

Incidence and Predictors for Delirium in Hospitalized Elderly Patients: a Retrospective Cohort Study

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ABSTRAK

Tujuan: untuk menentukan insidens dan prediktor delirium serta mengembangkan model prediksi delirium pada pasien rawat inap berusia lanjut di Indonesia. **Metode:** suatu penelitian kohort retrospektif dilakukan pada pasien berusia lanjut (usia 60 tahun atau lebih) dan merupakan pasien rawat inap di bangsal penyakit dalam dan ruang rawat akut Rumah Sakit Cipto Mangunkusumo. Penelitian ini dilakukan sejak bulan Januari 2008 hingga bulan Desember 2010. Pasien tidak mengalami delirium saat masuk rumah sakit. Dua belas prediktor terjadinya delirium yang telah didefinisikan sebelumnya diidentifikasi pada saat pasien masuk rumah sakit. Prediktor independen untuk delirium diidentifikasi dengan analisis regresi Cox proportional hazard dan setiap faktor independen dikuantifikasi untuk mengembangkan suatu model prediksi delirium. Kemampuan kalibrasi dari model tersebut ditentukan dengan uji Hosmer-Lameshow dan kemampuan diskriminasinya ditentukan dengan menghitung area under curve (AUC) dari receiver operating curve. **Hasil:** subyek penelitian terdiri atas 457 pasien, sebagian besar (52,5%) merupakan pasien laki-laki berusia 60-69 tahun (55,8%), dengan rerata usia 69,6 tahun (SB 7,09). Delirium terjadi pada 86 pasien (insidens kumulatif 18,8%, insidens densitas 0,021 per orang-hari) dalam empat belas hari pertama perawatan di rumah sakit. Tiga prediktor independen delirium diidentifikasi, yakni: infeksi (tanpa sepsis, adjusted HR 1,83 (IK 95%:0,82-4,10); dengan sepsis, adjusted HR 4,86, IK 95%, 2,14-11,04), gangguan kognitif (adjusted HR 3,12; IK 95% 1,89-5,13) dan penurunan status fungsional (adjusted HR 1,74; IK 95% 1,07-2,82). Model prediktif dilakukan dengan menggunakan model akhir analisis multivariat dan distratifikasi menjadi tiga kelompok tingkatan risiko: rendah (tingkat delirium 4,4%), sedang (32,8%), dan tinggi (54,7%). Uji Hosmer-Lemeshow menunjukkan presisi yang baik (nilai $p=0,066$) dan AUC menunjukkan kemampuan diskriminasi yang baik (0,82, IK 95% 0,78-0,88). **Kesimpulan:** insidens delirium adalah sebesar 18,8% pada pasien rawat inap berusia lanjut dengan insidens densitas 0,021 per orang-hari, infeksi gangguan kognitif, dan penurunan status fungsional saat masuk ke rumah sakit merupakan prediktor independen terjadinya delirium selama perawatan di rumah sakit.

Kata kunci: usia lanjut, delirium, model prediksi.

ABSTRACT

Aim: to determine the incidence and predictors for delirium and to develop a prediction model for delirium in hospitalized elderly patient in Indonesia. **Methods:** a retrospective cohort study was conducted in elderly patients (aged 60 years and older) who were hospitalized in Internal Medicine Ward and Acute Geriatric Ward Cipto Mangunkusumo Hospital from January 2008 until December 2010. Patients were not delirious on admission. Twelve predefined predictors for development of delirium during hospitalization were identified on admission. Independent predictors for delirium were identified by Cox's proportional hazard regression analysis and each independent predictor was quantified to develop delirium prediction model. The calibration performance of the model was tested by Hosmer-Lameshow test and its discrimination ability was determined by calculating area

under the receiver operating characteristic curve (AUC). **Results:** subjects consist of 457 patients, predominantly male (52.5%) and were in 60-69 age group (55.8%), with mean age of 69.6 (SD 7.09) years old. Delirium developed in 86 patients (cumulative incidence 18.8%, incidence density 0.021 per person-days) during first fourteen-days of hospitalization. Three independent predictors for delirium were identified, including: infection (without sepsis, adjusted HR 1.83 (95% CI 0.82-4.10); with sepsis, adjusted HR 4.86, 95% CI 2.14-11.04), cognitive impairment (adjusted HR 3.12; 95%CI 1.89-5.13) and decrease of functional status (adjusted HR 1.74; 95% CI 1.07-2.82). Predictive model was performed using the final model of multivariate analysis and stratified into three levels: low- (rate of delirium 4.4%), intermediate- (32.8%), and high-risk (54.7%) groups. The Hosmer-Lemeshow test revealed good precision (p-value 0,066) and the AUC showed good discrimination ability (0.82, 95% CI 0.78-0.88). **Conclusion:** incidence of delirium is 18.8% in hospitalized elderly patients, with incidence density of 0.021 per person days. Infections, cognitive impairment, and decrease of functional status on admission are independent predictors for the development of delirium during hospitalization.

Key words: elderly, delirium, incidence, prediction model.

INTRODUCTION

Increasing elderly population will be followed by numerous health problems, as it is seen in increasing rate of hospitalization among this population. Comparable to other developing countries, in Indonesia, percentage of hospitalized elderly patient at internal medicine inpatient unit Cipto Mangunkusumo hospital (RSCM) in 2001 and 2002 was as high as 26.3 and 28.7%, respectively.¹ Delirium, or acute confusional state, is a common diagnosis with serious complications in hospitalized elderly patients.^{2,3} Prevalence of delirium on admission were varies from 14 to 56% with associated hospital mortality rate of 25-30%.^{3,4} In Acute Geriatric Ward RSCM the incidence of delirium were around 17% with prevalence of up until 47.3%.^{5,6}

Delirium is a mental disorder presented with global cognitive dysfunction, alter of consciousness, sleep cycle, and psychomotor activity in acute setting and fluctuated.⁷ Delirious patients have increased morbidity, decreased functional status, prolonged hospital stay and increased risk of entering long-term care on discharge from hospital compared with patients without delirium.^{3,4,8-11} A systematic literature study showed mean hospitalization and associated mortality rates after 6 months period were 36% and 26%, respectively.³ Delirium occurs as consequences of interrelation of predisposing factors (risk factors) and precipitating factors (triggering factors). In general, the risk factors were age, dementia, hypoalbuminemia, usage of anticholinergic, and psychoactive medications,

decreasing functional status, vision and hearing impairments. Precipitating factors identified were metabolic disturbance, infection, cardiovascular disease, imbalance of electrolytes and primary disease of the brain.^{8-10,12,13} Several studies have been conducted to identify independent predisposing and precipitating factors,¹⁴⁻¹⁶ but there was no study aimed to quantify those factors comprehensively and to develop predictive model of delirium during hospitalization.

The aims of this study aims are to determine the incidence of delirium and to determine independent predictors for delirium development in elderly patient hospitalized at internal medicine inpatient ward. We try to quantify these factors to derive a prediction rule for occurrence of delirium during first 14 days of hospitalization among elderly patients treated in acute ward, which can stratify patients into different risk levels. This stratification will lead to a better management of hospitalized elderly patients, and in turn, will decrease the incidence of delirium as well as morbidity and mortality associated with delirium.

METHODS

Design, Setting, and Population

A retrospective-cohort study was conducted among elderly patients who were hospitalized during January 2008 until December 2010 period at Internal Medicine Inpatient Unit and Acute Geriatric Ward Cipto Mangunkusumo Hospital (RSCM), Jakarta, a national referral hospital in Indonesia. Data extraction from medical records was performed on March and April 2011. Patients

were excluded if there was any evidence or diagnosis of delirium or acute confusional state on admission.

Assessment of Predictors

We determined 12 predictors which from the literatures have been identified as predisposing or precipitating factors for development of delirium, including: age, sex, hypoalbuminemia, anemia, anticholinergic drugs, decrease of functional status (measured by Barthel index of activity of daily living [AOL]), stroke, metabolic disturbance (including electrolytes and acis-base disturbances, and/or hypoglycemia), infection (with and without sepsis), heart diseases, and hypoxia. All of predictors were assessed through medical records at the date of admission.

Determination of Delirium Occurrence

From the medical record, we retrospectively followed-up patients since the admission until fourteen days afterward for the occurrence of delirium during hospitalization. Diagnosis of delirium was made by treating doctors (i.e. internists and/or geriatricians), which usually based on the presence of acute mental change in patients with previously fully alert marked by disorientation, sleep disturbance, and/or agitation, especially if happened fluctuatively.

Data Analyses

Data were analyzed using SPSS 17.0. Numerical data was presented in means with their standard deviations (SD), where categorical data was presented as proportion. Incidence of delirium presented as cumulative incidence and incidence density. We performed survival analysis with Kaplan-Meier method to determine survival for developing delirium during first 14-days of hospitalization and also the mean of survival. We used Cox's proportional hazard regression analysis (Cox's regression), both in bivariate and multivariate analyses, to determine independent predictors for developing delirium. Predictors which had p-value <0.20 on bivariate analysis will be included in multivariate analysis. Predictors were considered significant for delirium in hospitalized elderly patients if p-value <0.05. Hazard ratios (and the 95% confidence intervals) presented for each independent predictors.

As there was some missing data from the medical records on the predictors and not included the missing data on analysis will

resulted in two weaknesses, i.e. underpowered of prediction model and biases if the missing data was differential, we imputed the missing values as suggested by Janssen et al. and Donders et al.^{17,18}

Independent predictors which determined by multivariate analysis were then included to derive a prediction model. A scoring system for practical use developed from the final model. Calibration power of the model was tested using Hosmer-Lameshow test and its discriminative power was determined through area under receiver operating characteristic curve (AUC).

RESULTS

From January 2008 until December 2010, there were 457 elderly patients hospitalized in Internal Medicine Ward RSCM which fulfill inclusion criteria. Of 457 patients, 240 (52.5%) were male and 255 (55.8%) were in age group 60-69 years old (mean age 69.6 [SD 7.09] years old). Demographic and clinical characteristic of the subject are presented in **Table 1**.

Eighty seven patients experienced delirium during their first 14-days of hospitalization (cumulative incidence 18.8%, incidence density 0.021 per person-days). Survival for not developing delirium within 14-day of hospitalization among elderly patients is 75.5% (standard error [SE] 2.5%) with mean of survival is 11.8 days (95% CI 11.4-12.3). Kaplan-Meier curve shows cumulative survival of delirium during hospitalization (**Figure 1**).

As we expected, some data in several variables are missing due to incompleteness of medical records. Before we continue with main analysis, we did the missing value analysis to determine whether the missing data was related to bias in data collection. **Table 2** shows how the comparability of missing data in each missing variables. Out of 5 predictors which have missing data, 2 of them (cognitive impairments and hypoxia) have different proportions of missing data based on whether subjects will experience delirium or not. We did the estimation and maximalization (EM) method to impute the missing data in order to maintain study power, and used the complete data to do further analyses.

Bivariate analyses showed that predictors which related to delirium in elderly hospitalized patients are infections, decrease of functional status, cognitive impairment, hypoalbuminemia,

Table 1. Subjects characteristics (n=457)

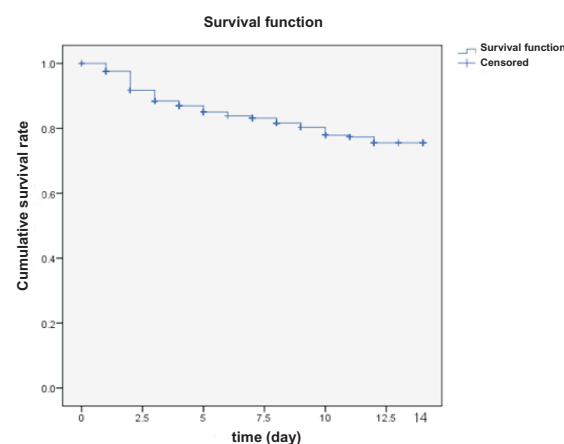
Characteristic	n (%)
Demographic	
Sex	
- Male	240 (52.5)
- Female	217 (47.5)
Mean age (SD)	69.56 (7.09)
Age	
- >80 years	46 (10.1)
- 70-79 years	156 (34.1)
- 60-69 years	255 (55.8)
Education	
- None/<6 years	32 (7.0)
- Primary school	118 (25.8)
- Junior High School	99 (21.7)
- Senior High School	138 (30.2)
- Academy/University	68 (14.9)
Activities	
- House wife	151(33.0)
- Pensioner	161 (35.2)
- Private	67 (14.7)
- None	78 (17.7)
Clinical Characteristics	
Comorbidities	
- Malignancy	36 (7.9)
- Cardiac disease	183 (40.0)
- Liver cirrhosis	49 (10.2)
- Cerebrovascular disease	57 (12.5)
- Renal disease	211 (46.2)
- Diabetes mellitus	143 (31.3)
- Lung infectio	260 (56.9)
- Urinary tract infection	55 (12)
Laboratory results	
- Hemoglobin, mean (SD)	10.8 (2.66)
- Leucocyte count, mean (SD)	11285 (13275)
- Thrombocyte, mean (SD)	254972 (130711)
- Ureum, mean (SD)	70.3 (57.44)
- Creatinin, mean (SD)	2.2 (2.84)
- ALT, mean (SD)	57.2 (139.18)
- AST, mean (SD)	40.7 (69.27)
- Albumin, mean (SD)	3.0 (0.66)
- Blood sugar, mean (SD)	157 (9.24)
- Natrium, mean (SD)	136.9 (7.22)
- Mean of ADL score (SD)	12.4 (5.49)
- Mean of MMSE score (SD)	24.6 (5.16)

Abbreviation: SD=Standard deviation, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, ADL=Activity Daily Living, MMSE=Mini Mental State Examination

cardiovascular disease, stroke, hypoxia, and metabolic disturbance. Analysis with Cox's proportional hazard regression revealed only infection (with and without sepsis), cognitive impairment, and decrease of functional status at admission are independent predictors of delirium during first 14-days of hospitalization among elderly patients (**Table 3**). Using logistic regression we then develop a model to calculate the probability for developing delirium based on these 3 independent predictors:

$$1 + e^{-3.2 + 0.64(\text{inf. w/o sepsis}) + 2.5(\text{inf. w/ sepsis}) + 0.94(\text{decr of func. st}) + 1.41(\text{cog. impairm})}$$

To simplify prediction of delirium probability based formula above, scoring system was created to easily apply in daily practice. Weighted score of each predictor were calculated by dividing regression coefficient with its standard error

**Figure 1.** Kaplan-Meier curve showed survival for delirium in elderly patients during first 14 days hospitalization**Table 2.** Case distribution in variables with missing data

Variable with missing data	Number of missing data (%)		
	All subject (n=457)	Subject without delirium (n=371)	Subject with delirium (n=86)
Albumin	51 (11%)	43 (11.5%)	8 (9.3%)
Cognitive impairment	41 (8.9%)	20 (5.4%)	21 (24.4%)
Decrease of functional status	16 (3.5%)	14 (3.7%)	2 (2.3%)
Metabolic disturbance	50 (10.9%)	41 (11.0%)	9 (10.5%)
Hypoxia	100 (21.8%)	95 (25.6%)	5 (5.8%)

Table 3. Multivariate analysis of delirium predictors

Predictor	HR (CI 95%)	P-value
Male sex	1.16 (0.74-1.84)	0.52
Hypoalbuminemia	1.28 (0.79-2.08)	0.32
Anemia	1.05 (0.67-1.64)	0.82
Decrease of functional status	1.74 (1.07-2.82)	0.02
Cognitive impairment	3.12 (1.89-5.13)	0.00
Stroke	1.40 (0.81-2.40)	0.22
Cardiac disease		0.16
None	1.00 (reference)	
CAD, benign arrhythmia, CHF fc I-II	0.61 (0.33-1.16)	0.13
ACS, malignant arrhythmia, CHF fc III-IV	1.27 (0.73-2.22)	0.40
Infections		0.00
- None	1.00 (reference)	
- Without sepsis	1.83 (0.82-4.10)	0.14
- With sepsis	4.86 (2.14-11.04)	0.00
Metabolic disturbance	1.04 (0.67-1.63)	0.85
Hypoxia	1.27 (0.80-1.98)	0.30

Abbreviation: CAD = coronary arterial disease, CHF = congestive heart failure, ACS= acute coronary syndrome

(**Table 4**). Based on the score above, we classified the risk of delirium into low, intermediate and high (**Table 5**).

Hosmer-Lameshow test showed that the prediction model have good precision (p-value 0.066) and good discrimination ability (AUC 0.823; 95% CI 0.776-0.877) (**Figure 2**).

DISCUSSION

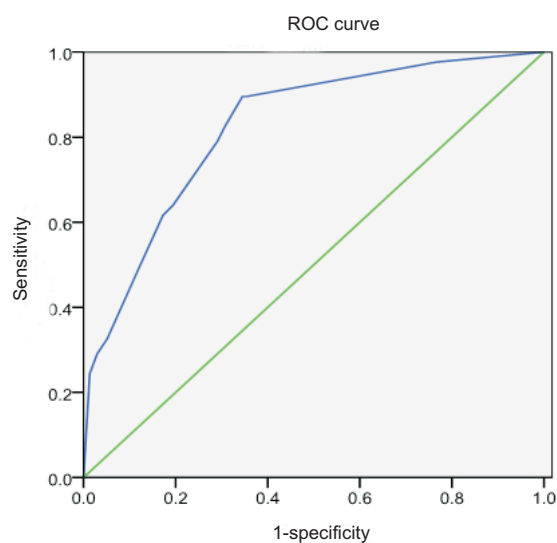
In this retrospective cohort study we found that the incidence of delirium during first 14-days hospitalization was 18.8% (95% CI 15.2-22.4%) with incidence density of 0.021 perperson-day. This finding was not different with other studies where incidences of delirium among hospitalized elderly patients were between 3 and 29%.¹⁴⁻¹⁶

A study conducted in 2004 found incidence of delirium in hospitalized elderly in RSCM were 17.93%.⁵ Inouye et al. (1993) found 25% of 107 elderly hospitalized patients were delirious.¹⁴ An advance study by the same author in 1996 found incidence of delirium were 18% of 196 subjects.¹⁶ Pisani et al. who performed a study at intensive care unit found a higher incidence, 71%.¹⁷

Survival of elderly patient to develop delirium within first 14-days of hospitalization in this study was 75.5% (SE 2.5%), with mean of survival 11.8 days (95% CI 11.4-12.3 days). Out of 86 patients who developed delirium, 59.3% patients occurred within first 3-days and 81.4% within first 7-days of hospitalization. Most of

Table 5. Performance of delirium predicting score

Score	Risk Class	Probability for delirium
<2	Low	4.4%
2 – 5	Intermediate	32.8%
>5	High	54.7%

**Figure 2.** Receiver operating characteristic (ROC) curve with AUC 0.823 (95% CI 0.776-0.877).**Table 4.** Multivariate analysis to develop delirium prediction score

Predictor variable	Coefficient regression (B)	SE	B/SE	Score	Rounded score	P-value
Infection						<0.001
Without sepsis	0.639	0.424	1.507	1	1	
With sepsis	2.504	0.463	5.408	3.590	3.5	
Decrease of functional status	0.941	0.299	3.147	2.088	2	0.002
Cognitive impairment	1.410	0.295	4.780	3.17	3	<0.001
Constanta	-3.202	0.410				

the study focuses on survival of delirium were being related with mortality or other outcome of delirium,¹⁷⁻¹⁹ and to our knowledge, this is the first study that performed survival analysis with delirium as an outcome. Inouye et al showed in her study, that the median of event (delirium) was at day four.¹⁴ Schor et al. found 31.3% of 291 elderly hospitalized patient became delirious during treatment; and among delirious patients, 46.2% occurred within first 3-days and 91.2% on 7-days of hospitalization.¹⁵ These evidences showed how usually elderly patients came to the hospital with advanced condition and they have high-risk for developing delirium during early period of hospitalization.

In this study we showed that infections, cognitive impairment, and low functional status at admission are independent predictors for developing delirium during first 14-day of hospitalization among elderly patients. These findings are comparable with previous studies on delirium in elderly.

In his cohort study, Schor et al. showed that symptomatic infection is an independent risk factor for in-hospital delirium (OR 2.96, 95% CI 1.42-6.15).¹⁵ Although did not attain statistical significance, in a case-controlled study, George et al. found that infection is the most common cause of delirium (accounting 34% from all delirious patients).¹³ Korevaar et al. also found infection as the most common risk factors besides decrease of functional status and cognitive impairment, even though there were not statistically significant.²⁰

Infection will increase the production of cytokines specifically interleukin-1, 2, 6 and 8, tumor necrosis factor alpha (TNF- α) and interferon (IF). These cytokines will increase the permeability of blood brain barrier and disturb various neurotransmitters in the brain, especially acetylcholine. The elevated cytokines concentration is widely accepted as one of the basics mechanisms of various neuropsychiatric disorders such as cognitive imbalance in dementia, depression, fatigue, and cognitive imbalance in cancer.²¹

Cognitive impairment or dementia were the most common studied risk factors of delirium and had close correlation with delirium.²² In our study, cognitive impairment was identified in 20.2% of all subjects and showed significant correlation with delirium both on bivariate and multivariate analyses. Schor et al. found

significant association between cognitive impairment and delirium (OR 8.9, 95% CI 3.99-20.14).¹⁵ Inouye et al. created delirium prediction model and cognitive impairment was one of the independent predicting factor. Risk of delirium is 3.5 fold higher in patient with recognized cognitive impairment.¹⁶ Korevaar et al. proved that cognitive impairment is the strongest risk factor for development of delirium (HR 9.48; 95% CI 2.27- 39.54).²⁰

Cognitive impairment such as dementia is a very strong predictor for delirium and demented patient carrying 2-5 fold greater risk to develop delirium. Moreover, there is evidence that more than half of delirious patient were previously demented. The relationship between dementia and delirium is very strong, but the pathophysiology is not fully understood yet. Some studies showed that cognitive function of delirious patient never fully recover.^{21,23} Dementia is thought to be caused by decreasing of acetylcholine and somatostatin level, whereas both had vital roles in cognitive function like attention and sleep-wake cycle. Demented patients are prone to develop delirium, especially if there were triggering factor like hypoxia or anticholinergic usage.²¹

Another independent predictor for development of delirium in this study is decrease of functional status. A study by Francis which used ADL as an instrument to measure functional status, found that decrease of functional status associated with delirium (OR 2.7, 95% CI 1.2-5.8).¹⁸ Inouye et al. also used ADL and instrumental ADL and came out with relative risk (RR) of a delirious patient who needed at least one assistance in term of IADL were 1.5, and 1.8 for patient who needed two or more assistance.¹⁴ Yuniastuti used ADL and showed that the higher the level of dependence the stronger association with presence of delirium.⁵ Korevaar et al also proved significance correlation between decreasing functional status and delirium.²⁰ High level of dependency in elderly patient is commonly caused by of general health status and chronic illnesses, and therefore become a predictor for delirium as comorbidity itself also correlates with delirium.²⁴

Prediction model was derived in our study based on only three statistically significant predictors included in the final model, i.e. infections, cognitive impairment, and decrease of functional status. The result of this research can

be easily applied when managing hospitalized elderly patient in daily practice. Delirium usually occurs within 10-14 first day of hospitalization. Early precaution and recognition are needed to manage the disease. Probability of a patient for developing delirium can be calculated using the formula or scoring system and incorporated this important information when educating patient and family and become an integral part in patient management. Two of three significant predictors, decreased of functional status and cognitive impairment, were domains in Comprehensive Geriatric Assessment (CGA) and therefore strengthened the importance of CGA in evaluating elderly patients. Results of this study can be used as a basis for including CGA as a standard operational procedure in the management hospitalized elderly patients.

To our knowledge, this is the first study in Indonesia which have aim to determine incidence density (ID) of developing delirium in hospitalized elderly patient. Incidence density provides better information than cumulative incidence because it informs us how fast delirium develops during hospitalization. Besides, this is a first prognostic study with retrospective cohort design which succeeded creating scoring system to predict delirium in hospitalized elderly patients in Indonesia, which has different characteristics with elderly patient in other region.

Limitation of the research is the incompleteness data on medical records. Data limited in terms of predictors and other factors which influences study like socio economic factors. In addition, bias (especially information bias) is exist, as if in a retrospective-designated cohort analysis. To overcome this limitation, we did data imputation which is also to maintain power of the study.

CONCLUSION

Incidence of delirium in elderly patients is 18.8% during first 14-day of hospitalization, with incidence density of 0.021 per person-day. Infection (with or without sepsis), cognitive impairment, and decreased of functional status are significant predictors for development of delirium during first 14-day of hospitalization among elderly patients. Infection with sepsis had a greatest contribution towards probability of delirium during hospitalization followed by

cognitive impairment, decreased of functional status, and infection without sepsis. Prediction model (scoring system) has been developed and can be used to stratify risk of delirium into low (4.4%), moderate (32.8%) and high (54.7%); with its good calibration and discrimination ability.

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