t = 4.038$; $p < 0.001$) and lymphocytes ($t = 4.903$; $p < 0.001$).

The mean CRP levels in those who survived were 30.3 ± 42.5 ng/L, whereas in the diseased they were 75.6 ± 54.0 ng/L. There was a statistically significant difference in the median CRP levels ($Z_U = 5.328$; $p < 0.001$). Those with lethal outcome had significantly higher median CRP levels.

Table 2 shows regression coefficient of bivariate logistic regression analysis. Statistically significant predictors of lethal outcome in bivariate logistic regression models were age, pneumonia, number of white blood cells, portion of granulocytes in leukocyte formula, as well as CRP concentration. A portion of lymphocytes and a portion of monocytes were protective factors.

Table 3 presents regression coefficient of the final logistic multivariate regression model including predictors: age, pneumonia and CRP. Counts of white blood cells, granulocyte, lymphocyte and monocyte portions were not included in the final model, since after the introduction of CRP as predictor these variables did not contribute significantly to the predictive power of the model. From statistical point of view, this model had significantly higher predictive power comparing to the null model ($\chi^2 = 28.298$, df = 3, $p < 0.001$, pseudo-R2Cox-Snell = 0.331) and could accurately classify 80% of cases (comparing to 66.7 in null model).

Table 1

Characteristics and treatment outcomes of patients with delirium

Variables	Patients (n = 120)		Statistics			
	survived (n = 80)	deceased (n = 40)	T	χ^2	Z_U	p
Age (years), x̄ ± SD	46.8 ± 11.6	57.3 ± 13.2	4.462			< 0.001
Gender, n (%)						
female	12 (15)	11 (27.5)		2.689		0.101
male	68 (85)	29 (72.5)				
Pneumonia, n (%)	13 (16.3)	23 (57.5)		21.607		< 0.001
Urinary infection, n (%)	28 (35)	15 (37.5)		0.072		0.788
Total leukocytes, x̄ ± SD *3.5−10 $\times 10^9$/L	9.7 ± 4.3	11.9 ± 5.6			-2.45	0.014
CRP, x̄ ± SD, *0−5 ng/L	30.3 ± 42.5	75.6 ± 54.0			5.328	< 0.001
Granulocytes, x̄ ± SD *43.0−76.0%	75.7 ± 8.9	84.3 ± 8.9	4.976			< 0.001
Monocytes, x̄ ± SD *4.3−10.0%	5.7 ± 2.1	4.0 ± 2.1	4.038			< 0.001
Limphocytes, x̄ ± SD *17.0−48.0%	18.7 ± 7.5	11.7 ± 7.0	4.903			< 0.001
Type of delirium, n (%)						
withdrawal	67 (83.7)	17 (42.5)		21.607		< 0.001
organic	13 (16.3)	23 (57.5)				

***Interval of reference values of laboratory parameters; CRP – C-reactive protein; x̄ – arithmetic mean; SD – standard deviation.**

Table 2

Bivariate logistic regression model of significant predictors of lethal outcome

Predictors	B	SE(B)	*p*	OR	CI 95% (OR)	
Age	0.074	0.019	< 0.001	1.077	1.037	1.119
Pneumonia	1.942	0.441	< 0.001	6.973	2.940	16.538
Leukocytes	0.093	0.042	0.026	1.098	1.011	1.192
Granulocytes	0.113	0.027	< 0.001	1.119	1.062	1.180
Lymphocytes	-0.139	0.034	< 0.001	0.871	0.815	0.930
Monocytes	-0.380	0.105	< 0.001	0.684	0.556	0.841
CRP	0.018	0.004	< 0.001	1.019	1.010	1.028

CRP – C-reactive protein; B – coefficient for usefulness of predictors; SE – standard error; OR – the ratio-change in the odds of the event of interest for a one-unit change in the predictor; CI 95% – confidence interval for 95%.

Table 3

Regression coefficient of final logistic multivariate regression model of predictors of lethal outcome

Predictors	B	SE(B)	*p*	OR	CI 95% (OR)	
Age	0.080	0.022	< 0.001	1.083	1.037	1.131
Pneumonia	1.916	0.552	0.001	6.793	2.304	20.028
CRP	0.013	0.005	0.012	1.013	1.003	1.023

For abbreviations see under Table 2.

It is evident, in the patients diagnosed with delirium that every year of age increases lethal outcome rate for 8.3% when it is controlled for other factors in the model. Pneumonia increases the risk for lethal outcome 6.8 times when controlled for other factors. For any increase in CRP by 1 mg/L the risk for lethal outcome in delirium diagnosed patients increases for 1.3% when controlled for other factors.

Discussion

In the currently available literature, so far there has not been studies especially examining leading risk factors for mortality of patients with delirium. Previous studies mostly investigated mortality of patients with delirium within certain diagnostic categories.

This study took into consideration age, gender, the type of delirium and markers of inflammation as risk factors for mortality of patients diagnosed with delirium in an intensive psychiatric care unit.

In the year 2013 Zhang et al. [9] published results of meta-analysis of delirium treatment outcomes in inpatients treated in the intensive care unit. Meta-analysis included 14 studies in which the data on mortality were found. Nine studies [10–18] showed the significant relation between delirium and mortality. The increase of mortality in these studies was controlled by the increase of age and seriousness of illness, including infections. The first European report [19] on mortality risk factors in the intensive care units was also published in the year 2013. This study confirmed the significant relation between delirium and mortality rate defining delirium as an independent risk factor for unfavorable outcome (institutionalization and death) during one month period of follow up.

Our study also showed that older and more seriously ill patients diagnosed with delirium die more frequently, but having in mind that patients in this study were, on the average, significantly younger than the patients in studies whose results we compared with ours. The reason is probably that studied patients were hospitalized in the psychiatric institution or already previously treated for some psychiatric disorder. Namely, the previous psychiatric disorder created base for development of delirium in the context of reduced cerebral reserve. Delirium itself is the result of interaction between precipitating factors and acute illnesses added to vulnerability. Higher age directly determines the degree of vulnerability of an individual. That is to say that the level of dependence and comorbidity increases with age [20]. Patients with worse premorbid functional status who develop delirium die significantly more frequently, *ie* delirium directly or indirectly converts vulnerability to unfavorable outcome [2]. The seriousness of illness makes a significant influence on mortality rate in patients with delirium [18, 21, 22]. In contrast to most of authors who tried to measure the seriousness of illness with indexes, this was not possible in our study due to the study design (the data were obtained retrospectively).

In our study, the inflammation syndrome is considered as a potential risk factor for death. Clinical and laboratory markers of inflammation are individually analyzed.

Pneumonia is a frequent disease being a cause of more than one million hospitalizations *per* year in the USA. In this country it is the ninth leading cause of death [23]. It is clinically characterized by a group of signs and symptoms that can vary intensively. Having this in mind, the diagnosis of pneumonia itself can be doubtful and difficult. Although it has very clear respiratory symptoms and marks, pneumonia may have totally atypical clinical course as well, without elevated body temperature, typical respiratory sounds or typical radiologic findings. This occurs most frequently in older people who also have high mortality rates of pneumonia, precisely

for lacking of accurate diagnosis [24]. For this group of patients it is very characteristic that pneumonia is manifested with clinical features of delirium only [25].

In our study, when the presence of pneumonia is taken in consideration, every year of age increases the risk of lethal outcome in patients with delirium for 8.3%. The presence of pneumonia in patients with delirium increases the risk for lethal outcome almost seven times after controlling for age and CRP blood level.

The results of the study by Calle et al. [24] carried out in geriatric intensive care unit, published in 2014, show that the mortality of people with pneumonia is significantly higher if they develop delirium. This rate increases significantly when the variable of consciences disorders is included in the model, and this is explained by the presence of hypoactive form of delirium that often remains unrecognized, and therefore consequently inadequately treated [26–28].

CRP levels as well as total of white blood cells and granulocytes were significantly higher in deceased patients compared to those who survived delirium. This confirms results of previous studies [4, 29, 30]. In other words, elevated level of CRP and granulocytes are significantly correlated to infection, inflammation response and mortality rate in patients with delirium in the intensive care. However, in the logistic multivariate model of prediction the CRP level and granulocytes have no value as lethal outcome predictors. In this model they are overridden by pneumonia. After being controlled for age and other factors in the model, the elements of leukocyte formula do not significantly contribute to prediction in the multivariate regression model. When controlled for age, CRP is a statistically significant predictor of lethal outcome, but only in patients without pneumonia. Every increase in CRP level by 1 mg/L increases the risk for lethal outcome for 1.3%. In patients with pneumonia, after controlling for age, the CRP does not contribute significantly to predictive power of multivariate regression model. CRP is a significant predictor of lethal outcome only in patients with no pneumonia, and this points to possible role of CRP as a predictor of lethal outcome in other diseases. CRP is significantly correlated with elevated risk for myocardial infarction and sudden cardiac death in seriously ill patients [31] as well as with acute renal failure in patients before dialysis [32], and as such could be valid early marker of morbidity and mortality in patients having multiple organ damages. Some future studies should yet clarify the role of CRP in prediction of lethal outcome in infective syndromes, but with look upon other markers as well, such are procalcitonin and Il-6 (3.29 pg/mL).

Delirium is a syndrome that can be prevented in 30–40% of cases [33]. High mortality rates are consequences of frequent overlooking of this diagnosis, especially in hypoactive form. In any case, the British guidance which states that every sudden change of behavior and mental status in both psychiatric patients and those who are not is considered delirium, until proven otherwise, seems useful [1]. According to that concept, in patients with such changes, as well as in patients clearly diagnosed with delirium, it would be useful to conduct comprehensive diagnostic procedures in order to exclude pneumonia or some other infective syndrome, renal and cardiac failure. Etiologic treatment would help to avoid complications of delirium and would also help to prevent bad outcomes such as institutionalization, cognitive deterioration and high mortality of patients with delirium. In this way, the number of days spent in a hospital, patients' personal characteristics, as well as overall costs of treatment that are in charge of health insurance would be significantly reduced. In our country these costs have never been estimated; The data from the USA could serve as an illustration, where costs go from 164 billion dollars *per* year [34], or over 182 billion dollars in eighteen European countries together [35, 36].

The limitation of our study is its retrospective design, which excluded the possibility to consider some significant variables (procalcitonin, Il–6…).

Another limitation could be heterogeneity of the sample (withdrawal deliriums were also included in the study).

Conclusion

Aiming to better and more precise diagnostics of this complicated and still unclear neuropsychiatric syndrome it would be useful to consider introduction of more precise diagnostics in every unit of intensive care. That would significantly reduce the number of delirium diagnosis overlook, especially of hypoactive forms, decrease complication of clinical features and would also reduce the unfavorable outcome rate, therefore consequently the total cost of treatment.

R E F E R E N C E S

1. *Gelder GM, Andreasen CN, Lopez-Ibor JJ, Geddes RJ.* New Oxford Text book of Psychiatry. Oxford, UK: Oxford University Press; 2009.
2. *Eeles EM, Hubbard RE, White SV, O'Mahony M, Savva GM, Bayer AJ.* Hospital use, institutionalisation and mortality associated with delirium. Age Ageing 2010; 39(4): 470−5.
3. *McGrane S, Girard TD, Thompson JL, Shintani AK, Woodworth A, Ely WE,* et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care 2011; 15(2): R78.
4. *Lobo SM, Lobo FR, Bota DP, Lopes-Ferreira F, Soliman HM, Mélot C,* et al. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest 2003; 123(6): 2043−9.
5. *Pepersack T, de Breucker S.* Could geriatric comprehensive assessment predict the outcome of pneumonia in the very old. Age Ageing 2007; 36(4): 455−9.
6. *Zhang Z, Pan L, Deng H, Ni H, Xu X.* Prediction of delirium in critically ill patients with elevated C-reactive protein. J Crit Care 2014; 29(1): 88−92.
7. *MacDonald A, Adamis D, Treloar A, Martin F.* C-reactive protein levels predict the incidence of delirium and recovery from it. Age Ageing 2007; 36(2): 222−5.
8. *Tsuruta R, Nakahara T, Miyauchi T, Kutsuna S, Ogino Y, Yamamoto T,* et al.. Prevalence and associated factors for delirium in

critically ill patients at a Japanese intensive care unit. Gen Hosp Psychiatry 2010; 32(6): 607−11.
9. *Zhang Z, Pan L, Ni H.* Impact of delirium on clinical outcome in critically ill patients: a meta-analysis. Gen Hosp Psychiatry 2013; 35(2): 105−11.
10. *Salluh JI, Soares M, Teles JM, Ceraso D, Raimondi N, Nava VS,* et al. Delirium epidemiology in critical care (DECCA): an international study. Crit Care 2010; 14(6): R210.
11. *Ely WE, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE,* et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004; 291(14): 1753−62.
12. *Lin SM, Liu CY, Wang CH, Lin CH, Huang CD, Huang PY,* et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med 2004; 32(11): 2254−9.
13. *Lin SM, Huang CD, Liu CY, Lin HC, Wang CH, Huang PY*, et al. Risk factors for the development of early-onset delirium and the subsequent clinical outcome in mechanically ventilated patients. J Crit Care 2008; 23(3): 372−9.
14. *Ouimet S, Riker R, Bergeron N, Bergeon N, Cossette M, Kavanagh B,* et al. Subsyndromal delirium in the ICU: evidence for a disease spectrum. Intensive Care Med 2007; 33(6): 1007−13.
15. *Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely WE.* Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010; 38(12): 2311−8.
16. *Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely WE.* Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilatet patients. Crit Care 2005; 9(4): R375−81.
17. *van den Boogaard M, Peters SA, van der Hoeven JG, Dagnelie PC, Leffers P, Pickkers P,* et al. The impact of delirium on the prediction of in-hospital mortality in intensive care patients. Crit Care 2010; 14(4): R146.
18. *van den Boogaard M, Schoonhoven L, van der Hoeven JG, van Achterberg T, Pickkers P.* Incidence and short-term consequences of delirium in critically ill patients: A prospective observational cohort study. Int J Nurs Stud 2012; 49(7): 775−83.
19. *Mariz J, Santos NC, Afonso H, Rodrigues P, Faria A, Sousa N,* et al. Risk and clinical-outcome indicators of delirium in an emergency department intermediate care unit (EDIMCU): an observational prospective study. BMC Emerg Med 2013; 13(1): 2.
20. *Yamaguchi T, Tsukioka E, Kishi Y.* Outcomes after delirium in a Japanese intensive care unit. Gen Hosp Psychiatry 2014; 36(6): 634−6.
21. *Sharma A, Malhotra S, Grover S, Jindal SK.* Incidence, prevalence, risk factor and outcome of delirium in intensive care unit: a study from India. Gen Hosp Psychiatry 2012; 34(6): 639−46.
22. *Siddiqi N, House AO, Holmes JD.* Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006; 35(4): 350−64.
23. *Dusemund F, Chronis J, Baty F, Albrich CY, Brutsche MH.* The outcome of community-acquired pneumonia in patients with chronic lung disease. Swiss Med Wkly 2014; 144: w14013.
24. *Calle A, Márquez MA, Arellano M, Pérez LM, Pi-Figueras M, Miralles R.* Geriatric assessment and prognostic factors of mortality in very elderly patients with community-acquired pneumonia. Arch Bronconeumol 2014; 50(10): 429−34. (English, Spanish)
25. *Marrie T.* Community-Acquired Pneumonia in the Elderly. Clin Infect Dis 2000; 31(4): 1066−78.
26. *Ewig S, Kleinfeld T, Bauer T, Seifert K, Schäfer H, Göke N.* Comparative validation of prognostic rules for community-acquired pneumonia in an elderly population. Eur Respir J 1999; 14(2): 370−5.
27. *Riquelme R, Torres A, el-Ebiary M, Mensa J, Estruch R, Ruiz M,* et al. Community-acquired pneumonia in the elderly. Clinical and nutritional aspects. Am J Respir Crit Care Med 1997; 156(6): 1908−14.
28. *de Zuazu HM, López GT, Barandiaran FA, Irujo OV, López MA.* Neumonía en el anciano. Factores relacionados con la mortalidad durante el episodio y tras el alta hospitalaria. Med Clin 2004; 123(9): 332−6. (Italian)
29. *Adamis D, Treloar A, Darwiche F, Gregson N, Macdonald AJ, Martin FC.* Associations of delirium with in-hospital and in 6-months mortality in elderly medical inpatients. Age Ageing 2007; 36(6): 644−9.
30. *Reny JL, Vuagnat A, Ract C, Benoit MO, Safar M, Fagon JU.* Diagnosis and follow-up of infections in intensive care patients: value of C-reactive protein compared with other clinical and biological variables. Crit Care Med 2002; 30(3): 529−35.
31. *Stenvinkel P.* Inflammatory and atherosclerotic interactions in the depleted uremic patient. Blood Purif 2001; 19(1): 53−61.
32. *Panichi V, Migliori M, de Pietro S, Taccola D, Bianchi AM, Norpoth M,* et al. C-reactive protein as a marker of chronic inflammation in uremic patients. Blood Purif 2000; 18(3): 183−90.
33. *Inouye SK, Westendorp RG, Saczynski JS.* Delirium in elderly people. Lancet 2014; 383(9920): 911−22.
34. *Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK.* One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008; 168(1): 27−32.
35. WHO Regional Office for Europe. European hospital morbidity database. Copenhagen: WHO Regional Office for Europe; 2012.
36. Organization for Economic Co-operation and Development. OECD health data 2012. Paris: Organization for Economic Co-operation and Development; 2012.

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