The effect of exacerbations on lung density in relation to patient characteristics in the RAPID-RCT trial of alpha-1 antitrypsin therapy

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Introduction

- Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) may temporarily induce changes that could impact lung density, affecting 15th percentile lung density (PD15) accuracy
- To date, the optimal length of the exacerbation-free period prior to a computed tomography (CT) scan has not been determined

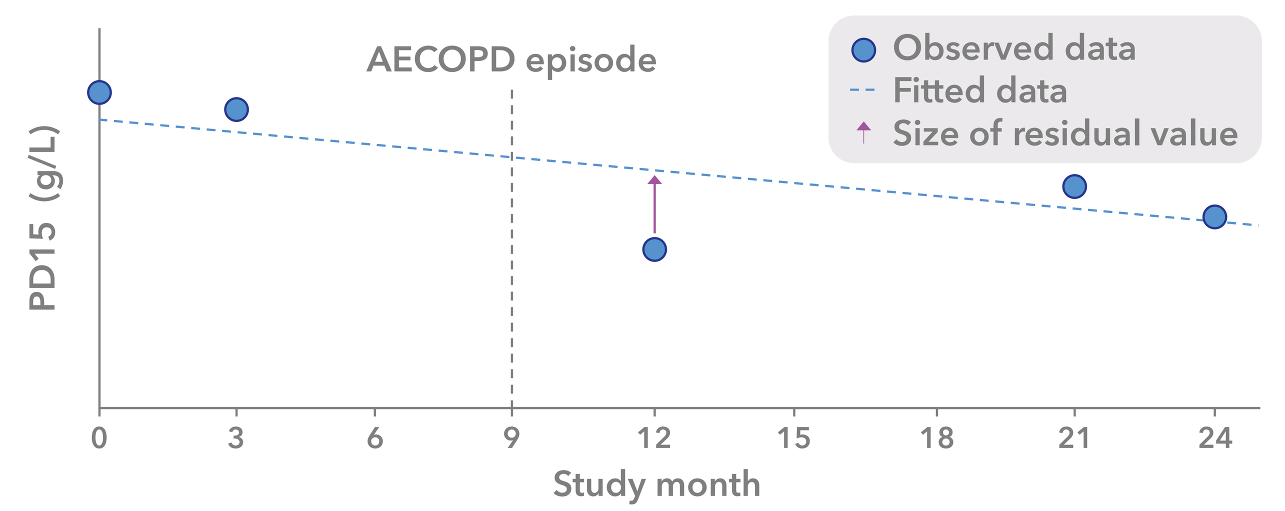
Aim

- Assess the influence of AECOPD and patient characteristics on CT lung density

Methods

- In the RAPID-RCT, CT scans were performed at baseline and at months 3, 12, 21 and 24[1]
- Raw marginal residuals were calculated (**Figure 1**)
- Residuals were compared by patient characteristics: age, sex, inhaled corticosteroid (ICS) use, alpha-1 antitrypsin (AAT) treatment group and baseline lung function parameters/PD15
- Histograms and density estimates were used in categorical assessment of patient characteristics; p-values were calculated using the Wilcoxon rank sum test
- Scatterplots present residual PD15 values *vs.* days since last exacerbation with a penalized B-Spline
- Residuals were grouped as large or small (> or <2 g/L in either direction) and presented by patient characteristics in categorical analyses
- A stepwise logistic regression analysis was conducted to determine which parameters were significantly associated with the frequency of large residuals (at least ±2 g/L)

Figure 1: Calculation of raw marginal residuals for PD15



Raw marginal residuals are defined as the difference between fitted and observed PD15 values. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PD15, 15th percentile lung density

Results

Data

- Data from 132 patients with at least three CT scans (633 CT scans; 333 without an AECOPD and 300 with a previous AECOPD at any time) were included in the analyses

Effect of prior AECOPD on PD15

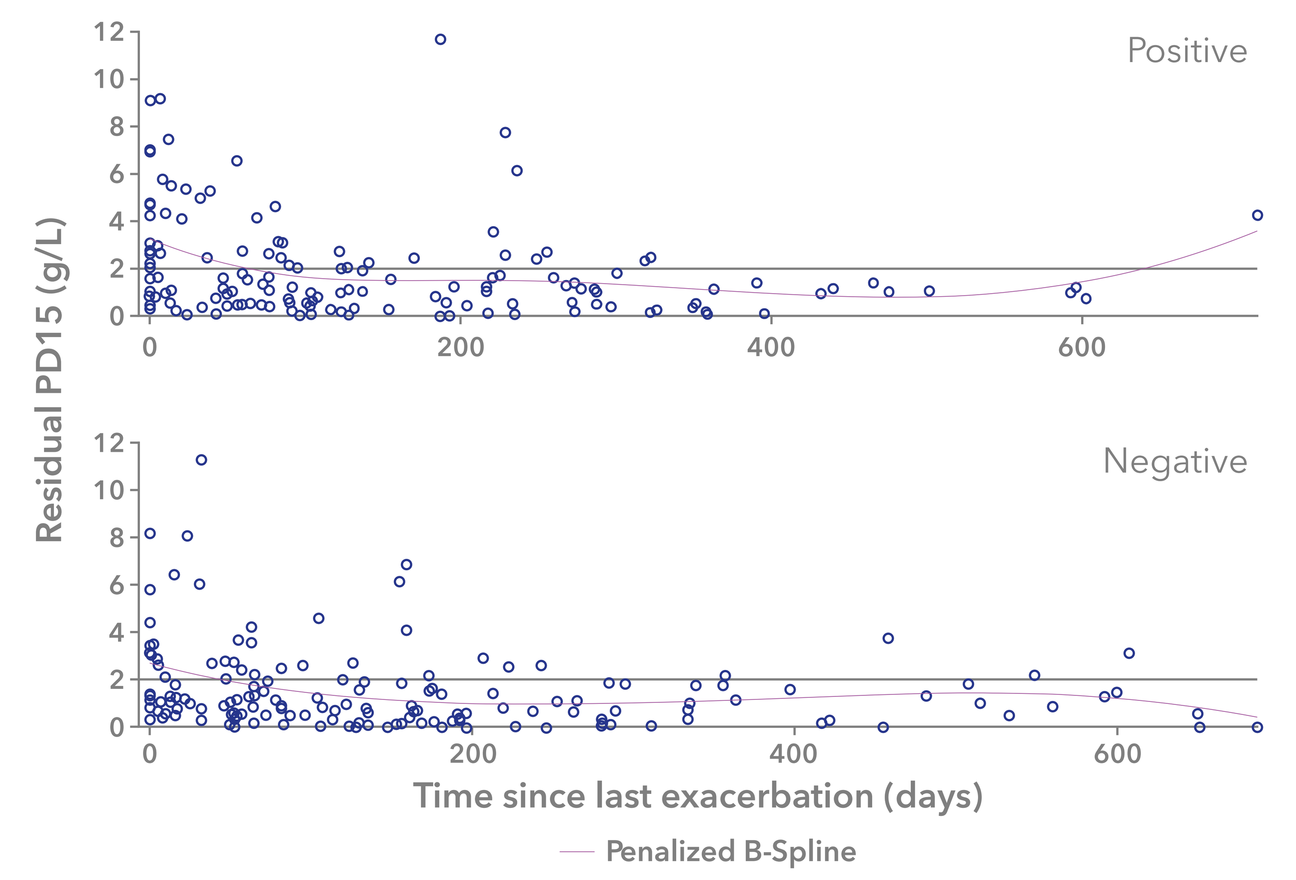
- Mean residuals were larger the closer the CT scan was to an exacerbation, and decreased with time (**Table 1** and **Figure 2**)

Table 1: Mean residual PD15 according to presence/timing of AECOPD

Weeks since last AECOPD	N	Mean PD15 (g/L)	SD
Any AECOPD	300	0.12	2.641
≤2	55	**0.83**	3.744
>2	245	-0.05	2.302
≤4	67	**0.52**	3.771
>4	233	0.00	2.209
≤6	76	**0.35**	3.965
>6	224	**0.04**	2.009
No AECOPD	333	-0.02	1.715

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PD15, 15th percentile lung density; SD, standard deviation

Figure 2: Raw marginal residual PD15 values relative to time since AECOPD



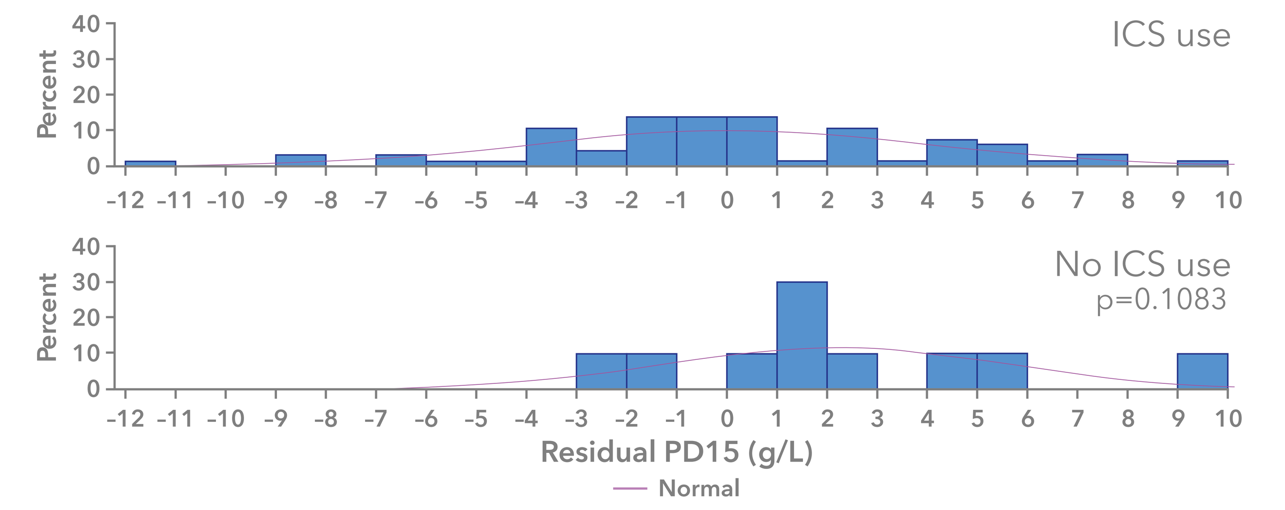
Positive (top) and negative (bottom) raw marginal residual PD15 values and spline. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PD15, 15th percentile lung density

- Positive and negative residuals were observed, likely reflecting inflammation and air trapping (**Figure 2**)

Effect of patient baseline parameters on residuals

- ICS use potentially influenced the size of residuals within 6 weeks of AECOPD, with a shift towards positive residuals in patients not receiving ICS (**Figure 3**) (p=0.11)
- Categorical analysis suggested that several baseline parameters were associated with a higher frequency of large residuals where there were:
  - AECOPD within 6 weeks – AAT treatment
  - No AECOPD within 6 weeks – Female sex, baseline PD15 ≥47.3 g/L (median)
- Logistic regression analysis revealed factors that influenced the frequency of large residuals; baseline PD15 and AECOPD within the last 6 week were the most significant factors (**Table 2**)

Figure 3: Effect of ICS use on residual PD15 values with an AECOPD within 6 weeks



AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; PD15, 15th percentile lung density

Table 2: Logistic regression analysis of parameters influencing the frequency of large residuals

	Odds ratio			p-value (Wald)
	Estimate	Lower 95% CI	Upper 95% CI	
Baseline PD15	1.030	1.017	1.044	<0.0001
Exacerbation within last 6 weeks: Yes *vs.* No	5.707	3.375	9.652	<0.0001
Sex: Female *vs.* Male	1.765	1.181	2.636	0.0055
Treatment group: AAT *vs.* Placebo	1.736	1.159	2.600	0.0074

Data presented relate to all residuals, independent of AECOPD. AAT, Alpha 1 Antitrypsin; CI, confidence interval; PD15, 15th percentile lung density

Conclusions

- AECOPD can affect PD15 values; however, the effect is small and greatest in the first 2 weeks following an AECOPD
- The influence of patient baseline parameters is equally minimal
- A 6-week exacerbation-free period represents a conservative approach to obtain reliable lung density data in future AAT deficiency trials

References

1. Chapman K *et al. Lancet* 2015;286:360–368

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Conflicts of interest: MH, XZ, YC and OV are employees of CSL Behring; MW is a consultant to CSL Behring

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