# INCIDENCE AND PREDICTORS OF EXTUBATION FAILURE IN PATIENTS WITH SEVERE PNEUMONIA AT CIPTO MANGUNKUSUMO GENERAL HOSPITAL

Kartika Juwita1, Gurmeet Singh2, Adhrie Sugiarto3, Hamzah Shatri4
1Department of Internal Medicine, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia
2Respirology and Critical Care Medicine Division, Dept.of Internal Medicine, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia
3Department of Anesthesiology and Intensive Care, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia
4Psychosomatic Division, Department of Internal Medicine, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia

## ABSTRACT

**Background:** Pneumonia is a common respiratory tract infection which is considered as one of the top causes of death. Patients with severe pneumonia often require intubation in order to achieve adequate ventilation. Extubation failure, however, is associated with increased complications and mortality. We aim to determine the predictors associated with extubation failure in patients with severe pneumonia.
**Methods:** A retrospective cohort study was conducted, which included patients with severe pneumonia intubated in the intensive care unit of Ciptomangunkusumo General Hospital over the period of 2015-2019. Patient characteristics, laboratory values and outcomes were retrieved from medical records. Relationships between variables and extubation outcomes were assessed in bivariate analysis and multivariate cox regression model.
**Results:** A total of 192 subjects with severe pneumonia was included in this study. Incidence of extubation failure among patients with severe pneumonia was 70.3%, with a mortality rate of 85.2%. Bivariate analyses found that age of >60 years, smoking history, moderate-to-severe Charlson Comorbidity Index, renal replacement therapy, not having neuromuscular disease, procalcitonin >2 ng/mL, and APACHE II score of ≥25 were associated with extubation failure. In multivariate analysis, moderate-to-severe Charlson Comorbidity Index (HR 2.254, 95% CI 1.353-3.755, p=0.002) and procalcitonin > 2 ng/mL (HR 1.859, 95% CI 1.037-3.333) were found to be independent predictors of extubation failure in patients with severe pneumonia.
**Conclusion:** Moderate-to-severe Charlson Comorbidity index and procalcitonin level of >2 ng/mL were independent predictors of extubation failure in patients with severe pneumonia.
**Keywords:** severe pneumonia, extubation failure, Charlson Comorbidity Index, procalcitonin

## ABSTRAK

**Latar Belakang:** Pneumonia berat adalah infeksi saluran napas yang masih memiliki angka mortalitas yang tinggi. Pasien pneumonia berat sering kali memerlukan intubasi untuk mencapai ventilasi yang adekuat. Terjadinya kegagalan ekstubasi dapat meningkatkan komplikasi dan mortalitas pada pasien. Penelitian ini bertujuan untuk mengetahui faktor yang dapat memprediksi kegagalan ekstubasi pada pasien pneumonia berat
**Metode:** Studi ini merupakan studi kohort retrospektif yang melibatkan pasien dengan pneumonia berat yang terintubasi dan dirawat di ICU RSCM pada tahun 2015-2019. Data pasien, hasil pemeriksaan laboratorium diambil, dan luaran pasien diambil dari rekam medis. Hubungan antara variabel dan luaran ekstubasi dianalisis dalam analisis bivariat dan multivariat dengan uji regresi cox.
**Hasil:** Sebanyak 192 subjek pasien pneumonia berat dilibatkan dalam penelitian ini. Insidensi kegagalan ekstubasi pada pasien pneumonia berat di RSCM adalah 70,3%, dengan angka mortalitas sebesar 85,2%. Dari analisis bivariat, didapatkan usia >60 tahun, merokok, Charlson Comorbidity Index sedang-berat, tidak adanya penyakit neuromuskular, terapi pengganti ginjal, prokalsitonin > 2 ng/mL, dan skor APACHE II ≥25 sebagai variabel yang berhubungan signifikan dengan kegagalan ekstubasi. Selanjutnya, analisis multivariat menemukan bahwa Charlson Comorbidity Index sedang-berat (p=0,002, HR 2,254, IK95% 1,353-3,755), dan prokalsitonin > 2 ng/mL (p<0,001, HR 1,859, IK95% 1,037-3,333) merupakan prediktor independen terhadap kegagalan ekstubasi pada pasien pneumonia berat.
**Kesimpulan:** Charlson Comorbidity Index sedang-berat dan kadar prokalsitonin > 2 ng/mL merupakan prediktor independen kegagalan ekstubasi pada pasien pneumonia berat
**Kata kunci:** pneumonia berat, kegagalan ekstubasi, Charlson Comorbidity Index, prokalsitonin

**Correspondence :**
Kartika Juwita,
Faculty of Medicine, Universitas Indonesia, Jl. Salemba Raya No. 6, RW 5, Kenari, Kec. Senen, Kota Jakarta Pusat, Jakarta 10430, Indonesia.
E-mail: kartika.kj@gmail.com,
No. Telp: 62 821-2240-8483

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## INTRODUCTION

Pneumonia is still considered as one of the leading cause of deaths globally, remaining as a major challenge in healthcare facilities and critical care units.[1] A recent report revealed that incidence of pneumonia in Indonesia has increased from 1,6% to 2,0%.[2] Despite healthcare improvements in the last decades, mortality from pneumonia remains high, especially in those with more severe form of disease. A study by Buharman et al found that the mortality rate of pneumonia patients with a CURB-65 score of 2 or more amounted to 60,8%.[3]

Patients with severe pneumonia often required mechanical ventilation in order to achieve adequate ventilation. Oktariani et al found that pneumonia with a CURB-65 score >2 indicated a higher probability of needs for mechanical ventilation.[4] After illness resolution, patient is progressively removed from the ventilator through the weaning process and eventually undergo extubation. However, under several conditions, extubation failure may occur, which is defined as the inability to maintain spontaneous breathing after removal of ventilatory support such that reintubation is needed within 72 hours.[5] Unfortunately, extubation failure is associated with increased risk of complications and mortality. Yu et al reported that extubation failure occurred in 34,4% of patients with severe pneumonia, with a mortality rate of 58,4%.[6]

Several studies have investigated factors associated with extubation failure, including demographic factors and various comorbidities.[7–9] However, results were inconsistent and reasons for intubation in the population varied instead of focusing on those with pneumonia. Considering the adverse outcomes associated with extubation failure, it is therefore crucial to promptly recognize the risk factors associated with extubation failure. For that reason, this study aims to determine the predictors associated with extubation failure in patients with pneumonia.

## STUDY DESIGN AND METHODS

### *Study population*

We conducted a retrospective cohort study using medical records of patients with severe pneumonia who were intubated in the intensive care unit (ICU) of Cipto Mangunkusumo General Hospital between January 2015 to December 2019. Patients were included if they were 18 years or above and fulfilled the criteria of severe pneumonia in accordance to American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA)[10] who were intubated within <24 hours and admitted in ICU after the diagnosis was made. Diagnosis of severe pneumonia was made if one major criteria (septic shock requiring vasopressors or respiratory failure requiring mechanical ventilation) or three or more minor criteria (respiratory rate ≥30 breaths/minute, $PaO_2/FiO_2 \leq 250$, multilobar infiltrates, confusion or disorientation, blood urea nitrogen ≥20 mg/dL, white blood cell count <4,000 cells/μL, thrombocyte count <100,000/μL, body temperature <36 $^oC$ and hypotension which requires aggressive fluid resuscitation).[10] We excluded patients if they had active malignancy within last 12 months, on immunosuppressant therapy and were intubated for non-pneumonia etiology of respiratory failure. This study has been approved by Medical Ethics Commission of the Faculty of Medicine University of Indonesia number KET 640/UN2.F1/ETIK/PPM.00.02/2021.

### *Study variables*

Data extracted from each record included gender, age, smoking status, comorbidities, body mass index (BMI), renal replacement therapy, underlying lung disease, neuromuscular disease, physiological and laboratory parameters needed to calculate APACHE II score, procalcitonin and hemoglobin to determine anemia status. BMI was classified into underweight (<18.5 $kg/m^2$),

normal (18.5-22.9 kg/m$^2$) and overweight and obese (>22.9 kg/m$^2$). Severity of comorbidity was calculated with Charlson Comorbidity Index (CCI), and was classified into three groups: mild, with CCI scores of 1-2; moderate, with CCI scores of 3-4; and severe, with CCI scores of ≥5. Underlying lung disease included active tuberculosis and chronic obstructive pulmonary disease. Physiology and laboratory parameters recorded were those obtained within 24 hours of ICU admission. Outcomes of extubation failure or success were also extracted. Extubation failure was defined as either failure of spontaneous breathing trial, unavoidable reintubation after successful extubation, extubation was not possible after 19 days in ICU, death while on ventilator or death occurring within 48 hours after extubation.

***Statistical analysis***

All analyses were performed with Statistical Package for the Social Sciences 20.0. Chi-square test or Fischer test was performed between each variable and extubation outcome. Variables with p value of ≤ 0,25 or variables with p value of >0,25 but was determined to be clinically important were subsequently analyzed in the multivariate cox regression. A variable is said to be significantly associated with extubation failure if a p value of <0,05 was obtained.

## RESULTS

***Patient characteristics***

A total of 192 severe pneumonia patients were included in the study after selection with the pre-defined inclusion and exclusion criteria. Most of the subjects were ≤ 60 years and had BMI of overweight or obese, but the proportion of males to females as well as smokers to non-smokers were similar. Most subjects had severe Charlson Comorbidity Index, procalcitonin level of >2 ng/mL, did not have renal replacement therapy, lung disease, and neuromuscular disease, had anemia, and APACHE II score of 11-15 and 16-20. Patients' demographic and clinical characteristics are further detailed in Table 1. Extubation failure occurred in 135 subjects (70.3%) and 115 of them (85.2%) died. Median length of extubation was 6 days (Table 2).

**Table 1.** Demographic and clinical characteristics

| Variables | N = 192 (%) |
|---|---|
| Gender, n (%) | |
| Male | 110 (57.3) |
| Female | 82 (42.7) |
| Age, n (%) | |
| >60 years | 65 (33.9) |
| ≤ 60 years | 127 (66.1) |
| BMI, n (%) | |
| Underweight | 42 (21.9) |
| Normal | 56 (29.2) |
| Overweight dan obese | 94 (49.0) |
| Smoking history, n (%) | |
| Yes | 104 (54.2) |
| No | 88 (45.8) |
| Charlson Comorbidity Index, n (%) | |
| Mild | 58 (30.2) |
| Moderate | 50 (26.0) |
| Severe | 84 (43.8) |
| Renal replacement therapy, n (%) | |
| Yes | 40 (21.1) |
| No | 150 (78.9) |

| | |
|---|---|
| Underlying lung disease, n (%) | |
| Yes | 34 (17.7) |
| No | 158 (82.3) |
| Neuromuscular disease, n (%) | |
| Yes | 16 (8.5) |
| No | 172 (91.5) |
| APACHE II score, n (%) | |
| 0-5 | 9 (4.7) |
| 6-10 | 32 (16.8) |
| 11-15 | 44 (23.0) |
| 16-20 | 43 (22.5) |
| 21-25 | 29 (15.2) |
| 25-30 | 17 (8.9) |
| >30 | 17 (8.9) |
| Procalcitonin (n=154), n (%) | |
| ≤ 2 ng/mL | 35 (22.7) |
| > 2 ng/mL | 119 (77.3) |
| Anemia, n (%) | |
| Yes | 122 (64.6) |
| No | 67 (35.4) |

**Table 2.** Outcomes of subjects

| **Outcomes** | **N = 192 (%)** |
|---|---|
| Duration of extubation (days) | 6 (4-19) |
| Extubation failure, n (%) | |
| Yes | 135 (70.3) |
| No | 57 (29.7) |
| Mortality, n (%) | |
| Yes | 115 (85.2) |
| No | 20 (14.8) |

***Factors associated with extubation failure***

From bivariate analyses, it was found that propotion of subjects with age of >60 years (96.9% vs 56.7%, p <0.001), smokers (82.7% vs 55.7%, p <0.001), moderate-to-severe Charlson Comorbidity index (86.6% vs 32.8%, p <0.001), had renal replacement therapy (85.0% vs 66.7%, p =0.024), not having neuromuscular disease (72.1% vs 43.8%, p=0.024), procalcitonin level of > 2 ng/mL (79.0% vs 37.1% p <0.001), and APACHE II score ≥25 (84.6% vs 66.4%, p=0.027) were significantly higher in extubation failure group. The unadjusted relative risk (RR) and its confidence interval (CI) was calculated for each variable, as detailed in Table 3. Subsequently, in the multivariate model, it was found that only moderate-to-severe CCI (HR 2.254, 95% CI 1.353-3.755; p=0.002) and procalcitonin level of > 2 ng/mL (HR 1.859, 95% CI 1.037-3.333; p<0.001) remained significantly associated with extubation failure (Table 4).

**Table 3.** Bivariate analysis between variables and extubation outcome

| **Variables** | **Extubation outcome** | | **RR (95% CI)** | **p value** |
|---|---|---|---|---|
| | **Fail** | **Success** | | |
| Gender, n (%) | | | | |
| Male | 79 (71.8) | 31 (28.2) | 1.05 (0.87-1.27) | 0.597 |

| | | | | |
|---|---|---|---|---|
| Female | 56 (68.3) | 26 (31.7) | | |
| Age, n (%) | | | | |
| >60 years | 63 (96.9) | 2 (3.1) | 1.71 (1.46-2.00) | **<0.001** |
| ≤ 60 years | 72 (56.7) | 55 (43.3) | | |
| BMI, n (%) | | | | |
| Abnormal | 101 (74.3) | 35 (25.7) | 1.22 (0.97-1.54) | 0.062 |
| Normal | 34 (60.7) | 22 (39.3) | | |
| Smoking history, n (%) | | | | |
| Yes | 86 (82.7) | 18 (17.3) | 1.49 (1.21-1.83) | **<0.001** |
| No | 49 (55.7) | 39 (44.3) | | |
| Charlson Comorbidity Index, n (%) | | | | |
| Moderate-severe | 116 (86.6) | 18 (13.4) | 2.64 (1.82-3.84) | **<0.001** |
| Mild | 19 (32.8) | 39 (67.2) | | |
| Renal replacement therapy, n (%) | | | | |
| Yes | 34 (85.0) | 6 (15.0) | 1.28 (1.07-1.52) | **0.024** |
| No | 100 (66.7) | 50 (33.3) | | |
| Underlying lung disease, n (%) | | | | |
| Yes | 21 (61.8) | 13 (38.2) | 0.86 (0.65-1.14) | 0.319 |
| No | 114 (72.2) | 44 (27.8) | | |
| Neuromuscular disease, n (%) | | | | |
| Yes | 7 (43.8) | 9 (56.3) | 0.61 (0.35-1.07) | 0.024 |
| No | 124 (72.1) | 48 (27.9) | | |
| APACHE II score | | | | |
| ≥25 | 33 (84.6) | 6 (15.4) | 1.27 (1.07-1.52) | **0.027** |
| <25 | 101 (66.4) | 51 (33.6) | | |
| Procalcitonin, n (%) | | | | |
| > 2 ng/mL | 94 (79.0) | 25 (21.0) | 2.13 (1.37-3.31) | **<0.001** |
| ≤ 2 ng/mL | 13 (37.1) | 22 (62.9) | | |
| Anemia | | | | |
| Yes | 91 (74.6) | 31 (25.4) | 1.22 (0.98-1.51) | 0.055 |
| No | 41 (61.2) | 26 (38.8) | | |

**Table 4**. Multivariate analysis

| Variable | P | HR (95% CI) |
|---|---|---|
| CCI | **0.002** | 2.254 (1.353-3.755) |
| Procalcitonin | **<0.001** | 1.859 (1.037-3.333) |

## DISCUSSION

The proportion of failed extubation among patients with severe pneumonia in this study was found to be 70.3% with a mortality rate of 85.2%. This number is higher in comparison to previous similar study by Yu et al, in which proportion of extubation failure was found to be 34.4% with a mortality of 58.4%.[6] This is probably due to the difference in the definition of extubation failure used in this study, as we included death while on ventilator into the failed extubation group, in contrary to most other studies which only included patients requiring reintubation after extubation.

From the findings of our study, we demonstrated that the following factors were found to be predictors of extubation failure: moderate-to-severe CCI and higher procalcitonin levels (> 2 ng/mL).

In our study, comorbidity burden was calculated with the Charlson Comorbidity Index. CCI is a validated method of estimating risk of death from comorbid conditions and have been widely used for prognostication and prediction of long-term survival. The scoring system takes into account a number of comorbidities, including cardiovascular, respiratory, renal, neurological, malignancy,

immunosuppressive and cerebrovascular diseases.[11] In line with our study, Verceles et al found that a higher comorbidity burden, as demonstrated by higher CCI scores, was associated with a lower chance of successful weaning from mechanical ventilation.[9] When patient was extubated, a series of physiological changes occur following the transition from mechanical ventilation to spontaneous breathing. This would result in increased work of breathing, increased oxygen demand and increased sympathetic tone. In patients with multiple comorbidities, such challenge might drive them into respiratory compromise, resulting in increased risk of complications including the need for reintubation.[12]

Another predictor of extubation failure was higher procalcitonin level. Procalcitonin a peptide produced in response to bacterial infection and is widely used as a bacterial infection biomarker.[13] Furthermore, procalcitonin was found to be associated with severity of pneumonia and organ dysfunction, hence was also used as a prognostic marker of morbidity and mortality.[14] Higher procalcitonin level was found to be associated with longer duration of ventilator use.[15] In our study, a cut-off of 2 ng/mL was used. Threshold values, however, differed between studies. Bloos et al found that initial procalcitonin level of >1.1 ng/mL was predictive for mortality in patients with severe pneumonia.[14] Another study by Krüger et al used a threshold of 0.228 ng/mL, and it was found that procalcitonin level on admission predict the outcome of community-acquired pneumonia with an accuracy higher compared with C-reactive protein and leukocyte count.[16] Together, these results corroborate our findings, suggesting the utilization of high procalcitonin level as a predictor for extubation failure and poorer outcomes, although further research regarding the optimal cut-off value for use in severe pneumonia patients is still needed.

This study has several limitations. First, it was conducted in a single center and considering that our center was a national referral hospital with higher complexity of diseases, the results might be different from that of the general population. Second, our sample size was relatively small, which potentially led to inaccuracy in the determination of independent risk factors or miss potential risk factors which are of clinical importance. Third, as this study was retrospective in nature and data were extracted from medical records, issues of incomplete or inaccurate data might be a source of bias.

## CONCLUSION

Moderate-to-severe Charlson Comorbidity index and procalcitonin level of >2 ng/mL were independent predictors of extubation failure in patients with severe pneumonia. Early identification of these factors would help to identify patients at risk of extubation failure.

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