Pattern of lung function is not associated with prior or future morbidity in children with sickle cell anemia

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On-Line Supplement

Results:

Does consideration of the FEF25-75 affect the association between SCD morbidity and lung function pattern?

Given recent studies that have investigated whether measurement of the $FEF_{25\text{-}75}$ offers additional information that could contribute to clinical decision making(1, 2), we examined the extent to which adding patients who were categorized in the “normal” group but had a reduced $FEF_{25\text{-}75}$ to the “obstruction” group would change the associations between this lung function pattern and morbidity.

We found 14 additional participants in the “normal” group who would have been reclassified as having obstruction (9% of the total cohort) using $FEF_{25\text{-}75}$<LLN criteria in spite of having a normal FEV_1/FVC ratio. (Of note, we also found 6 patients with a reduced FEV_1/FVC ratio who had an $FEF_{25\text{-}75}$ at or above the LLN). Repeating our analyses of factors associated with baseline lung function showed that including $FEF_{25\text{-}75}$<LLN criteria did not change the results – prior morbidity was not associated obstruction (Table E4). Similarly when we repeated our multivariable models examining the associations between lung function pattern and prospective morbidity, there were no associations between obstruction and future rates of pain or ACS (Table E4).

Table E1. Final negative binomial regression models for prospective rates of ACS and vaso-occlusive pain in children with SCA who had at least 12 months of prospective follow-up (N=121)

	IRR	**95% CI**	**P Value**
E2a. Prospective rates of ACS			
Retrospective rate of ACS events per year	18.98	8.92-70.35	<0.001
Obstructive pattern	0.89	0.42-1.89	0.77
Restrictive pattern	1.99	0.46-2.14	0.99
Non-specific pattern	1.58	0.23-1.45	0.24
E2b. Prospective rates of pain			
Age (years)	1.07	0.995-1.15	0.07
Retrospective rate of pain events per year	2.21	1.72-2.84	<0.001
Obstructive pattern	0.67	0.33-1.37	0.26
Restrictive pattern	0.58	0.32-1.03	0.06
Non-specific pattern	0.89	0.41-1.95	0.77

Table E2. Final negative binomial regression models for prospective rates of ACS and vaso-occlusive pain in children with SCA, including HU as a covariate (N=136)

	IRR	**95% CI**	**P Value**
E3a. Prospective rates of ACS			
Taking HU	2.04	1.14-3.64	0.02
Retrospective rate of ACS events per year	12.24	6.28-23.86	<0.001
Obstructive pattern	0.86	0.42-1.76	0.67
Restrictive pattern	1.12	0.53-2.37	0.78
Non-specific pattern	0.50	0.19-1.30	0.15
E3b. Prospective rates of pain			
Age (years)	1.07	1.01-1.14	0.022
Taking HU	2.17	1.22-3.85	0.008
Retrospective rate of pain events per year	2.08	1.67-2.58	<0.001
Obstructive pattern	0.66	0.36-1.21	0.18
Restrictive pattern	0.62	0.33-1.18	0.15
Non-specific pattern	0.95	0.40-2.25	0.91

Table E3. Logistic regression models of the association between retrospective rates of ACS and pain and having obstruction (defined as FVC $\geq$ LLN with FEV_1/FVC <LLN or FEF_{25-75} < LLN; N=35 with obstruction versus 79 with normal lung function)

	Model 1*	Model 2†	Model 3‡	Model 4§
	OR (95% CI) P Value	OR (95% CI) P Value	OR (95% CI) P Value)	OR (95% CI) P Value
Retrospective ACS Rate	2.18 (0.49-9.74) 0.31	2.30 (0.48-10.97) 0.29	2.30 (0.47-11.22) 0.39	1.60 (0.28-9.12) 0.60
Retrospective Pain rate	0.65 (0.30-1.43) 0.29	0.66 (0.30-1.45) 0.30)	0.69 (0.29-1.62) 0.39	0.84 (0.37-1.89) 0.84

* Unadjusted model
† Model adjusted for age and gender
‡ Model adjusted for age, gender, and SCD factors (hemoglobin [g/dL], white blood cell count, and reticulocyte %)
§ Model adjusted for age, gender, and pulmonary factors of interest (has asthma, bronchodilator response >12%, early life ETS exposure, ln (IgE))

Table E4. Alternate* negative binomial regression models for prospective rates of ACS and vaso-occlusive pain in children with SCA, (N=136)

	IRR	**95% CI**	**P Value**
E3a. Prospective rates of ACS			
Retrospective rate of ACS events per year	13.90	7.33-26.42	<0.001
Obstruction pattern	1.07	0.56-2.04	0.85
Restriction pattern	1.08	0.51-2.30	0.84
Non-specific pattern	0.58	0.22-1.51	0.26
Has BD response $\geq$ 12%	1.48	0.85-2.59	0.17
E3b. Prospective rates of pain			
Retrospective rate of pain events per year	2.29	0.80-2.90	<0.001
Obstruction pattern	1.02	0.61-1.73	0.93
Restriction pattern	0.66	0.37-1.15	0.14
Non-specific pattern	1.08	0.55-2.12	0.82
Age	1.06	0.99-1.13	0.10
Hb (g/dL)	1.15	0.95-1.39	0.16
WBC	1.06	0.99-1.13	0.12

*Using alternate classification scheme in which the Obstruction pattern group includes those with either an FEV_1/FVC ratio below the LLN or the FEF_{25-75} below the LLN

1. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making. *Eur Respir J* 2014; 43: 1051-1058.
2. Lukic KZ, Coates AL. Does the FEF25-75 or the FEF75 have any value in assessing lung disease in children with cystic fibrosis or asthma? *Pediatr Pulmonol* 2015; 50: 863-868.