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LETTER

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# Circulating pentraxin 3 in severe COVID-19 or other pulmonary sepsis

## 1 | INTRODUCTION

The long pentraxin 3 (PTX3), described initially as a microvascular inflammation marker, is an acute-phase protein released by several cell types in response to infection or tissue damage. It contributes to resistance to bacteria, fungi, viruses and inflammation regulation.[1] Circulating PTX3 was abnormally high (>2 ng/ml) in all 958 patients with severe sepsis or septic shock included in a pre-planned sub-study of the Albumin Italian Outcome Sepsis (ALBIOS) trial.[2] At multivariable analyses, it was associated with the severity of the disease, the occurrence of new organ failures and death. The strongest predictors of higher PTX3 were a diagnosis of septic shock, a higher initial serum level of lactate and a shorter time from enrolment to blood sampling. Albumin supplementation was associated with lower PTX3 in patients with septic shock.[2]

Pulmonary vasculitis and excessive inflammation may play a crucial role in the novel coronavirus disease (COVID-19).[3-6] Therefore, we hypothesized that circulating PTX3 is exceptionally high during severe COVID-19. Herein, we describe the plasma levels of PTX3 in patients with COVID-19 admitted to the Intensive Care Unit (ICU) and compare them with those in patients with other pulmonary sepsis enrolled in the ALBIOS trial.

## 2 | MATERIALS AND METHODS

This study was approved by our institutional review board (protocol number 465/20). Informed consent was obtained according to local regulations.

Plasma concentration of PTX3 was measured with sandwich ELISA[2] every other day in 59 consecutive adults (≥18 years of age) admitted to our ICU with laboratory-confirmed COVID-19 from 1 March to 31 May 2020. Here, we present values obtained 1 ± 1 days and 7 ± 1 days after ICU admission (or at ICU discharge, whichever came first). Some of these data were presented in another publication showing that the initial circulating PTX3 can predict 28-day mortality in hospitalized patients with COVID-19.[7] Four (6.6%) patients with COVID-19 received low-dose corticosteroids and two (3.3%) the interleukin 6 (IL-6) inhibitor tocilizumab, before admission to the ICU. No patients received these drugs during their stay in the ICU, as per our local policy at that time. Albumin was never prescribed.

The ALBIOS trial was a multicentre randomized controlled trial where 1818 patients with severe sepsis or septic shock received crystalloids and 20% albumin (targeting a serum albumin level of ≥ 30 g/L) or crystalloids alone for fluid resuscitation.[8] It was approved by the institutional review boards of all participating centres. Written informed consent was obtained from each patient. Severe sepsis was defined as a proven or suspected infection with at least two signs of systemic inflammation and at least one severe and acute organ dysfunction. Septic shock was defined as severe sepsis with a Sequential Organ Failure Assessment (SOFA) cardiovascular sub-score of ≥ 3. All patients fulfilled the third international consensus definition for sepsis (Sepsis-3) published after the conclusion of the ALBIOS trial. In a pre-planned sub-study on 958 patients from 40 centres, circulating PTX3 was measured on days 1, 2 and 7 after study entry (or at ICU discharge, whichever came first).

As part of another research project, we measured the initial plasma IL-6 level in 56 of the patients with COVID-19, those with plasma stored at −80°C. We used a custom-designed plate on an ELLA-automated immunoassay system (Bio-Techne). IL-6 was not available for patients enrolled in the ALBIOS trial. According to the test manufacturer, circulating IL-6 in healthy subjects is < 10 pg/ml. Reference values for critically ill subjects[9] are reported in the Discussion.

Reporting of the study conforms to broad EQUATOR guidelines.[10]

### 2.1 | Statistical analysis

The sample size of the study was the number of consecutive patients admitted to our ICU from 1 March to 31 May 2020 (first regional outbreak of COVID-19).

Data are reported as mean (SD), median (IQR) or proportion.

Circulating PTX3 in 59 patients with COVID-19 was compared with that in 269 (out of 958) patients enrolled in the ALBIOS trial who fulfilled the following inclusion criteria: (i) reason for ICU admission was 'medical'; (ii) sepsis originated from the lungs; and (iii) PTX3 was measured on days 1 and 2. Exclusion criteria were (i) reason for ICU admission was 'elective surgery' or 'emergency surgery'; (ii) sepsis originated outside of the lungs; and (iii) PTX3 was not measured on day 1 or 2. Data were analysed with Mann-Whitney or Pearson's chi-squared tests (IBM SPSS version 25.0; Armonk NY, USA). Propensity scores were generated for pulmonary disease (COVID-19 or other pulmonary sepsis) with logistic regression analysis, adjusting for the following variables: age (years); sex (female or male); body mass index, the ratio between body weight and the square of body height ($kg/m^2$); the number of pre-existing medical conditions (none, one, two or more)—essential baseline characteristics of the study population; the ratio between arterial oxygen tension and inspired oxygen fraction ($PaO_2/FiO_2$) (mmHg)—probably the most widely used marker of severity of hypoxemia; initial diagnosis of septic shock (SOFA cardiovascular sub-score $\geq$ 3) (yes or no); and initial serum lactate concentration (mmol/L)—the strongest predictors of circulating PTX3 in the ALBIOS trial.[2] 'Initial' referred to ICU admission for patients with COVID-19 and study entry for those in the ALBIOS trial. Individuals in the two groups were matched 1:1 using the nearest neighbour method without replacement (R plugin for SPSS 'PSMatching' and 'MatchIT'). Data collected on day 1 or 2, and day 7 (or at ICU discharge) from patients with COVID-19 were compared with those collected on the same days from propensity score-matched patients enrolled in the ALBIOS trial.

A two-tailed p value $< 0.05$ was considered statistically significant.

## 3 | RESULTS

Thirty-one/59 (52.5%) patients with COVID-19 presented with pulmonary sepsis as originally defined in the ALBIOS trial. Fifty-nine/59 (100%) fulfilled the current updated definition of sepsis (Sepsis-3).

Before matching, patients with COVID-19 differed from those with other pulmonary sepsis for several characteristics, including body mass index, the number of pre-existing medical conditions, initial serum lactate concentration and initial diagnosis of septic shock (Table 1). They also had lower heart rate, higher albumin concentration, higher haemoglobin concentration, lower white blood cell count and less severe coagulation and kidney dysfunction. More patients with COVID-19 were treated with norepinephrine, but only 3/59 (5.1%) had a serum lactate level $\geq$ 2 mmol/L compared with 125/269 (46.5%) enrolled in the ALBIOS trial ($P$ <.001). One-hundred thirty-one/269 (48.7%) patients in the ALBIOS trial received albumin.

After matching, patients with COVID-19 no longer differed from those with other pulmonary sepsis for most of their baseline characteristics (Table 2). Several markers of severity of the disease, including the degree of hypoxemia, the initial circulating lactate and the Simplified Acute Physiology Score (SAPS) II, did not differ between groups. Even so, patients with COVID-19 still had a lower heart rate, similar albumin concentration, higher haemoglobin concentration, similar white blood cell count and less severe extrapulmonary organ dysfunction. More patients with COVID-19 were treated with norepinephrine, but only 3/59 (5.1%) had a serum lactate level $\geq$ 2 mmol/L compared with 14/59 (23.7%) enrolled in the ALBIOS trial ($P$ =.009). Thirty/59 (50.8%) of the patients in the ALBIOS received albumin.

In this propensity score-matched cohort, patients with COVID-19 tended to have a lower, not higher, plasma concentration of PTX3 compared to patients with other pulmonary sepsis, both on day 1 or 2 and day 7 (or ICU discharge) (Figure 1). Initial circulating PTX3 was similarly 'low' in patients with COVID-19 who did (20 [15-42] ng/mL; n = 31) or did not (20 [11-43] ng/mL; n = 28) fulfil the diagnostic criteria for pulmonary sepsis used in the ALBIOS trial ($P$ =.627). Twenty-eight-day non-survivors of COVID-19 (30 [19-64] ng/mL; n = 14) presented with higher circulating PTX3 than survivors (18 [11-36] ng/mL; n = 45) ($P$ =.030).

Initial circulating IL-6 in patients with COVID-19 was 115 (58-233) pg/ml, higher than the reference values for healthy subjects in 54/56 (96.4%) patients.

## 4 | DISCUSSION

In contrast to our hypothesis, circulating PTX3 was not higher in patients with severe COVID-19 than those with other pulmonary sepsis enrolled in the ALBIOS trial.

The role of inflammation in the pathogenesis of COVID-19 remains controversial. Early reports have consistently shown that the circulating levels of many pro-inflammatory cytokines are higher in patients with COVID-19 than in healthy subjects and even more in those with severe or fatal disease.[5] Based on this finding, many authors have assimilated COVID-19 to cytokine storm,[3,4] a syndrome characterized by excessive systemic inflammation leading to multi-organ dysfunction.[11] Subsequent reports, comparing patients with severe COVID-19 to those with other well-known systemic inflammatory syndromes, have shown that the circulating levels of pro-inflammatory cytokines are elevated in the former group, but usually no more than in the latter group.[9,12,13] For instance, in a recent meta-analysis of 37 studies, the estimated pooled mean circulating IL-6 was 55 pg/ml in critically ill patients with COVID-19 (n = 367), 460 pg/ml in

**TABLE 1** Description of the aggregate cohort

| | | | COVID-19 (n = 59) | ALBIOS (n = 269) | P value |
|---|---|---|---|---|---|
| Age | Years | Mean ± SD | 62 ± 11 | 64 ± 16 | 0.317 |
| Sex | Female | N (%) | 11 (18.6%) | 99 (36.8%) | 0.077 |
| Body mass index | $kg/m^2$ | Mean ± SD | 31 ± 8 | 26 ± 5 | <0.001 |
| Pre-existing conditions | None | N (%) | 50 (84.7%) | 150 (55.8%) | <0.001 |
| | One | N (%) | 8 (13.6%) | 88 (32.7%) | |
| | Two or more | N (%) | 1 (1.7%) | 31 (11.5%) | |
| Pre-existing conditions | Liver disease | N (%) | 0 | 3 (1.1%) | 0.415 |
| | COPD | N (%) | 2 (3.4%) | 52 (19.3%) | 0.003 |
| | Chronic renal disease | N (%) | 1 (1.7%) | 9 (3.3%) | 0.504 |
| | Immunodeficiency | N (%) | 0 | 48 (17.8%) | <0.001 |
| | Congestive or ischaemic heart disease | N (%) | 7 (11.9%) | 43 (16.0%) | 0.425 |
| $PaO_2/FiO_2$ | mmHg | Median[IQR] | 162 [123-218] | 146 [100-212] | 0.205 |
| With ARDS | | N (%) | 59 (100%) | 243 (90.3%) | 0.242 |
| With shock | | N (%) | 42 (71.2%) | 126 (46.8%) | 0.001 |
| Lactate | mmol/L | Median[IQR] | 1.0 [0.9-1.4] | 1.9 [1.1-3.2] | <0.001 |
| SAPS II score | | Mean ± SD | 40 ± 7 | 45 ± 15 | 0.012 |
| Heart rate | Bpm | Mean ± SD | 83 ± 16 | 101 ± 21 | <0.001 |
| Mean arterial pressure | mmHg | Mean ± SD | 80 ± 9 | 77 ± 15 | 0.097 |
| Albumin | g/L | Median[IQR] | 27 [25-29] | 25 [22-30] | 0.044 |
| Bilirubin | mg/dl | Median[IQR] | 0.9 [0.7-1.4] | 0.7 [0.4-1.3] | 0.007 |
| Creatinine | mg/dl | Median[IQR] | 0.9 [0.6-1.1] | 1.3 [0.8-2.1] | <0.001 |
| Haemoglobin | g/dl | Median[IQR] | 12.7 [11.7-13.5] | 11.0 [9.9-12.6] | <0.001 |
| With noradrenaline | | N (%) | 42 (71.2%) | 110 (40.9%) | <0.001 |
| Platelets | $10^3/mm^3$ | Median[IQR] | 256 [179-357] | 174 [113-249] | <0.001 |
| White blood cells | $10^3/mm^3$ | Median[IQR] | 8.7 [6.9-10.5] | 12.3 [6.3-19.0] | 0.002 |
| SOFA Score | Total | Median[IQR] | 6 [5-8] | 7 [4-9] | 0.100 |
| | Respiration | Median[IQR] | 3 [2-3] | 3 [2-3] | 0.279 |
| | Coagulation | Median[IQR] | 0 [0-0] | 0 [0-1] | <0.001 |
| | Liver | Median[IQR] | 0 [0-1] | 0 [0-1] | 0.504 |
| | Cardiovascular | Median[IQR] | 3 [0-4] | 3 [0-4] | 0.123 |
| | Kidney | Median[IQR] | 0 [0-0] | 2 [2-3] | <0.001 |
| ICU mortality | | N (%) | 16 (27.6%) | 79 (29.4%) | 0.786 |
| 28-day mortality | | N (%) | 14 (23.7%) | 82 (30.9%) | 0.272 |
| Hospital mortality | | N (%) | 16 (27.6%) | 92 (34.2%) | 0.331 |
| Days in ICU | | Median[IQR] | 13 [6-23] | 11 [6-21] | 0.326 |
| Renal replacement therapy | | N (%) | 3 (5.1%) | 52 (19.3%) | 0.008 |

*Note:* Data refer to ICU admission for patients with COVID-19 and study entry, generally corresponding to sepsis diagnosis, for those in the ALBIOS trial. Variables were defined as in the original study protocol of the ALBIOS trial (8). Body mass index denoted the ratio between body weight and the square of body height; liver disease the presence of cirrhosis, portal hypertension or previous episodes of liver insufficiency; immunodeficiency the presence of immunosuppressive diseases or receipt of immunosuppressive therapies. Congestive or ischaemic heart disease was defined as New York Heart Association class II (class III and class IV were original exclusion criteria). $PaO_2/FiO_2$: arterial oxygen tension to inspired oxygen fraction ratio. The Acute Respiratory Distress Syndrome (ARDS) was defined as a $PaO_2/FiO_2 \leq 300$ mmHg with positive end-expiratory pressure (invasive ventilation) or continuous positive airway pressure (non-invasive ventilation) $\geq 5$ $cmH_2O$. The Simplified Acute Physiology Score (SAPS) II was used to assess the severity of systemic illness at baseline. Scores range from 0 to 163, with higher scores indicating more severe illness. The Sequential Organ Failure Assessment (SOFA) score includes sub-scores ranging from 0 to 4 for each of six components (neurological, respiration, coagulation, liver, cardiovascular and renal components), with higher scores indicating more severe acute organ dysfunction. In the original ALBIOS trial, and herein, this scoring system was slightly modified by excluding the assessment of the neurological component, and by decreasing to 65 mmHg the mean arterial pressure threshold for a cardiovascular sub-score of 1. Shock was defined as a SOFA cardiovascular sub-score $\geq 3$ that is treatment with noradrenaline (any dosage), adrenaline (any dosage) or dopamine (more than 5.0 mcg/kg/min). Outcome measures are shown as additional markers of severity of the disease. P values refer to the Mann-Whitney or Pearson's chi-squared tests.

**TABLE 2** Description of the propensity score-matched cohort

| | | | COVID-19 (n = 59) | ALBIOS (n = 59) | P value |
|---|---|---|---|---|---|
| Age * | years | Mean ± SD | 62 ± 11 | 62 ± 16 | 0.815 |
| Sex * | Female | N (%) | 11 (18.6%) | 11 (18.6%) | 0.999 |
| Body mass index * | $kg/m^2$ | Mean ± SD | 31 ± 8 | 29 ± 7 | 0.104 |
| Pre-existing conditions * | None | N (%) | 50 (84.7%) | 46 (78.0%) | 0.615 |
| | One | N (%) | 8 (13.6%) | 11 (18.6%) | |
| | Two or more | N (%) | 1 (1.7%) | 2 (3.4%) | |
| Pre-existing conditions | Liver disease | N (%) | 0 | 1 (1.7%) | 0.315 |
| | COPD | N (%) | 2 (3.4%) | 8 (13.6%) | 0.047 |
| | Chronic renal disease | N (%) | 1 (1.7%) | 0 | 0.315 |
| | Immunodeficiency | N (%) | 0 | 2 (3.4%) | 0.154 |
| | Congestive or ischaemic heart disease | N (%) | 7 (11.9%) | 4 (6.8%) | 0.342 |
| $PaO_2/FiO_2$ * | mmHg | Median[IQR] | 162 [123-218] | 147 [122-198] | 0.434 |
| With ARDS | | N (%) | 59 (100%) | 56 (94.9%) | 0.242 |
| With shock * | | N (%) | 42 (71.2%) | 37 (62.7%) | 0.328 |
| Lactate * | mmol/L | Median[IQR] | 1.0 [0.9-1.4] | 1.1 [0.9-1.9] | 0.513 |
| SAPS II score | | Mean ± SD | 40 ± 7 | 40 ± 13 | 0.945 |
| Heart rate | bpm | Mean ± SD | 83 ± 16 | 93 ± 18 | 0.001 |
| Mean arterial pressure | mmHg | Mean ± SD | 80 ± 9 | 79 ± 14 | 0.571 |
| Albumin | g/L | Median[IQR] | 27 [25-29] | 27 [22-30] | 0.424 |
| Bilirubin | mg/dl | Median[IQR] | 0.9 [0.7-1.4] | 0.7 [0.4-1.2] | 0.017 |
| Creatinine | mg/dl | Median[IQR] | 0.9 [0.6-1.1] | 1.3 [0.8-2.6] | 0.002 |
| Haemoglobin | g/dl | Median[IQR] | 12.7 [11.7-13.5] | 11.6 [9.9-13.0] | 0.001 |
| With noradrenaline | | N (%) | 42 (71.2%) | 29 (49.2%) | 0.015 |
| Platelets | $10^3/mm^3$ | Median[IQR] | 256 [179-357] | 169 [119-243] | <0.001 |
| White blood cells | $10^3/mm^3$ | Median[IQR] | 8.7 [6.9-10.5] | 10.1 [6.0-16.2] | 0.136 |
| SOFA Score | Total | Median[IQR] | 6 [5-8] | 7 [5-9] | 0.053 |
| | Respiration | Median[IQR] | 3 [2-3] | 3 [2-3] | 0.534 |
| | Coagulation | Median[IQR] | 0 [0-0] | 0 [0-1] | <0.001 |
| | Liver | Median[IQR] | 0 [0-1] | 0 [0-0] | 0.342 |
| | Cardiovascular | Median[IQR] | 3 [0-4] | 3 [0-4] | 0.999 |
| | Kidney | Median[IQR] | 0 [0-0] | 1 [1-2] | <0.001 |
| ICU mortality | | N (%) | 16 (27.6%) | 11 (18.6%) | 0.251 |
| 28-day mortality | | N (%) | 14 (23.7%) | 12 (20.3%) | 0.657 |
| Hospital mortality | | N (%) | 16 (27.6%) | 11 (18.6%) | 0.251 |
| Days in ICU | | Median[IQR] | 13 [6-23] | 11 [6-20] | 0.463 |
| Renal replacement therapy | | N (%) | 3 (5.1%) | 8 (13.6%) | 0.113 |

*Note:* Data refer to ICU admission for patients with COVID-19 and study entry, generally corresponding to sepsis diagnosis, for those in the ALBIOS trial. Individuals in the two groups were matched 1:1 based on their propensity score obtained with logistic regression analysis using (*) as covariates. Variables were defined as in the original study protocol of the ALBIOS trial (8), and as reported in the legend of Table 1. P values refer to the Mann-Whitney or Pearson's chi-squared tests.

those with the acute respiratory distress syndrome unrelated to COVID-19 (n = 2767), 984 pg/ml in those with sepsis (n = 5320) and 3111 pg/ml in those with the chimeric antigen receptor T cell-induced cytokine release syndrome (n = 72).[9] In the present cohort of patients with severe COVID-19, the average initial circulating IL-6 was 115 (58-233) pg/ml: abnormally high but not that high. Results were similar when IL-6 expression in cells isolated from the broncho-alveolar lavage fluid was compared between patients with COVID-19, other pneumonia or no pneumonia, all treated with invasive

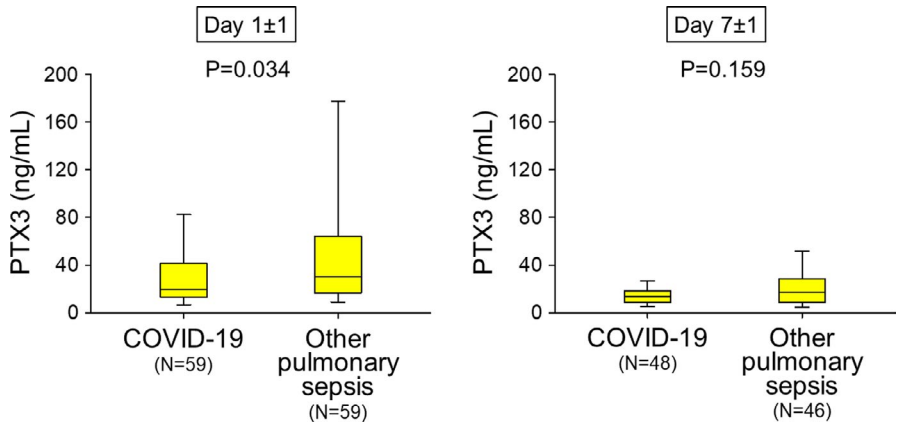


**FIGURE 1** Circulating PTX3 with severe COVID-19 and other pulmonary sepsis. The plasma concentration of PTX3 was measured in 59 patients with severe COVID-19 and 59 propensity score-matched patients with other pulmonary sepsis enrolled in the ALBIOS trial. Circulating PTX3 was measured 1 ± 1 days and 7 ± 1 days after ICU admission for patients with COVID-19 or study entry, generally corresponding to the diagnosis of sepsis, for those in the ALBIOS trial. Results are presented as box plots where the boundary of the box closest to zero indicates the 25th percentile, the line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers (error bars) above and below the box indicate the 90th and 10th percentiles. In patients with COVID-19, circulating PTX3 was 20 (13-42) and then 13 (8-18) ng/ml; in those with other pulmonary sepsis, it was 30 (16-64) and then 17 (9-28) ng/ml. P values refer to the Mann-Whitney test

mechanical ventilation in the ICU.[14] As this evidence is growing, some authors have suggested that cytokine storm is probably not the typical phenotype of severe COVID-19. Immune suppression may be more common.[15]

From a clinical perspective, excessive inflammation is generally associated with fever, tachycardia, hypotension with signs of hypoperfusion, hypoalbuminemia and anaemia, thrombocytopenia and multi-organ dysfunction.[11] These signs are very common during sepsis.[8] Before matching, patients with COVID-19 presented with severe hypoxemic respiratory failure but no other distinctive signs of hyper-inflammation. After matching, patients with COVID-19 continued to appear *no more* inflamed and with *no more* severe extra-pulmonary organ dysfunction than those enrolled in the ALBIOS trial. Again, even if several authors have noted clear signs of hyper-inflammation in some neonates, children and adults with severe COVID-19, these are not a constant finding.

Like C-reactive protein, PTX3 is a component of the innate humoral immunity typically induced by inflammation.[1] In patients with sepsis or septic shock enrolled in the ALBIOS trial, PTX3 was markedly elevated.[2] In those with COVID-19, it was elevated as well, but to a lesser degree. This result may reflect a different origin of infection (more commonly bacterial in patients in the ALBIOS trial) or a different role of PTX3 in the two syndromes' pathogenesis. Nonetheless, based on the data discussed above, it may also suggest that COVID-19 is not always associated with cytokine storm. This may be relevant, as hyper-inflammation is regarded as a possible therapeutic target for COVID-19.[3,4]

Some of the limitations of our study deserve a comment. First, patients with COVID-19 or other pulmonary sepsis were matched for a limited number of covariates. Even so, their baseline characteristics, the overall severity of the disease and the strongest predictors of circulating PTX3 were reasonably comparable between the two groups. Other studies comparing COVID-19 with other critical illnesses did not make such an effort to diminish confounding. Second, PTX3 is only one of many circulating biomarkers of inflammation. D-dimer, C-reactive protein and ferritin are elevated with severe COVID-19, usually more than in other critical illnesses.[9] This may indicate that (vascular [6]) inflammation has an essential role in the pathogenesis of COVID-19 and that circulating PTX3 does not correctly reflect it. Third, although cytokine storm does not seem to be the rule, it may still occur in some patients with severe COVID-19.

In conclusion, circulating PTX3 was not higher with severe COVID-19 than with other pulmonary sepsis.

## KEYWORDS

Acute-phase reaction, Coronavirus infections, Inflammation, Pneumonia

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