Research Square

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Pulmonary Embolism as a Risk Factor for Necrotizing Pneumonia in Mechanically Ventilated Patients With Severe COVID-19: A Matched Case–Control Study

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Abstract

Background

Necrotizing pneumonia (NP) is an uncommon but life-threatening complication of pulmonary infection characterized by parenchymal liquefaction and cavitation. During the COVID-19 pandemic, we observed a high incidence of NP among mechanically ventilated patients (MVP) with severe disease. We sought to identify risk factors associated with NP in this population.

Methods

We conducted a retrospective matched case–control study including adult ICU patients with laboratory-confirmed COVID-19 requiring invasive mechanical ventilation between March 2020 and June 2021. Cases were patients who developed NP based on radiologic or surgical findings. Controls were matched 3:1 by duration of mechanical ventilation (± 2 days). Conditional logistic regression was used for univariate and multivariate analyses.

Results

Among 936 mechanically ventilated patients, 42 (4.5%) developed NP. Mortality was significantly higher in patients with NP compared with those without NP (71% vs 44%). Thirty-seven cases were matched to 111 controls. In univariate analysis, male sex, lower body mass index, hypertension, elevated D-dimer levels, pulmonary embolism (PE), pulmonary infarction, and repeated isolation of the same bacterial species were associated with NP. In a multivariable model adjusting for a pre-specified set of clinically relevant covariates, PE during hospitalization remained associated with NP (adjusted OR 5.45; 95% CI 1.85–16.06; P = .002).

Conclusions

Pulmonary embolism is associated with the development of necrotizing pneumonia in mechanically ventilated patients with severe COVID-19, consistent with a potential thrombotic-ischemic mechanism underlying lung necrosis with subsequent infection.

Trial registration

Not applicable. This was a retrospective observational study, not a healthcare intervention trial.

Background

Severe coronavirus disease 2019 (COVID-19) frequently leads to acute hypoxemic respiratory failure requiring invasive mechanical ventilation [1, 2]. Critically ill patients with COVID-19 are at high risk for secondary bacterial infections and thrombotic complications, both of which contribute substantially to morbidity and mortality [3–6].

Necrotizing pneumonia (NP) represents a severe form of pulmonary infection characterized by progressive parenchymal destruction, cavitation, and liquefaction [7, 8]. Traditionally associated with virulent pathogens such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, and anaerobic bacteria, NP is thought to result from a combination of bacterial cytotoxicity, intense inflammatory response, and vascular compromise [7–9]. Pulmonary vascular thrombosis and infarction have been recognized contributors to parenchymal necrosis in severe bacterial pneumonia [10].

COVID-19 is strongly associated with endothelial dysfunction and hypercoagulability [11–13]. Autopsy studies demonstrate widespread pulmonary microvascular thrombosis and endothelial injury, while clinical studies report pulmonary embolism (PE) in up to 20–30% of critically ill patients despite thromboprophylaxis [14–16]. The coexistence of severe inflammation, secondary infection, and thrombotic obstruction raises the possibility that ischemic lung injury may predispose to parenchymal necrosis.

During the COVID-19 pandemic, we identified a notably high incidence of necrotizing pneumonia (4.5%) among mechanically ventilated patients with severe COVID-19 [17]. Given the limited data regarding this complication, we conducted a matched case–control study to identify clinical and microbiological risk factors associated with its development.

Methods

We performed a retrospective matched case–control study at a tertiary care hospital in Colombia. The study included patients admitted between March 1, 2020, and June 30, 2021.

Eligible patients were adults (≥ 18 years) with laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR for SARS-CoV-2) requiring invasive mechanical ventilation.

Cases were defined as patients with imaging or surgical findings documenting NP (cavitation and/or parenchymal necrosis consistent with established radiologic criteria) [18] during hospitalization. Controls were mechanically ventilated COVID-19 patients who did not develop NP. Controls were matched to cases in a 3:1 ratio according to duration of mechanical ventilation prior to NP diagnosis (± 2 days) to account for differential time at risk.

Data were extracted from electronic medical records, including demographics (age, sex, body mass index [BMI]), comorbidities (hypertension, Charlson comorbidity index, immunosuppression), severity scores (APACHE II, SOFA), oxygenation parameters (PaO_2/FiO_2 ratio), laboratory markers (D-dimer, C-reactive protein, leukocyte and lymphocyte counts), diagnosis of pulmonary embolism or pulmonary

infarction (confirmed by CT angiography), prior pneumonia (community-acquired, ventilator-associated, hospital-acquired), microbiology data from tracheal aspirate or bronchoalveolar lavage (BAL), and antibiotic exposure prior to NP diagnosis (or matched time in controls).

Repeated bacterial isolation was defined as isolation of the same bacterial species on more than one occasion before NP diagnosis.

Statistical analysis was performed using Stata software. Continuous variables are reported as mean (SD); categorical variables as frequency (%). Conditional logistic regression accounting for matched sets was used to assess univariate associations between candidate variables and NP. A multivariable conditional logistic regression model was then constructed using a pre-specified set of covariates selected a priori based on clinical and biological plausibility as potential confounders of the association between PE and NP (sex, BMI, hypertension, and repeated bacterial isolation), rather than through statistical selection procedures. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was defined as $P < 0.05$.

The institutional ethics committee approved the study and waived informed consent. A generative AI tool (ChatGPT, OpenAI) was used solely to assist in generating the explanatory schematic in Fig. 1; it was not used for data collection, analysis, interpretation, or drafting of the manuscript text.

Results

Among 936 mechanically ventilated patients with severe COVID-19, 42 (4.5%) developed necrotizing pneumonia. Mortality among NP patients was 71%, compared with 44% among mechanically ventilated patients without NP. Thirty-seven NP cases were successfully matched to 111 controls.

Mean age was similar between cases and controls (64.1 vs 62.9 years; $P = 0.61$). Cases were more frequently male (81% vs 52%; OR 3.91; 95% CI 1.54–9.92; $P < 0.01$). BMI was lower among cases (26.1 vs 28.9 kg/m²; OR 0.88 per unit increase; 95% CI 0.81–0.97; $P < 0.01$). Hypertension was more common among cases (24% vs 9%; OR 3.20; 95% CI 1.17–8.77; $P = 0.02$). APACHE II, SOFA scores, and oxygenation parameters did not differ significantly.

Elevated D-dimer levels were associated with NP. ICU admission D-dimer > 10,000 ng/mL was more frequent among cases (21% vs 4%; OR 8.80; $P = 0.02$).

Pulmonary embolism occurred in 40.5% of cases compared with 9.9% of controls (OR 6.10; 95% CI 2.32–15.89; $P < 0.01$). Pulmonary infarction was observed exclusively in cases (10.8% vs 0%; $P < 0.01$).

Repeated isolation of the same bacterial species occurred more frequently among cases (48.6% vs 27.9%; OR 2.64; 95% CI 1.18–5.92; $P = 0.02$). The overall number of bacterial species isolated was not significantly associated with the development of NP. Table 1.

Table 1
Baseline characteristics of cases and controls

Variable	**Cases (n = 37)**	**Controls (n = 111)**	**OR (IC95%)**	***p-value***
Age – mean (± SD)	64.14 (12.25)	62.87 (12.82)	1.01 (0.98–1.04)	0.61
Male sex - n (%)	30 (81.08)	58 (52.25)	3.91 (1.54–9.92)	< 0.01
BMI – mean (± SD)	26.14 (4.23)	28.88 (5.46)	0.88 (0.81–0.97)	< 0.01
Charlson score > 3 - n (%)	2 (5.41)	9 (8.11)	0.64 (0.13–3.17)	0.57
Smoker - n (%)	18 (48.65)	54 (48.65)	1.00 0.46–2.16)	1.00
Obesity - n (%)	15 (40.54)	49 (44.14)	0.86 (0.41–1.83)	0.70
Hypertension - n (%)	9 (24.32)	10 (9.01)	3.20 (1.17–8.77)	0.02
Immunosuppression - n (%)	1 (2.70)	6 (5.41)	0.47 (0.05–4.19)	0.47
Steroid use - n (%)	37 (100)	109 (98.20)	1.04 (0.11–10.27)	1.00
Steroid days – mean (± SD)	10.62 (3.92)	10.58 (4.18)	1.00 (0.91–1.10)	0.95
COVID-19 vaccination - n (%)	3/29 (10.34)	22/89 (24.72)	0.40 (0.11–1.49)	0.14
Days of symptoms on admission – mean (± SD)	9.49 (5.46)	7.75 (4.19)	1.07 (0.99–1.15)	0.07
ICU admission PaFIO2 – mean (± SD)	104 (53.74)	104 (66.08)	1.00 (0.99–1.01)	0.96
Lowest PaFIO2 – mean (± SD)	83.14 (32.88)	83.75 (36.60)	1.00 (0.99–1.01)	0.92
Prior NIMV or HFNC - n (%)	18 (48.65)	37 (33.33)	1.76 (0.86–3.58)	0.12
Reintubation - n (%)	1 (2.70)	4 (3.60)	0.75 (0.08–6.71)	0.79
ICU admission APACHE – mean (± SD)	16.41 (9.68)	16.90 (6.58)	0.99 (0.94–1.04)	0.72

Variable	Cases (n = 37)	Controls (n = 111)	OR (IC95%)	*p-value*
ICU admission SOFA– mean (± SD)	5.08 (2.77)	4.88 (2.71)	1.03 (0.90–1.17)	0.71
ICU admission leukocytes – mean (± SD)	13.605 (5281)	11.919 (4633)	1.00 (0.99-1.00)	0.07
ICU admission lymphocytes – mean (± SD)	766 (613)	912 (1088)	1.00 (0.99-1.00)	0.38
Lymphocyte nadir – mean (± SD)	397 (226)	420 (323)	1.00 (0.99-1.00)	0.70
ICU admission D-dimer > 10000 - n (%)	5/24 (20.83)	3/70 (4.29)	8.80 (0.99–78.16)	0.02
Highest ICU D-dimer – mean (± SD)	20502 (29784)	7471 (17077)	1.00 (1.00–1.00)	< 0.01
Highest ICU CRP – mean (± SD)	32.01 (8.15)	31.36 (10.64)	1.01 (0.97–1.05)	0.70
PE diagnosis - n (%)	15 (40.54)	11 (9.91)	6.10 (2.32–15.89)	< 0.01
Pulmonary infarction - n (%)	4 (10.81)	0 (0.0)	16.5 (1.86–145.9)	< 0.01
Shock - n (%)	37 (100)	99 (89.19)	4.94 (0.63–39.07)	0.12
Prior* CAP - n (%)	6 (16.22)	7 (6.31)	2.57 (0.86–7.65)	0.1
Prior* VAP - n (%)	6 (16.22)	7 (6.31)	2.57 (0.86–7.65)	0.09
Prior* HAP - n (%)	2 (5.41)	11 (9.91)	0.46 (0.09–2.45)	0.34
Number of prior pneumonia episodes – mean (± SD)	0.70 (0.66)	0.77 (0.67)	0.86 (0.49–1.53)	0.61
Antibiotics prior to diagnosis - n (%)	36 (97.30)	104 (93.69)	2.48 (0.29–21.20)	0.36
Positive bacterial culture prior to diagnosis - n (%)	33 (89.19)	86 (77.48)	2.50 (0.79–7.95)	0.10
Number of bacterial species isolated – mean (± SD)	1.22 (1.00)	1.03 (1.00)	1.21 (0.84–1.77)	0.31
Same bacterial species isolated > once - n (%)	18 (48.65)	31 (27.93)	2.64 (1.18–5.92)	0.02

Variable	Cases (n = 37)	Controls (n = 111)	OR (IC95%)	*p-value*
Number of bacterial species isolated > once – mean (± SD)	0.62 (0.76)	0.32 (0.56)	2.09 (1.15–3.81)	0.01
Resistant bacterial species - n (%)	9 (24.32)	17 (15.32)	1.71 (0.71–4.11)	0.24
Number of resistant bacterial species – mean (± SD)	0.35 (0.72)	0.19 (0.50)	1.56 (0.86–2.82)	0.15
BMI (Body Mass Index), SD (Standard deviation), NIMV (Non-invasive mechanical ventilation), HFNC (High-flow nasal cannula), ICU (Intensive care unit), CRP (C-reactive protein), PE (pulmonary embolism), CAP (Community acquired pneumonia), VAP (ventilator-associated pneumonia), HAP (hospital-acquired pneumonia)				

In the multivariable model adjusting for sex, BMI, hypertension, and repeated isolation of the same bacterial species, PE remained associated with NP (adjusted OR 5.45, 95% CI 1.85–16.06; P = 0.002); none of the other covariates reached statistical significance in this adjusted model. Table 2.

Table 2
Risk factors for NP, multivariate model

Variable	Odds Ratio	95% CI		P value
Male gender	2.808	0.864	9.125	0.086
Body mass index	0.924	0.835	1.034	0.168
Hypertension	2.468	0.758	8.140	0.138
Pulmonary embolism	5.445	1.846	16.061	0.002
Isolation of same bacterial species > 1 occasion	1.373	0.171	11.022	0.765
Number of overall bacterial species isolated	1.433	0.318	6.459	0.639
*Figure created with the assistance of ChatGPT (OpenAI, San Francisco, CA, USA).				

Discussion

In this matched case–control study of mechanically ventilated patients with severe COVID-19, pulmonary embolism was associated with necrotizing pneumonia after adjustment for other clinically relevant covariates. Although pulmonary infarction—a complication of pulmonary embolism—could not be analyzed due to the absence of cases in the control group, its exclusive presence among cases suggests that it may represent an additional risk factor.

The observed NP incidence (4.5%) is notable given that NP is generally uncommon in viral pneumonia [7]. Although mortality is already high for critically ill patients with severe COVID-19 pneumonia, mortality

was 27% higher in patients with this complication, underscoring its clinical severity.

Given the well-established association between COVID-19 and thrombotic complications [11–13], our findings support a thrombotic–ischemic model of lung necrosis with subsequent superinfection. COVID-19–associated coagulopathy is characterized by endothelial injury, elevated D-dimer levels, and both macrovascular and microvascular thrombosis [11–13]. Autopsy studies have demonstrated diffuse pulmonary microangiopathy and widespread vascular injury [11].

In our cohort, pulmonary embolism was documented in 40.5% of patients with necrotizing pneumonia compared with 9.9% of patients without NP. Pulmonary infarction was observed exclusively among patients who developed NP. This pattern was further reflected by admission D-dimer levels, which were approximately threefold higher in patients who subsequently developed NP.

Impairment of pulmonary and bronchial vascular supply may lead to regional parenchymal ischemia and tissue necrosis. In this setting, bacterial colonization of poorly perfused lung tissue may be facilitated, while reduced vascular delivery of antibiotics may limit effective antimicrobial activity [7, 9]. The resulting cycle of ischemia, infection, and impaired host defense may promote progressive tissue destruction. Figure 1.

The strong association between PE and NP in our cohort suggests that macrovascular thromboembolism may represent a clinically detectable marker of more extensive thrombotic pulmonary injury predisposing to necrosis and subsequent infection. (Proposed pathophysiology model of necrotizing pneumonia in severe COVID-19 on Fig. 1)

Repeated isolation of the same bacterial species was significantly associated with subsequent development of necrotizing pneumonia (NP) in univariate analysis. This finding may reflect persistent colonization as an early marker of unrecognized underlying parenchymal necrosis, or ongoing infection insufficiently responsive to antimicrobial therapy due to impaired antibiotic penetration into poorly perfused tissue. Although this variable did not retain statistical significance after multivariable adjustment, it may represent a clinically relevant signal warranting heightened suspicion for NP in mechanically ventilated patients with recurrent isolation of the same pathogen.

These findings have practical implications. Mechanically ventilated COVID-19 patients with confirmed PE may warrant closer radiologic surveillance for necrotizing complications, particularly in the presence of persistent inflammation or repeated isolation of the same bacterial species. Whether intensified anticoagulation strategies could reduce NP incidence requires further investigation.

This study has several limitations. First, it was conducted at a single center and employed a retrospective design, which may limit generalizability. Second, chest imaging was performed according to clinical indication rather than a standardized protocol, potentially introducing detection bias. Third, the relatively small sample size limits the precision of effect estimates and the number of variables that could be included in multivariable models. Finally, the observational design precludes causal inference.

Despite these limitations, the strong and biologically plausible association between PE and NP supports further prospective evaluation.

Conclusions

Necrotizing pneumonia is an underrecognized but serious complication of severe COVID-19, associated with substantially higher mortality than non-complicated disease. Our findings suggest that thrombotic pulmonary injury—evidenced by the strong association with preceding pulmonary embolism—may contribute to its pathogenesis. Early recognition is therefore important, as timely diagnosis may allow targeted interventions before irreversible lung destruction occurs. Clinicians should maintain a high index of suspicion for NP in mechanically ventilated patients who develop pulmonary embolism, particularly when the same bacterial species is persistently isolated from tracheal aspirate or BAL cultures.

Abbreviations

NP
Necrotizing pneumonia
PE
Pulmonary embolism
COVID-19
Coronavirus disease 2019
SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2
ICU
Intensive care unit
BMI
Body mass index
SD
Standard deviation
OR
Odds ratio
CI
Confidence interval
RT-PCR
Reverse transcription polymerase chain reaction
NIMV
Non-invasive mechanical ventilation
HFNC
High-flow nasal cannula
CRP

C-reactive protein
CAP
Community-acquired pneumonia
VAP
Ventilator-associated pneumonia
HAP
Hospital-acquired pneumonia.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Ethics Committee of Hospital Pablo Tobón Uribe (approval number: 2022.069), which waived the requirement for individual informed consent given the retrospective, de-identified nature of the data. This research was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

A.H.: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Project administration. C.A.: Methodology, Formal analysis, Writing – review & editing. I.R.: Investigation, Data curation, Writing – review & editing. S.P.: Investigation, Data curation, Writing – review & editing. J.A.: Investigation, Data curation. D.M.: Investigation, Data curation. P.V.: Investigation, Data curation. G.D.R.: Conceptualization, Supervision, Writing – review & editing.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality and institutional data-sharing restrictions but are available from the corresponding author on reasonable request.

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Figures

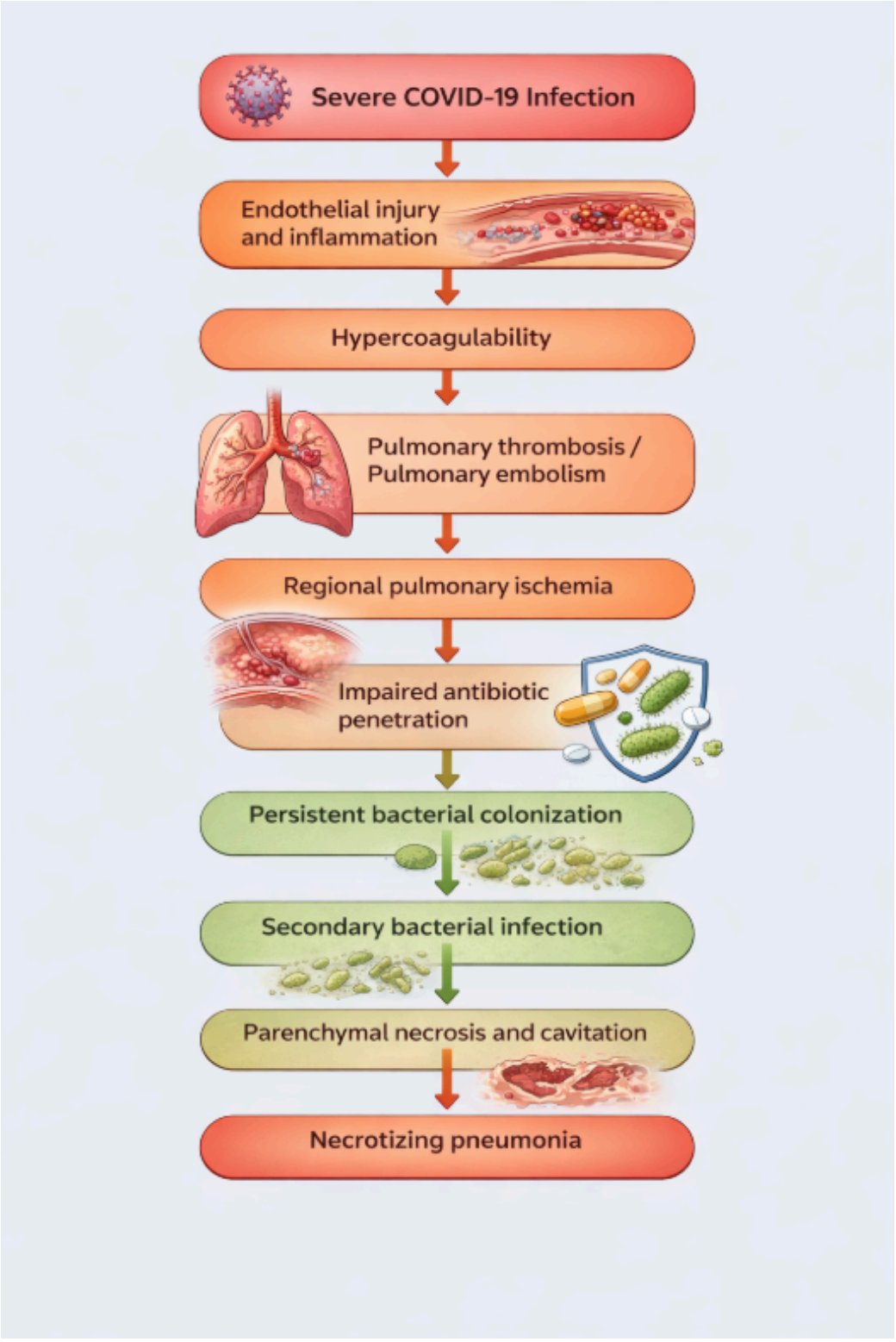


Figure 1

Proposed pathophysiology model of necrotizing pneumonia in severe COVID-19

*Figure created with the assistance of ChatGPT (OpenAI, San Francisco, CA, USA).