Iron Deficiency is Associated with Shorter Time to Next Pulmonary Exacerbation in Cystic Fibrosis

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Background

- Iron deficiency (ID) is common in cystic fibrosis (CF) (prevalence of 40%-80%) [1]
- Clinical impact of ID in CF poorly understood
- Small, pre-modulator study found association between ID severity and shorter time to antibiotics [2]
- Unknown if ID persists and relationship between ID and pulmonary exacerbations while on modulators

Objective

Characterize the effects of ID on subsequent time to pulmonary exacerbations in a large cohort, including patients on highly effective CFTR modulator therapy

Methods

- Retrospective review of 182 adults (without history of transplantation) at single center from 2012-2022
- ID definition: transferrin saturation (TSAT) < 20% or serum iron level < 60 ug/dl [1], pulmonary exacerbation definition: antibiotics for new pulmonary symptoms
- Used novel multivariable restricted time model to analyze recurrent event data in which both predictors (ID status) and outcomes (exacerbations) have repeated measurements (see Figure 1) [3]
- Used generalized estimating equations to model the correlated time-to-first- exacerbation outcomes
- This approach accounts for correlation between recurrent event times contributed by the same individual

Results

Table 1: Baseline characteristics. N=182.

Variable	Mean (SD) or Percent
Age (years)	31.23 (11.15)
Sex (male)	42%
PI	97%
Baseline ppFEV1	63.70 (26.65)
Baseline BMI	22.93 (4.10)
Baseline TSAT	17.24 (13.28)
HomoF508del	41%
Modulator (ever)	36%
CKD (ever)	4%
Cancer (ever)	1%
Pregnancy (ever)	2%
Bleeding (ever)	10%
MRSA (ever)	57%
PsA (ever)	86%
DM (ever)	39%

Key: PI = pancreatic insufficiency, ppFEV1 = percent predicted FEV1, BMI = body mass index, TSAT = percent transferrin saturation, CKD = chronic kidney disease, MRSA = sputum methicillin resistant staph aureus, PsA = sputum pseudomonas, DM = diabetes mellitus, PEx = pulmonary exacerbations

Table 2: ID is associated with a 5.9 day shorter time to next exacerbation (p = 0.028), adjusted for key clinical characteristics including age, ppFEV1, CFTR modulator use, BMI, sputum bacteria, and others.

	Est. (days)	95% CI	P-value
ID (yes/no)	-5.9	(-11.19,-0.632)	0.028*
ppFEV1	0.2	(-0.014,0.416)	0.067
Age	0.4	(-0.060,0.800)	0.092
BMI	0.3	(-1.221,1.735)	0.733
Sex (M)	-2.0	(-11.27,7.199)	0.666
Pregnancy	-5.6	(-21.01,9.792)	0.475
Cancer	18.1	(-27.14,63.42)	0.432
HomoF508del	12.7	(2.383,23.02)	0.016*
PEx/year	0.5	(-0.539,1.603)	0.330
Modulator	7.9	(1.687,14.06)	0.013*
CKD	-0.7	(-7.740,6.272)	0.837
DM	-13.6	(-21.02,-6.082)	<0.001***
PI	-25.3	(-65.67,15.13)	0.220
MRSA	-31.6	(-55.36,-7.870)	0.009**
PsA	-33.9	(-49.25,-18.61)	<0.001***
Bleeding	4.6	(-4.716,13.97)	0.332

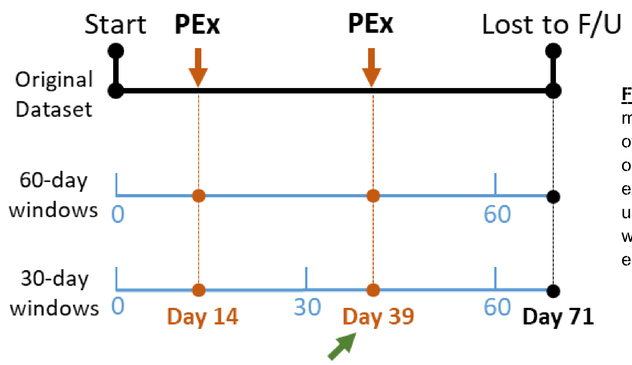

Figure 1: Visual representation of novel model applied to a single subject's data over a 71 day period, illustrating 60-day or 3-day pseudo-observations. The exacerbation at Day 39 would be lost using the original data or the 60-day window for the final generalized linear equation modeling.

Conclusions

- Iron deficiency persists with modulator therapy, with an independent association between ID and shorter time to subsequent pulmonary exacerbation
- First step in assessing the prognostic value of ID for relevant CF-specific outcomes
- Understanding clinical impact of ID in CF will help guide diagnosis, as well as subsequently design trials to address treatment

Future Directions

- Further work needed to determine optimal biomarkers to define clinically relevant ID in CF
- Further analysis needed to determine other key clinical outcomes of ID in CF, such as functional capacity, fatigue, and mortality
- Prospective clinical trials needed to evaluate safest and most effective therapy for iron repletion in CF

Bibliography

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