BMJ Open Respiratory Research

Prognostic indicators for in-hospital mortality in COPD with acute exacerbation in Thailand: a retrospective cohort study

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ABSTRACT

Background Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common and deteriorating event leading to in-hospital morbidity and mortality. Identification of predictors for in-hospital mortality of AECOPD patients could aid clinicians in identifying patients with a higher risk of death during their hospitalisation.

Objective To explore potential prognostic indicators associated with in-hospital mortality of AECOPD patients.

Setting General medical ward and medical intensive care unit of a university-affiliated tertiary care centre.

Methods A prognostic factor research was conducted with a retrospective cohort design. All admission records of AECOPD patients between October 2015 and September 2016 were retrieved. Stratified Cox's regression was used for the primary analysis.

Results A total of 516 admission records of 358 AECOPD patients were included in this study. The in-hospital mortality rate of the cohort was 1.9 per 100 person-day. From stratified Cox's proportional hazard regression, the predictors of in-hospital mortality were aged 80 years or more (HR=2.16, 95% CI: 1.26 to 3.72, p=0.005), respiratory failure on admission (HR=2.50, 95% CI: 1.12 to 5.57, p=0.025), body temperature more than 38°C (HR=2.97, 95% CI: 1.61 to 5.51, p=0.001), mean arterial pressure lower than 65 mm Hg (HR=4.01, 95% CI: 1.88 to 8.60, p<0.001), white blood cell count more than 15 x 10^9/L (HR=3.51, 95% CI: 1.90 to 6.48, p<0.001) and serum creatinine more than 1.5 mg/dL (HR=2.08, 95% CI: 1.17 to 3.70, p=0.013).

Conclusion Six independent prognostic indicators for in-hospital mortality of AECOPD patients were identified. All of the parameters were readily available in routine practice and can be used as an aid for risk stratification of AECOPD patients.

Key messages

What is the key question?
► What are the prognostic indicators for in-hospital mortality in AECOPD patients?

What is the bottom line?
► Several indicators associated with in-hospital mortality in AECOPD included those aged more than 80 years old, respiratory failure on admission, high initial body temperature (≥38°C), low mean arterial pressure (≤65 mm Hg), high white blood cell count (≥15 x 10^9/L) and increased serum creatinine level (≥1.5 mg/dL).

Why read on?
► The knowledge of these prognostic indicators could aid clinicians in identifying patients with a higher risk of death during their hospitalisation and thus resulting in better overall patient care and survival.

2013,[2] and the prevalence of COPD was also higher in the rural (6.8%) compared with urban (3.7%) regions.[3] Although biomass fuels and other environmental factors might contribute to COPD, especially in developing countries,[4] the most common risk factor for COPD in Thailand is cigarette smoking.[5]

Acute exacerbation of COPD (AECOPD) is defined as an acute worsening of respiratory symptoms in COPD patients who subsequently require additional therapy.[6] AECOPD considerably affects the disease progression and the deterioration of overall pulmonary function, impairs quality of life and increases the risk of further exacerbations and mortality.[7–9] Prevention of the occurrence of AECOPD is, therefore, a vital goal in the management and care of patients. However, a large proportion of COPD patients still experience recurrent exacerbations,[6] and approximately 30% require hospitalised care,[7 10] which results in an even higher risk of mortality.[11]

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. It was estimated to be the third leading cause of death worldwide by the year 2020.[1] In Thailand, the prevalence of COPD was reported at 177 per 100 000 population in

Several prognostic factors associated with in-hospital mortality of AECOPD patients were reported and they included patients' demographics and comorbidities (age,[10 12 13] male sex,[10 13] cigarette smoking,[14] low body mass index (BMI),[13 15] atrial fibrillation,[16] cardiac failure,[17] coronary heart disease[18] and stroke[18]), history and physical examination (impaired neurological status,[10 19] tachycardia[19] and lower limb oedema[10]), COPD-specific severity features (baseline dyspnoea grade,[10 20] low forced expiratory volume in 1 s (FEV1),[13] cor pulmonale,[14] laboratory investigation (eosinopenia,[16] abnormal blood gas values,[12 14] acidaemia, hypercapnia,[14] hypoxia[14] and higher blood urea nitrogen (BUN)[19]), hypoalbuminemia[13]), acute kidney injury[21] and pneumonia.[8 13 20]

However, the effect and significance of each predictor on mortality varied across different studies.[15 22] This study aims to explore the prognostic indicators for in-hospital mortality in AECOPD patients admitted to a tertiary care centre in Thailand, a developing country.

METHODS

Study design and setting

We conducted prognostic factor research with retrospective cohort design in a university-affiliated tertiary care centre, Suratthani Hospital, Thailand.

Study participants

All admission records of AECOPD patients aged 40 years or more, admitted to the general medical wards or medical intensive care unit (MICU) of Suratthani Hospital between October 2015 and September 2016, were included. The diagnosis of AECOPD was based on the 'principal diagnosis' by the International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) codes J44.0, J44.1 and J44.9 in the discharge summary. All admission charts were externally audited and AECOPD diagnosis was confirmed by a pulmonologist. If any admission was diagnosed and summarised to 'pneumonia' as the principal cause of hospitalisation and 'COPD' as comorbidity, they would not be included in this study. However, patients with AECOPD as a principal diagnosis (major cause of admission) and had consolidation in chest radiography were eligible for our study. They were recognised as 'pneumonic exacerbation' in some studies.[8] Patients with spirometry results inconsistent with COPD, FEV1/forced vital capacity (FVC) ratio of more than 0.7 and other active pulmonary disease (acute respiratory distress syndrome, lung cancer or acute pulmonary embolism) were excluded. The unit of observation in this study was each hospitalised admission for each COPD patient. Thus, the data were, therefore, collected in multiple records for patients with recurrent admissions during the study period.

Data collection

Patients' demographic and clinical data associated with the investigation and treatment of each admission were extracted from medical records. Demographic and baseline characteristic data included gender, age, BMI, smoking status, comorbidities diagnosed before the index admission, the severity of COPD evaluated by spirometry (the closest result to the index admission), current inhaled controller medications and the history of influenza vaccination. The number of COPD-related events in the previous year, including both hospitalised visits and emergency department visits, were also collected. Clinical parameters including initial vital signs (body temperature (BT), heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and respiratory rate (RR)), admission to MICU, the presence of respiratory failure requiring intubation, initial chest radiography interpreted by attending physicians, laboratory investigations within the first 24 hours of hospitalisation and therapeutic profile were retrieved from each admission record. All patient admission records were separated into two groups: non-survived admissions and survived admissions based on the survival status of the patient.

Prognostic factors threshold

All the prognostic factors thresholds were chosen based on previous literature and clinical experiences: (1) age ≥ 80 years; advance age,[23] (2) BT≥38°C; represent fever,[24] (3) MAP <65 mm Hg; international sepsis guideline,[25] (4) serum creatinine (SCr) ≥1.5 mg/dL; presence of initial renal insufficiency. Although the [26]Kidney Disease: Improving Global Outcomes (KDIGO) on acute kidney injury (AKI) suggested the increase in SCr (>1.5 times of baseline) rather than single SCr value, we recognised that many COPD patients did not have baseline SCr information on evaluation. Thus, an assumption was made that most previously stable COPD patients should have a well-preserved renal function or SCr less than or equal to 1, (5) white blood cell (WBC) count ≥15 x 10^9/L; increase the chance of having a bacterial infection,[27] (6) neutrophil count ≥9 x 10^9/L, eosinophil count <50/mm^3, haemoglobin <120 g/L, BUN >20 mg/dL; DECAF score for AECOPD[16], (7) serum sodium <135 mmol/L and serum chloride <95 mmol/L; represent hyponatremia and hypochloremia.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or funding of this research.

Statistical analysis

All statistical analyses were performed using Stata Statistical Software: Release V.16 (StataCorp LLC). Prior to statistical modelling, clinical characteristics and associated parameters were compared between survived and

non-survived admissions with descriptive statistics. For normally distributed data, mean and SD were used for description, and Student's t-test was used for comparison. For skewed data, median and IQR were used for description, and the Mann–Whitney test was used for comparison. Categorical data were presented as frequency and percentage. The comparison of categorical data was made using the exact probability test. Variables with more than 20% missing were excluded from statistical modelling. All analyses were two-sided with a p value <0.05 as a critical value for statistical significance. The continuous data were dichotomised based on threshold values as described earlier. For multiple time data with marginal risk sets, Cox's proportional hazard (PH) regression was used. The model was stratified by order of admission to allow the hazard function to vary on each visit (sequence or order-specific).[28 29] Radiographic consolidation and admission to the MICU on admission were included as a confounder in the model for adjustment of probable pneumonia status. As the main objective of this study was exploratory, only HRs of the potential predictors were presented in the results. Cluster variance based on an individual patient was used to account for within-patient correlation. We assessed for PH assumption via statistical testing using Schoenfeld residuals. HR and its 95% CI were estimated for each of the potential prognostic indicators.

As the main focus was on the parameters of each admission, length of hospital stay and the duration of mechanical ventilation were omitted from the analysis. A univariable stratified Cox's regression was modelled for each potential predictor reported in prior studies. Predictors with p value <0.1 from the univariable model were included in the final multivariable stratified Cox's model, where multivariable or adjusted HRs were reported. Multiple imputations was done for variables with missing data of less than 20%. As the imputed model showed no significant difference from the non-imputed model, we chose to report the complete-case analysis. Sensitivity analysis with the single-record approach, where readmission visits were excluded, was performed to investigate the robustness of the primary results, which was derived from the multiple-record approach with stratified Cox's regression.

RESULTS

A total of 527 admissions of AECOPD were retrieved. Of this number, 11 admissions with inconsistent spirometry results, FEV1/FVC>0.7, were excluded. Finally, 516 admission records of 358 patients were included for analysis. During the study period, 67 patients died, and 291 survived the admission. The cumulative in-hospital mortality of the cohort was 18.7% (67/358), while the rate of in-hospital mortality was 1.9 per 100 person-day. Fifty-five patients (10.7%) were admitted to the MICU, and the mortality was 32.7%. The baseline clinical characteristics of AECOPD patients within the study cohort

(n=358) and missing data were shown in table 1. The use of inhaled controller medications in survived and non-survived admissions (n=516) was shown in online supplementary table 1. The patients were predominantly men (86.3%) with the mean age of 74 years (±SD 11.1). There was a higher proportion of patients aged ≥80 years in the non-survived group compared with the survived group (52.2% vs 34.1%, p=0.006). Ninety-four per cent of the patients were either current or past smokers. Only 22.9% of the patients had spirometry results. The mean of FEV1/FVC was 0.50 (±SD 0.11). Influenza vaccine was administered in 23 (6.4%) patients before hospitalisation.

Several clinical parameters and initial laboratory investigations revealed significant differences that included BT, SBP, DBP, MAP, presence of respiratory failure, radiographic consolidation, serum sodium, serum chloride, BUN, SCr, serum albumin, haemoglobin, WBC count, neutrophil count, eosinophil count and hypoglycaemia (table 2). Besides, the median duration of mechanical ventilation and the median length of hospital stay were significantly longer in non-survived admissions than survived admissions.

Overall, 90.7% of admissions were treated with antibiotic agents. Ceftriaxone (51.0%) and clarithromycin (42.6%) were the most prescribed drugs. Only the prescription of clarithromycin during admission was significantly different between those who did not survive and those who survived (29.9% vs 44.5%, p=0.025) (online supplementary table 2).

The potential prognostic variables were selected based on both previously reported factors and factors with significant univariable testing. Patients aged ≥80 years old, respiratory failure requiring intubation, BT ≥38°C, MAP <65 mm Hg, WBC count ≥15 x 10^9/L, neutrophil count ≥9 x 10^9/L, eosinophil count <0.05 x 10^9/L, haemoglobin <120 g/L, SCr ≥1.5 mg/dL, BUN >20 mg/dL, serum sodium <135 mmol/L and serum chloride <95 mmol/L were individually included in univariable analysis (table 3). According to the analysis plan, the arterial blood gas results, serum albumin and glucose values were excluded from the analysis due to more than 20% missing data. On multivariable stratified Cox's PH regression, the predictors of in-hospital mortality of AECOPD patients were those aged ≥80 years old (HR=2.16, 95% CI: 1.26 to 3.72, p=0.005), had respiratory failure requiring intubation on admission (HR=2.50, 95% CI: 1.12 to 5.57, p=0.025), had high initial BT ≥38°C (HR=2.97, 95% CI: 1.61 to 5.51, p=0.001), had MAP <65 mm Hg (HR=4.01, 95% CI: 1.88 to 8.60, p<0.001), had WBC count ≥15 x 10^9/L (HR=3.51, 95% CI: 1.90 to 6.48, p<0.001) and had SCr ≥1.5 mg/dL (HR=2.08, 95% CI: 1.17 to 3.70, p=0.013) (table 3).

The result of the sensitivity analysis is shown in online supplementary table 3. All the estimated values (HRs), both in terms of direction and magnitude, were consistent between the multiple-record cohort and the single-record cohort (excluded readmission visits). The full

Table 1 Baseline clinical characteristics of COPD patients with acute exacerbation within the study cohort (n=358 patients)

Characteristics	Missing data n (%)	AECOPD patients (n=358)	
Male (n, %)	0 (0)	309	−86.3
Age ≥80 years (n, %)	0 (0)	131	−36.6
Age, years, mean (±SD)	0 (0)	74	±11.1
Body mass index, kg/m², mean (±SD)	171 (47.8)	20.4	±4.2
Smoking status			
Never smoker (n, %)	0 (0)	20	−5.6
Ex-smoker (n, %)		292	−81.6
Active smoker (n, %)		46	−12.9
Underlying diseases (n, %)			
Present (any)	0 (0)	296	−82.7
Hypertension	0 (0)	145	−40.5
Diabetes mellitus	0 (0)	44	−12.3
Dyslipidemia	0 (0)	48	−13.4
Ischaemic heart disease	0 (0)	36	−10.1
Atrial fibrillation	0 (0)	20	−5.6
Left ventricular dysfunction	0 (0)	6	−1.7
Chronic kidney disease	0 (0)	27	−7.5
Cerebrovascular disease	0 (0)	27	−7.5
COPD status			
Spirometry done (n, %)	0 (0)	82	−22.9
FEV1, % predicted, median (IQR)	276 (77.1)	38	29.0 to 57.0
FVC, % predicted, median (IQR)	277 (77.4)	64	51.0 to 84.0
FEV1/FVC ratio, mean (±SD)	276 (77.1)	0.5	±0.1
GOLD severity of airflow limitation (n, %)			
I: FEV1 ≥80% predicted	276 (77.1)	6	−1.7
II: FEV1 50–79% predicted		20	−5.6
III: FEV1 30–49% predicted		33	−9.2

Continued

Table 1 Continued

Characteristics	Missing data n (%)	AECOPD patients (n=358)	
IV: FEV1 <30% predicted		23	−6.4
Long-term oxygen therapy, (n, %)	0 (0)	26	−7.3
Cor pulmonale (n, %)	0 (0)	12	−3.4
Number of events in previous year			
Hospitalisation, median (IQR)	25 (7.0)	0	0 to 1
ED visit, median (IQR)	37 (10.3)	0	0 to 2
Influenza vaccination	0 (0)	23	−6.4

AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; ED, emergency department; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

multiple-record data that were analysed with stratified Cox's regression revealed higher statistical power and precision with narrower CIs. Therefore, the primary analysis was valid and robust to changing of assumption.

DISCUSSION

In this study, six independent predictors of in-hospital mortality of AECOPD patients were identified. They were aged 80 years or more and had respiratory failure requiring intubation on arrival, BT higher than 38°C, MAP lower than 65 mm Hg, WBC count more than 15 x 10^9/L and SCr more than 1.5 mg/dL. These factors could prognosticate mortality during admission of AECOPD patients regardless of pneumonic status and whether the patients were admitted to the MICU or general medical ward on admission, as these factors were adjusted in the final regression model.

Previous studies reported a varying range of in-hospital mortality from 2% (mixed urban and rural hospital)[19] to 29% (only intensive care units (ICUs)).[15] The cumulative in-hospital mortality in this study was 18.7%. Interestingly, ICU mortality (33%) in our study was similar to the overall cumulative ICU mortality (29%) in a systemic review and meta-analysis.[15] Marked differences in short-term mortality between pneumonic (12.1%) and non-pneumonic (8.3%) acute exacerbation patients were reported in one study.[10] Our cohort had a higher proportion of pneumonic exacerbation from chest radiography (51.2%) and a higher rate of respiratory failure on admission (68.8%) than those of studies that reported a lower incidence of death during the hospitalised period.[8 10 20]

For patients' demographic data, aged patients and the presence of comorbidities had been widely reported as significant prognostic factors for in-hospital mortality.

Table 2 Dynamic clinical parameters during survived and non-survived admissions with acute exacerbation of chronic obstructive pulmonary disease (n=516 admissions)

Clinical parameters	Missing data, n (%)	Non-survived admissions (n=67)		Survived admissions (n=449)		P value
Initial vital signs						
BT, °C, median (IQR)	1 (0.2)	37.2	37 to 38	37	36.7 to 37.4	0.001
HR, per minute, median (IQR)	0 (0)	100	88 to 120	102	88 to 118	0.615
SBP, mm Hg, mean (±SD)	1 (0.2)	117.7	±29.0	136.4	±25.1	<0.001
DBP, mm Hg, mean (±SD)	1 (0.2)	73.7	±18.4	80.9	±14.9	<0.001
MAP, mm Hg, mean (±SD)	1 (0.2)	88.4	±20.5	99.4	±16.7	<0.001
RR, per minute, mean (±SD)	0 (0)	26.2	±5.1	25.4	±5.3	0.253
Admission to MICU (n, %)	0 (0)	18	−26.9	37	−8.2	<0.001
Respiratory failure on admission (n, %)	0 (0)	61	−91	294	−65.5	<0.001
Radiographic consolidation (n, %)	0 (0)	50	−74.6	214	−47.7	<0.001
Laboratory investigations						
pH, mean (±SD)	420 (81.4)	7.31	±0.21	7.37	±0.13	0.144
PaO$_2$, mm Hg, median (IQR)	425 (82.4)	130	75.1 to 262	151	92.2 to 216	0.363
PaCO$_2$, mm Hg, median (IQR)	420 (81.4)	37.2	26.9 to 43.4	37.1	26.9 to 47.2	0.791
Sodium, mmol/L, mean (±SD)	11 (2.1)	136.6	±8.0	138.6	±4.4	0.003
Potassium, mmol/L, mean (±SD)	11 (2.1)	4.1	±0.8	4	±0.6	0.121
Chloride, mmol/L, mean (±SD)	12 (2.3)	93.6	±8.7	97.6	±5.6	<0.001
Bicarbonate, mmol/L, mean (±SD)	11 (2.1)	24.9	±7.9	24.3	±5.0	0.36
Blood urea nitrogen, mg/dL, median (IQR)	11 (2.1)	21	15 to 32	15	11 to 21	<0.001
Serum creatinine, mg/dL, median (IQR)	9 (1.7)	1.1	0.8 to 1.5	0.9	0.8 to 1.2	0.03
Serum albumin, g/dL, mean (±SD)	193 (37.4)	3.4	2.9 to 3.7	3.9	3.5 to 4.2	<0.001
Haemoglobin, g/L, mean (±SD)	8 (1.6)	121	107 to 132	130	117 to 140	0.004
WBC count, x 10^9/L, median (IQR)	8 (1.6)	15.1	10.4 to 19.4	12.6	9.4 to 16.3	0.022
Neutrophil count, x 10^9/L median (IQR)	0 (0)	13.76	8.35 to 17.1	10. 25	6.8 to 14. 45	0.014
Eosinophil count, x 10^9/L, median (IQR)	0 (0)	0.01	0 to 0.07	0.05	0 to 0.29	<0.001
Platelet count, x 10$^{9/L}$, median (IQR)	8 (1.6)	232.5	158.0 to 328.0	244. 0	193.0 to 302.0	0.569
Peak glucose, mg/dL, median (IQR)	195 (37.8)	214	160 to 272	192	151 to 247	0.102
Hypoglycaemia (glucose <55 mg/dL)	213 (41.3)	15	−27.3	15	−6.1	<0.001
Mechanical ventilator duration, days, median (IQR)	0 (0)	7	3 to 18	2	0 to 4	<0.001
Length of hospital stay, days, median (IQR)	0 (0)	7	2 to 20	4	2 to 6	<0.001

BT, body temperature; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; MICU, medical intensive care unit; WBC, white blood cell.

Increasing age[10 13 30] or patients aged more than 75 years[12] were significantly associated with death during hospitalisation, as the patients' FEV1 declines at a more accelerated rate in older COPD patients than younger ones.[31] Comorbidities were not significantly different among survived and non-survived admissions, which was similar to one study reported that no association between the number of comorbidities and mortality in AECOPD patients.[32] This finding was in contrast to the result of another study, which showed that the higher number of comorbidity from the Deyo-adapted Charlson Index was a significant predictive factor of in-hospital mortality.[30] A vast majority of patients in this study were men, which was similar to the previous report in North-eastern Thailand in 2014.[33] The explanation was probably due to a higher proportion of smokers in men than women. Also, the misdiagnosis of COPD as asthma in female patients due to gender bias was common.[34]

Acute respiratory failure on admission and requirement of mechanical ventilation were consistently reported to be essential prognostic factors for both in-hospital mortality and postdischarge mortality.[35] Acidotic respiratory failure reflects the severity of the exacerbation. This condition is modifiable if it is early identified, via blood gas analysis, and properly managed. Non-invasive ventilation had been proven to be an immediate intervention that can effectively reduce mortality in patients with acute acidotic respiratory failure due to exacerbation of COPD.[35] Nonetheless, this non-invasive approach was not widely available in our limited-resource setting.

Table 3 Prognostic factors associated with in-hospital mortality among hospitalised AECOPD patients by univariable and multivariable stratified Cox's PH regression analysis with variance correction

Prognostic factors	Univariable model		Multivariable model	
	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age ≥80 years	1.78 (1.05 to 3.03)	0.032	2.16 (1.26 to 3.72)	0.005
Respiratory failure (intubation)	2.26 (0.99 to 5.14)	0.052	2.50 (1.12 to 5.57)	0.025
BT ≥38.0°C	2.12 (1.21 to 3.69)	0.008	2.97 (1.61 to 5.51)	0.001
MAP <65 mm Hg	5.38 (2.44 to 11.87)	<0.001	4.01 (1.88 to 8.60)	<0.001
WBC count ≥15 x 10^9/L	2.39 (1.42 to 4.01)	0.001	3.51 (1.90 to 6.48)	<0.001
Neutrophil count ≥9 x 10^9/L	1.36 (0.80 to 2.34)	0.258	–	–
Eosinophil count <0.05 x 10^9/L	1.63 (0.95 to 2.80)	0.077	1.61 (0.82 to 3.18)	0.167
Haemoglobin <120 g/L	0.90 (0.52 to 1.56)	0.714	–	–
Serum creatinine ≥1.5 mg/dL	2.19 (1.19 to 4.04)	0.012	2.08 (1.17 to 3.70)	0.013
Blood urea nitrogen >20 mg/dL	1.74 (0.99 to 3.04)	0.053	1.55 (0.74 to 3.23)	0.248
Serum sodium <135 mmol/L	1.21 (0.67 to 2.18)	0.520	–	–
Serum chloride <95 mmol/L	1.38 (0.82 to 2.31)	0.222	–	–

The models were adjusted for radiographic consolidation status and admission to the medical intensive care unit on admission.
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BT, body temperature; MAP, mean arterial pressure; WBC, white blood cell.

Most of the patients still required invasive endotracheal intubation for mechanical ventilation and even carried a higher risk of in-hospital mortality. In Thailand, not all patients with acute respiratory failure could be initially admitted to the MICU because of ICU overcrowdedness. Most patients were treated and mechanically ventilated in general medical wards. For this reason, the multivariable model was adjusted for the admission status of each patient to properly explore for risk factors that were independent of the place that the patients were admitted.

Pneumonia, or the presence of radiographic consolidation, was considered as another factor of poor outcomes in AECOPD patients.[8 20] However, chest radiography was commonly known as an insensitive test for identifying early pneumonia.[36] Thus, the presence of pneumonia in AECOPD patients should not rely entirely on radiographic consolidation but other possible clinical signs of pneumonia, such as higher BT and increased WBC count from initial complete blood count. In this study, both BT higher than 38°C and WBC count more than 15 x 10^9/L were included in the multivariable analysis. They yielded a significant result for the prediction of in-hospital mortality independent of consolidation status. Previous studies supported that higher neutrophil counts[37] and pneumonia[8 13] can be used as predictors for in-hospital mortality. In contrast, one integrative review of low-quality studies reported contradicting results that BT and WBC variables could not predict intermediate-term mortality in a specific group of AECOPD patients who require ICU admission.[22]

On initial univariable analysis, our study demonstrated that all of the blood pressure components were significantly lower in non-survived admissions compared with those who survived. In statistical analysis, only the MAP was included in the regression model due to the highest OR and the presence of collinearity among the blood

pressure components. MAP lower than 65 mm Hg was identified as the strongest independent predictor of in-hospital mortality (HR=4), which was supported by a previous study of AECOPD requiring ICU admission.[38] The cause of hypotension in AECOPD could be either cardiogenic or non-cardiogenic in origin. In patients with high pulmonary pressure, right-sided heart failure or cor pulmonale is common and considered a terminal event for COPD patients. Identifying the exact aetiology of hypotension could provide the proper preventive strategy or early management; however, this was beyond the scope of our study.

Several laboratory parameters were explored for their potential prognostic properties in this study, but only the rising of SCr or the presence of acute kidney injury was confirmed as a significant predictor for in-hospital mortality, in concordance with the previous report.[21] Although the final multivariable analysis did not fulfil other prior hypotheses of those laboratory parameters, some of our observations were supported by past studies such as hypoalbuminemia,[16 39] hyponatremia,[39] hypochloremia,[40] eosinopenia[16] and anaemia.[41] Hyponatremia is a common predictive marker of mortality and morbidity of AECOPD patients, although the effect found in our study was modest and non-significant.[40]

Generally, all admitted AECOPD patients are administered with systemic corticosteroids during their admission in our setting, both intravenous and oral route. Prehospitalised use of inhaled corticosteroids was identified in about 65% of all admission records (online supplementary table 1). Both the use of systemic corticosteroids in the recent admission[42] and prehospitalised inhaled corticosteroid[43 44] might explain the low level of eosinophil in this study. Recently, one study had reported an increased risk of sepsis after the use of oral corticosteroids, but not for inhaled corticosteroid.[45] This sepsis risk could sustain

for approximately 5 months after corticosteroid exposure. As our prognostic factors for AECOPD mortality are overlapped with features associated with sepsis, recent use of systemic corticosteroids could likely confound our results. Therefore, in our analysis, low eosinophil count, a probable marker of steroid use, was incorporated in the multivariable model, thereby adjusting its effect when interpreting others. Our Cox's analysis was stratified by order of admission, which allows the comparison of prognostic factors among patient visits with similar baseline risk for in-hospital mortality.

Our study reported a set of independent prognostic factors of in-hospital mortality for AECOPD patients admitting in a tertiary care centre in Thailand, where the burden and spectrum of disease were substantially different from those of previous research. These factors could aid clinicians in risk stratification for optimal management. For example, an elderly patient with the presence of organ dysfunctions (respiratory failure, shock or renal insufficiency) should be considered as a high-risk patient who required continuous monitoring and admission to an ICU. For patients with fever or leucocytosis, we should suspect systemic infection or sepsis. Prompt septic workup and adequate empirical antimicrobial treatment are crucial.

The strength of our study was gained from multiple-record data collection and multiple failure-time survival analysis of the primary outcome; these allow us to quantify marginal risk for the study population with the preservation of statistical power. Another critical point was the adjustment of radiographic consolidation and admission to the MICU within the analysis model, which enable the consideration of each factor independent of pulmonary consolidation status and differential severity of the patient. The included predictors were also objective and routinely available on admission. This study carried some limitations. First, the data collection was retrospective. Data on some clinically relevant factors such as clinical dyspnoea scale and home oxygen therapy status were unavailable. Second, only a small proportion of patients had spirometry results prior to the index admissions (22.5%) and had blood samples taken for blood gas analysis (18.6%). As this study excluded the patients with inconsistent spirometry results from the analysis, the presence of selection bias was possible. However, this represents real-life clinical practice, as spirometry results were available only in 19–50% of COPD patients,[46–48] and only 11 patients (3.1%) were excluded from this study based on the spirometry result. Finally, our study result was based on a single tertiary referral centre. Thus, this limited the generalisability to non-tertiary care centres.

Although we recognised that spirometry was essential for diagnosis and provided useful information about the severity of stable COPD,[6] in real life the spirometry services were not sufficiently done and properly documented. Interestingly, these problems seemed to be global. The National Committee for Quality Assurance of the USA showed that spirometry was infrequently used and had been done only in one-third of the patients.[49] Another data from a large

Welsh COPD Primary Care Audit also reported that only 19% of COPD patients had been verified with the 'gold standard' post-bronchodilator FEV1/FVC.[48] Currently, in Thailand, COPD patients were diagnosed by physicians based on symptoms, signs, risk factors (advanced age and smoking status) and chest radiographic results that were compatible with COPD (diffuse pulmonary hyperinflation). In this study, the diagnosis of COPD was based primarily on the ICD-10 codes, as there was a study in the UK that supported the use of specific diagnostic codes to accurately identify COPD patients.[50] The COPD definition used in this study was, therefore, pragmatic rather than deterministic. We believed that our estimated set of indicators could be suitably generalised to settings where COPD diagnosis relies mainly on clinical profiles.

It was clearly identified that there was a very low number of hospitalised AECOPD patients who were properly evaluated with arterial blood gas within the first 24 hours. There were some explanations for this clinical defect. First, arterial blood gas analysis would not generally be done in AECOPD patients who were not intubated. Second, the imbalance in the number of physicians and patient workload impeded the chance that the patients would receive arterial puncture within the first 24 hours. As we aimed to explore for prognostic indicators that were readily available in all patients on admissions, arterial blood gas was not included in the model.

In conclusion, the prognostic indicators for in-hospital mortality in AECOPD patients admitting to a tertiary care centre in Thailand included patients aged 80 years or more, and those who had the following characteristics: acute respiratory failure on admission, BT higher than 38°C, MAP lower than 65 mm Hg, initial WBC count more than 15 x 10^9/L and SCr more than 1.5 mg/dL.

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