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Original Article

Pain in adults with cystic fibrosis – Are we painfully unaware?

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ABSTRACT

Background: A previous Australia-wide pilot study identified pain as a significant burden in people with CF (pwCF). However, the prevalence, frequency and severity have not been evaluated using validated tools.

Methods: Australian adults, pwCF and healthy controls (HC) were invited to complete an online questionnaire from July 2023 – February 2024, consisting of four validated tools: Brief Pain Inventory, Pain Catastrophising Scale, PAGI-SYM and PAC-SYM. The questionnaire, disseminated via Cystic Fibrosis Australia, CF Together and online social media groups, explored experiences surrounding pain and its management using closed and free text entries.

Results: There were 206 respondents, consisting of 117 CF patients and 89 HC. Over 70 % ($n = 69$) of pwCF reported pain compared to 28 % ($n = 21$) of HC ($p = <0.001$). Further, significantly higher pain frequency per month was reported for pwCF than HC (40 % vs. 10 %; $p < 0.001$). Symptom clustering was also observed where at least three other locations of pain were reported, and pain was reported to trigger other physiological and psychological symptoms. Notably, there was no significant difference in the locations, occurrence, frequency or severity of pain between those on a CFTR modulator or not ($p = 0.625$). PwCF also reported significantly lower relief from over-the-counter therapies ($p = 0.002$) and expressed themes of unmet symptom and management needs.

Conclusions: This study identified a high prevalence of pain affecting multiple body parts in pwCF compared to HC and suggests that pain is sub-optimally managed, impairing their quality of life. Increased awareness and early recognition within the CF clinics and the development of clinical pathways are critically needed to better manage and monitor pain in pwCF, leading to improved quality of life and health outcomes.

1. Introduction

Cystic fibrosis (CF) has a complex disease phenotype with a broad spectrum of physical and psychological manifestations [1]. The most prominent clinical manifestations include chronic pulmonary infections leading to bronchiectasis, exocrine pancreatic insufficiency, gastrointestinal obstruction, male infertility and chronic hepatobiliary disease, with substantial phenotypic variation [2]. In addition, people with CF (pwCF) have historically been reported to experience pain [3]. Regardless of the source or location of the pain, it is related to an increased risk of mortality independent of disease severity [4]. In addition to affecting mortality rates, it significantly impacts quality of life [5]. Yet, in the last ten years, there has been a paucity of evidence in the literature surrounding pain, a lack of clinical guidelines surrounding pain management strategies and no standardised measurement specific to CF [6].

In a recent study, among other symptoms, pain was reported as a significant contributor to the burden of the disease [7]. Despite pharmacological advances (including CFTR modulators), early diagnosis and multidisciplinary care, there is still a distinct lack of current evidence in the literature pertaining to the diverse types of pain, associated clinical symptoms, frequency and severity of pain [8]. In addition, research has

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been conducted sparingly in single centres, whereby no case-control studies have been conducted in adults or children in the last 36 years. There have been no case control studies utilising validated tools to compare the significance of pain of pwCF to that of the general population. In particular, there is also a lack of knowledge surrounding the effectiveness of pain medication or interventions and the effects of modulator therapies on the burden of pain. Research into the experiences of pain in pwCF has been conducted but is limited by small sample sizes, and a call for larger qualitative studies describing pain management competencies in healthcare providers was called for [6].

The disease burden, clinical profile and symptom patterns in CF have dramatically shifted in the last decade to reflect a comparatively healthier older population of pwCF [9]. As this profile shifts, knowledge and a deeper understanding of these changing patterns are critical not only to the development of appropriate therapeutics but also to increasing the individual's quality of life and driving patient-orientated outcomes.

Therefore, this study aims to address the significance of pain in CF compared to the general population, identify the prevalence, severity and frequency of pain, and evaluate the effects of modulator therapies on pain in CF. Further, it adds to the body of evidence surrounding unmet pain management needs and the effectiveness of pain medications in pwCF. The study's secondary aim was to identify discrete patterns of patient-reported pain in pwCF to develop patterns or hierarchical clustering to inform clinical practice.

This study was designed to collect and collate data to address the aforementioned gaps in the literature, respond to the research priorities outlined by pwCF and inform future clinical pathways or resources for pain management in CF.

2. Methods

2.1. Survey development and design

The survey was designed and developed by the research team (AW, RM, GD, CO, NR), a statistician, a Pain Medicine Specialist (GD) who specialises in complex pain and an individual living with CF. The target population included adults living with CF and a control group of gender and age-matched adults who had not been previously diagnosed with CF. The study was approved by the Southern Cross University Human Research Committee (Ethics Approval Number: 2023/026). The online survey started with a detailed participant information sheet (PIS) for both cohorts (Appendix A) and used an implied consent model.

2.2. Pain-related outcomes

Four validated scales were utilised in this study: 1- the Brief Pain Inventory short-form (BPI) [10], 2 - the Pain Catastrophising Scale (PCS) [11], 3 - the Patient Assessment of Gastrointestinal Disorder Symptom Severity Index (PAGI-SYM) [12], and 4 - the Patient Assessment of Constipation-Symptoms (PAC-SYM) [13]. The PAGI-SYM and PAC-SYM were chosen because gastrointestinal pain has been widely documented in pwCF, and we wanted to explore this within our cohort also. However, we wanted to ensure that we are not just assessing for GI pain by including other validated tools such as the BPI, where previous research has demonstrated its reliability and validity in pwCF [[3,5,14]]. Supplementary file one details the reasoning behind using the tools employed and reliability in previous CF research.

Questions relating to current medications and pain management were included (Appendix B). When asked to comment on overall and mental health, the response scales consisted of a five-point Likert scale, which ranged from 1 ("Very poor") to 5 ("Excellent"). Locations of pain were systematically clustered and visually represented using pain body maps. Open-ended qualitative questions were also asked to pwCF about their experiences accessing treatment and communication in the healthcare setting.

Table 1
Demographic analysis of individuals living with cystic fibrosis (CF) and healthy controls ($n = 206$).

Respondent Characteristics		People Living with CF		Healthy Controls		
		Count	Mean ± SD	Count	Mean ± SD	*p*-Value
Gender	Female	85 (73 %)		65 (74 %)		
	Male	29 (24 %)		23 (25 %)		
	Not disclosed	3 (2 %)		1 (1 %)		
Age			41 ± 14		42 ± 15	0.957
Height (cm)			163.1 ± 13.8		168.2 ± 10.4	0.519
Weight (kg)			69.4 ± 23.9		74.7 ± 14.7	**0.006***
BMI (kg/m^2)			25 ± 7		26 ± 4	**0.005***
CF Genotype##						
ΔF508/ ΔF508		56 (56 %)				
ΔF508/other		36 (36 %)				
Other/other		15 (15 %)				
Suffers from anxiety or depression		67 (57 %)		33 (37 %)		**0.003***
Mean patient-reported overall health**			3.68 ± 0.99		4.15 ± 0.63	**<0.001***
Mean patient-reported mental health**			3.17 ± 1		3.49 ± 0.97	**0.022***
On CFTR modulator therapy		78 (67 %)				
Self-reported FEV%			72 % predicted (SD 24, range 29–135)			

* $p < 0.05$.
** Likert scale of one to five.
\## Eight missing data points.

2.3. Recruitment

Recruitment of pwCF was conducted in conjunction with community-facing peak bodies (Cystic Fibrosis Australia, CF Together) through social media platforms. The survey link was provided using an online survey platform (https://www.qualtrics.com), from the 15th of July 2023 to 12th of February 2024. The control cohort was recruited via social media platforms, including Facebook, LinkedIn and Instagram.

The inclusion criteria included >18 years old, living in Australia, a formal diagnosis of CF, and being cognitively competent for the CF cohort, and identical for the healthy control (HC) cohort with the exclusion of being diagnosed with CF. The exclusion criteria for both cohorts included having a chronic disease or another chronic disease in the case of CF.

G Power software was used for sample size calculations (significance level (alpha)0.05, power 0.80, effect size $f = 0.3$). A sample size estimation of 140 respondents (70 pwCF and 70 controls) was required to be statistically significant.

2.4. Statistical analysis

The response data from both cohorts were downloaded via the Qualtrics platform and collated together into tables in MS Excel formats. Separate tables for individual cohort analyses were also created. The data were then cleaned to remove any missing values and exported into IBM SPSS statistics. Standard statistical methods were utilised (refer to Supplementary file one). The methodology utilised by Dubin et al. [8]

Table 2
Comparison of self-reported locations of pain experienced in people with cystic fibrosis (CF) ($n = 117$) and healthy controls ($n = 89$).

Location	pwCF ($n = 117$) n (%)	HC ($n = 89$) n (%)	Total ($n = 206$) n (%)	Pearson Chi-square	p Value
Back pain	65 (56)	34 (38)	99 (48)	6.098	**0.014***
Headaches	65 (56)	32 (36)	97 (47)	7.794	**0.005***
Joint pain	65 (56)	29 (33)	94 (46)	10.751	**<0.001***
Gastrointestinal	52 (44)	6 (7)	58 (28)	35.522	**<0.001***
Chest pain	45 (38)	2 (2)	47 (23)	37.645	**<0.001***
Sinus pain	42 (36)	5 (6)	47 (23)	26.317	**<0.001***
Cervical pain	20 (17)	4 (5)	24 (12)	7.796	**0.005***

* $p < 0.05$.

for thematic analysis was employed for the free-text responses. The authors used an inductive approach to allow patterns to emerge from the data and iteratively analysed the data, refining codes and themes. Multiple layers of coding were constructed, refining the codes and themes. The data were stored in compliance with Southern Cross University's institutional requirements and compliance with the National Statement of Ethical Conduct in Human Research.

3. Results

3.1. Response rate of the study sample and respondent characteristics

Upon activation of the survey, 266 people (164 pwCF and 102 in the control group) accessed the survey. Forty-seven (29 %) did not progress past the PIS. The remaining 71 % ($n = 117$) of pwCF fully completed the survey. A total of 89 (87 %) of the control respondents completed the survey, with 13 % ($n = 13$) stopping at the PIS. The median time of 9.23 min was taken to complete the survey by pwCF compared to the median time of 6.13 min for the control cohort. Table 1 summarises the demographics and anthropometrics for both cohorts.

3.2. Respondent's health characteristics

Furthermore, 35 % ($n = 40$) of pwCF had been hospitalised multiple times in the last year (e.g., 63 % ($n = 25$) were pulmonary exacerbations, and other issues included neurological manifestations, miscarriage and severe pain) with a mean stay of 13.05 (± 12.31) days in hospital. Comparatively, 11 % ($n = 10$) of the control group reported only one hospitalisation ($p = 0.038$) where hospital admission was reported for day procedures (e.g., double mastectomy, tonsillitis infection and removal and knee arthroscopy) and acute events (e.g., an ectopic rupture and concussion).

3.3. Pain locations and characteristics

When reporting the overall presence of pain using the BPI, there were 174 (99 pwCF and 75 HC) total responses. Eighteen and 14 data points were missing from the pwCF and HC cohorts, respectively. Over 70 % ($n = 69$) of pwCF described suffering from pain compared to 28 % ($n = 21$) of HC ($p = <0.001$). Table 2, Fig. 2 and Fig. 3 depict the locations of pain described by both cohorts.

When analysing the pwCF data, specifically between genders, cervical or neck pain was significantly higher in the female cohort ($p = 0.005$). There were no significant differences between genders in the pwCF cohort relating to severity, frequency, catastrophising, or gastrointestinal symptoms relating to pain. In the pwCF cohort, there was a significant relationship observed between overall health and mental health ($p = <0.001$), pain severity and feelings of overall health ($p = 0.030$) and pain severity and pain interference ($p = <0.001$).

The frequency of exacerbations is described in Fig. 1, whereby significant differences were reported when describing the prevalence of pain in pwCF compared to HCs ($p = <0.001$). Further, 43 % ($n = 46$) of pwCF reported that pain triggered other symptoms, such as increased anxiety and fatigue, a decrease in sleep, and heightened stress levels. Table 4 describes the individual chi-square tests conducted to analyse the significance of the severity, interference, catastrophising, and effects on constipation and gastrointestinal symptoms. It also details the individual pain interference scores.

In the analysis of individual pain locations, headaches were associated with sinus, cervical, back, and chest pain (56 % ($n = 65$) of pwCF vs

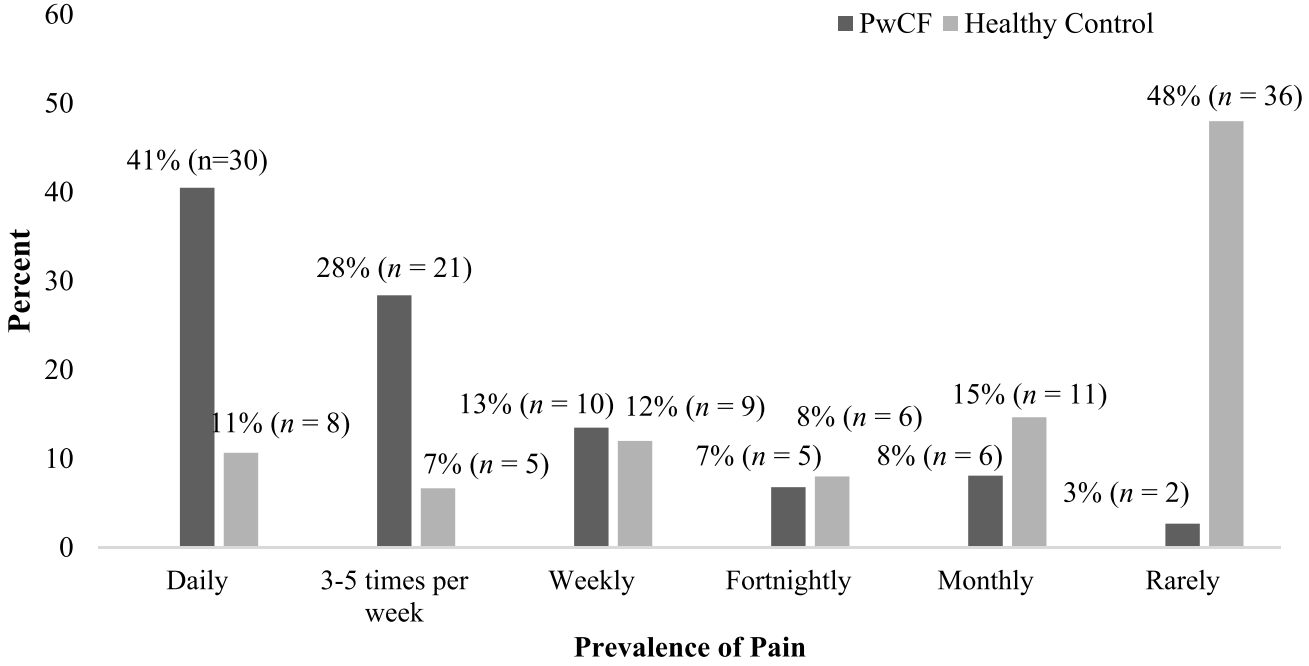

Fig. 1. Comparison of the self-reported prevalence of pain in people with cystic fibrosis (CF) ($n = 74$) and healthy controls ($n = 75$).

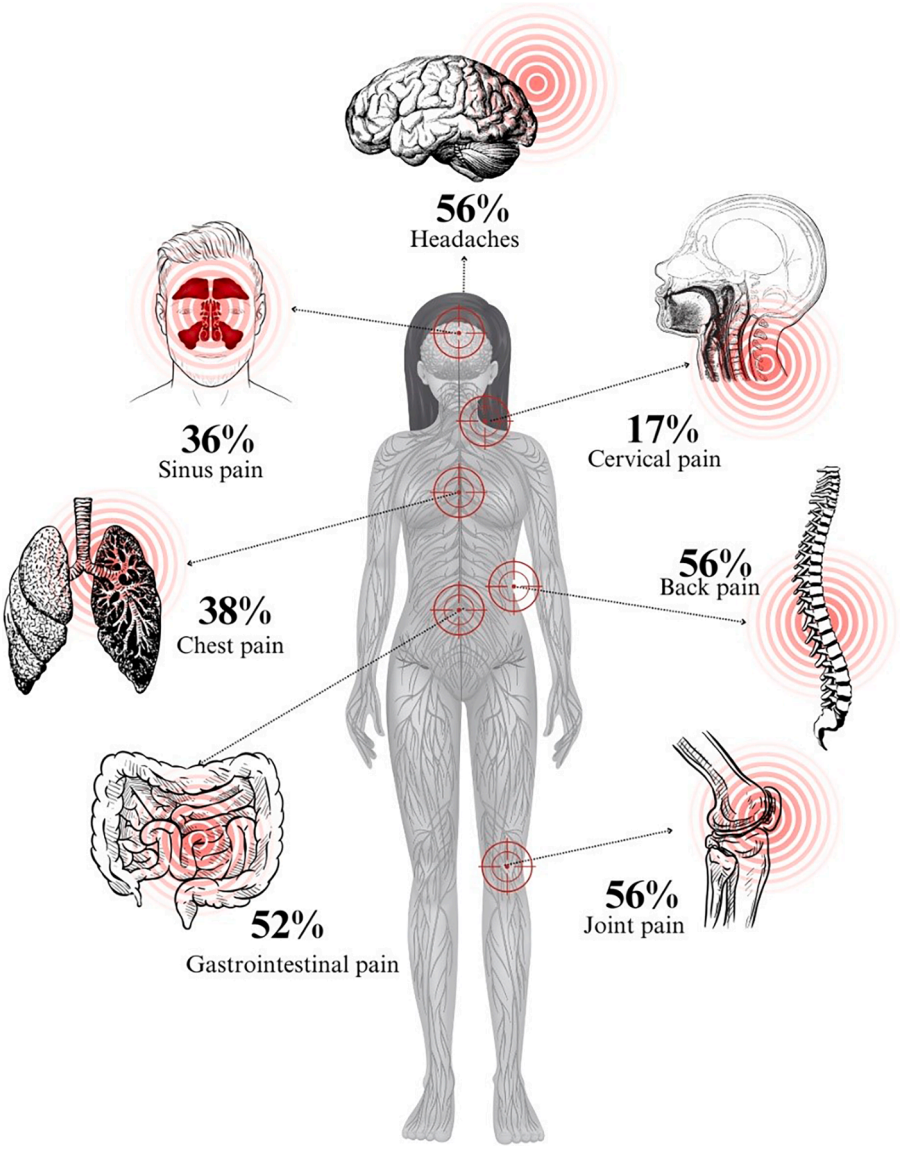

Fig. 2. Self-reported locations of pain experienced in people with cystic fibrosis (CF) ($n = 117$).

36 % ($n = 32$) of HC, $p = 0.005$), sinus pain (36 % ($n = 42$) of pwCF vs 5 % ($n = 5$) of HC, $p < 0.001$) was associated with headaches and gastrointestinal, back, joint and chest pain, joint pain (56 % ($n = 65$) of pwCF vs 32 % ($n = 29$) of HC, $p < 0.001$) was associated with sinus, cervical, back and chest pain, cervical pain (19 % ($n = 20$) of pwCF vs 5 % ($n = 4$) of HC, $p = 0.005$) was associated with headaches and sinus, back and joint pain, gastrointestinal pain (44 % ($n = 52$) of pwCF vs 7 % ($n = 6$) of HC, $p < 0.001$) was associated with headaches and sinus and chest pain, back pain (56 % ($n = 65$) of pwCF vs 38 % ($n = 34$) of HC, $p = 0.014$) was associated with headaches and sinus, cervical, joint and chest pain and chest pain (38 % ($n = 45$) of pwCF vs 2 % ($n = 2$) of HC, $p < 0.001$) was associated with sinus, back, joint and gastrointestinal pain. Fig. 3 details the severity levels of specific pain locations of pwCF. Data from all pwCF ($n = 117$) was used in a clustering approach to develop a pictorial representing the severity and associated pain, as described in Supplementary File 1.

3.4. Pain characteristics and age

A Pearson correlation coefficient was computed to assess the various relationships in the pwCF cohort between age and the pain characteristics investigated. There were significant medium positive relationships between age and BMI ($r = 0.31$, $p = < 0.001$), BPI ($r = 0.24$, $p = 0.023$) and Total Pain Interference scores ($r = 0.22$, $p = 0.023$). No correlations were observed between age and the patient's perceived effectiveness of medications.

3.5. Pharmacologic and non-pharmacologic pain management

Medications consumed specifically for pain and the effectiveness reported in both cohorts are described in Table 3.

3.6. Concomitant CFTR modulators

Over 67 % ($n = 78$) of pwCF reported that they were taking CFTR modulators. Of those who reported taking CFTR modulators, 93 % were taking elexacaftor/tezacaftor/ivacaftor. There was no significant difference in the locations, occurrence, frequency or severity of pain between those on a CFTR modulator and not ($p = 0.625$).

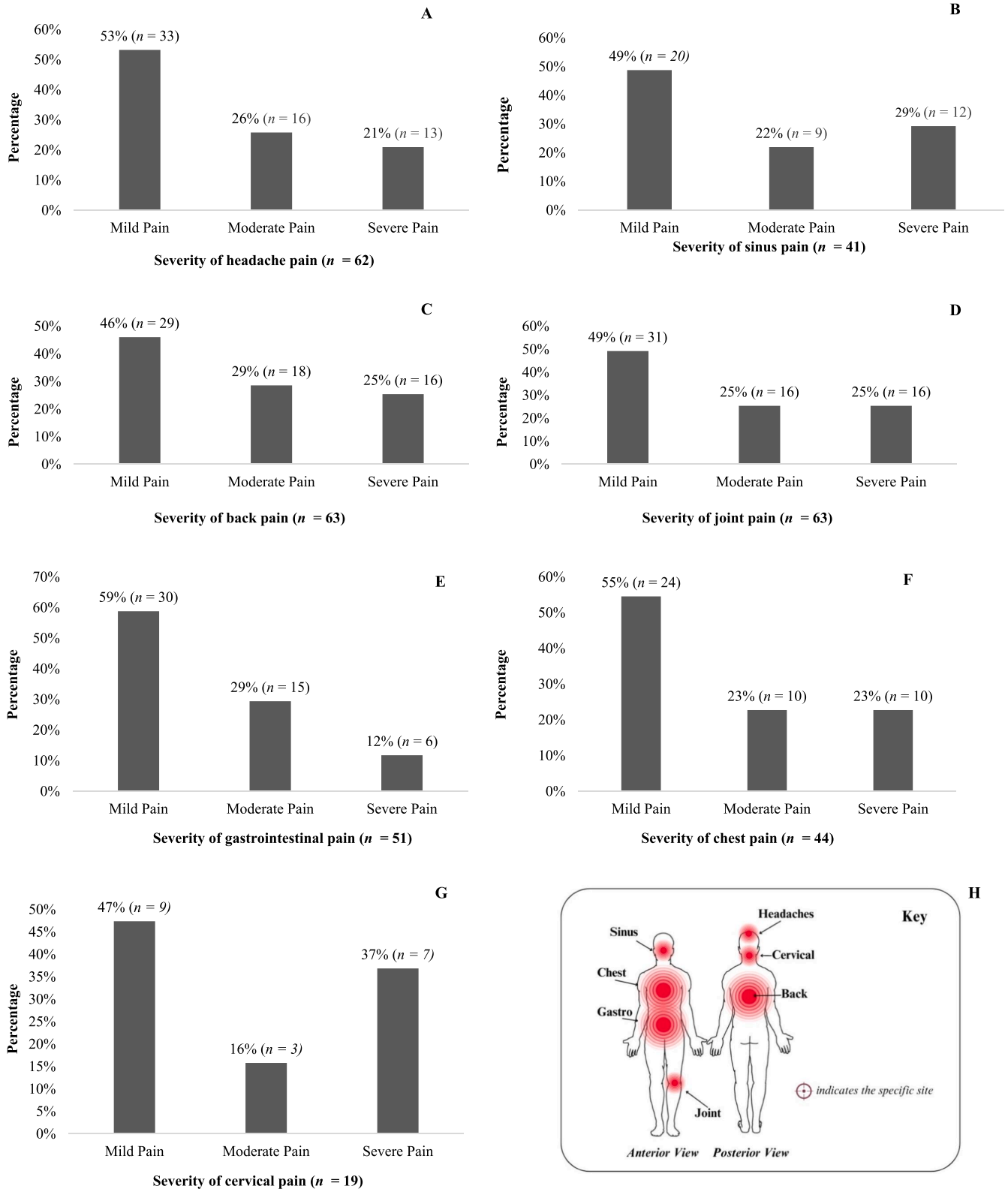

Fig. 3. Self-reported pain severity in pwCF. A describes the severity levels reported by pwCF experiencing headache pain. B describes the severity levels reported by pwCF experiencing sinus pain. C describes the severity levels reported by pwCF experiencing back pain. D describes the severity levels reported by pwCF experiencing joint pain. E describes the severity levels reported by pwCF experiencing gastrointestinal pain. F describes the severity levels reported by pwCF experiencing chest pain. G describes the severity levels reported by pwCF experiencing cervical pain, and H is the key to the pain locations.

Table 3
Comparison of pain management relief (reported on a scale of 0 – 10, 0 being no relief at all to 10 being complete relief from pain) in people with cystic fibrosis (CF) (n = 117) and healthy controls (n = 89).

Pain management strategy	pwCF using pain management strategy Count	Relief rating for People Living with CF Mean ± SD	Controls using pain management strategy Count	Relief rating for Healthy Controls Mean ± SD	p-Value of relief rating
OTC	96 (82 %)	6.83 ± 2.62	53 (60 %)	8.67 ± 2.01	**0.002***
Caffeine	12 (10 %)	5.36 ± 3.67	8 (9 %)	5.88 ± 2.59	**0.012***
Medicinal cannabis	12 (10 %)	9.10 ± 1.45	2 (2 %)	8.00 ± 4.24	**0.012***
Prescribed analgesics	40 (34 %)	8.25 ± 1.81	7 (8 %)	8.00 ± 3.63	0.157
Exercise	49 (42 %)	6.40 ± 2.21	29 (33 %)	7.44 ± 2.58	0.690
Nerve blocks	6 (5 %)	7.60 ± 1.95	–	–	
TENS machine	6 (5 %)	5.67 ± 2.07	5 (6 %)	8.40 ± 3.13	0.603
Stress management	16 (14 %)	5.33 ± 2.02	1 (1 %)	8.00	
Meditation	20 (17 %)	5.47 ± 2.00	5 (6 %)	6.50 ± 3.79	0.136

Abbreviations: OTC (Over the counter medications)*;* TENS machine (Transcutaneous electrical nerve stimulation).
* $p < 0.05$.

3.7. Concerns surrounding pain management

Only 34 % (n = 34) of pwCF reported having a formal pain diagnosis compared to 18 % (n = 14) of HC (p = 0.009). When asked to describe their satisfaction with their pain management plan, pwCF were significantly less satisfied than HC (p = 0.002). Following on, when asked to describe how comfortable respondents are discussing pain with their healthcare practitioner, pwCF were significantly less comfortable (p = <0.001).

The open-ended questions answered by the pwCF cohort surrounding any challenges to addressing pain are summarised in Table 5. Four major themes were identified, including "pain is under-recognised", "fear of stigmatisation", "concerns surrounding ageing" and "desire for holistic pain management". The modal theme described feelings of being dismissed (n = 24), followed by pain being undermanaged (n = 17). Over 15 % of respondents expressed a desire for a holistic team to manage their pain.

4. Discussion

This is the first-ever case-control study to be conducted on pain in CF using validated tools (Brief pain inventory, Pain Catastrophising Scale, PAGI-SYM and PAC-SYM). Multiple pain locations were investigated, including the impacts and effectiveness of medication, specifically CFTR modulators, on pain profiles in CF. This research highlights that the majority (69 %) of pwCF are suffering from almost daily pain as compared with approximately 20 % of the adult population of Australia [15]. Further, this study highlights the bidirectional relationship between daily function in pwCF, pain and mental health. Notably, pain was often associated with at least four other locations and exacerbated or triggered other clinical associations such as anxiety, depression, nausea, and fatigue. Of notable concern, pain is reportedly under-recognised, poorly managed by treating health care practitioners and is ineffective or poorly responsive to pain therapies. This study accentuates the current lack of emphasis and priority on recognising pain or developing proper pain management strategies in CF.

The pwCF who responded to the open-ended questions were extremely forthcoming in their experiences surrounding seeking and managing pain management strategies, with a few respondents expressing gratitude and acknowledging that this is a hugely under-researched yet critical area of investigation. The respondents provided rich, detailed insights into their experiences surrounding their desire for a holistic approach, feelings of being judged or labelled, ageing concerns and feelings that their pain is under-recognised and under-managed. Quantitative studies cannot capture these self-reported details of their experiences alone. Previous research has identified that pwCF in America are also concerned with symptom management needs and fear reprisal over seeking adequate pain relief [8]. This is congruent with the current findings in this study, whereby similar themes were expressed when exploring how pain is addressed in the clinic and barriers to discussing pain with their CF team or healthcare practitioners. Whilst new standards of care have been developed for accessing pain management [16], there is no standard assessment tool for this population that specifically measures CF-related pain and its co-morbidities. The lack of assessment tools, pwCF's fear of reprisal or stigmatisation when seeking pain management therapies and undermanagement of pain when it is reported warrants immediate attention from health care providers. Policies, procedures, and protocols for assessing overall health at initial screening or routine check-ups need reviewing and amending to highlight pain as a significant burden of the disease.

Previous research has demonstrated that pain is an important aspect of CF and is associated with worse clinical outcomes [17]. However, this is the first case-control to confirm the significance of pain in adults with CF versus HC and classify them alongside pain interference and catastrophising. Similar to the findings of Sawicki et al. [18], our study highlighted that over 69 % of pwCF were experiencing pain at a much greater frequency than HC, where most pwCF were experiencing it almost daily. The HC data surrounding the prevalence and incidence of pain was comparable to recent epidemiological research in chronic pain [19] and, therefore, was reliable as a comparison dataset. However, this research has also highlighted the clinical risk factors, including multi-morbidity and the presence of another site of pain, in developing chronic pain [19,20], depicted in this study.

Comparable to research conducted by Flume et al. [14], our findings demonstrated the significance of pain severity on interference with daily functioning and the effects of pain severity and level of pain catastrophising. Particularly affecting sleep and subsequent effects on mood, the association is known to be multi-directional, whereby pain causes poor sleep and increases the intensity and duration of pain [21]. This was also observed in this study, where the greater the severity of pain, the greater the inference with sleep and associations with self-reported mood disorders such as anxiety and depression. Previous general pain studies outline the links between depression and negative beliefs surrounding pain, which lead to a poorer prognosis of recovery [22]. The bidirectional relationship between daily functioning, pain and mental health issues highlights the importance of recognising pain and screening for all three domains should be considered in one assessment tool.

The most commonly reported pain locations include headaches, joint and back aches, and gastrointestinal pain. These findings differed from the findings of Blackwell et al. [23], who reported that gastrointestinal pain was the most commonly reported location; however, they were comparable to the findings of Festini et al. [24], who also reported that headaches were the most commonly reported followed by gastric and back pain. Many studies have highlighted that joint and back pain are frequent and reported as severe [24]. Further, frontal pain or headaches often accompany nasal polyps or chronic sinusitis, known co-morbidities of CF, and therefore may explain the high incidence.

Table 4
Pain-related measures in people with cystic fibrosis (CF) ($n = 117$) and healthy controls ($n = 89$).

		PwCF			Healthy Controls			*p*-Value
Pain-related outcomes		*n (%)*	Mean	Median	*n (%)*	Mean	Median	
Brief Pain Inventory								
Pain severity score		96 (82.05)	4.09		70 (78.65)	2.89		**<0.001***
	Mild Pain	57 (48.72)			53 (59.55)			
	Moderate Pain	22 (18.80)			14 (15.73)			
	Severe Pain	17 (14.53)			3 (3.37)			
Pain interference		117 (100)	4.30	3.86	89 (100)	2.33	1.43	**<0.001***
	General activity	97 (82.91)	4.47	4.00	70 (78.65)	2.67	1.00	**0.002***
	Mood	96 (82.05)	4.92	4.50	70 (78.65)	2.84	1.00	**<0.001***
	Walking ability	96 (82.05)	3.77	3.00	70 (78.65)	2.23	1.00	**<0.001***
	Normal work	97 (82.91)	4.18	3.00	70 (78.65)	2.24	1.00	**<0.001***
	Relationships	95 (81.19)	3.51	2.00	70 (78.65)	1.60	1.00	**<0.001***
	Sleep	97 (82.91)	4.46	4.00	70 (78.65)	2.57	1.00	**<0.001***
	Enjoyment of life	97 (82.91)	4.53	4.00	70 (78.65)	2.13	1.00	**<0.001***
Pain Catastrophising Scale		94 (80.34)			70 (78.65)			**<0.001***
	Low (0–9)	0 (0)			1 (1.12)			
	Moderate (10–19)	39 (33.33)			49 (55.06)			
	High (20–39)	41 (35.04)			15 (16.85)			
	Very High (40–52)	14 (11.97)			0 (0)			
Rumination		94 (80.34)	7.68		70 (78.65)	5.97		**0.004***
Magnification		94 (80.34)	5.59		70 (78.65)	4.44		**0.009***
Helplessness		94 (80.34)	11.13		70 (78.65)	4.20		**<0.001***
Patient Assessment of Constipation Symptoms		50 (42.74)	25.96		6 (6.74)	23.5		0.65
Rectal symptoms		50 (42.74)	4.94		6 (6.74)	4.17		0.42
Abdominal symptoms		50 (42.74)	10.20		6 (6.74)	10.83		0.71
Stool symptoms		50 (42.74)	10.82		6 (6.74)	8.50		0.29
Patient Assessment of Gastrointestinal Disorder Symptom Severity Index		50 (42.74)	53.29		6 (6.74)	46.83		0.50
Heartburn/regurgitation		50 (42.74)	15.44		6 (6.74)	10.50		0.20
Nausea/vomiting			6.56			7.00		**0.04***
Lower abdominal pain			6.44			5.67		0.48
Upper abdominal pain			5.58			4.50		0.42
Post-prandial fullness/early satiety			12.40			11.50		0.67
Bloating			7.50			7.67		0.90

* $p < 0.05$.

This study reports clustering using pain body maps in pwCF. Future research is needed to explore clustering fully using machine learning algorithms or hierarchical clustering. Hierarchical clustering is a powerful machine-learning technique that can identify distinct subgroups of patients based on pain characteristics, location and quality of life [25]. Further, using clustering methods at first patient visits predicted outcomes at three-month follow-up, which allowed for the identification of patients at risk of poor outcomes. Recent work surrounding pain biomarkers suggests that combining pain clustering with genetics, neuroimaging, and sensory profiling may contribute to personalised/precision pain management and diagnosis [26].

In the era of CFTR modulators, this study reflects the contemporary adult with CF taking CFTR modulators, with a higher median age reflecting the ever-improving survival rates versus the historical representation of CF. This study highlights the increasing burden of CF, in particular pain, its severity and the interference in their daily lives in the ageing pwCF. When describing the use of CFTR modulators and rating pain severity, frequency or effectiveness of pain medication, no significant differences were observed. There has been no previous research to the authors' knowledge on the patient perceived effectiveness of medication on pain severity and frequency. Further, only a few studies report the effects of modulators on pain limited to the gastrointestinal system

Table 5
Qualitative themes of the pain experiences in people with cystic fibrosis (CF)(n = 86).

Theme	Summary Code	Quote
Pain is under-recognised	Pain is dismissed	"My CF team are not really helpful in any sort of pain management. They will refer me to myriad doctors but not pain management" *(52 years old, FEV1 % >70 on a modulator therapy, moderate severity and high pain interference)*
		"The team are very busy, and I have assumed it's not something they care about or are supposed to treat" *(66 years old, FEV1 % >70 on a modulator therapy, moderate severity and high pain interference)*
		"Medical practitioner-based gaslighting - All the organ care comes first, and pain is not reviewed or, if mentioned, no reviews or further investigation/ support offered" *(41 years old, not on a modulator therapy, severe pain and high pain interference)*
		"Tried in the past, dismissed or not taken seriously" *(41 years old, on a modulator therapy, moderate severity and moderate pain interference)*
		"They seem to target lungs, indigestion and endocrinology problems, nothing else" *(58 years old, FEV1 % <70 on a modulator therapy, severe pain and high pain interference)*
		"The dismissiveness of the team at the Hospital is a barrier, and any request for pain medication is considered an addiction" *(55 years old, FEV1 % >70 not on a modulator therapy, severe pain and high pain interference)*
		"They tend to downplay the pain and palm it off on other factors… e.g. aging" *(63 years old, FEV1 % <70 on a modulator therapy, moderate pain and low pain interference)*
	Pain is undermanaged	"I have always explained my symptoms and concerns, and nothing seems to get better" *(23 years old, FEV1 % >70 on a modulator therapy, moderate pain and low pain interference)*
		"I am always told it's not that bad, people are worse off, and that they can't help me" *(20 years old, FEV1 % <70 on a modulator therapy, moderate pain and high pain interference)*
		"Pain is hard to quantify and is therefore perceived as being "in my head" *(48 years old, on a modulator therapy, severe pain and high pain interference)*
		"They know I have pain, but no suggestions have been made to address it" *(53 years old, FEV1 % <70 on a modulator therapy, moderate pain and high pain interference)*
		"Pain is usually associated with my stomach, and my CF team are respiratory physicians and do not seem to understand the pain" *(28 years old, FEV1 % >70 on a modulator therapy, mild pain and mild pain interference)*
Fear of stigmatisation	Fear of being judged as drug seeking or as complaining	"Sometimes, it doesn't seem sufficient enough to bring up, and there are already so many other things they're taking care of, not wanting to overload them with more" *(35 years old, FEV1 % >70 on a modulator therapy, mild pain and mild pain interference)*
		"I don't like to cause a fuss" *(20 years old, FEV1 % <70 on a modulator therapy, and mild pain)*
		"Don't want to feel like I am painkiller shopping" *(47 years old, on a modulator therapy, mild pain, and high pain interference)*
		"I have felt very quickly judged regarding being on narcotics by the CF team. And even if I explained until I was blue in the face, I would get another new person to come in with another judgy comment about why I didn't try physical therapy or something. It was really upsetting. I hated going to the clinic because of it" *(40 years old, FEV1 % >70, not on a modulator therapy, moderate pain, and high pain interference)*
Concerns surrounding ageing		"Only one issue per consult, please", which is ridiculous for a 59-year-old CF person in pain. Clinics are lacking in "aging CF" person profoundly, which causes me great sadness" *(59 years old, on modulator therapy, severe pain, and high pain interference)*
Desire for holistic pain management		"Pain and its discussion and understanding by dr/CF nurse practitioners aren't at the centre of CF care. I still do not have a holistic treatment plan. Pain is generally outsourced to a GP without input or regular discussion from the CF healthcare team" *(46 years old, FEV1 % <70 on a modulator therapy, mild pain and moderate pain interference)*

[27]. This study highlights that pain is a significant burden on CF regardless of modulator therapy. Where modulator therapies have drastically changed the course of the disease, pain, however, remains a critical unresolved issue not altered by modulators. Previous research has also described headaches, oropharyngeal and abdominal pain as adverse events related to the consumption of modulator therapies [28, 29]. Therefore, without the clinical history of the respondents, no CF-specific screening tool or measurement for pain prior to taking modulators and further follow-up, it cannot be definitively attributed to the modulator therapy as an adverse event or related to CF as another symptom.

The most commonly reported medication for both cohorts, over-the-counter medications, were significantly less effective for the pwCF cohort and were not affected by CFTR modulator consumption, indicating other potential interactions, such as genomic variations. This study, including the clustering of different pain locations and stratification of pain, may serve as a baseline for future research into genomic variations and the differential pain profiles associated with CF. With the

rise of pharmacogenetics and research into drug efficacy, having a comprehensive understanding of variations in genes related to pain or drug metabolising enzymes will guide drug selection and subsequent dosing, dramatically affecting pwCF's quality of life by maximising therapeutic effects and minimising toxicity.

5. Limitations and strengths

A major strength of this study included the question set surrounding medications or interventions specifically used for pain in conjunction with the NRS rating the effectiveness of the intervention. Further, using validated pain tools ensured accuracy and consistency so that they were comparable across the cohorts and could be used in future research when evaluating the effectiveness of interventions such as CFTR modulator therapies.

Limitations of this study included internet accessibility, digital literacy requirements, and gender imbalance among participants, with a higher number of females than males in both cohorts. Further, being an online questionnaire, the study was also subject to self-selection bias and a lack of screening to verify the inclusion or exclusion criteria were met. Recommendations for the future would be to recruit patients in dedicated CF clinics and administer the survey with their healthcare professionals. This would provide deeper insights into the types of pain and any clinical associations that may have been missed due to the self-reporting nature of the questionnaire. Overall, comprehensive clinical and psychological data together will add to the rigour of future studies in this area.

6. Conclusion

The study is the first to be published to describe self-reported pain severity and frequency in addition to qualitative themes on accessing pain management strategies in CF. It presents a much-needed insight into an underrecognised and undermanaged symptom– pain. Prospective body map clustering and pain profiling should be integrated into the current clinical workup of a pwCF. Further research whereby biosignatures, or pain profiling, in CF, will allow for personalised pain management strategies to be developed for improved long-term care.

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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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2025.01.009.

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