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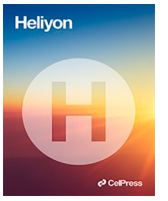

Research article

Evaluating CRMS/CFSPID phenotypes and outcomes: A retrospective study from a large UK cystic fibrosis centre☆

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ABSTRACT

Background: Cystic fibrosis transmembrane conductance regulator metabolic syndrome/cystic fibrosis screen-positive, inconclusive diagnosis (CRMS/CFSPID) is a designation given following a positive newborn screen for cystic fibrosis (CF) when CF is not excluded but cannot be confirmed. We describe the long-term clinical outcomes of a CRMS/CFSPID cohort.

Methods: A retrospective, single centre study of children with a current or previous diagnosis of CRMS/CFSPID. Study period extended from February 1, 2007 to August 1, 2022. Baseline and longitudinal data were assessed.

Results: 30 children were designated as CRMS/CFSPID between 2007 and 2021. At baseline, 13 CFTR variants were identified, of which F508del and R117H 7T/9T were most common (occurring in 25 and 20 children respectively). Initial mean immunoreactive trypsinogen and sweat chloride were 82.8 mmol/L and 34.3 mmol/L respectively. During longitudinal assessment ($n = 27$), occurring over a mean duration of 8.5 years, five children progressed to CF at a mean age of 9.5 years. All children were pancreatic sufficient except one who reclassified to CF. Four isolated *Pseudomonas aeruginosa* and 12 isolated *Staphylococcus aureus*, of which one and two progressed to CF respectively. All recent Z-scores for weight and spirometry were above −2. Initial mean sweat chloride was higher in those who progressed to CF versus those who did not, although this did not reach statistical significance (38.4 mmol/L versus 32.0 mmol/L respectively, $p = 0.105$).

Conclusions: Most children with CRMS/CFSPID remained well with a low progression rate to CF. This supports a less intensive medical surveillance approach. Our results highlight the importance of assessment in a dedicated CRMS/CFSPID clinic during adolescence to detect progression to CF after 6 years of age.

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Abbreviations

(CF) Cystic fibrosis
(CFTR) Cystic fibrosis transmembrane conductance regulator
(UK) United Kingdom
(NBS) Newborn blood spot
(CRMS/CFSPID) Cystic fibrosis transmembrane conductance regulator related metabolic syndrome/cystic fibrosis screen-positive, inconclusive diagnosis
(STROBE) Strengthening the Reporting of Observational Studies in Epidemiology
(IRT) Immunoreactive trypsinogen
(VVCC) Variants of varying clinical consequence
(VUS) Variants of unknown significanc
(*S. aureus)* *Staphylococcus aureus*
(*P. aeruginosa*) *Pseudomonas aeruginosa*
(BMI) Body mass index
(FEV1) Forced expiratory volume in the 1st second
(FVC) Forced vital capacity
(CNS) Chrispin-Norman score
(CXR) Chest X ray
(CT) Computerised tomography
(SD) Standard deviation
(IQR) Interquartile range
(R117H 7T/9T) R117H associated with poly T tract variants 7T and 9T

1. Introduction

Cystic Fibrosis (CF) is a common life-limiting autosomal recessive condition caused by variants in the CF transmembrane conductance regulator (CFTR) gene. Since being rolled out across the United Kingdom (UK) in 2007, the newborn blood spot (NBS) screening programme has led to earlier diagnosis of CF in asymptomatic or minimally symptomatic individuals, thus enabling earlier intervention and increasing survival [2]. Most infants who screen positive for CF are subsequently diagnosed with CF via CFTR genetic analysis or sweat testing. However, for infants who are not found to have two CF-causing variants nor a raised sweat chloride level, the diagnosis can remain unclear [3]. In these cases, further CFTR functional testing and extended genetic analysis may or may not provide diagnostic clarity. Infants who screen positive for CF but do not demonstrate clinical features consistent with a diagnosis of CF are termed as CFTR-related metabolic syndrome/CF screen-positive, inconclusive diagnosis (CRMS/CFSPID). This global harmonised designation now supersedes previous diagnostic terms [4].

Although most CRMS/CFSPID children will remain asymptomatic, some children will progress to a diagnosis of CFTR-related disorder or CF. This can occur either through conversion, whereby a child develops clinical features of CF such as pathognomonic symptoms or a raised sweat test, or through reclassification, whereby a child's genotype is deemed causative of CF following advances in our understanding of the pathogenicity of specific CFTR variants [5]. There is much uncertainty surrounding prognosis, with prospective studies reporting a progression rate from CRMS/CFSPID to CF between 11 % and 44 % [6–8]. Prognostic factors are also

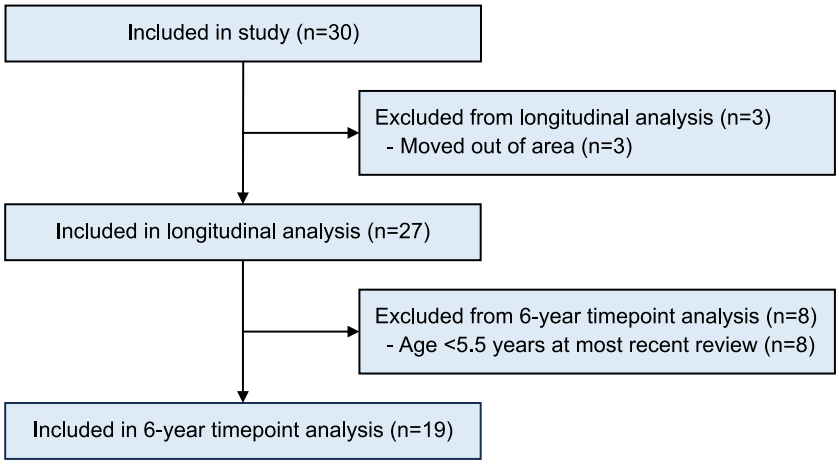

Fig. 1. STROBE diagram. Abbreviation: STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

unclear, making it difficult to predict which children are more likely to progress to CF. This prognostic uncertainty causes challenges in determining the intensity of medical surveillance, as well as having significant emotional, behavioural and mental health impacts on children and their families [9,10].

Given the significant variability in NBS programmes globally, CRMS/CFSPID children from different regions may have unique clinical characteristics consequential to the different genetic and physiological parameters incorporated in their local NBS programmes [11]. To our knowledge, there have not been any studies investigating the clinical characteristics of a UK-based CRMS/CFSPID cohort until now. In this study, we aim to advance our understanding of CRMS/CFSPID by describing the phenotypes and clinical outcomes of a cohort of CRMS/CFSPID children from a large UK CF centre.

2. Materials and methods

The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and fulfilled the criteria outlined in the STROBE checklist [12]. The STROBE diagram is shown in Fig. 1. Children born between 2007 and 2021 with a current or previous retrospective diagnosis of CRMS/CFSPID under the care of Birmingham Women's and Children's NHS Foundation Trust, a regional multidisciplinary paediatric CF centre, were eligible for inclusion. The diagnostic criteria for CRMS/CFSPID are summarised in Fig. 2. Eligible children were identified by reviewing local databases, consulting department leads and reviewing clinic lists. Number of CF cases diagnosed following a positive NBS in our centre during the study period was obtained from local departmental records, which were contemporaneously updated at the time of patient diagnosis. A retrospective analysis of clinical records from February 1, 2007 to August 1, 2022 was performed. Children who had not been reviewed within the previous 1.5 years were included in the baseline analysis (n = 30) but excluded from longitudinal analysis (n = 27). Children who had investigations performed between 5.5 and 7 years of age were included in the 6-year timepoint analysis (n = 19). This timepoint was chosen due to current guidance which recommends that children with CRMS/CFSPID have an extensive evaluation at 6 years of age [4,13]. Frequency of follow up appointments varied between children across the study period. Following its publication in 2020, our centre adopted the European Cystic Fibrosis Society standard of care for children with CRMS/CFSPID, setting up a dedicated local CRMS/CFSPID clinic [4]. All children who progressed to CF subsequently received specialist CF care.

Demographic, genetic, physiological, microbiological, radiological and clinical data were extracted from local health records. All respiratory clinic letters were reviewed for validation. For children under shared care with another trust, all local letters and reports were reviewed where available. These clinical records were not de-identified prior to data collection. A positive NBS result was defined as a referral via the screening pathway for clinical and diagnostic assessment for CF following a raised immunoreactive trypsinogen (IRT) level detected on a dried blood sample within the first week of life. Genetic variants were classified as CF-causing, variants of varying clinical consequence (VVCC), variants of unknown significance (VUS) or non-CF according to the cftr2 online database at the time of the affected child's birth [14]. Sweat testing was performed as per guidelines [15]. Normal, intermediate and raised sweat chloride results were defined as <30 mmol/L, 30–59 mmol/L and ≥60 mmol/L respectively [16]. Children with normal and intermediate sweat chloride results were classified as Group A CRMS/CFSPID and Group B CRMS/CFSPID respectively, as per guidance from the European Cystic Fibrosis Society [4,17]. Pancreatic sufficiency was defined as a faecal pancreatic elastase level of >200 μg/g or reported as normal. *Staphylococcus aureus* (*S. aureus)* and *Pseudomonas aeruginosa* (*P. aeruginosa*) infections were identified by bacterial isolation on sputum culture, cough plate or cough swab obtained during routine clinic visits. Z-scores and percentiles for height, weight and body mass index (BMI) were determined according to the LMS Parameters for UK World Health Organization growth charts using the childsds R package [18,19]. BMI was reported at age two years and above. Forced expiratory volume in the 1st second (FEV1) and forced vital capacity (FVC) measurements were identified through spirometry. Results obtained with variable, suboptimal or poor child technique, as documented in the physiology report, were excluded. Z-scores and percentage of predicted values for age, sex and ethnicity were calculated as per Global Lung Function Initiative standardised reference equations using the rspiro R package [20,21]. Modified Chrispin-Norman score (CNS) on chest X rays (CXR) were reported by a specialist radiologist. Modified CNS assesses respiratory disease progression in CF, ranging from 0 (normal) to 38 (pathological) [22]; note that in our clinical practice, the highest score we tend to see in children with CF is 22. CXRs obtained during episodes of acute illness were excluded. Presence and severity of bronchiectasis on computerised tomography (CT) thorax scans were reported by a specialist radiologist.

Data was collected in Microsoft Excel and de-identified prior to analysis to avoid potential bias. All analyses were performed in R

			Sweat Chloride		
			Normal	Intermediate	Raised
CFTR variants	CF causing	CF causing	CF	CF	CF
	CF causing, VVCC or VUS	VVCC or VUS	CRMS/CFSPID Group A	CRMS/CFSPID Group B	
	CF causing, VVCC or VUS	Non-CF causing	Carrier		
	Non-CF causing	Non-CF causing	Not suspected		

Fig. 2. Diagnostic aid for children undergoing clinical and diagnostic assessment for CF. Abbreviations: CRMS/CFSPID: cystic fibrosis transmembrane conductance regulator related metabolic syndrome/cystic fibrosis screen-positive, inconclusive diagnosis; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; VVCC: variants of varying clinical consequence; VUS: variants of unknown significance.

(version 4.3.1) [23]. Descriptive summaries of continuous data are provided as means and standard deviation (SD) for normally and uniformly distributed data and as median and interquartile range (IQR) for nonparametric distributed data. Comparisons for continuous data were made using Student's *t*-test for normally distributed data and Mann-Whitney *U* test for nonparametric distributed data. Comparisons for categorical data were made using Fisher's exact test. For sweat chloride and modified CNS results, the slope of a linear regression model relating the time of each test to the result was calculated for children with at least two results (thus reflecting the trend throughout the study whilst standardising for differences in test time intervals between children).

3. Results

3.1. Baseline assessment

30 children born between 2007 and 2020 were identified with an initial diagnosis of CRMS/CFSPID. 26 (86.7 %) children had a positive NBS result. All four (13.3 %) children with a negative NBS result had a first-degree relative with CF which prompted their referral for CF clinical and diagnostic assessment. On assessment they were found to have an inconclusive CF diagnosis, fulfilling all other aspects of the CRMS/CFSPID diagnostic criteria. Therefore, following expert senior input, they were diagnosed with and managed as CRMS/CFSPID. During the study period, 252 children in our centre were diagnosed with CF following a positive NBS, equating to a CF:CRMS/CFSPID ratio of 9.7 following a positive NBS.

Baseline characteristics are displayed in Table 1. 13 different CFTR variants were identified via genetic testing. All children had one CF-causing variant, of which F508del was the most common (83.3 %), and one VVCC or VUS, of which R117H associated with poly T tract variants 7T and 9T (R117H 7T/9T) was the most common (66.7 %). On initial sweat test, one third of children had a normal result (CRMS/CFSPID Group A) and the remaining two thirds of children had an intermediate result (CRMS/CFSPID Group B). 14 (46.7 %) children had an antibiotic prophylaxis prescription documented in their clinical records.

3.2. 6-Year assessment

Of the children who received regular follow up, 19 children reached the 6-year assessment timepoint. Their characteristics are displayed in Table 1. Only one child had progressed to CF by this timepoint via reclassification of their CFTR variant. On spirometry, all Z-scores for FEV1 and FVC were above −2. It is noteworthy that nine spirometry reports were excluded from this analysis due to poor or suboptimal technique. Only one child had Z-scores for weight and height below −2. Extended anthropometry and spirometry data are displayed in Table S1. Only one child had a CT thorax at this timepoint, which showed no bronchiectasis.

3.3. Longitudinal assessment

27 children received regular follow up, whilst three children moved out of the area and were excluded from longitudinal analysis. Their characteristics are displayed and compared in Table 1. Mean follow-up duration across the cohort was 8.53 years since birth (range 1.95–15.3 years), totalling 230 years of follow-up time. Follow-up duration was significantly longer for children who progressed to CF than for those who did not (mean of 13.3 and 7.44 years respectively, $p = 0.00261$), which is assumed to be due to the likelihood of CF progression increasing with age.

22 children (81.5 %) remained as CRMS/CFSPID, whilst five children (18.5 %) progressed to a CF diagnosis at a mean age of 9.49 years (range 6.40–12.3 years). One of these children reclassified to CF, as the R785X variant was subsequently classified as CF-causing on July 22, 2013. The other four children converted to CF through developing clinical features: one child developed a raised sweat test, one child developed both a raised sweat test and mild bronchiectasis on CT thorax, and two children developed mild bronchiectasis confirmed on CT thorax (alongside intermediate sweat test results). The latter two children were classified as CF (as opposed to CFTR-RD) due to the development of clinical features of CF plus evidence of CFTR dysfunction.

At the endpoint sweat test, the overall chloride change since initial testing was significantly higher in children who progressed to CF than in those who did not (median change of 20.5 and 3.00 mmol/L respectively, $p < 0.001$). Across the study duration, when standardised for differences in test time intervals between children, sweat chloride increased more rapidly in children who progressed to CF than in those who did not (median slope of 1.77 and 0.854 respectively, $p = 0.138$). The endpoint modified CNS was significantly higher in children who progressed to CF than in those who did not (mean of 7.60 and 5.20 respectively, $p = 0.0438$). Across the study duration, modified CNS increased significantly more rapidly in children who progressed to CF than in those who did not (median slope of 0.363 and 0.0964 respectively, $p = 0.024$). Ten children underwent CT scans at a mean age of 10.6 years. Of these children, two had possible/probable mild bronchiectasis (all of whom remained as CRMS/CFSPID) and three had confirmed mild bronchiectasis (all of whom converted to CF). On endpoint spirometry, all Z-scores for FEV1 and FVC were above −2. On endpoint anthropometry, all Z-scores for weight were above −2 and all but one Z-scores for height were above −2. Extended anthropometry and spirometry data are displayed in Table S1. Only one child was pancreatic insufficient with a low pancreatic faecal elastase and steatorrhea; this child reclassified to CF. Four children isolated *P. aeruginosa* (risk of 14.8 %) and 12 isolated *S. aureus* (risk of 44.4 %). 14 children had at least one comorbidity, including all five children who progressed to CF. The most common comorbidity was atopy (occurring in five children, two of whom has asthma), followed by vitamin D insufficiency and anxiety (both occurring in two children). 16 of the 27 children (59.3 %) were under shared care with another trust.

It is worthwhile to ask if there are any apparent associations between newborn characteristics and progression to CF. Of the 10 children who had a normal initial sweat test result, and therefore classified as CRMS/CFSPID Group A, only one child converted to CF,

Table 1
Comparison of characteristics of children with initial diagnosis of CRMS/CFSPID at baseline, 6-year and endpoint assessment (the latter stratified by current diagnosis of CRMS/CFSPID or CF).

		Baseline	6-year	Endpoint		
				CRMS/CFSPID	CF	P-value
		(n = 30)	(n = 19)	(n = 22)	(n = 5)	
Initial visit data	**Newborn Characteristics**					
	Sex, female, n (%)	16 (53.3)	12 (63.2)	11 (50.0)	4 (80.0)	0.342
	Ethnicity, Caucasian, n (%)	26 (86.7)	18 (94.7)	19 (86.4)	4 (80.0)	1
	Ethnicity, other, n (%)	4 (13.3)	1 (5.3)	3 (13.6)	1 (20.0)	1
	NBS, IRT (mmol/L), mean ± SD	82.8 ± 29.9	79.6 ± 26.8	83.1 ± 33.0	86.0 ± 25.8	0.858
	NBS, positive result, n (%)	26 (86.7)	16 (84.2)	18 (81.8)	5 (100)	0.561
	CFTR variant 1 (CF-causing)					
	F508del, n (%)	25 (83.3)	16 (84.2)	18 (81.8)	4 (80.0)	1
	621+1G- > T, n (%)	2 (6.7)	1 (5.3)	2 (9.1)	0 (0)	1
	Other[a], n (%)	3 (10.0)	2 (10.5)	2 (9.1)	1 (20.0)	0.474
	CFTR variant 2 (VVCC or VUS)					
	R117H, 7T/9T, n (%)	20 (66.7)	15 (78.9)	16 (72.7)	3 (60.0)	0.616
	D1152H, n (%)	2 (6.7)	2 (10.5)	1 (4.5)	1 (20.0)	0.342
	F1099L, n (%)	2 (6.7)	0 (0)	2 (9.1)	0 (0)	1
	p.Arg810Ser, n (%)	2 (6.7)	0 (0)	0 (0)	0 (0)	NA
	Other[b], n (%)	4 (13.3)	2 (10.5)	3 (13.6)	1 (20.0)	1
	Initial sweat test					
	Age (weeks), median (IQR)	5.29 (33.7)	6.00 (43.9)	8.29 (46.9)	4.43 (2.71)	0.382
	Chloride (mmol/l), mean ± SD	34.3 ± 8.59	33.5 ± 8.26	32.0 ± 7.63	38.4 ± 7.92	0.105
	Normal result, n (%)	10 (33.3)	7 (36.8)	9 (40.9)	1 (20.0)	0.621
	Intermediate result, n (%)	20 (66.7)	12 (63.2)	13 (59.1)	4 (80.0)	0.621
Follow up visit data	Follow up duration (years), mean ± SD			7.44 ± 3.74	13.3 ± 2.32	0.00261
	Repeat sweat test					
	Age (years), median (IQR)		5.88 (0.415)	5.66 (7.31)	11.9 (1.85)	0.0212
	Chloride (mmol/L), mean ± SD		34.2 ± 9.50	34.3 ± 7.95	61.8 ± 19.2	<0.001
	Normal result, n (%)		1 (5.3)	6 (27.3)	0 (0)	0.539
	Intermediate result, n (%)		5 (26.3)	13 (59.1)	2 (40.0)	0.589
	Raised result, n (%)		0 (0)	0 (0)	2 (40.0)	0.0237
	Overall chloride change (mmol/L), median (IQR)		4.00 (2.75)	3.00 (13.5)	20.5 (9.25)	<0.001
	Missing, n (%)		13 (68.4)	3 (13.6)	1 (20.0)	
	Sweat test trend across study duration					
	Number of sweat tests, mean ± SD			2.58 ± 0.961	3.00 ± 0	NA
	Chloride slope, median (IQR)			0.854 (2.46)	1.77 (0.733)	0.138
	Missing, n (%)			3 (13.6)	1 (20.0)	
	CXR					
	Age (years), mean ± SD		6.01 ± 0.423	6.90 ± 3.69	11.9 ± 3.20	0.011
	Modified CNS (units), mean ± SD		7.06 ± 1.92	5.20 ± 2.24	7.60 ± 2.30	0.0438
	Missing, n (%)		2 (10.5)	2 (9.1)	0 (0)	
	CXR trend across study duration					
	Number of CXRs, mean ± SD			6.58 ± 3.53	10.4 ± 3.78	0.0452
	Modified CNS slope, median (IQR)			0.0964 (0.223)	0.363 (0.114)	0.024
	Missing, n (%)			3 (13.6)	0 (0)	
	Spirometry					
	Age (years), mean ± SD		6.23 ± 0.371	9.59 ± 2.94	13.2 ± 2.34	0.0247
	FEV1 z-score, mean ± SD		0.111 ± 0.858	0.323 ± 0.678	0.280 ± 0.482	0.899
	FVC z-score, mean ± SD		0.256 ± 0.976	0.492 ± 0.690	0.780 ± 1.09	0.509
	Missing, n (%)		10 (52.6)	9 (40.9)	0 (0)	
	Anthropometry					
	Age (years), mean ± SD		6.00 ± 0.286	7.27 ± 3.83	13.3 ± 2.32	0.00252
	Weight z-score, mean ± SD		−0.0846 ± 1.10	−0.0165 ± 1.05	0.129 ± 1.32	0.792
	Height z-score, mean ± SD		−0.0841 ± 1.05	−0.124 ± 0.758	0.234 ± 1.08	0.739
	Missing, n (%)		1 (5.3)	0 (0)	0 (0)	
	Clinical characteristics					
	Pancreatic sufficiency, n (%)			22 (100)	4 (80.0)	0.185
	P. aeruginosa infection, n (%)			3 (13.6)	1 (20.0)	1
	S. aureus infection, n (%)			10 (45.5)	2 (40.0)	1
	Comorbidities, n (%)			9 (40.9)	5 (100)	0.0407

Abbreviations: CRMS/CFSPID: Cystic fibrosis transmembrane conductance regulator related metabolic syndrome/cystic fibrosis screen-positive, inconclusive diagnosis; CF: Cystic fibrosis; NBS: Newborn screen; IRT: immunoreactive trypsinogen; CFTR: cystic fibrosis transmembrane conductance regulator; VVCC: variants of varying clinical consequence; VUS: variants of unknown significance; CXR: Chest X ray; CNS: Chrispin-Norman score; FEV1: Forced expiratory volume in the 1st second, FVC: Forced vital capacity; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus*.

[a] All other CF-causing variants occurred in one child each. These are G542X, G551D and P67L.

[b] All other VVCC or VUS variants occurred in one child each. These are F575Y, P750L, R1070W and R785X. Note that R785X was subsequently classified as CF-causing on July 22, 2013.

resulting in a Group A progression risk of 10.0 %. For the remaining 17 children who had an intermediate initial sweat test result, and therefore classified as CRMS/CFSPID Group B, four children progressed to CF, resulting in a Group B progression risk of 23.5 %. However, this difference in progression to CF between Group A and Group B was not statistically significant ($p = 0.621$). Across the longitudinal cohort, the initial sweat chloride level was higher in children who progressed to CF than those who did not, although this also did not reach statistical significance (mean of 38.4 and 32.0 mmol/L respectively, $p = 0.105$). On NBS, IRT was slightly higher in children who progressed to CF than those who did not, but not significantly so (mean of 86.0 and 83.1 mmol/L respectively, $p = 0.858$). All children who progressed to CF had a positive NBS result. F508del frequency was similar between children who progressed to CF and those who did not (80.0 % and 81.8 % respectively, $p = 1$). R117H 7T/9T frequency was lower in children who progressed to CF compared to those who did not, but this did not reach statistical significance (60.0 % and 72.7 % respectively, $p = 0.616$).

4. Discussion

The NBS screening programme has led to earlier diagnosis of CF, enabling earlier intervention and increasing survival [2]. An unintended consequence of the NBS programme is the identification of children who screen positive for CF but do not demonstrate clinical features consistent with a diagnosis of CF, termed CRMS/CFSPID [4]. In this retrospective study, we described the phenotypes and longer-term outcomes of a cohort of children with CRMS/CFSPID. To our knowledge, this is the first clinical study a UK-based CRMS/CFSPID cohort. We show that despite their variable follow up periods, most children in this cohort remained well with a low progression rate to CF.

We included four children who had a negative NBS result but had a first-degree relative with CF which prompted their referral for CF clinical and diagnostic assessment. They were found to have an inconclusive CF diagnosis, fulfilling all other aspects of the CRMS/CFSPID diagnostic criteria. For these children, there is currently a lack of evidence regarding their long-term clinical outcomes, as well as a lack of guidance regarding their diagnostic designation and management strategy. Following expert senior input, these children were diagnosed with and managed as CRMS/CFSPID, and therefore included in this study. It is noteworthy that all four of these children remained well and none of them progressed to CF during their follow up periods. We advise further evaluation of this group of children who have an inconclusive CF diagnosis in the context of a negative NBS, in order to clarify their diagnostic designation and management strategy. De-medicalisation of these children could reduce unnecessary anxiety and worry for patients and their families.

At baseline assessment, a wide range of CFTR variants were identified, with all children having one CF-causing variant and one VVCC or VUS, of which F508del and R117H 7T/9T were the most common respectively. One third of children had a normal initial sweat test result and were therefore classified as CRMS/CFSPID Group A, whilst the remaining two thirds of children had an intermediate result and were therefore classified as Group B. Current guidance recommends extensive evaluation at 6 years of age [4,13]. By this timepoint, only one child in our cohort had progressed to CF via reclassification of a CFTR variant, and no child had converted to CF via developing clinical features. Anthropometry and spirometry results were reassuring, portraying a well cohort at this timepoint. A substantial number of spirometry reports were excluded from our analysis due to poor or suboptimal technique. This highlights the potential limitations of performing and interpreting spirometry at 6-years of age in a clinical setting, as young children may not be able to provide reliable results. This is especially true of this cohort where they will be seen less frequently and therefore have had less coaching than the CF cohort. Overall, the low levels of progression to CF by this timepoint, as well as the tendency for unreliable spirometry results, suggests that the extensive evaluation at 6 years of age may have limited usefulness. This highlights the importance of undertaking a full clinical assessment in adolescence, as suggested by current guidance [4,13]. This will be essential to inform the configuration of adult services to cater for this unique cohort.

Longitudinal assessment, which encompassed a mean duration of 8.53 years, revealed a progression rate from CRMS/CFSPID to CF of 18.5 %. This is relatively low and is in keeping with prospective studies, which reveal progression rates between 11 % and 44 % [6–8]. The mean age of progression to CF was 9.49 years, which is later than previous studies suggest [6,24–27]. This may partly be due to the later age at which detailed investigations such as CT scans were undertaken in this cohort. Nevertheless, this finding further highlights the importance of undertaking a full clinical assessment in adolescence. All children were pancreatic sufficient except for one child who was reclassified to CF. Given that previous studies have shown that all children with CRMS/CFSPID are pancreatic sufficient, the fact that this child was reclassified to CF is somewhat unsurprising [6,26,28]. The infection rate for *P. aeruginosa,* an important CF pathogen associated with morbidity and mortality, was relatively low at 14.8 % [29]. There was no evidence of impaired lung function. These reassuring results are in keeping with prospective studies [6–8]. They portray a generally well cohort, supporting current guidance which recommends a less intensive medical surveillance approach for CRMS/CFSPID children compared to CF [4,13].

Across the study duration, sweat chloride increased more rapidly in children who progressed to CF than those who did not. This is in keeping with previous studies and highlights the usefulness of repeat sweat testing, which could help evaluate CF progression risk [27,30]. In addition, across the study duration, modified CNS increased significantly more rapidly in children who progressed to CF than those who did not. This shows that modified CNS is a useful tool in monitoring for radiographical evidence of respiratory disease progression and could help evaluate CF progression risk. To our knowledge, modified CNS progression in CRMS/CFSPID has not been previously studied.

Although only a small number of children in our cohort progressed to CF, which limits the statistical significance of our results, our results suggest that some newborn characteristics may have prognostic value regarding progression to CF. Our results suggest that a

higher initial sweat chloride, reflected in both the sweat chloride value and a Group B CRMS/CFSPID designation, may be predictive of CF progression risk. These findings support previous studies which suggest using initial sweat chloride result as a biomarker, allowing for early identification of subjects at risk of progression to CF [8,31,32]. Some studies also suggest that IRT may have prognostic value [31,33]. Although our results did show a higher IRT in children who progressed to CF versus those who did not, this difference was only slight. Our results also suggest that R117H 7T/9T may be less pathogenic than other VVCC or VUS variants. This supports previous studies which propose the withdrawal of R117H 7T/9T from NBS CFTR mutation panels due to its low penetrance [34,35]. This is especially important when considering which variants to use in NBS protocols which involve next generation sequencing. Further research studies to evaluate the predictive values of these newborn characteristics in larger cohort sizes would be of benefit, as they may help guide medical surveillance intensity and mitigate prognostic uncertainty for affected children and their families.

Strengths of our study include the prolonged follow up duration, with multiple children being reviewed well into their adolescence. Our study also has the advantage of complete case ascertainment as it is from a single paediatric network; this is significant given the variability in NBS programmes between different networks [11]. Whilst this variability in NBS programmes limits the generalisability of our findings, our results remain valuable and relevant, particularly within the UK. Limitations of our study include the retrospective design, variance in management strategies and frequency of follow up appointments, missing investigation results and small sample size. No child in our cohort underwent functional CFTR testing such as nasal potential difference or intestinal current measurements, which is recommended by the consensus guidelines from the CF Foundation [4]. However, given the limited availability and invasive nature of these tests, our cohort is reflective of the reality for numerous CRMS/CFSPID patients who do not have these results available.

In conclusion, despite their variable follow up periods, most CRMS/CFSPID children in this study remained well with a low progression rate to CF. This supports a less intensive medical surveillance approach for CRMS/CFSPID children compared to CF. Our results highlight the importance of assessment in a dedicated CRMS/CFSPID clinic during adolescence to detect progression to CF after 6 years of age. This will be essential to inform the configuration of adult services to cater for this unique cohort. As this cohort progresses into adulthood, ongoing monitoring and evaluation will be valuable to assess longer-term outcomes and to appraise transition into adult services.

CRediT authorship contribution statement

Alison Mansfield: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Christopher Hine:** Writing – review & editing, Resources, Project administration. **Prasad Nagakumar:** Writing – review & editing, Resources. **Benjamin Davies:** Writing – review & editing, Resources. **Maya Desai:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Conceptualization.

Ethics declarations

This study was registered with the Institution's Research & Development office (local reference: 23/BWC/LA/Hine) and in accordance with the UK National Research Ethics Service guidance, neither individual informed consent nor formal research ethics committee review was required as the study was undertaken by the direct clinical care team using information previously collected in the course of routine care. Clinical records were not de-identified prior to data collection. Data was subsequently de-identified prior to analysis.

Data availability statement

Data associated with this study has not been made publicly available as it contains confidential information. Additional patient-specific data would not be available if requested from the corresponding author due to the small numbers of patients in this data set.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39935.

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