Development and Validation of a Clinical Prediction Model for Community-Onset Pneumonia caused by Extended-Spectrum Beta-lactamase-Producing Enterobacterales

ABSTRACT

Objective

The study aims to identify specific risk factors associated with developing pneumonia cause by ESBL producing organisms and develop a Clinical scoring model base on the risk factors identified to be able to provide guidance on appropriate empiric antibiotic therapy

Methods

We conducted a single-center retrospective cohort study in a tertiary hospital on Pasig City, Philippines including 150 patients admitted with Community onset Pneumonia from 2018 to 2019

Results

Among 150 patients admitted with Community onset Pneumonia, 70.2% their respiratory isolates were K. Pneumoniae followed be E. coli at 14.57%. The Total ESBL rate among all the respiratory isolate was 45.3%. Univariate analysis of all the risk factors showed significant statistical difference in female Sex (OR 0.49; 5% CI: 0.26-0.96), Charlson Score (OR 26.00; 95% CI: 10.66-63.39), Recent Hospitalization (OR: 29.35; 95% CI: 11.53-74.46), Recent Antibiotic Use (OR 84.49; 95% CI: 28.66 – 251.87), Prior History of ESBL (OR: 57.14; 95% CI: 12.96 – 525.01), and Frequent ED visits (OR:45.88; 95% CI; 15.92 – 132.23). Multivariate analysis was done to generate the final model. The results shows that Charlson Score (OR 11.86, 95%CI: 2.55 – 55.18, p value 0.002), Recent Antibiotic Use (OR:31.09, 95%CI: 5.36-180.44, p value <0.001). and Frequent ED visits (OR 6.52; 95% CI 1.04-41.07) were found to be significant predictor of ESBL. The final model of the three risk factors has a performance AU ROC Curve of 0.9780 at distinguishing between the positive and negative samples.

Conclusion

The results of this study suggest a simple and easy-to-use prediction model to predict Community-onset pneumonia caused by ESBL-producing Enterobacterales.

Introduction

Pneumonia is a significant problem worldwide and remains one of the major causes of death among young and old patients.

Beta-Lactamase-producing species of the Enterobacterales family are notoriously resistant to penicillin, extended-spectrum cephalosporins and carbapenems, which severely limits the therapeutic options for treating patients with infections caused by resistant pathogens.

The impact of these microorganisms with these forms of antibiotic resistance poses a challenge to the clinician. The presence of these resistant strains increases the likelihood of inadequate empirical coverage especially in the community setting. Inadequate empirically coverage, on the other hand, is associated with impaired survival and increase in length of hospital stay.

Efforts should be made to increase the probability of providing appropriate initial antimicrobial treatment in patients with infections related to MDR bacteria, and to reduce subsequent emergence of resistance. At the same time, improving antibiotic prescribing and use is critical to effectively treat infections, protect patients from harm caused by unnecessary antibiotic use, and combat antibiotic resistance.

Methodology

This is a single-center retrospective cohort study of adult patients with community-onset pneumonia at The Medical City, Ortigas between January 2018 to December 2019. Patients with Community Onset Pneumonia who met the inclusion criteria with clinical data upon hospitalization (sociodemographic, clinical signs and symptoms, laboratory findings) are followed-up to check for the presence of ESBL producing Enterobacterales from samples taken within 48 hours of admission

Inclusion and Exclusion criteria

Inclusion criteria

- Adult patients (>18 years old)
- Sputum or Endotracheal/tracheal aspirate taken within 48 hours of admission.
- Diagnosed with Community-Onset Pneumonia defined as pneumonia with its onset occurring among non-hospitalized patient or less than 48 hours from index admission guided by clinical, radiologic and laboratory parameters
  - Imaging – New chest infiltrates (Chest Xray, CTscan, or Ultrasound)
  - Clinical – Fever, Productive cough, dyspnea, pleuritic chest pain, tachypnea, tachycardia, hypoxemia, hypotension, delirium
  - Laboratory parameters – Leukocytosis, CRP, Procalcitonin
- Respiratory cultures that grew Enterobacterales

Exclusion criteria

- Patients with missing or incomplete medical data for analysis
- Age of 18 years old and below
- Pneumonia occurring after 48 hours of index admission
- Respiratory cultures that did not grew Enterobacterales.

Data Collection and definition of Variables

Predictor variables included patient characteristics at hospital admission, demographic information, important past medical history and chronic comorbidities. Sputum or endotracheal cultures, will be taken into account if measured upon admission or within 48 hours after admission. These candidate predictors are selected *a priori* as based on demonstrated variable associations from previous studies, clinical knowledge, the ease, reliability and practicality of measurement in clinical practice (table 1).

Statistical analysis

8 independent predictor variables was added to multivariable regression analyses. LASSO regression was employed which performed both variable selection and regularization in order to enhance the performance accuracy by dealing with multicollinearity and overfitting problems. Chosen variables identified by LASSO regression analysis were put into a logistic regression model, and those statistically significant variables makes up the prediction model. The discriminative ability of the risk score model was measured using the concordance (or c) statistics and presented under the receiver-operator characteristic curve (AUC). Internal validation was derived from the original study sample using bootstrapping technique with a total of 1000 boostrap data sets.

Results/Findings

A total of 150 hospitalized adult patients admitted consecutively with community-onset pneumonia from The Medical City, Pasig City, Philippines' electronic database between January 2018 to December 2019

The mean age of patients included was 74.43 ± 14.88 years old. There are more males than females accounting for 55.33% of the total number of patients. Majority of the respiratory samples were via sputum submission accounting to 88.7% of all respiratory samples. The most common symptoms noted was cough (77.3%) followed by dyspnea (52.6%) and the most common sign is fever (56.6%) followed by hypoxemia (40%). The most common radiologic finding is bilateral lung infiltrates (58.6%) and most common laboratory finding is Neutrophilia/Bandemia (81.3%) followed by leukocytosis (60%).

Among the organisms isolated, Klebsiella Pneumoniae comprises 70.2% of the total samples, followed by Escherichia coli at 14.57%.

Signs and symptoms of tachypnea, tachycardia, hypoxemia, hypotension and delirium are more common with the ESBL cohort. Radiologic findings of bilateral infiltrates and pleural effusion, as well as, laboratory findings of elevated procalcitonin and Neutrophilia/Bandemia are more common with the ESBL Cohort (Table 2)

A univariate analysis was conducted to see the significant predictors of ESBL and Non-ESBL cohort.

The results shows that female gender (OR 0.49; 95% CI: 0.26-0.96), Charlson Score of 4 and above (OR 26.00; 95% CI: 10.66-63.39), Recent Hospitalization (OR: 29.35; 95% CI: 11.53-74.46), Recent Antibiotic Use (OR 84.49; 95% CI: 28.66 – 251.87), Prior History of ESBL (OR: 57.14; 95% CI: 12.96 – 525.01), and Frequent ED visits (OR:45.88; 95% CI; 15.92 – 132.23) was found to be a significant predictor of ESBL (Table 3)

A multivariate analysis to make the final model was made to see which among the factors that are significant in univariate analysis will be included. The results show that Charlson Score of 4 and above (OR 11.86, 95%CI: 2.55 – 55.18, p value 0.002), Recent Antibiotic Use (OR: 31.09, 95%CI: 5.36-180.44, p value <0.001). and Frequent ED visits (OR 6.52; 95% CI 1.04-41.07) were found to be significant predictor of ESBL (table 4)

Model Performance

Model performance was performed by assessing its discrimination and calibration. C statistics was measured with AU ROC curve. The three significant variables combined recorded an **AU ROC** of **0.9780** which means that the model has excellent performance in distinguishing between the positive and negative classes (figure 1)

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and AUC for each variable is shown in Table 5

Table 1. Independent Variables included in the analysis

Age	Age at time of hospitalization
Gender	Biological aspects of an individual as determined by their anatomy which is produced by their chromosomes, hormones and their interactions
Charlson Score >3	predicts the one-year mortality for a patient who may have a range of comorbid conditions
Recent Hospitalization	During the 12 months preceding index hospitalization
Recent Antibiotic use	Includes treatment with B-lactam/B-lactamase inhibitor combinations, cephlosporins, and/or fluoroquinolones during the 3 months preceding index admission
History of prior ESBL infection/colonization	Includes prior history within 1 year of Index admission
Immunosuppression	Includes immunosuppressive therapy during the 3 months preceding the index admission(defined as glucocorticoids [equivalent to prednisone at 20 mg or above for at least 2 weeks] or more than 48 h of any of the following: tacrolimus, sirolimus, cyclosporine, mycophenolate, or antithymocyte globulin) and chemotherapy (defined as alkylating agents) during the 3 months preceding the index admission.
Frequent ED visit	Defined as 3 or more ED visits annually

Table 2. Baseline Characteristics

Variable	All N=150	ESBL Cohort N=68 (45%)	Non-ESBL Cohort N=83 (55%)	p-value
Age (Mean ± SD)	74.43 ± 14.88	75.09 ± 16.34	73.89 ± 13.63	0.218[k]
Sex				
Male	83 (55.33)	44 (64.71)	39 (47.56)	0.035
Female	67 (44.67)	24 (35.29)	43 (52.44)	
Respiratory Sample				
Endotracheal Aspirate	13 (8.67)	9 (13.24)	4 (4.88)	0.083
Sputum	133 (88.67)	56 (82.35)	77 (93.9)	
Tracheal Aspirate	4 (2.67)	3 (4.41)	1 (1.22)	
Signs/Symptoms				
cough	116 (77.33)	48 (70.5)	68 (81.92)	0.101
fever	85 (56.67)	34 (50)	51 (61.44)	0.158
body malaise	55 (36.67)	24 (35.29)	31 (61.44)	0.794
pleuritic chest pain	18 (12)	7 (10.29)	11 (13.25)	0.575
dyspnea	79 (52.67)	41 (60.2)	38 (45.78)	0.750
tachypnea	51 (34)	31 (47.05)	21 (25.3)	0.009
tachycardia	34 (22.67)	22 (32.35)	12 (14.45)	0.008
hypoxemia	60 (40)	39 (57.35)	21 (25.3)	0.000
hypotension	23 (15.33)	16 (23.52)	7 (8.43)	0.010
delirium	19 (12.67)	14 (20.58)	5 (6.02)	0.007
others	72 (48)	27 (39.7)	45 (54.21)	0.075
Radiographic findings				
clear	8 (5.33)	2 (2.94)	6 (7.22)	0.242
Unilateral infiltrates	46 (30.67)	17 (25)	29 (34.93)	0.186
Bilateral infiltrates	88 (58.67)	48 (70.58)	40 (48.19)	0.005
Pleural effusion	52 (34.67)	31 (45.58)	21 (25.30)	0.009
others	2 (1.33)	0 (0)	2 (2.4)	0.197
Laboratory findings				
Leukocytosis	90 (60)	41 (60.29)	49 (59.03)	0.872
Elevated Procalcitonin	13 (8.67)	10 (14.70)	3 (3.61)	0.015
Elevated ESR/CRP	2 (1.33)	1 (1.4)	1 (1.2)	0.888
Neutrophilia/Bandemia	122 (81.33)	61 (89.7)	61 (73.49)	0.011
Organism				
Citrobacter Species	3 (1.99)	1 (1.47)	2 (2.41)	0.009
E. coli	22 (14.57)	15 (22.06)	7 (8.43)	
Enterobacter Species	13 (8.61)	2 (2.94)	11 (13.25)	
K. Pneumonia	106 (70.2)	50 (73.53)	56 (67.47)	
Proteus Species	2 (1.32)	-	2 (2.41)	
S. marcescens	5 (3.31)	-	5 (6.02)	
Recent hospitalization	80 (52.98)	61 (89.71)	19 (22.89)	0.000
Recent antibiotic use	71 (47.02)	62 (91.18)	9 (10.84)	0.000
Prior History of ESBL	42 (28)	40 (58.82)	2 (2.44)	0.000
Immunosupression	17 (11.33)	17 (25.37)	-	0.000
Frequent ED Visits	55 (36.67)	50 (74.63)	5 (6.02)	0.000
Charlson Score				
3 and below	88 (59.06)	16 (23.53)	72 (88.89)	0.000
4 and above	61 (40.94)	52 (76.47)	9 (11.11)	

Table 3. Univariate logistic regression

	Odds Ratio	SE	z-score	p-value	[95% Confidence Interval]
Age	1.01	0.01	0.49	0.623	0.98-1.03
Sex (female)	0.49	0.17	-2.09	0.037	0.26-0.96
Charlson score 4 and above	26.00	11.82	7.17	0.000	10.66-63.39
Recent hospitalization	29.35	14.00	7.09	0.000	11.53-74.76
Recent antibiotic use	84.96	47.11	8.01	0.000	28.66-251.87
Prior history of ESBL	57.14	43.26	5.34	0.000	12.96-252.01
Frequent ED visits	45.88	24.78	7.08	0.000	15.92-132.23

Table 4. Multivariate logistic regression

	Odds Ratio	SE	z-score	p-value	[95% Confindence interval]
Sex (female)	0.57	0.42	-0.77	0.443	0.13-2.42
Charlson score 4 and above	11.86	9.30	3.15	0.002	2.55-55.18
Recent hospitalization	2.05	1.77	0.83	0.405	0.38-11.10
Recent antibiotic use	31.09	27.90	3.83	0.000	5.36-180.44
Prior history of ESBL	2.03	2.19	0.66	0.510	0.25-16.74
Frequent ED visits	6.52	6.12	2	0.046	1.04-41.07

Figure 1. Area under the curve of the Model's Performance (using the three variables)

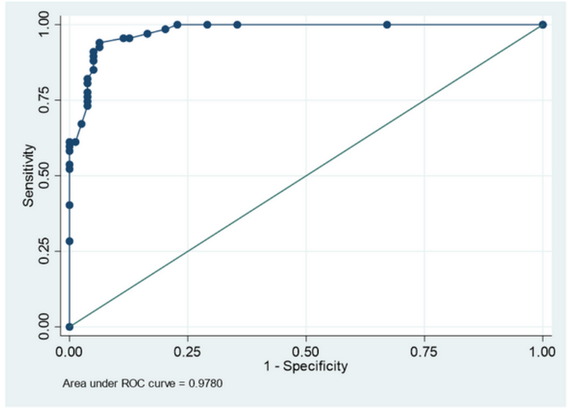

Table 5

	Sensitivity	Specificity	PPV	NPV	ROC Area
Charlson score of 4 and above	85.25	81.82	76.47	88.89	82.68
Recent Antibiotic use	87.32	92.50	91.18	89.16	90.17
Frequent ED visits	90.91	82.11	74.63	93.98	84.30

Conclusion and Recommendation

This study was able to develop a clinical prediction tool to estimate the risk of developing Community-onset pneumonia cause by ESBL-producing Enterobacterales. **Recent Antibiotic use**, **Charlson score of 4 and abov**e and Frequent ED visits were identified to be significant predictive factors in the final prediction model. This prediction model will ultimately guide clinicians on decision making in terms of initial empiric antibiotic therapy to use to among patients with community-onset pneumonia

We recommend to test the model's performance using other data sets for external validation. A prospective cohort design using the model will be best to test its applicability in medical practice. Increasing the number of the samples included in the study is also recommended

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