A marker of human neutrophil elastase mediated club cell secretory protein-16 degradation (CC16-HNE) is associated with mortality and pulmonary hypertension in idiopathic pulmonary fibrosis

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BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is characterized by epithelial injury, fibrosis, and an aberrant immune response. Club cells are essential for lung homeostasis by repairing the injured epithelium and secreting the anti-inflammatory club cell secretory protein-16 (CC16). Additionally, activated neutrophils release human neutrophil elastase (HNE) during inflammation.

Aim: Investigate if serum measurements of CC16 degradation by HNE (CC16-HNE) were related to IPF mortality and pulmonary hypertension (PH).

METHODS

Serum CC16-HNE was assessed at baseline in 99 prevalent IPF subjects by the neoepitope-specific ELISA nordicCC16-HNE™ along with pulmonary function and PH. Mortality was registered for at least three years and up to five years. Serum CC16-HNE was compared in subjects with or without PH by a linear regression model adjusting for age and sex. Additionally, subjects were dichotomised into low vs high baseline serum CC16-HNE at the median and analysed by Kaplan-Meier and Cox proportional hazard model for survival association. CC16-HNE association with smoking status was assessed by Kruskal-Wallis test with Dunn's multiple comparisons.

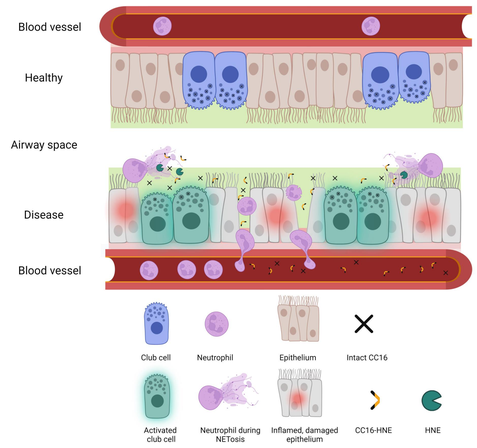


Figure 1 CC16 is secreted as upkeep of lung milieu homeostasis. In disease, the epithelium permeability can increase due to injury. Neutrophils are recruited as first responders to inflammatory injury inflammation and, upon activation, form neutrophil extracellular traps (NETosis), secreting various compounds such as human neutrophil elastase (HNE). HNE can cleave CC16, releasing the CC16-HNE fragment that can be measured in blood samples.

Demographics

	Patients with IPF
n	99
Age (years), mean (SD)	72.6 (6.0)
Male sex, n (%)	79 (79.8%)
Smoking status: never/former/current, n (%)	27(27.3%)/67(67.7%)/5 (5.0%)
FVC (% predicted), mean (SD)	83.9 (24.7)
Emphysema, n (%)	48 (48.9%)
Pulmonary hypertension, n (%)	13 (13.13%)

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; SD, standard deviation

Take-home messages

- Low serum CC16-HNE at baseline was associated with:
  - increased risk of mortality
  - a PH complication in IPF
- These results indicate that a neutrophil immune response and degradation of CC16 is relevant for disease outcome. CC16 degradation by HNE could serve as a prognostic biomarker for IPF and diagnostic for a PH complication.

RESULTS

Lower baseline CC16-HNE was associated with PH in IPF

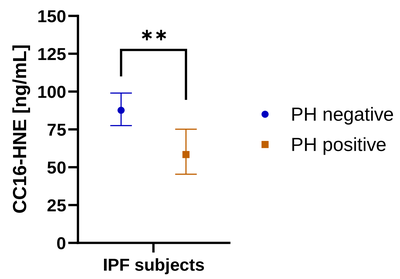
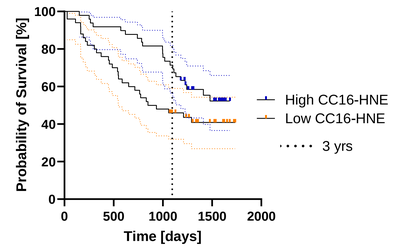


Figure 2 Diagnostically, serum CC16-HNE was lower in IPF subjects with PH (adjusted geometric mean 58.4 [95%CI: 45.4-75.2] ng/mL) when compared to those without (adjusted geometric mean 87.7 [95%CI: 77.5-99.1] ng/mL, p = 0.004).

Data are shown as geometric means ±95% confidence interval (95%CI).

Lower baseline CC16-HNE was associated with a worse survival prognosis



	BL	1 yrs	2 yrs	3 yrs
High:	49	46	44	36
Low:	50	40	30	21

Figure 3 Prognostically, lower serum levels of CC16-HNE was associated with worse survival in IPF when compared to higher levels (hazard ratio 1.79 [95%CI 1.03-3.13; p=0.04).

All-cause mortality for all subjects were monitored from baseline (BL) and at least up to three years (yrs).

CC16-HNE was not associated to smoking status

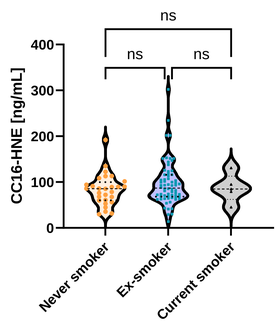


Figure 4 Serum CC16-HNE was not associated with smoking status in IPF (p>0.05), where statuses included: never smoker (median 85.6 [IQR: 60.0-99.7] ng/mL), ex-smoker (median 86.8 [68.2-115.9] ng/mL), and current smoker (median 85.0 [IQR: 62.0-113.0] ng/mL). Data are shown as violin plots.

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Disclosures: AHH, FBS, MAK, DJL, JMBS are employed at Nordic Bioscience and may be shareholders.

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