CLINICAL ARTICLE

Early Detection of Pneumonia with the Help of Dementia in Geriatric Hip Fracture Patients

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Objective: To investigate the role of dementia in pneumonia among geriatric patients with hip fracture and further develop an algorithm for stratifying risk of developing postoperative pneumonia.

Methods: The algorithm was developed after retrospectively analyzing 1344 hip fracture patients in the National Clinical Research Center for Orthopedics, Sports Medicine, and Rehabilitation from 1992 to 2012. Twenty-eight variables were analyzed for evaluating the ability to predict postoperative pneumonia. The validation of the algorithm was performed in the MIMIC-III database after enrolling 235 patients.

Results: One thousand five hundred and seventy-nine patients were enrolled, 4.69% patients had postoperative pneumonia in our hospital, and 17.02% suffered pneumonia in the MIMIC-III database. Dementia patients had more postoperative pneumonia (12.68% *vs* 4.24%, $P = 0.0075$), as compared with patients without dementia. The algorithm included nine predictors: dementia, age, coronary heart disease, the American Society of Anesthesiologists score, surgical method, mechanical ventilation, anemia, hypoproteinemia, and high creatinine. Internal validation showed the algorithm with dementia could improve predictive performance, while external validation found the algorithm with or without dementia both had similar and good predictive ability.

Conclusions: The algorithm has the potential to be a pragmatic risk prediction tool to calculate risk of pneumonia in clinical practice and it may also be applicable in critically ill hip fracture patients with dementia.

Key words: Dementia; Geriatric hip fracture; Pneumonia; Prevention; Risk algorithm

Introduction

Dementia and hip fractures have becoming common significant public health issues among the elderly due to the growing aging population[1,2]. Approximate 0.5% of the worldwide population and more than 35 mn people suffered from dementia globally[3]. One and a half mn hip fractures occur per year and this number will continue to increase to 4.5 mn by 2050[4]. Dementia patients had an odds ratio of 6.9 to develop hip fractures, and hip fractures could also in turn increase the risk of dementia[5]. The recent study showed that antipsychotic drugs were associated with an increased risk of hip fractures among dementia patients[6] and elderly dementia adults needed home care services more often than elderly adults who did not have dementia[7].

Patients with advanced dementia and hip fracture or pneumonia had a relatively poor prognosis. More explicitly, 6-month mortality was up 50%[8] and dementia patients with hip fracture suffered from a higher risk of postoperative mortality, as compared with patients without dementia[1,2,9–11]. Pneumonia is also the most common complication of hip fractures[12]. Studies have reported 4.23% to 8.80% of hip fracture patients developed pneumonia in hospital[13,14], which significantly increased the risk of mortality and reduced patients' quality of life[4,15–18]. Pneumonia was associated with various risk

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factors in hip fracture patients, such as age, gender, albumin, body mass index (BMI), nutrition status, preexisting pulmonary diseases, multiple-organ failure, and mechanical ventilation[13,14,19,20]. Besides, dementia has been proved as a predictor for pneumonia among elderly populations[21]. However, some studies showed no significant association between pneumonia and dementia/cognitive impairment after adjusting other risk factors especially among patients with hip fractures[13–15]. Therefore, the role of dementia in pneumonia among geriatric hip fracture patients requires further elucidation. Identifying predictors for pneumonia is vital for risk stratification and it can also provide insight into therapeutic strategies.

Therefore, this study aimed to i) perform a subgroup analysis of patients with and without dementia, ii) create and validate a risk algorithm to predict the risk of postoperative pneumonia among elderly patients with hip fracture, iii) further compare the algorithm including and excluding the variable of dementia.

Patients and Methods

Study Population

The study retrospectively analyzed 2066 patients in the National Clinical Research Center for Orthopaedics, Sports Medicine, and Rehabilitation from January 1992 to December 2012. All hip fracture patients with a hospital diagnosis of femoral neck fracture or femoral intertrochanteric fracture (ICD-9-CM [International classification of disease, ninth revision, clinical modification]: 820) were entered into the national center's hip fracture database. We continuously included all hip fracture patients who meet the following inclusion criteria: (1) patients diagnosed with a femoral neck or intertrochanteric fracture; (2) patients treated with surgery in our department. Patients were excluded if (1) age less than 65 years; (2) radiograph-confirmed pneumonia after admission within 48 h; (3) conservative treatments; (4) history of pneumonia before hospitalization within 3 months. Figure 1 shows the patients' enrollment flowchart. Patients in our hospital were used to develop and internally validate the algorithm.

The study also externally validated the algorithm after analyzing 58,976 patients in the MIMIC-III database. This database was a large and freely available database containing deidentified health-related data from medical records associated with patients who were admitted to critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012[22]. The PhysioNet approved researchers have data access to the MIMIC-III database[23].

The Medical Research Ethics Board of the Chinese PLA General Hospital approved the study protocol and waived patients' consent for review of medical records and images, as all data were anonymized and retrospective. This study was conducted in accordance with the Declaration of Helsinki.

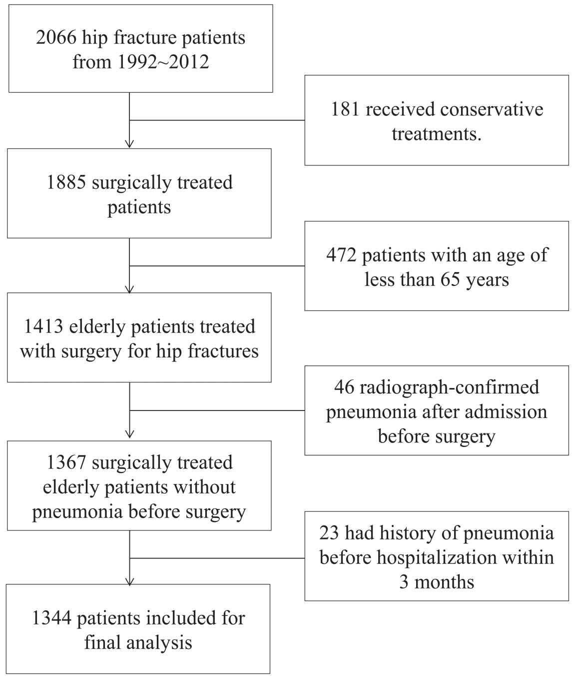

Fig. 1 The patient enrollment flowchart

Subgroup Analysis of Patients with and without Dementia

Dementia was a condition characterized by a decline in memory, language, problem-solving, and other thinking skills that affect a person's ability to perform everyday activities. Patients with a diagnosis of dementia including Alzheimer's disease and vascular dementia were assigned to total dementia group. Other patients without a diagnosis of dementia were considered as non-dementia group. Characteristic distributions (patient's general information, comorbidities, clinical interventional factors, and laboratory examinations) were compared between the two groups. Besides, the univariate and multiple analyses were performed to evaluate the relationships between the above-mentioned clinical variables and dementia.

Outcome of Interest: Postoperative Pneumonia

Postoperative pneumonia was defined that new infiltrations were shown in chest X-ray and one or more following symptoms appeared after surgery during hospitalization[24]: (1) presence of new and/or progressive and persistent respiratory symptoms including coughing and expectoration; (2) presence of fever or hypothermia; (3) physical examination showing lung consolidation signs and/or moist rale; (4) a white cell count of greater than 10×10^9/L or less than 4×10^9/L; and (5) pathogen isolation from blood culture or sputum.

Potential Predictors

Candidate predictor variables were identified based on a review of the literature, and variables available from medical records were collected. Variables considered for creating the algorithm included patients' general characteristics, comorbidities, clinical interventional characteristics, and laboratory examinations. We identified 28 possible variables: age, gender, BMI, fracture type, history of smoking, Chronic Obstructive Pulmonary Disease (COPD), asthma, diabetes, hypertension, coronary heart disease, prior myocardial infarction, arrhythmia, prior stroke, cerebral sequelae, dementia, Parkinson's disease, digestive system disorders, renal diseases, rheumatologic disease, tumor, American Society of Anesthesiologists (ASA) scores, surgical method, mechanical ventilation, anemia (a hemoglobin level of less than 12.0 g/dl in male and 11.0 g/dl in female), hypoproteinemia (an albumin level of less than 3.0 g/dl), high creatinine (a serum creatinine level of more than 1.2 mg/dl), RDW (red blood cell distribution width), and any electrolyte disorders. The patients' general characteristics and comorbidities were collected at presentation. The clinical interventional characteristics and laboratory examinations were collected before surgery.

Algorithm Development

In the study, the 28 variables were analyzed for their ability to predict postoperative pneumonia. The Least Absolute Shrinkage and Selection Operator (LASSO) method combined with 10-fold cross-validation was used to further reduce the number of candidate variables. The LASSO method could minimize the residual sum of squares subject to the sum of the absolute value of the variable coefficients being less than a constant[25]. Compared with other logistic regression, the LASSO method had the advantage of shrinking coefficients toward zero, thus it could efficiently reduce the number of predictors without affecting the interpretability of the algorithm[26]. In the study, the significant characteristics with a relative low coefficient value (≤0.005) were excluded. The values for the included significant characteristics in the algorithm were obtained from the coefficient values according to the LASSO method. In detail, the values were 10 times the estimate (coefficient value) of each characteristic divided by the total of the estimates of the nine included characteristics in the algorithm. The final scores were rounded off to the closest integer. The total prognostic score of each patient represented the sum of all the scores from the included significant characteristics. Internal and external validation of the algorithm was placed in the supplementary material (Appendix S1). External validation was performed in the MIMIC-III database, and we extracted patients according to ICD-9-CM code (Table S1). Figure S1 shows the patient's enrollment flowchart in the MIMIC-III database.

Statistical Analysis

Statistical descriptions of all patients were presented. Quantitative variables were shown as mean ± standard deviation. Differences between the dementia patients and the non-dementia patients were compared by the *t* test or Wilcoxon rank test for continuous variables and by the chi-square test for categorical variables. The simple and multiple logistic regression analyses were performed to evaluate the relationships between the clinical variables and dementia. The algorithm's validation was evaluated by discrimination and calibration. Regarding external validation cohort, to replace the missing albumin values, we imputed five times to generate five data sets by using the PROC MI (multiple imputations) procedures. All variables were included in the imputation algorithm to improve accuracy in generating replacements of missing albumin values. A *P*-value of 0.05 or less was considered statistically significant, and analyses were performed in SAS 9.2 software (SAS Institute Inc., Cary, NC) and R version 3.5.3 for Windows XP.

TABLE 1 Patient demographics

Characteristics	Patients ($n = 1344$)
Age (years)	78.15 ± 7.28
Gender, female (%)	65.18 (876/1344)
BMI (kg/m^2)	22.66 ± 3.36
Fracture type, intertrochanteric (%)	55.95 (752/1344)
History of smoking (%)	4.39 (59/1344)
Comorbidities	
COPD (%)	3.79 (51/1344)
Asthma (%)	2.31 (31/1344)
Diabetes (%)	26.49 (356/1344)
Hypertension (%)	58.04 (780/1344)
Coronary heart disease (%)	22.99 (309/1344)
Prior myocardial infarction (%)	3.27 (44/1344)
Arrhythmia (%)	9.08 (122/1344)
Prior stroke (%)	18.38 (247/1344)
Cerebral sequelae (%)	3.27 (44/1344)
Dementia (%)	5.28 (71/1344)
Parkinson's disease (%)	1.64 (22/1344)
Digestive system disorders (%)	4.76 (64/1344)
Renal diseases (%)	2.98 (40/1344)
Rheumatologic disease (%)	2.98 (40/1344)
Tumor (%)	4.61 (62/1344)
Clinical interventional characteristics	
ASA scores, III/VI (%)	45.91 (617/1344)
Surgical methods	
Intramedullary fixation (%)	37.28 (501/1344)
Hip replacement (%)	50.07 (673/1344)
Other procedures (%)	12.65 (170/1344)
Mechanical ventilation (%)	36.98 (497/1344)
Laboratory examinations	
Anemia (%)	29.94 (389/1344)
Hypoproteinemia (%)	31.99 (430/1344)
High creatinine (%)	2.83 (38/1344)
RDW	
≤12.49 (%)	22.02 (296/1344)
12.50–12.99 (%)	22.32 (300/1344)
13.00–13.79 (%)	29.91 (402/1344)
≥13.80 (%)	25.74 (346/1344)
Any electrolyte disorders (%)	61.61 (828/1344)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; RDW, red blood cell distribution width.

TABLE 2 The comparison of characteristics between the dementia group and non-dementia group

Characteristics	Non-dementia (*n* = 1273)	Dementia (*n* = 71)	*P* values
Age (years)	78.10 ± 7.30	79.07 ± 6.96	0.27
Gender, female (%)	65.75 (837/1273)	54.93 (39/71)	0.06
BMI (kg/m^2)	22.65 ± 3.40	22.76 ± 2.61	0.79
Fracture type, intertrochanteric (%)	55.54 (707/1273)	63.38 (45/71)	0.20
History of smoking (%)	4.40 (56/1273)	4.23 (3/71)	0.94
Comorbidities			
COPD (%)	4.01 (51/1273)	0.00 (0/71)	0.16
Asthma (%)	2.28 (29/1273)	2.82 (2/71)	0.78
Diabetes (%)	27.02 (344/1273)	16.90 (12/71)	0.06
Hypertension (%)	58.29 (742/1273)	53.52 (38/71)	0.43
Coronary heart disease (%)	22.86 (291/1273)	25.35 (18/71)	0.63
Prior myocardial infarction (%)	3.30 (42/1273)	2.82 (2/71)	0.82
Arrhythmia (%)	9.35 (119/1273)	4.23 (3/71)	0.14
Prior stroke (%)	17.05 (217/1273)	42.25 (30/71)	<0.01
Cerebral sequelae (%)	2.67 (34/1273)	14.08 (10/71)	<0.01
Parkinson disease (%)	1.65 (21/1273)	1.41 (1/71)	0.87
Digestive system disorders (%)	4.79 (61/1273)	4.23 (3/71)	0.82
Renal diseases (%)	2.83 (36/1273)	5.63 (4/71)	0.22
Rheumatologic disease (%)	2.99 (38/1273)	2.82 (2/71)	0.93
Tumor (%)	4.24 (54/1273)	11.27 (8/71)	0.02
Clinical interventional characteristics			
ASA scores, III/VI (%)	44.78 (570/1273)	66.20 (47/71)	<0.01
Treatment methods			
Intramedullary fixation (%)	37.78 (481/1273)	28.17 (20/71)	0.05
Hip replacement (%)	50.04 (637/1273)	50.70 (36/71)	
Other procedures (%)	12.18 (155/1273)	21.13 (15/71)	
Mechanical ventilation (%)	36.45 (464/1273)	46.48 (33/71)	0.09
Laboratory examinations			
Anemia (%)	28.91 (368/1273)	29.58 (21/71)	0.90
Hypoproteinemia (%)	31.11 (396/1273)	47.89 (34/71)	<0.01
High creatinine (%)	2.75 (35/1273)	4.23 (3/71)	0.47
RDW			
≤12.49 (%)	22.07 (281/1273)	21.13 (15/71)	0.90
12.50–12.99 (%)	22.39 (285/1273)	21.13 (15/71)	
13.00–13.79 (%)	30.01 (382/1273)	28.17 (20/71)	
≥13.80 (%)	25.53 (325/1273)	29.58 (21/71)	
Any electrolyte disorders (%)	62.06 (790/1273)	53.52 (38/71)	0.15
Postoperative pneumonia (%)	4.24 (54/1273)	12.68 (9/71)	<0.01

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; RDW, red blood cell distribution width.

Results

Patient Demographics

In the database from the National Clinical Research Center for Orthopedics, Sports Medicine, and Rehabilitation, 1344 patients were finally enrolled. Postoperative pneumonia was observed in 4.69% of patients. The mean age was 78.15 ± 7.28 years, and 65.18% of patients were women. The majority of comorbidity was hypertension (58.04%), followed by coronary heart disease (22.99%) and prior stroke (18.38%). Regarding laboratory examinations, patients with anemia, hypoproteinemia, and high creatinine were 29.94%, 31.99%, and 2.83%, respectively. Table 1 shows the patients' demographics.

Subgroup Analysis

Subgroup analysis showed patients with dementia were more likely to develop postoperative pneumonia as compared with patients without dementia (4.24% *vs* 12.68%, $P = 0.0075$). Multivariate analysis further confirmed dementia patients had an odds ratio of 2.24 (95% *CI*: 1.01–4.96) to develop pneumonia (Table S2). Moreover, dementia patients also had higher rates of prior stroke (17.05% *vs* 42.25%, $P < 0.01$), cerebral sequelae (2.67% *vs* 14.08%, $P < 0.01$), ASA score of III/IV (44.78% *vs* 66.20%, $P < 0.01$), tumor (4.24% *vs* 11.27%, $P = 0.02$), and hypoproteinemia (31.11% *vs* 47.89%, $P < 0.01$), while other variables were similarly distributed between the two groups (Table 2).

TABLE 3 Lasso parameter estimates and corresponding scores

Parameters	Estimates	Values[a]	Scores
Intercept	−0.063989	−0.063989	
Age (years)			
≥65 and <75	0.013367	0.718146	0
≥75 and <85			1
≥85			1
Coronary heart disease			
Yes	0.009498	0.510283	1
No			0
Dementia			
Yes	0.029301	1.574205	2
No			0
ASA score			
I/II	0.023393	1.256796	0
III/VI			1
Surgical methods			
Intramedullary fixation	0.011543	0.62015	0
Hip replacement			1
Other procedures			1
Mechanical ventilation			
Yes	0.005884	0.316120	1
No			0
Anemia			
Yes	0.014672	0.788258	1
No			0
Hypoproteinemia			
Yes	0.017650	0.948252	1
No			0
High creatinine			
Yes	0.011004	0.591193	1
No			0

Abbreviation: ASA, American Society of Anesthesiologists; [a] The values are 10 times of the estimate of each characteristic divided by the total of the estimates of the nine included characteristics in the model. That is the values = 10 × (the estimate of each characteristic/ the total of the estimates of the nine included characteristics). An example: a 86-year-old (1 point) female with coronary heart disease (1 point) but without dementia (0 points) treated with intramedullary fixation (0 points) due to hip fracture. Her ASA score was III (1 point) and she did not perform with mechanical ventilation (0 points) during surgery. Laboratory examinations showed that her hemoglobin (0 points), albumin (0 points), and creatinine (0 points) were normal before surgery. Therefore, the total prognostic score of the female patient was 3 points

Algorithm Development

Of the 28 potential risk variables, 12 variables were significant after the LASSO model combined with the 10-fold cross validation and the three variables were discarded due to low coefficient value (value ≤0.005). Therefore, the nine variables, namely, dementia, age, coronary heart disease, ASA score, surgical method, mechanical ventilation, anemia, hypoproteinemia, and high creatinine, were used to develop the final algorithm.

The values for the nine significant characteristics were obtained from the coefficient values (Table 3). Prognostic score was assigned to each variable and the total prognostic score of the algorithm ranged from 0 to 10 points. An example of calculation of total prognostic score was shown in Table 3. The number of patients with different scores was normally distributed. Higher scores indicated higher rates of postoperative pneumonia (Fig. 2). According to the risk of pneumonia in each score, three risk groups were created: group A had a postoperative pneumonia rate of 1.44%, group B had a pneumonia rate of 9.42%, and group C had a pneumonia rate of 44.44% ($P < 0.001$, chi-square test, Table 4).

Internal Validation

The AUROC for the algorithm with dementia was 0.79, and the AUROC for the algorithm without dementia was 0.78 (Fig. 3). The correct classification rates of the two algorithms were 93.8% and 81.5%, respectively (Table 5). The discrimination slope was 0.071 (95%*CI*: 0.057-0.085) in the algorithm with dementia and 0.060 (95%*CI*: 0.048-0.073) (Fig. 4) in the algorithm without dementia. The above-mentioned results indicated the algorithm with dementia had better discrimination abilities as compared with the algorithm without dementia.

A similar tread was also observed in terms of calibration ability: the algorithm with dementia also showed good calibration, with a calibration slope of 0.93(95%*CI*: 0.78-1.07), an X-intercept of −0.0038 (95%*CI*: −0.017-0.0067), and a Y-intercept of 0.0035 (95% *CI*: −0.0068-0.014) (Table 6 and Fig. 5). The algorithm without dementia had a calibration slope of 0.88 (95%*CI*: 0.73-1.02), an X-intercept of −0.0033 (95%*CI*: −0.017-0.0075), and a Y-intercept of 0.0029 (95%*CI*: −0.0072-0.013). The *P* values obtained from the goodness-of-fit test were both more than 0.05, which indicated good agreement between the predicted matrix and the observed matrix.

External Validation

In the MIMIC-III database, 235 patients were finally enrolled. Table S3 shows the patients' demographics. As compared with geriatric hip fracture patients in the national center hip fracture database, in which data were collected in general hospital wards, patients in the MIMIC III database had significantly higher burden of comorbid conditions (Table S4).

According to the availability of variables in the MIMIC III database, some revisions of the algorithm were made (Table S5): coronary heart disease was changed to myocardial infarction, ASA score was changed to the number of comorbidities, and intramedullary fixation in the surgical method was changed to closed reduction of fracture. Notably, the corresponding estimates in each parameter were the same as the original algorithm.

External validation of the algorithm was performed in the cohort with missing data and imputed data. In the external validation cohort with missing data, the AUROC for the algorithm with and without dementia were both 0.80 (Figure S2 and Table 5). After imputing data, the AUROC for the algorithm with and without dementia both decreased to 0.73. A similar trend was found in the discrimination slope (Figure S3). The results indicated validation with missing data might overestimate the discrimination ability of this

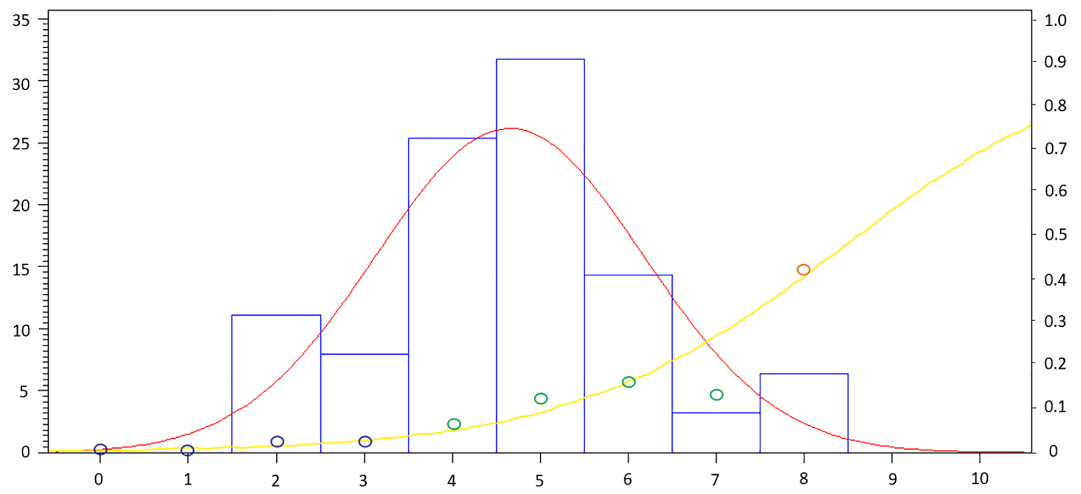

Fig. 2 Histogram plot of the number of patients against each score. The red line indicated that the number of patients with different scores was normally distributed. The yellow line meant that patients with higher scores had a higher risk of developing postoperative pneumonia. The dot showed the observed probabilities of postoperative pneumonia in each score.

TABLE 4 Number of patients and rates of postoperative hospital-required pneumonia in patients with the same score

Scores	Patients (*n* = 1344)	Rates	Groups	Patients (*n* = 1344)	Rates
0	25	0.00% (0/25)	A	12/836	1.44%
1	157	0.00% (0/157)	A		
2	334	2.09% (7/334)	A		
3	320	1.56% (5/320)	A		
4	268	5.97% (16/268)	B	47/499	9.42%
5	160	12.50% (20/160)	B		
6	56	16.07% (9/56)	B		
7	15	13.33% (2/15)	B		
8	9	44.44% (4/9)	C	4/9	44.44%
9	0	0.00% (0/0)	C		
10	0	0.00% (0/0)	C		

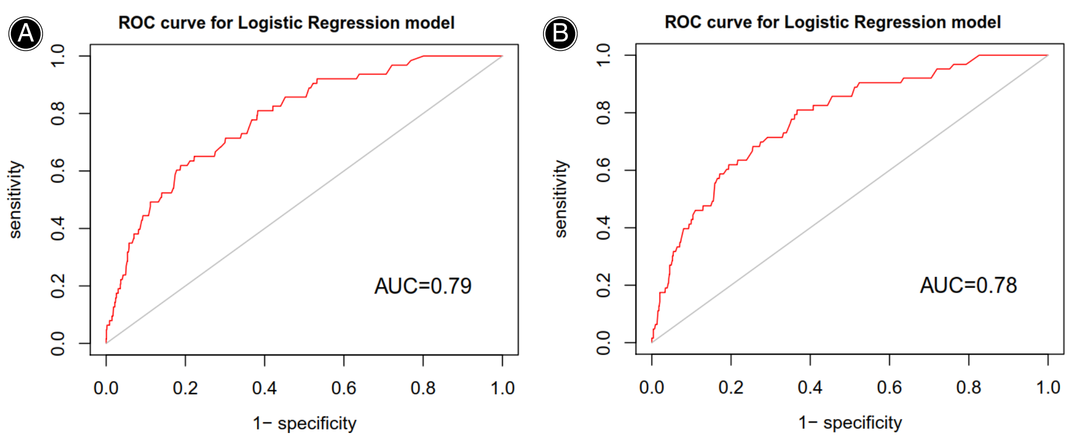

Fig. 3 ROC curves for the two models: (A) the model with dementia (C value = 0.79); (B) the model without dementia (C value = 0.78)

TABLE 5 Discrimination performances of the model with and without dementia

Validation	Models	AUROC	Slope	95% *CI*	CCR	Sensitivity	Specificity
Internal	Model*	0.79	0.071	0.057-0.085	93.8%	14.3%	97.7%
	Model†	0.78	0.060	0.048-0.073	81.5%	52.4%	83.0%
External‡	Model*	0.80	0.034	−0.009-0.078	82.1%	26.1%	93.2%
	Model†	0.80	0.027	−0.015-0.069	82.1%	26.1%	93.2%
External§	Model*	0.73	0.032	0.012-0.053	83.2%	16.5%	97.0%
	Model†	0.73	0.025	0.0055-0.045	82.8%	31.5%	93.5%

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confident interval; CCR, correct classification rate; * Indicates the model including dementia; † Indicates the model excluding dementia; ‡ Indicates external validation with missing data; § Indicates external validation with imputed data.

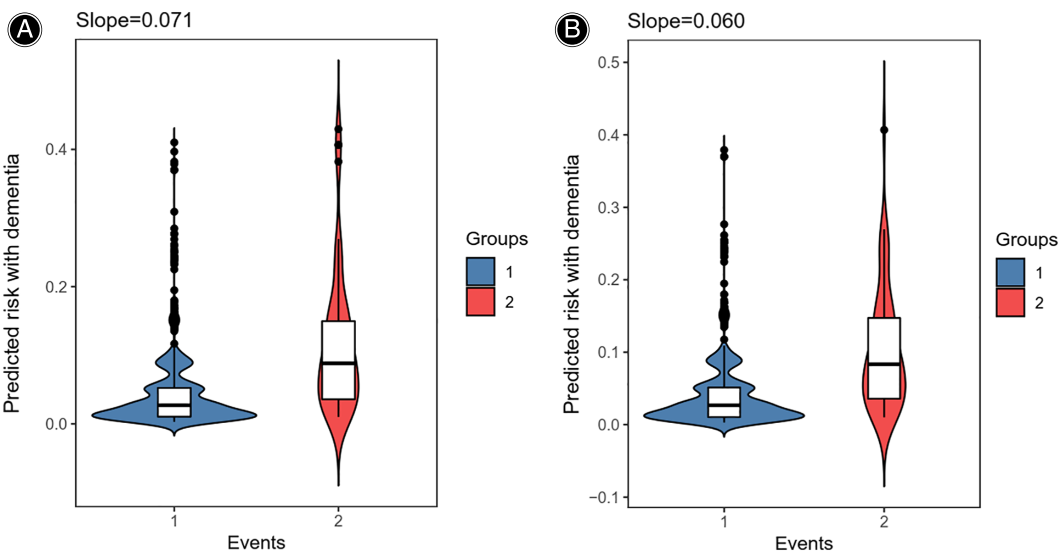

Fig. 4 Violin plots of predicted probabilities in the two models: (A) the model with dementia (Slope = 0.071); (B) the model without dementia (Slope = 0.060). Discrimination slope was defined as the difference between the mean predicted probability with postoperative pneumonia (2) and without it (1).

TABLE 6 Calibration performances of the model with and without dementia

Validation	Groups	Slope	95% *CI*	X-intercept	95% *CI*	Y-intercept	95% *CI*	*P*¶
Internal	Model*	0.93	0.78-1.07	−0.0038	−0.017-0.0067	0.0035	−0.0068-0.014	0.32
	Model†	0.88	0.73-1.02	−0.0033	−0.017-0.0075	0.0029	−0.0072-0.013	0.78
External‡	Model*	1.07	−0.13-2.28	0.059	−∞-0.14	−0.063	−0.28-0.15	0.09
	Model†	1.06	0.019-2.10	0.063	−5.54-0.14	−0.067	−0.26-0.12	0.56
External§	Model*	1.32	−0.52-3.17	0.069	−∞-0.15	−0.091	−0.42-0.24	0.44
	Model†	1.22	−0.34-2.79	0.068	−∞-0.15	−0.083	−0.36-0.20	0.73

Abbreviation: *CI*, confident interval; * Indicates the model including dementia; † Indicates the model excluding dementia; ‡ Indicates external validation with missing data; § Indicates external validation with imputed data; ¶ Indicates the goodness-of-fit test.

algorithm and the algorithm had similar and excellent discrimination ability regardless of including or excluding dementia.

In the cohort with missing data, we found the AUROC of mechanical ventilation alone was up to 0.72 (Figure S2), which was even higher than the AUROC of the combination

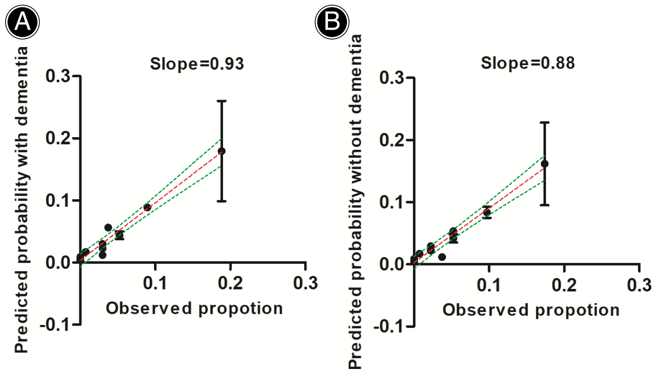

Fig. 5 Calibration plot of the two models developed using the deciles of the predicted probability of postoperative pneumonia risk against the observed risk in each decile and fitted a smooth line: (A) the model with dementia (slope = 0.93); (B) the model without dementia (slope = 0.88)

of all other variables in the algorithm. In the external validation cohort with imputed data, we also found the similar trend: the AUROC of mechanical ventilation alone was up to 0.68. The results indicated mechanical ventilation might play the most important role in developing pneumonia in critically ill setting.

Regarding calibration in the external validation with missing data, the slope was 1.07 in the algorithm with dementia and 1.06 in the algorithm without dementia (Figure S4 and Table 6). After data imputation, the calibration ability decreased, which was consistent with the trend of discrimination ability. The algorithm without dementia had slightly better calibration ability as compared with the algorithm with dementia.

Discussion

Role of Dementia in Pneumonia

In elderly populations, some studies have shown dementia was a significant predictor for pneumonia[21] possibly because degenerative neurologic diseases could develop oropharyngeal dysphagia[27]. However, some studies showed no significant association between pneumonia and cognitive impairment after adjusting for other potential risk factors among elderly patients with hip fractures[13,14]. Thus, whether dementia plays an important role in developing pneumonia needs deep investigations. We speculated that the heterogeneity of populations might contribute to the difference. Our study confirmed the importance of dementia in developing postoperative pneumonia in non-critically ill elderly patients with hip fracture. However, as for critically ill patients, we found that mechanical ventilation might be the greatest predictor for pneumonia and the importance of dementia in developing pneumonia obviously decreased. In our previous study, multivariate analyses did not find dementia to be significantly associated with postoperative pneumonia in hip fracture patients[15]. However, when patients with an age of less than 65 years were excluded for analysis, dementia was included in the algorithm with the largest estimate, which indicated that this variable was essential in determining postoperative pneumonia among the elderly. Subgroup analysis also confirmed that patients with dementia were more likely to develop postoperative pneumonia as compared with patients without dementia. The multivariate analysis further confirmed that dementia patients had an odds ratio of 2.24 to develop postoperative pneumonia.

Important Significance of the Algorithm

A simple scoring system is essential for the identification of patients at high risk of pneumonia in clinical practice. Ji *et al.*[28] created a risk score for predicting hospital-acquired stroke-associated pneumonia after intracerebral hemorrhage. The risk score included 11 risk factors: age, current smoking, excess alcohol consumption, COPD, pre-stroke dependence, admission GCS (Glasgow Coma Scale) score, admission NIHSS (National Institutes of Health Stroke Scale) score, dysphagia, infratentorial location, extension into ventricles, and hematoma volume. Even though the above-mentioned score could potentially predict pneumonia, it was developed based on patients with intracerebral hemorrhage. To our knowledge, models addressing prediction of postoperative pneumonia among hip fracture patients were scarce.

Our study developed an algorithm in a series of 1344 patients. The predictors included in the final algorithm were dementia, age, coronary heart disease, ASA score, surgical method, mechanical ventilation, anemia, hypoproteinemia, and high creatinine. Pneumonia could be prevented and/or better managed when people at a high risk were identified early. Some targeted measures for dementia, coronary heart disease, anemia, hypoproteinemia, and high creatinine might be useful in reducing the risk of developing postoperative pneumonia. Internal validation of the algorithm also proved that dementia included in the algorithm could improve the effectiveness and accuracy of the algorithm. Similar results were obtained in assessing the calibration of the algorithm. External validation showed the algorithm also had good discrimination and calibration ability.

Clinical Application Value

Some potential risk factors have been identified to select the patients at high risk of pneumonia. Chawla[19] found that male patients with preexisting pulmonary diseases, multiple-organ failure, or mechanical ventilation were more likely to develop pneumonia. Guzmán-Herrador *et al.*[20] indicated that therapeutic interventions, such as mechanical ventilation, were the major risk factors for developing pneumonia, but previous infection, chronic renal failure, and anemia were weak prognostic factors for pneumonia. However, the above-mentioned risk factors were not specific for predicting pneumonia after hip fracture surgery. Thus, the clinical application value of those variables among this particular population was limited. Our algorithm was especially designed for those patients, and it contained nine parameters which were easy to obtain. The algorithm had a total prognostic score ranging from 0 to 10. Patients with higher prognostic scores were more likely to develop postoperative pneumonia. Besides, three risk groups were created. Patients in group A had the lowest postoperative pneumonia rate, some measures for avoiding the nine risk factors should be recommended to those patients. Patients in group B had a relatively high postoperative pneumonia rate, and preventive use of antibiotics might be considered among those patients. Patients in group C had the largest risk for developing postoperative pneumonia, and robust preventive measures, such as adequate antibiotics, might need to be considered for those patients. Therefore, the individual prevention of postoperative pneumonia might be realized clinically according to the algorithm, but the clinical utility of the algorithm still needs further consideration.

Expansion of Application Scope

In order to expand the application of the algorithm, we tested its effectiveness among critically ill patients. External validation of the algorithm was performed in the MIMIC-III database. External validation showed the algorithm also had good predictive performance, which indicated that this algorithm was also applicable among critical ill patients with hip fracture.

In that database, the rate of pneumonia was 17.02% among patients from the MIMIC-III database, which was significantly higher than that among patients from the national center hip fracture database possibly due to higher disease burden in critical ill setting. The algorithm with or without dementia both had relative similar discrimination and calibration ability, which indicated dementia might not play an important role in critical ill patients with hip fractures. Patients in the MIMIC III database were older and had higher burden of comorbid conditions, as compared with patients from the national center's hip fracture database. Thus, we speculated that, among so many comorbidities, the importance of dementia in developing pneumonia decreased in critically ill patents. We further found that mechanical ventilation was the greatest predictor for pneumonia in critically ill patients. Mechanical ventilation has been shown to be significantly associated with pneumonia in various other studies[19,20].

Limitations

This study had several limitations. First, the study did not include all potential risk factors for predicting pneumonia, such as urinary catheter, tracheostomy, total parenteral nutrition, hand hygiene, health workers' skills, and patient compliance. Some factors may also play roles in developing pneumonia. Second, this study excluded patients with an age of less than 65 and we only included patients treated with surgery. The majority of hip fractures needed surgical treatments despite the trend that biodegradable materials were booming. Therefore, the reproducibility and applicability of the algorithm needs further investigation among patients with an age of less than 65 years and patients without surgical treatments. Third, we only include data from 1992 to 2012 and more recent data were still under collections. Four, external validation was performed in the MIMIC-III database, which contained of data from medical records associated with patients admitted to critical care units. The distribution of main characteristics between patients in the national clinical center's hip fracture database and the MIMIC III database were significantly different. However, despite the difference, external validation showed the algorithm also had excellent predictive performance and it indicated this algorithm was also applicable in critically ill patients.

Conclusions

The algorithm has the potential to be a pragmatic risk prediction tool to calculate risk of pneumonia in clinical practice and it is also applicable in critically ill hip fracture patients with dementia. Some interventions for dementia, coronary heart disease, surgery type, avoiding unnecessary mechanical ventilation, anemia, hypoproteinemia, and high creatinine may be useful in reducing the risk of developing postoperative pneumonia. Preventive use of antibiotics may be considered among patients with a high risk of developing postoperative pneumonia.

Conflict of Interest

None.

Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher's web-site:

Figure S1. The patient enrollment flowchart in the MIMIC III database

Figure S2. ROC curves for the two models in the external validation before and after data imputation. Before data imputation: (A) the model with dementia (C value = 0.80); (B) the model without dementia (C value = 0.80); after data imputation: (C) the model with dementia (C value = 0.73); (D) the model without dementia (C value = 0.73). (E) ROC curve for mechanical ventilation alone (C value = 0.72, green line) and other variables except mechanical ventilation combined (C value = 0.68, blue line) in the external validation before data imputation. (F) ROC curve for mechanical ventilation alone (C value = 0.68, green line) and other variables except mechanical ventilation combined (C value = 0.63, blue line) in the external validation after data imputation.

Figure S3. Violin plots of predicted probabilities in the two models in external validation before and after data imputation. Before data imputation: (A) the model with dementia (slope = 0.034); (B) the model without dementia (slope = 0.027). After data imputation: (C) the model with dementia (slope = 0.032); (B) the model without dementia (slope = 0.025). Discrimination slope was defined as the difference between the mean predicted probability with postoperative pneumonia (2) and without it (1)

Figure S4. Calibration plots of the two models before and after data imputation. Before data imputation: (A) the model with dementia (slope = 1.07); (B) the model without dementia (slope = 1.06); after data imputation: (C) the model with dementia (slope = 1.32); (B) the model without dementia (slope = 1.22)

Table S1. ICD-9-CM procedure codes for hip fractures
Table S2. Univariate and multivariate analyses of characteristics for dementia in geriatric patients with hip fractures (n = 1344)
Table S3. Patient demographics in external validation group from the MIMIC III database
Table S4. The comparison of main characteristics in geriatric hip fracture patients obtained from the two databases
Table S5. The comparison of the nine included characteristics in the original and revised model

Appendix S1. Supporting Information

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