Predictors of Mortality in COPD Exacerbation Cases Presenting to the Respiratory Intensive Care Unit

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Research

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Abstract

Background:

Studies report high in-hospital mortality of chronic obstructive pulmonary disease (COPD) exacerbations especially for those who requiring intensive care unit (ICU) admission. Recognizing factors associated with mortality in those patients could reduce healthcare costs and improve end-of-life care.

Methods: This retrospective cohort study included 384 patients with AECOPD admitted to the respiratory ICU (RICU) of a tertiary hospital in Beijing from Jan 1, 2011 to Dec 31, 2018. Patients demographic characteristic, blood test results and comorbidities were extracted from the electronic medical record system and compared between survivors and non-survivors.

Results: We finally enrolled 384 AECOPD patients, 44 (11.5%) patients died in hospital and 340 (88.5%) were discharged. The most common comorbidity was respiratory failure (294 (76.6%)), followed by hypertension (214 (55.7%)), coronary heart disease (CHD, 115 (29.9%)) and chronic heart failure (CHF, (76 (19.8%)). Multiple logistic regression analysis revealed the independent risk factors associated with in-hospital mortality included lymphocytopenia, leukopenia combined with CHF and the requirement for invasive mechanical ventilation (IMV).

Conclusions:

The in-hospital mortality of patients with COPD exacerbation requiring RICU admission is high. Lymphocytes<0.8×10^9/L, leukopenia, requirement for IMV, combined with CHF could be identified as risk factors associated with increased mortality rates.

Introduction

Chronic obstructive pulmonary disease(COPD) is a worldwide public health challenge because of high prevalence and related disability and mortality, and World Health Organization projections predict that COPD-related mortality and disability will continue to increase worldwide until at least 2030.\(^1\) Acute exacerbation of COPD (AECOPD), defined as the worsen of respiratory symptoms and the requirement of additional clinical treatment, tends to be a critical factor leading to poor outcomes. The exacerbation of COPD reduces lung function and quality of life, and is accompanied by an increased burden of disease and a high hospital mortality.\(^2\text{–}4\) Several studies have identified factors independently associated with in-hospital mortality due to COPD exacerbations, including cardiac organ system dysfunction, duration of hospital stay, older age, comorbid conditions and nutritional status, arterial oxygen (PaO2 ) and carbon dioxide tension at entry. However, independent prognostic factors are quite variable between studies.\(^5\text{–}8\) In addition, only few studies did specifically target patients admitted in RICU. The purpose of our study was to determine the hospital mortality rate and the factors affecting mortality for patients requiring ICU admission.
Methods

Study design and subjects

The electronic medical records of all patients admitted to the RICU with a diagnosis of AECOPD from Beijing Hospital during the period Jan 1, 2011 and Dec 31, 2018 were actively reviewed. COPD was defined as a ratio of the FEV\textsubscript{1} to the forced vital capacity (FVC) of less than 0.70 after bronchodilation according to the Global Initiative for Obstructive Lung Disease. If this information was unavailable in this time, previous data was gathered from the stable stage. Exacerbation was defined by the presence of at least two of the three following symptoms: dyspnea, cough, and increasing of sputum purulence. Patients were excluded from the study if they were COPD patients admitted for diagnoses other than exacerbation. Patients whose duration of hospitalization less than 24 hours, re-admission within 1 month were also excluded. Laboratory examination results within 24 hours of admission were used in this study. The criteria for the management of AECOPD in the RICU did not change during the study period.

Data collection

Data were collected from the electronic medical record system, including demographic characteristic, routine blood examination, biochemical test, arterial blood gas (ABG), pulmonary function test and comorbidities. Demographic characteristic includes age, gender, body mass index (BMI), smoking status, long-term home oxygen therapy, the admission index of activities of daily living (ADL), requirement for invasive mechanical ventilation (IMV) and ventilator service time. Blood examination includes leukocyte, neutrophil, lymphocyte, eosinophil, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimer, creatinine, uric acid, etc. All blood samples were collected within 24 hours and sent to the laboratory in the time for testing. Comorbidity include respiratory failure, hypertension, CHD, CHF, atrial fibrillation, diabetes, and CKD. In addition, all treatment regimens were determined by doctors in accordance with the latest guidelines. The criteria for the management of AECOPD in the RICU did not change during the study period. The endpoint of the research was all-cause hospital mortality.

Statistical analysis

All data were analyzed by using SPSS 25.0 (IBM, NY, USA). Continuous variables were expressed as mean and standard deviation (SD). Categorical variables were presented as percent. The differences of continuous variables among groups were examined by one-way ANOVA. Categorical variables were expressed as percent. The differences of characteristics or factors between survivors and non-survivors were examined by using t-test or Chi-square tests. Univariable and multivariable logistic regression analysis were used to explore the risk factors of AECOPD in-hospital mortality. Variables in univariate analyses with p value < 0.1 were included in the multivariable logistic regression analysis to evaluate the independent risk factors for in-hospital mortality. A p-value < 0.05 was considered statistically significant.

Results
452 patients were hospitalized in RICU with AECOPD between January 2011 and December 2018. After excluding 4 patients with less than 24 hours of hospitalizations, 26 patient's re-admission within one month and 38 patients with unavailable key data in the electronic medical record, we included 384 patients in the final analysis. 44 patients (11.5%) died during the hospital stay and 340 patients (88.5%) discharged.

**Clinical features and comorbidities in patients**

The present research included the data of 384 AECOPD patients admitted to the RICU. Patients were divided into survivor and non-survivor groups based on in-hospital mortality. Demographic characteristics and baseline data of patients in the survival and non-survival groups are presented in Table 1. The average age of all patients was 78.2 ± 8.2 years. There were more males (72.9%) than female (27.1%). Patients who died in the hospital had lower admission index of ADL (28.6 ± 28.9) than survivors (43.1 ± 30.0, p = 0.003). The ventilator service time was longer in non-survivors (438.3 ± 505.3 hours) than in survivors (269.7 ± 317.0 hours, p = 0.042). Requirement for IMV was significantly higher in the non-survivor group than the other group (65.9% vs. 7.1%, p < 0.001). The most common complication was respiratory failure (76.6%), followed by hypertension, CHD and CHF. Patients combined with CHF were higher in non-survivors than survivors (50.0% vs. 15.9%, p < 0.001).
Table 1
Clinical features and comorbidities between survivors and non-survivors.

| Variable                     | Total (N = 384) | Survivors (n = 340) | Non-survivors (n = 44) | P value |
|------------------------------|-----------------|---------------------|------------------------|---------|
| Age, years                   | 78.2 (8.2)      | 78.0 (8.2)          | 79.7 (7.6)             | 0.185   |
| Sex                          |                 |                     |                        |         |
| male                         | 280 (72.9%)     | 244 (71.8%)         | 36 (81.8%)             | 0.158   |
| female                       | 104 (27.1%)     | 96 (28.2%)          | 8 (18.2%)              |         |
| BMI, kg/m²                   | 23.2 (5.3)      | 23.3 (5.2)          | 22.7 (5.8)             | 0.579   |
| Smoking status               |                 |                     |                        | 0.073   |
| Never smoker                 | 85 (22.3%)      | 77 (22.8%)          | 8 (18.2%)              |         |
| Former smoker                | 242 (63.4%)     | 208 (61.5%)         | 34 (77.3%)             |         |
| Current smoker               | 55 (14.4%)      | 53 (15.7%)          | 2 (4.5%)               |         |
| Smoking exposure, pack-years | 35.6 (34.5)     | 35.3 (35.0)         | 38.3 (30.8)            | 0.593   |
| Long-term home oxygen therapy| 76 (19.8%)      | 68 (20.0%)          | 8 (18.2%)              | 0.776   |
| The admission index of ADL   | 41.3 (30.2)     | 43.1 (30.0)         | 28.6 (28.9)            | 0.003   |
| Requirement for IMV          | 53 (13.8%)      | 24 (7.1%)           | 29 (65.9%)             | < 0.001 |
| Ventilator service time, hours | 294.2 (354.5) | 269.7 (317.0)       | 438.3 (505.3)          | 0.042   |
| Comorbidity                  |                 |                     |                        |         |
| Respiratory failure          | 294 (76.6%)     | 258 (75.9%)         | 36 (81.8%)             | 0.382   |
| Hypertension                 | 214 (55.7%)     | 194 (57.1%)         | 20 (45.5%)             | 0.145   |
| CHD                          | 115 (29.9%)     | 102 (30.0%)         | 13 (29.5%)             | 0.951   |
| CHF                          | 76 (19.8%)      | 54 (15.9%)          | 22 (50.0%)             | < 0.001 |
| Atrial fibrillation          | 64 (16.7%)      | 55 (16.2%)          | 9 (14.1%)              | 0.474   |
| Diabetes                     | 97 (25.3%)      | 85 (25.0%)          | 12 (27.3%)             | 0.744   |
| CKD                          | 55 (14.3%)      | 47 (13.8%)          | 8 (18.2%)              | 0.437   |

Date is presented as mean ± standard deviation (SD) for continuous variable and percentages for categorical variables, BMI: body mass index, IMV: Invasive mechanical ventilation, CHF: chronic heart failure, CHD: coronary heart disease, CKD: chronic kidney diseases.
Laboratory examination of patients on admission

The mean value of leukocyte count of non-survivors was significantly higher than that of survivors (10.2 ± 6.3 × 10⁹/L vs. 8.2 ± 3.3 × 10⁹/L, p = 0.043). Lymphocytes were significantly lower in non-survivors than survivors (0.84 ± 0.89 × 10⁹/L vs. 1.09 ± 0.60 × 10⁹/L, p = 0.020). 65.9% patients with lymphocytopenia (lymphocytes were less than 0.8 × 10⁹/L) in survivors and 33.4% in non-survivors. The mean value of platelet in survivors was 188.3 ± 79.0 × 10⁹/L, whereas the mean value of platelet in non-survivors was 178.7 ± 96.5 × 10⁹/L. NLR and PLR were calculated from the absolute numbers of lymphocyte, neutrophils and platelets, which were significant differences between the survival and non-survival groups. CRP, NT-proBNP, and D-dimer were significantly greater in non-survivors than in survivors. Albumin and PaCO₂ were lower in non-survivors than in survivors. Significant differences in lung function were not observed. The laboratory examination was shown in Table 2.
Table 2
Laboratory examination of patients on admission.

| Variable                          | Total (N = 384) | Survivors (n = 340) | Non-survivors (n = 44) | P value |
|-----------------------------------|-----------------|---------------------|------------------------|---------|
| White blood cell count, ×10^9/L   | 8.4 (3.8)       | 8.2 (3.3)           | 10.2 (6.3)             | 0.043   |
| < 4                               | 20 (5.2%)       | 15 (4.4%)           | 5 (11.4%)              | 0.002   |
| 4–10                              | 270 (70.3%)     | 249 (73.2%)         | 21 (47.7%)             |         |
| > 10                              | 94 (24.5%)      | 76 (22.4%)          | 18 (40.9%)             |         |
| Neutrophil count, ×10^9/L         | 7.3 (7.8)       | 7.1 (8.0)           | 8.8 (6.4)              | 0.187   |
| Lymphocytes count, ×10^9/L        | 1.05 (0.65)     | 1.09 (0.60)         | 0.84 (0.89)            | 0.020   |
| < 0.8                             | 141 (37.2%)     | 112 (33.4%)         | 29 (65.9%)             | < 0.001 |
| ≥ 0.8                             | 243 (62.8%)     | 228 (66.6%)         | 15 (34.1%)             |         |
| Platelet count, ×10^9/L           | 187.2 (81.1)    | 188.3 (79.0)        | 178.7 (96.5)           | 0.460   |
| < 100                             | 40 (10.4%)      | 31 (9.1%)           | 9 (20.5%)              | 0.021   |
| ≥ 100                             | 348 (89.6%)     | 309 (90.9%)         | 35 (79.5%)             |         |
| NLR, %                            | 10.8 (17.3)     | 9.6 (16.7)          | 19.9 (19.5)            | < 0.001 |
| PLR, %                            | 253.1 (355.0)   | 240.8 (357.0)       | 362.4 (332.3)          | 0.033   |
| Eosinophil count, ×10^9/L         | 0.12 (0.19)     | 0.11 (0.14)         | 0.15 (0.40)            | 0.213   |
| CRP, mg /L                        | 5.1 (7.0)       | 4.7 (6.7)           | 8.4 (8.6)              | 0.002   |
| Albumin, g/L                      | 35.2 (5.5)      | 35.4 (5.4)          | 33.5 (5.9)             | 0.030   |
| NT-proBNP, pg/ml                  | 1123.3 (2586.0) | 948.0 (2280.2)      | 2474.3 (4066.3)        | 0.039   |
| D-dimer, ug/L                     | 726.6 (1075.8)  | 676.5 (1018.4)      | 1127.0 (1392.9)        | 0.009   |
| Creatinine, umol /L               | 83.4 (63.1)     | 81.0 (60.4)         | 102.2 (79.6)           | 0.099   |
| Uric acid, umol /L                | 260.5 (131.9)   | 254.9 (126.0)       | 304.1 (166.2)          | 0.067   |

**Arterial blood gas analysis**

|          |          |          |          |         |
|----------|----------|----------|----------|---------|
| pH       | 7.37 (0.07) | 7.37 (0.07) | 7.39 (0.06) | 0.186   |
| PaO₂, mmHg | 78.0 (25.9) | 77.9 (23.2) | 78.3 (41.4) | 0.960   |

Date is presented as mean ± standard deviation for continuous variable and percentages for categorical variables, NLR: neutrophil/lymphocyte ratio, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, FEV₁: forced expiratory volume in 1 s, FVC: forced vital capacity.
| Variable                  | Total     | Survivors  | Non-survivors | P value |
|---------------------------|-----------|------------|---------------|---------|
|                           | (N = 384) | (n = 340)  | (n = 44)      |         |
| PaCO₂, mmHg               | 52.8 (15.8) | 53.5 (16.1) | 47.7 (12.5)   | 0.022   |
| PaO₂/FiO₂, mmHg           | 275.7 (85.5) | 277.59 (83.9) | 260.7 (96.7)  | 0.225   |
| **Lung function test**    |           |            |               |         |
| Post-bronchodilator FEV₁, L | 0.94 (0.46) | 0.95 (0.46) | 0.82 (0.10)   | 0.705   |
| Post-bronchodilator FVC, L | 1.95 (0.69) | 1.95 (0.70) | 1.77 (0.42)   | 0.714   |
| Post-bronchodilator FEV₁/FVC, % | 47.16 (12.39) | 47.13 (12.39) | 48.61 (17.19) | 0.869   |

Date is presented as mean ± standard deviation for continuous variable and percentages for categorical variables, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, FEV₁: forced expiratory volume in 1 s, FVC: forced vital capacity

**Independent risk factors for in-hospital mortality**

Requirement for IMV, the admission index of ADL, CHF, WBC, lymphocyte, platelet, NLR, CRP, albumin, NT-proBNP, D-dimer and PaCO₂ were all significant in univariable analysis (Table 3). All variables with p < 0.1 would be included in the multiple logistic regression analysis. We found that the requirement for IMV (OR = 30.31, 95% CI: 8.29–110.74, p < 0.001), combined with CHF (OR = 7.63, 95% CI: 2.27–25.64, p = 0.001) and hypoleukocytemia (OR = 5.77, 95% CI: 1.05–31.74, p < 0.044) and lymphocytopenia (OR = 3.60, 95% CI: 1.10–11.76, p = 0.034) were the independent risk factors associated with in-hospital mortality.
Table 3
Logistic regression analysis of the in-hospital mortality of AECOPD requiring ICU admission.

| Variable                                      | Univariable OR (95%CI) | P value | Multivariable OR (95%CI) | P value |
|----------------------------------------------|------------------------|---------|--------------------------|---------|
| Age, years                                   | 1.03 (0.99–1.07)       | 0.185   | 30.31 (8.29–110.74)      | < 0.001 |
| Gender (M/F)                                  | 1.77 (0.79–3.95)       | 0.163   | 0.99 (0.97–1.02)         | 0.578   |
| Requirement for IMV                           | 25.46 (12.04–53.83)    | < 0.001 | 30.31 (8.29–110.74)      | < 0.001 |
| The admission index of ADL                   | 0.98 (0.97–1.00)       | 0.004   | 0.99 (0.97–1.02)         | 0.578   |
| Smoking status (ever vs.never)                | 1.33 (0.59–2.98)       | 0.491   |                          |         |
| CHF                                          | 5.30 (2.74–10.23)      | 0.001   | 7.63 (2.27–25.64)        | 0.001   |
| White blood cell count, ×10⁹/L                |                       |         |                          |         |
| < 4                                          | 3.95 (1.31–11.94)      | 0.015   | 5.77 (1.05–31.74)        | 0.044   |
| 4–10                                         | 1.00 (ref)             |         | 1.00 (ref)               |         |
| > 10                                         | 2.81 (1.42–5.54)       | 0.003   | 3.05 (0.90–10.31)        | 0.073   |
| Lymphocyte count, ×10⁹/L                      |                       |         |                          |         |
| < 0.8                                        | 3.85 (1.98–7.47)       | < 0.001 | 3.60 (1.10–11.76)        | 0.034   |
| ≥ 0.8                                        | 1.00 (ref)             |         | 1.00 (ref)               |         |
| Platelet count, ×10⁹/L                       |                       |         |                          |         |
| < 100                                        | 2.56 (1.23–5.82)       | 0.025   | 0.61 (0.11–3.28)         | 0.652   |
| ≥ 100                                        | 1.00 (ref)             |         | 1.00 (ref)               |         |
| NLR, %                                       | 1.02 (1.01–1.04)       | 0.008   | 1.01 (0.99–1.03)         | 0.292   |
| PLR, %                                       | 1.00 (1.00–1.00)       | 0.115   |                          |         |
| CRP, mg /L                                   |                       |         |                          |         |
| < 10                                         | 1.00 (ref)             |         | 1.00 (ref)               |         |
| ≥ 10                                         | 2.55 (1.21–5.45)       | 0.016   | 0.18 (0.03–1.00)         | 0.051   |
| Albumin, g/L                                 |                       |         |                          |         |
| < 35                                         | 1.93 (1.00–3.70)       | 0.049   | 0.55 (0.16–1.95)         | 0.356   |

IMV: Invasive mechanical ventilation, CHF: chronic heart failure.
| Variable               | Univariable OR (95%CI) | P value | Multivariable OR (95%CI) | P value |
|------------------------|------------------------|---------|--------------------------|---------|
| ≥ 35                   | 1.00 (ref)             |         | 1.00 (ref)               |         |
| NT-pro BNP; pg/L       | 1.00 (1.00–1.00)       | 0.014   | 1.00 (1.00–1.00)         | 0.163   |
| D-dimer; ug/L          |                        |         |                          |         |
| < 500                  | 1.00 (ref)             |         | 1.00 (ref)               |         |
| 500–1000               | 2.08 (0.98–4.42)       | 0.057   | 0.93 (0.23–3.76)         | 0.931   |
| > 1000                 | 2.97 (1.33–6.63)       | 0.008   | 1.84 (0.39–8.61)         | 0.441   |
| PaCO₂; mmHg            | 0.97 (0.95-1.00)       | 0.026   | 0.99 (0.94–1.05)         | 0.512   |

IMV: Invasive mechanical ventilation, CHF: chronic heart failure.

Discussion

The present study identified several risk factors for death in adults who were hospitalized with AECOPD in respiratory ICU (RICU). In particular, lymphocytes < 0.8 × 10⁹/L, leukopenia, requirement for IMV, combined with CHF were associated with higher odds of in-hospital death.

Knowledge about prognosis of disease and factors that predict poor outcome is important to enable physicians to advise patients on the expected natural course of an illness. Many risk factors that predict death from AECOPD have been identified before. C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) and other factors like D-dimer and N-terminal-pro hormone B-type natriuretic peptide (NT-pro BNP) were associated with in-hospital mortality in AECOPD patients.\textsuperscript{[9–14]} Additionally, to the best of our knowledge, predicting in-hospital mortality of ICU patients with AECOPD based on lymphocytopenia has been reported in only a few studies. The study showed that relative lymphocyte count ≤ 20% were significantly associated with higher risk of death in elderly patients with moderate-to-severe COPD.\textsuperscript{[15]} Xiong et al. and Yao et al. found that patients with COPD who died had lower lymphocyte count than patients who survived, but lymphocyte count was not an independent risk factor for in-hospital mortality of AECOPD patients.\textsuperscript{[16,17]} We observed that lymphocytopenia occurred in more than 65% of patients in non-survivors group and also an independent risk factor for in-hospital mortality (OR 3.60 (1.10-11.76)).

Mechanisms for lymphocytopenia predicting high risk of in-hospital death in patients with AECOPD remains unclear. Several facts should be considered. First, peripheral blood lymphocytes were relatively decreased in the elderly\textsuperscript{[18,19]} and older age was also a significant risk factor for COPD mortality as reported in previous studies.\textsuperscript{[20,21]} Second, relatively lower lymphocyte count as a biomarker of inflammation could increase the risk of infection which will cause death from AECOPD. As we know, lymphocytopenia was found in the critically ill patients with SARS-CoV infection because targeted
invasion by SARS-CoV viral particles damages the cytoplasmic component of the lymphocyte and causes its destruction.\textsuperscript{[22]} Additionally, lymphocytopenia is also common in the severe patients with MERS infection which is the result of apoptosis of lymphocytes.\textsuperscript{[23]} In the present study, lymphocyte count was determined to be a useful, widely available, and inexpensive predictor that can help identify AECOPD patients admitted to the RICU that are at high risk of in-hospital mortality. Whether the benefit of immunotherapy in patients with AECOPD is associated with low lymphocytes should be assessed in future studies.

Requirement for IMV was a significant predictor of in-hospital mortality of AECOPD.\textsuperscript{[21, 24]} In the Brown study, 38.7\% of patients required IMV and multivariate analysis showed the requirement for IMV was importantly associated with in-hospital death.\textsuperscript{[21]} Lindenauer PK et al. showed that in-hospital mortality was higher in COPD patients who required IMV than in patients with non-invasive ventilation (NIV).\textsuperscript{[25]} The results of the present study were consistent with previous studies. This finding is not surprising, typically, patients who require IMV rather than NIV are in a severe disease stage.

CHF is a common comorbidity of COPD.\textsuperscript{[26]} In the present study, combined with CHF was an important risk factor for predicting in-hospital mortality of AECOPD patients. Testa et al. found that patients with COPD and CHF had an increased risk of mortality compared with patients with either COPD or CHF alone.\textsuperscript{[27]} The results of the present study were consistent with their study. There are some potential pathophysiological mechanisms that could explain the interaction between COPD and cardiovascular disease. These include spillover of pulmonary inflammation directly leading to development of atheromatous plaque formation and arterial remodeling. With the deterioration of COPD, the increased pulmonary vascular resistance leads to pulmonary hypertension and right ventricular dysfunction. In addition, both hypoxia and acidosis can reduce the diastolic and systolic myocardial dysfunction.\textsuperscript{[28, 29]}

Our study also has several limitations. Firstly, the results may not be generalizable to other ICU patients because of single-center design. Secondly, management of respiratory insufficiency did not follow a prospective protocol and the individual preferences of the treating physician may have affected outcome. Although, our center applied the guidelines for clinical practice during the study period. Thirdly, we do not have precise information on nutritional status or quality of life prior to admission. Finally, the study is lack of post-hospital mortality data, which leads be mandatory for validation of the prognostic factors in our findings.

Hospitalization for acute COPD exacerbation is becoming more frequent, and it places an enormous burden on patients and health care systems. In conclusion, the current study has identified a number of variables associated with in-hospital mortality for AECOPD patients in RICU.

\textbf{Declarations}

\textit{Ethics approval and consent to participate}
Our study followed the Declaration of Helsinki and it was approved by the Ethics Committee of Beijing hospital (2019BJYYEC-018-02).

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Not applicable

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