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Pentraxin 3 As a Clinical Marker in Children With Lower Respiratory Tract Infection

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Summary. Background: Pentraxin 3 (PTX-3) is an acute-phase protein that increases in the plasma during inflammation. Objective: We aimed to evaluate the usefulness of PTX-3 as a clinical marker in children with lower respiratory tract infection (LRTI) and examine the correlation of PTX-3 with other biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT). Methods: We enrolled 117 consecutive patients admitted to Seoul St. Mary's Hospital with LRTI using the WHO criteria. We recorded data on fever duration and peak temperature before admission, duration of fever after admission, respiratory rate, heart rate, oxygen saturation upon admission, duration of oxygen supplementation, and duration of hospital stay. Upon admission, white blood cell (WBC) count, erythrocyte sedimentation rate, CRP level were measured. Multiplex respiratory virus polymerase chain reaction was performed using nasal swabs. PTX-3, PCT, and various cytokines were measured after the study had been completed. Results: We found that there was no significant difference in the level of PTX-3 according to the type of viral infection. PTX-3 levels showed a significant correlation with PCT levels, but not with levels of CRP. The level of PTX-3 showed a significant correlation with peak temperature and duration of fever before admission as well as interleukin (IL)-6 levels. PCT levels showed a significant correlation with IL-6 and granulocyte-colony stimulating factor levels, peak temperature, and duration of fever before admission, and duration of hospital stay. CRP levels showed a significant correlation with duration of fever before admission, total WBC count, and neutrophil count. PCT levels significantly predicted a hospital stay of 7 days or more. PTX-3, PCT, and CRP levels showed no correlation with any other clinical features. Conclusion: PTX-3 reflected disease severity but failed to predict length of hospital stay. Further studies evaluating the use of PTX-3 as a biomarker in mild LRTI would be useful. **Pediatr Pulmonol. 2016;51:42–48.**

Key words: pentraxin 3; children; inflammatory marker; lower respiratory infection; procalcitonin; C-reactive protein.

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INTRODUCTION

Lower respiratory tract infection (LRTI) is common, particularly in the first years of life.[1] In many cases, LRTIs are caused by viruses and have a mild course, unless they are complicated by bacterial superinfection.[2,3]

However, because some cases can proceed to a more severe course, early diagnosis and recognition of the disease severity are necessary for optimal care. Many inflammatory markers have been developed to serve this purpose such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and procalcitonin (PCT) levels.[4]

Pentraxin 3 (PTX-3) is a novel biomarker that behaves as an acute-phase protein: as its blood levels, which are low in normal conditions (<2 ng/ml in humans, 1.24 ng/ml [0.87–2.08] in children), rapidly increase in the plasma during inflammation (e.g., sepsis, endotoxin shock, and other inflammatory conditions).[5,6] PTX-3 is released in response to microbial recognition and can bind specific pathogens such as fungi, bacteria, and viruses.[5] A previous study found that plasma PTX-3 levels could be used to diagnose the

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severity of community acquired pneumonia with higher sensitivity compared to CRP, and also correlated with the length of hospital stay.[7] Another study found that a high concentration of PTX-3 helps to differentiate parapneumonic effusion from non-parapneumonic effusion.[8] However, no study has investigated the value of PTX-3 in viral infection, which is the most common cause of LRTI in children.

The aim of this study was to evaluate the usefulness of PTX-3 as a clinical marker in LRTI and examine the correlation of PTX-3 with other biomarkers such as CRP and PCT.

MATERIAL AND METHODS

Study Design

We enrolled 117 consecutive patients with LRTI admitted to the ward from the emergency department or outpatient department using the WHO criteria, that is, patients with fever, cough, a fast respiratory rate for their age, chest in-drawing, and rhonchi or crepitations on auscultation. Children were excluded if they had received antibiotics in the 10 days preceding admission or if they were suffering from an underlying chronic disease (e.g., anatomical abnormalities of the respiratory tract, immunological deficits, progressing neurological conditions, psychomotor retardation, congenital heart disease, or hemoglobinopathy), severe malnutrition, or other concurrent infections.

We recorded data on fever duration and peak temperature before admission, duration of fever after admission, respiratory rate, heart rate, oxygen saturation upon admission, duration of oxygen supplementation, and duration of hospital stay. Upon admission, total white blood cell (WBC) count, ESR, and CRP levels were measured from blood samples before any medical treatment and multiplex respiratory virus polymerase chain reaction (PCR) was performed using nasal swabs. Blood samples for measurement of PTX-3, PCT, cytokines, and chemokines were placed in tubes containing EDTA, immediately centrifuged at 2,500*g* and stored at −80°C. Assays were performed after the study was completed.

After admission, patients under 3 months of age received 60 mg/kg/day of intravenous amoxicillin sodium and potassium clavulanate (Moxicle injection; Daewoong Pharm., Seoul, Korea), patients between 3 months and 12 years of age received 90 mg/kg/day of intravenous amoxicillin sodium and potassium clavulanate, and patients over 12 years of age received 3,600 mg of intravenous amoxicillin sodium and potassium clavulanate. Patients with positive results upon *Mycoplasma pneumoniae* PCR received 15 mg/kg/day of oral clarithromycin (Klaricid dry syrup; Abbott Korea Limited., Seoul, Korea).

Study Subjects

Children with a medical diagnosis of LRTI admitted to Seoul St. Mary's Hospital from May 1, 2012 to November 30, 2013 were enrolled. Enrollment was conducted by pediatric pulmonologists. The Institutional Review Board of the Seoul St. Mary's Hospital approved the study (protocol no: KC13TISI0254). Written informed consent was obtained from parents or guardians; assent was obtained from invited children.

Detection of Viruses

The Resplex II assay (Qiagen, Hilden, Germany) simultaneously targets 12 viruses: respiratory syncytial virus (RSV), human rhinovirus (hRhV), influenza virus (IV), human metapneumovirus (hMPV), human coronaviruses (hCoV), parainfluenza virus (PIV), adenovirus (AdV), and human bocavirus (hBoV). Specimen-extracted RNAs were tested in a single reaction using the ResPlex II assay, following the protocol of the manufacturer, as described previously.[9]

Meausrement of Cytokines and Chemokines

Quantification of five cytokines: (interleukin [IL]- 1β, IL-2, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)- α), and four chemokines: (IL-8, granulocyte stimulating factor (G-CSF), MIG (CXCL9), and interferon gamma inducible protein-10) in sera was performed with the Bio-Plex Pro Human Cytokine assay (Bio-Rad Laboratories, Inc., Hercules, CA). Assays were carried out according to the manufacturer's instructions.

Mycoplasma pneumoniae Polymerase Chain Reaction

M. pneumoniae specimens were obtained from throat swabs and DNA was then extracted from subcultures or clinical specimens by centrifuging the samples at 14,000*g* for 20 min at 4°C in a refrigerated minicentrifuge and digesting the pellets with 200 μl proteinase K (1 mg/ml) lysis buffer for 1 hr at 60°C. Proteinase K was inactivated by incubation at 95°C for 10 min.

Detection of *Streptococcus pneumoniae* Urinary Antigen

We used the BinaxNOW *Streptococcus pneumoniae* Antigen Card (Binax, Portland, ME) to test for urinary pneumococcal antigen. This test detects the C- polysaccharide present on the cell wall of all pneumococcal strains. Urine was concentrated 25- fold by selective ultrafiltration (PM 15,000, Minicon Urifil-10 Concentrator; Millipore, Bedford, MA). The results were considered qualitatively as either positive or negative.

Measurement of Plasma PTX-3

We used a human PTX-3 ELISA Kit (Boster Biological Technology Co., Ltd., Fremont, CA) to measure plasma concentrations of PTX-3 in blood samples. For each plasma sample, 100 μl was directly transferred to the micro-test strip wells of the ELISA plate and subsequently incubated for 2 hr at room temperature. After three washing steps, a detection antibody was added, and the reaction system was incubated for 2 hr at room temperature. Antibody binding was detected with streptavidin-conjugated horseradish peroxidase and developed with a substrate solution. Next, the reaction was stopped, and the optical density was determined with a microplate reader set to 450 nm. Wavelength correction was set to 570 nm. Sample results were calculated from a standard curve generated by dilutions of a known amount of recombinant PTX-3 protein. Each standard or sample was assayed in duplicate.

Measurement of Serum PCT

PCT measurements were performed using a time-resolved amplified cryptate emission technology assay (Kryptor PCT; Brahms AG, Hennigsdorf, Germany) with a functional assay sensitivity of 0.06 g/L, which is about fourfold above normal mean levels.[10] The coefficients of variation at concentrations of 0.1, 0.25, 0.5, and 10 ng/ml were 16, 7, 5, and 3%, respectively. The assay time was less than 20 min and results were routinely available within 1 hr.

Pediatric Early Warning Score

The Pediatric Early Warning Score (PEWS) is an easily scored tool that is based on five domains: behavior, cardiovascular status, respiratory status, nebulizer use, and persistent postsurgical vomiting. The tool is further supported by an algorithmic response that is based on the score.[11] A critical PEWS is defined as a total score of 4 or a score of 3 in any of the PEWS domains which reflects a critical value that requires consultative action.[11] Each patient was scored according to the PEWS upon admission.

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). All continuous variables are expressed as mean ± SE, and numbers (n) with percentages are expressed for categorical variables. To compare PTX-3 levels in different types of viral infection, the Mann–Whitney U-test was performed for continuous variables that did not follow a parametric distribution, and the Wilcoxon signed-ranks test was used to compare categorical variables. A linear regression analysis was applied for correlations between PTX-3 and all of the clinical and laboratory variables of LRTI patients. Receiver operating characteristic (ROC) curves were generated to predict a hospital stay of 5 days or 7 days or more according to CRP, PCT, and PTX-3 levels. Statistical significance was defined at $P < 0.05$ in a two-tailed test.

RESULTS

Study Population

In total, 117 patients were included in the study. The mean age of the study population was 1.9 ± 2.6 years and there were 74 males. With regards to the clinical features of the patients, the mean duration of fever before admission was 2.4 ± 2.4 days, the mean peak temperature before admission was $38.9 \pm 0.7^{\circ}$C, the mean hospital stay was 4.5 ± 1.7 days, and the mean PEWS score was 1.7 ± 0.8. With regards to the laboratory data, the mean ESR was 38.1 ± 28.0 mm/hr, the mean WBC count was $10{,}195.9 \pm 4{,}401.8 \times 10^4$ cells, and mean number of neutrophils was $4{,}465.5 \pm 3{,}625.6 \times 10^4$ cells. The mean CRP level was 1.8 ± 3.5 mg/dl, the mean PCT level was 0.2 ± 0.6 ng/ml, and the mean PTX-3 level was 8.2 ± 9.1 ng/ml (Table 1).

Microbiology

Within the study population, causative agents were found in 90 patients. In those with positive PCR results, RSV was the most frequently isolated agent (47 cases). There were two cases of IV, eight cases of AdV, eight cases of hMPV, ten cases of PIV, ten cases of hRhV, two cases of hCoV, nine cases of hBoV, four cases of *M. pneumoniae* infection, and three cases of *S. pneumonia* infection (Table 2). There was no significant difference in the level of PTX-3 when cases with any type of causative agents were compared to those with no causative agent (Fig. 1). In the infected group, there were 11 cases with superinfection and 79 cases without superinfection. There was no significant difference in the level of PTX-3 according to superinfection (data not shown).

Correlation of Inflammatory Markers With Laboratory Data and Clinical Findings

PTX-3 levels showed a significant correlation with PCT levels, but not with the levels of CRP (Table 3). PTX-3 levels showed a significant correlation with the peak temperature and duration of fever before admission as well as IL-6 levels. PCT levels showed a significant correlation with the peak temperature and duration of fever before admission as well as hospital stay. PCT also showed a significant correlation with IL-6 and G-CSF levels. CRP levels showed a significant correlation with the duration of fever before admission, ESR, total WBC count, and neutrophils count (Table 4). However PTX-3,

TABLE 1— Subject Characteristics

Characteristics	All (n = 117)	Infected (n = 90)	Non infected (n = 27)	*P*-value*
Age, years	1.9 ± 2.6; 0–13	1.6 ± 2.5; 0–13	2.6 ± 2.9; 0–11	0.099
Male, n (%)	74 (62.2)	52 (57.8)	22 (81.5)	0.039
Fever duration before admission, days	2.4 ± 2.4; 0–10	2.5 ± 2.4; 0–10	2.1 ± 2.4; 0–10	0.428
Fever duration after admission, days	0.8 ± 1.0; 0–4	0.9 ± 1.1; 0–3	0.7 ± 0.9; 0–4	0.354
Total fever duration, days	3.2 ± 2.9; 0–12	3.3 ±2.9; 0–12	3.1 ± 3.1; 0–11	0.739
Peak temperature before admission, °C	38.9 ± 0.7; 37.8–40.0	38.9 ± 0.7; 37.8–40.0	39.0 ± 0.7; 38.0–40.0	0.790
Respiratory rate, % of normal value	107.7 ± 16.3; 100–210	31.8 ± 7.8; 100–210	30.0 ± 8.8; 100–160	0.312
Heart rate, % of normal value	108.1 ± 11.4; 100–164	125.2 ± 16.3; 100–164	119.1 ± 18.0; 100–145	0.040
O_2 saturation (n = 22)	96.0 ± 4.5; 79–100	96.1 ± 4.7; 79–100	95.0 ± 4.2; 96–99	0.596
O_2 supplementation, days (n = 16)	2.9 ± 1.9; 1–7	2.2 ± 2.1; 1–7	1.5 ± 2.1; 1	0.053
Hospital stay, days	4.5 ± 1.7; 1–12	4.5 ± 1.6; 3–12	4.6 ± 1.9; 3–11	0.929
Pediatric early warning score	0.6 ± 1.0; 0–4	0.6 ± 1.0; 0–4	0.5 ± 0.8; 0–3	0.685
ESR, mm/hr	38.1 ± 28.0; 2–120	36.8 ± 26.3; 2–120	41.6 ± 32.0; 4–120	0.439
Total WBC, cells x 10^4	10,195.9 ± 4,401.8; 3, 160–29,950	9,953.6 ± 3,845.9; 3,160–19,770	11,250.4 ± 5,910.9; 3,180–29,950	0.182
Neutrophil, cell x 10^4	4,465.5 ± 3,625.6; 50–19,960	4,152.3 ± 3,021.0; 50–12,620	5,742.2 ± 5,052.0; 520–19,960	0.045
C-reactive protein, mg/dl	1.8 ± 3.5; 0–23.0	1.8 ± 3.7; 0–23.0	2.1 ± 2.9; 0–10.0	0.703
Procalcitonin, ng/ml	0.2 ± 0.6; 0.0–5.8	0.2 ± 0.6; 0–5.8	0.1 ± 0.2; 0–0.6	0.600
Pentraxin 3, ng/ml	8.2 ± 9.1; 0.0–22.2	7.6 ± 9.0; 0–22.2	10.1 ± 9.2; 0–22.2	0.226

ESR, erythrocyte sedimentation rate; WBC, white blood cell.
Data expressed as mean ± SD or as n (%); range.
*P-value between infected versus non infected.

PCT, and CRP levels showed no significant correlation with the duration of fever after admission, respiratory rate, heart rate, oxygen saturation, or duration of oxygen supplementation. PTX-3, PCT, and CRP also showed no significant correlation with TNF-α, IL-1β, IL-8, IFN-γ, or IL-2 (Table 4).

TABLE 2— Causative Agents (n = 117)

Causative agent	N (%)
RSV	47 (41.2)
None	27 (23.1)
Parainfluenza	10 (8.4)
Rhinovirus	10 (8.4)
Bocavirus	9 (7.6)
Metapneumovirus	8 (6.7)
Adenovirus	8 (6.7)
Mycoplasma pneumoniae	4 (3.4)
Streptococcus pneumonia	3 (2.5)
Influenza	2 (1.7)
Coronavirus	2 (1.7)

Use of Inflammatory Markers to Predict Hospital Stays of 5 Days or 7 Days or More

We assessed the ability of inflammatory markers, PTX-3, PCT, and CRP in its ability to predict a hospital stay of 5 days or 7 days or more. PTX-3, PCT, and CRP did not

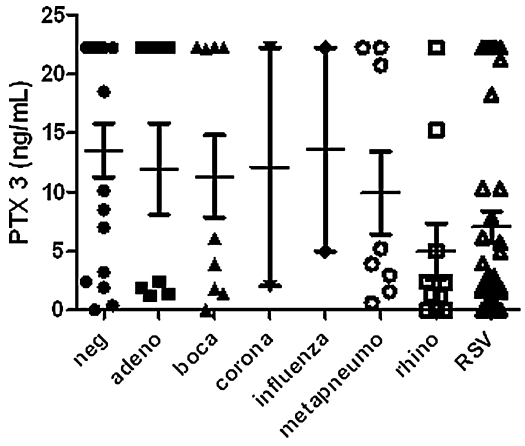

Fig. 1. Pentraxin 3 (PTX 3) level in virus infection.

TABLE 3—Correlation Between Procalcitonin, C-Reactive Protein, and Pentraxin 3

	Procalcitonin	C-reactive protein
Pentraxin 3	0.267 (0.004)	−0.035 (0.707)

Data presented as r (*P*-value).

significantly predict a hospital stay of 5 days or more. In addition, PTX-3 and CRP did not significantly predict a hospital stay of 7 days or more. However, PCT levels significantly predicted a hospital stay of 7 days or more (Table 5).

DISCUSSION

In this study, we aimed to evaluate the usefulness of PTX-3 as an inflammatory marker in LRTI and examine the correlation of PTX-3 with other biomarkers such as CRP and PCT. We found that there was no significant difference in the level of PTX-3 between cases with any type of viral infection and those with no causative agent. PTX-3 levels showed a significant correlation with the peak temperature and duration of fever before admission as well as IL-6 levels. PCT levels showed a significant correlation with the peak temperature and duration of fever before admission, as well as duration of hospital stay. PCT also showed a significant correlation with IL-6 and G-CSF levels. CRP levels showed a significant correlation with the duration of fever before admission, ESR, total WBC count, and neutrophil count. PCT levels significantly predicted a hospital stay of 7 days or more.

PTX-3 levels are known to be increased in various disease such as kidney disease, cardiovascular disease, and acute respiratory distress syndrome.[12–14] We found that the level of PTX-3 reflects disease severity in children with LRTI by showing a significant correlation with the peak temperature and duration of fever before admission. This result was similar to that reported in a previous study which found that plasma PTX-3 levels could be used to diagnose the severity of community acquired pneumonia in adults.[7] We also found that the PCT level reflects disease severity and prognosis in children with LRTI. Our findings support previous studies which reported similar findings.[15,16] There was a lack of correlation with other clinical signs of disease severity. This might be because the age of the study population and the disease category were different from previous studies which involved rather serious diseases such as acute respiratory distress syndrome, cardiovascular disease, and sepsis in adults.[13,14,17]

There was no difference in PTX-3 levels between those who were found to be infected with a causative agent and those who were not. One possible explanation for this finding is that it might have been due to the limitations of a nasopharyngeal swab: we presume that even patients with no detectable viruses might actually have been infected.[18]

TABLE 4—Correlation of Pentraxin 3, Procalcitonin, and C-Reactive Protein With Clinicopathologic Features in Lower Respiratory Tract Infection

	Pentraxin 3	Procalcitonin	C-reactive protein
Fever duration before admission	0.200 (0.030)	0.384 (<0.001)	0.245 (0.007)
Fever duration after admission	0.001 (0.788)	0.001 (0.804)	0.004 (0.510)
Total duration of fever	0.018 (0.144)	0.031 (0.056)	0.016 (0.510)
Peak temperature before admission	0.342 (0.009)	0.464 (<0.001)	0.074 (0.579)
Respiratory rate	0.014 (0.209)	0.003 (0.556)	0.026 (0.083)
Heart rate	0.013 (0.226)	0.000 (0.914)	0.014 (0.208)
O_2 saturation	0.004 (0.364)	0.001 (0.908)	0.003 (0.823)
O_2 supplementation, days	0.009 (0.727)	0.011 (0.699)	0.028 (0.530)
Hospital stay	0.034 (0.715)	0.202 (0.029)	−0.103 (0.265)
Pediatric early warning score	0.000 (0.877)	0.014 (0.197)	0.019 (0.142)
ESR	0.055 (0.554)	0.089 (0.340)	0.683 (<0.001)
Total WBC	0.155 (0.095)	0.036 (0.697)	0.302 (0.001)
Neutrophil	0.164 (0.077)	0.072 (0.443)	0.519 (<0.001)
IL-1ß	0.177 (0.059)	0.032 (0.735)	0.031 (0.739)
IL-2	0.042 (0.656)	−0.058 (0.539)	0.109 (0.242)
IL-6	0.214 (0.022)	0.319 (0.001)	0.079 (0.401)
IL-8	−0.027 (0.774)	−0.031 (0.747)	0.053 (0.575)
G-CSF	0.019 (0.837)	0.255 (0.006)	0.119 (0.202)
IFN-γ	0.112 (0.235)	−0.019 (0.838)	0.105 (0.261)
TNF-α	0.180 (0.053)	−0.019 (0.840)	0.048 (0.607)

ESR, erythrocyte sedimentation rate, WBC, white blood cell; IL, interleukin; G-CSF, granulocyte colony stimulating factor; IFN, interferon; TNF, tumor necrosis factor.
Data are presented as r (*P*-value).

TABLE 5— Inflammatory Markers to Predict Hospital Stay for 5 Days, and 7 Days or More

Hospital stay (days)	Pentraxin 3	Procalcitonin	C-reactive protein
5	0.512 (0.8245)	0.555 (0.3183)	0.568 (0.2118)
7	0.521 (0.8094)	0.649 (0.0351)	0.552 (0.5403)

AUC, area under curve.
Data are presented as AUC (*P*-value).

Our study also found that PTX-3 levels did not vary depending on the types of virus causing infection. This is because PTX-3 acts as a part of the innate immune system as a pattern recognition molecule. PTX-3 is also involved in resistance against some viral infections.[5] PTX-3 binds both human and murine cytomegalovirus (HCMV and MCMV, respectively) and reduces the viral infection of dendritic cells in vitro.[19] Accordingly, *ptx3 -/-* mice present a higher susceptibility to infections than wild-type mice, and the viral titer is reduced upon treatment with recombinant PTX-3.[19] Moreover, PTX-3 protects MCMV-infected mice from *Aspergillus fumigatus* superinfection and enhances the production of IL-12 and IFN-γ by dendritic cells and T cells, respectively.[19]

Finally, human and murine PTX-3 binds influenza virus (H3N2) through interaction between viral hemagglutinin glycoprotein and the sialic acid residue present on PTX-3.[20] PTX-3 inhibits virus-induced hemagglutination and viral neuraminidase activity and neutralizes virus infectivity.[20] Treatment with recombinant PTX-3 reduces mortality and viral load.[20] Further study will be needed to discover the differential effect of PTX-3 on different types of virus in vivo.

Our study found that PTX-3 level correlated with IL-6 levels. This result is similar to those of previous studies which found that PTX-3 correlated with IL-6 in patients with acute pancreatitis and obstructive sleep apnea.[21,22] However, PTX-3 showed no significant correlation with TNF-α, IL-1β, IL-8, IFN-γ, or IL-2 in the current study. This was different from previous studies which found that PTX-3 was produced in response to proinflammatory stimuli including IL-1β, TNF-α, microbial moieties, and toll-like receptor (TLR) engagement.[23]

There are some limitations to our study. The first is that the study population was limited to mild cases of LRTI: there were no cases requiring intensive care, and the mean PEWS score was 0.6 ± 1.0, having only one case with a score of 4. Secondly, the distribution of causative agents was concentrated to selected viruses.

A recent study examined the PTX-3 levels of induced sputum in asthmatic patients and another study investigated the usefulness of PTX-3 level in bronchoalveolar lavage fluid to discriminate microbiologically confirmed pneumonia in mechanically ventilated patients.[24,25] Further study involving local levels of PTX-3 in LRTI would be of interest.

In conclusion, PTX-3 reflected the disease severity of LRTI in children but failed to act as a prognostic marker. Further study in order to evaluate the use of PTX-3 as a biomarker in mild LRTI would be useful.

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