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Clinimetric evaluation of muscle function tests for individuals with cystic fibrosis: A systematic review ☆,☆☆

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ABSTRACT

Accurate testing of muscle function is essential in individuals with cystic fibrosis (CF). A literature search was conducted in MEDLINE, CENTRAL, CINAHL, PEDro, ScienceDirect and Web of Science according to PRISMA and COSMIN guidelines from inception to September 2019 to investigate the clinimetric properties of muscle tests in individuals with CF. The search identified 37 studies (1310 individuals) and 34 different muscle tests. Maximal inspiratory pressure, inspiratory work capacity and quadriceps strength measured by computerised dynamometry were identified as reliable tests of muscle function. The one-minute sit-to-stand test was found to have high reliability but its validity to measure quadriceps strength is unknown. The clinimetric properties of other routinely used tests have not been reported in people with CF. Very different measurement procedures were identified. Inspiratory muscle and quadriceps testing can be considered as reliable but high-quality studies evaluating tests of other muscles function (e.g. muscle endurance) are lacking.

1. Introduction

Cystic fibrosis (CF) is a genetic multisystemic disease caused by a mutation of the CFTR (Cystic Fibrosis Transmembrane Regulator) gene [1]. CF is associated with a progressive decline in lung function, but it also impacts on systemic functions, including muscle function [2]. Quadriceps strength (along with fat-free mass) is strongly related to reduced maximal aerobic capacity (measured by cardio-pulmonary exercise testing), which leads to a progressive reduction of quality of life and an increased rate of mortality [3–5]. The reduced lower limb strength that occurs in CF is mainly related to muscle atrophy, which can be attributed to various factors (systemic inflammation, lower levels of physical activity, impaired energy balance etc.) [2]. Numerous studies have reported reduced quadriceps maximal isometric force in individuals with CF compared to predicted values based on data from healthy peers [2,6]. However, evidence supporting reduced respiratory muscle (RM) strength is not consensual. The majority of studies (70%) have reported normal or above normal values of volitional RM strength in individuals with CF while the results of in-vitro measurements or non-volitional measurements of muscle function (transdiaphragmatic twitch pressure) suggested that RM function is altered in individuals with CF [7–9]. It is thus important to monitor mus-

Abbreviations: MIP, maximal inspiratory pressure; IWC, inspiratory work capacity; STST1', one-minute sit-to-stand test; RM, respiratory muscles; MEP, maximal expiratory pressure; MVC, maximal voluntary contraction; LLM, lower limb muscle; ULM, upper limb muscle; MRPD-MIP, maximal rate of pressure development of the inspiratory muscles; MRPD-MEP, maximal rate of pressure development of the expiratory muscles; MRR-MIP, maximal relaxation rate of the inspiratory muscles; MRR-MEP, maximal relaxation rate of the expiratory muscles; ICC, intra-class correlation coefficient; CR, coefficient of reliability; STST30", 30-seconds sit-to-stand test.

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cle function, as is recommended for chronic obstructive pulmonary disease (COPD) [10,11]. However, to date, there are no specific recommendations for the assessment of muscle function in individuals with CF.

According to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines, studies evaluating muscle function should employ robust outcome measures that have undergone clinimetric evaluation (validity, reliability, responsiveness and interpretability) within the population studied or have shown robustness in both healthy subjects or other individuals with lung disease [12,13]. Volitional measures of RM strength such as maximal inspiratory (MIP) and expiratory (MEP) mouth pressures are reliable and several studies have reported normative values in samples of healthy subjects [14,15]. Maximal voluntary contractions (MVC) of the quadriceps muscle measured using dynamometry or a strain gauge, as well as handgrip strength, have shown reliability in patients with COPD and normative values in healthy subjects are available [16–18]. Non-volitional measures of muscle function during evoked manoeuvres (phrenic or femoral magnetic nerve stimulation) have also been described in patients with COPD as such measures do not require patient collaboration and ensure maximal measurements [19]. However, none of these measures have yet been fully validated. Similarly, other methods to measure muscle strength, contractility or endurance have been described but have yet to be validated and evaluated for reliability in both healthy subjects and individuals with lung disease [10,11] (see Supplemental Table S1). The aim of this study was to identify muscle function tests that have undergone clinimetric evaluation for use in CF in order to help clinicians to choose the most appropriate outcome measures to ensure accurate measurements of muscle function.

We therefore undertook a systematic review: (1) to explore the clinimetric properties of muscle function tests for the respiratory muscles (RM), lower limb muscles (LLM) and upper limb muscles (ULM), (2) to report the relationships identified within the studies between muscle function and other outcomes and (3) to describe the testing procedures used to measure the different components of muscle function.

2. Methods

2.1. Design and objectives

This systematic review followed the Preferred Reporting Items for Systematic Review (PRISMA) and the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines [12,20]. The protocol for the systematic review was prospectively indexed in the International Prospective Register for Systematic Reviews (PROSPERO) (CRD42019127939). The following clinimetric properties were analysed: validity, reliability and responsiveness. Relationships between muscle function and other clinical outcomes were also evaluated.

2.2. Data search strategy

The research strategy included keywords associated with the medical condition (“cystic fibrosis”) as well as the different components of muscle function (endurance, strength, fatigue and contractility) to ensure all relevant records were identified. Search terms relating to muscle were: “muscle testing” OR “muscle assessment” OR “muscle function” OR “muscle strength” OR “muscle endurance” OR “respiratory muscles” OR “peripheral muscles” OR "muscle fatigue" OR "muscle fatigability" OR "muscle contractility". The following bibliographic databases were searched: MEDLINE; CENTRAL; CINAHL; PEDro, ScienceDirect and Web of Science from inception to September 2019. The references of the included studies were screened and references that met the inclusion criteria were also included.

2.3. Study selection

Muscle function is a wide term that encompasses different variables such as strength, endurance, fatigue or contractility. In order to enhance the usability of the results in clinical practice this review focused on muscle function tests (according to the abovementioned components of muscle function) that can be reasonably undertaken during routine clinical practice without involving invasive procedures (2). This encompasses non-volitional measurements of peripheral muscles function (e.g. femoral magnetic nerve stimulation) but only those that do not involve invasive measurements. The aim of this systematic review was to focus on muscle function, measures of structural muscle characteristics such as muscle volume or muscle mass were not included [21].

The inclusion criteria were therefore: 1) studies that included people (children, adults or both) with CF (with or without a comparison group of healthy peers); 2) prospective observational or cross-sectional studies that involved at least one RM, ULM or LLM function test and explored at least one of the review outcomes (clinimetric properties or relationship with other outcomes); 3) studies that included an intervention in order to evaluate certain clinimetric properties (construct validity or responsiveness); 4) studies published in English, French or Spanish.

Interventional studies (i.e. randomized controlled trials) that evaluated muscle function as an outcome measure but that did not evaluate the clinimetric properties of the test used were excluded. Abstracts, reviews, editorials or retrospective studies were also excluded.

2.4. Outcomes

Three clinimetric properties of muscle tests, validity, reliability and responsiveness, were evaluated as the primary outcome. Validity was defined as the extent to which a measurement tool actually measures the construct it purports to measure [12]. In order for a test to be considered as valid, it must meet the following three criteria: 1) construct validity (the degree to which a measurement tool is consistent with hypotheses based on the assumption that the tool actually measures the construct to be measured); 2) content validity (the degree to which the content of a measure is an adequate reflection of the construct to be measured) and 3) criterion validity (the degree to which the score of a tool is an adequate reflection of a gold standard or reference test) [12]. Due to the lack of defined reference tests for the measurement of muscle function in CF, guidelines from COPD were used [10,11]. The reference tests for respiratory muscle strength were maximal inspiratory (MIP) and expiratory pressures (MEP) [10]. The reference test for lower limb muscle strength was isometric testing using either a dynamometer or a strain gauge [11]. To our knowledge, no reference test has been determined for ULM strength. Similarly, no reference test has been determined for the measurements of other aspects of muscle function (endurance, contractibility or fatigue) or non-volitional strength. Reliability was defined as the extent to which repeated evaluations by 1) the same investigator (intra-observer), 2) different investigators (inter-observer) or 3) over time (test-retest) yielded similar results [12]. Responsiveness was defined as the ability of the method to detect change over time [12].

Secondary outcomes were relationships between muscle function and other outcomes. Only linear relationships (correlation coefficients) were considered. The strength of correlations was defined as follows: r=0 to 0.19: very weak, r=0.20 to 0.39: weak, r=0.40 to 0.59: moderate, r=0.60 to 0.79: strong and r=0.80 to 1.0: very strong [22]. The testing procedure used was reported for each

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study (i.e. number of trials, reference equations, accordance with international recommendations).

2.5. Study extraction

Studies were identified by two of the review authors (YC and CM). They independently screened article titles and removed duplicates. Abstracts and then relevant full texts were retrieved and assessed by the same authors who independently determined if they fulfilled the inclusion criteria. A third reviewer (GP) was consulted in case of disagreement. Corresponding authors were contacted if meaningful data were missing from any study.

The following information was extracted from each study: study details (authors, publication date and country); sample characteristics (number of individuals, sex ratio, age, weight, body mass index, *Pseudomonas aeruginosa* status and lung function); the clinimetric properties of the tests used (if evaluated); relationships with clinically outcomes (if evaluated) and the specific measurement procedures used. If the sample was analysed in subgroups according to sex or respiratory status, the data were pooled using the Cochrane Handbook equations for pooling the means of different groups [23].

2.6. Risk of bias assessment

Two authors (YC and CM) independently evaluated the risk of bias. Studies that reported on test validity were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [24]. Studies that reported on test reliability or reproducibility were assessed using the Quality Appraisal tool for studies of diagnostic Reliability (QAREL) [25]. In accordance with the PRISMA statement and the Cochrane Handbook, risk of bias was not analysed for studies that only reported data on relationships between muscle function and other outcomes and did not assess clinimetric properties [20,23].

2.7. Statistical analysis

A qualitative analysis of the clinimetric properties of muscle tests, and the relationship between muscle function and other outcomes was undertaken.

3. Results

3.1. Systematic review

The search generated 1998 records. Thirty-seven studies with a total of 1310 individuals fulfilled the inclusion criteria and were included (Fig. 1). Details of the studies are provided in Table 1. Four studies specifically evaluated the clinimetric properties of muscle tests [26–29]: 1 evaluated RM function tests [29], 3 evaluated LLM function tests [26–28] and none evaluated ULM function tests. The other 33 studies evaluated the relationship between muscle function and other outcomes [30–62]. Among all the studies included, 3 reported tests for RM, LLM and ULM [50,54,56]; 7 reported at least two tests [30,41,48,55,58,60,61]; 16 reported RM testing alone [29,31–33,36,39,40,42,44,46,47,49,51,52,59,62]; 11 reported LLM testing alone [26–28,34,35,37,38,43,45,53,57] and none reported ULM testing alone.

3.2. Primary outcome: clinimetric properties

The clinimetric properties of the different muscle function tests and procedures are reported in Table 2. All the studies of clinimetric properties included only adults with CF.

3.2.1. RM function

The clinimetric properties of 2 tests of RM function were evaluated: MIP (RM strength) and inspiratory work capacity (IWC) (RM strength and endurance) [29].

MIP was found to have high intra-observer reliability (intra-class correlation coefficient ICC=0.89) and test-retest reliability (coefficient of reliability CR=87% and 95% confidence interval (CI) limits of agreement = 1.5 to -8.6). Two measurements of MIP were conducted within 48 hours but a learning effect was not assessed. IWC was also found to have high intra-observer reliability (ICC=0.99) and test-retest reliability (CR=94% and 95% CI limits of agreement = 0.4 to -0.6) Two measurements of IWC were conducted within 48 hours and IWC was free of a learning effect [29].

3.2.2. Limb muscle function

The clinimetric properties of specific quadriceps isometric strength measurements were evaluated by one study that reported maximal voluntary contraction (MVC) measurements (LLM strength) and endurance time (LLM endurance) of the quadriceps muscle [28]. Clinimetric properties were also reported for five field tests: the one-minute sit-to-stand test (STST1'), the 30 second sit-to-stand test (STST30''), the vertical jump test, the stair climbing power test and the triple hop distance [26,27]. The STST30'', vertical jump test, stair climbing power test and triple hop distance test all had significant criterion validity for the measurement of quadriceps strength (r=0.55, r=0.62, r=0.84 and r=0.78 respectively) [26]. Other aspects of validity, reliability or responsiveness were not reported for these tests. Quadriceps MVC using an isometric ergometer had high test-retest relative reliability (ICC=0.88) and low variability (standard error of measurement 7.2%). Endurance time had high test-retest relative reliability, but higher variability compared to MVC (standard error of measurement 24.9%). Two measurements of quadriceps MVC and endurance time were reported six weeks apart and no learning effect was reported for either MVC or endurance time [28]. None of the components of validity were evaluated for the STST1'. The STST1' was found to have high intra-observer reliability (ICC=0.98) and test-retest reliability (coefficient of variation CV=3.84 and mean bias 1.36 and 2.29 respectively between three iterations of the test), although a significant learning effect was reported [27]. The STST1' was found to be responsive to change (Cohen's effect size 0.965) with a median difference of 7.7 repetitions after a 3-week pulmonary rehabilitation program [27].

3.3. Secondary outcomes: relationships between muscle function and other outcomes

Details of the correlations between muscle function and other outcomes for all the RM tests are reported in Table 3. In adults with CF, there was a moderate to strong correlation between MIP and limb muscle strength (correlation coefficients ranged from r=0.48 to 0.60 for handgrip and from r=0.56 to 0.73 for quadriceps strength) as well as lean body mass [39,47,54,58,61]. However MIP was only weakly or non-significantly correlated with lung function and body mass index (BMI) [39,46,51]. Two studies in children with CF reported moderate correlations between MIP and lung function and lean body mass [32,36]. Two studies of adults with CF reported strong to very strong correlations between IWC and handgrip strength (r=0.80) and lean body mass (r=0.70) [52,58]. One study reported significant correlations between MRPD, MIP and MEP measurements (measured during both MIP and MEP) and MIP (r=0.64 and r=0.65 respectively) and MEP (r=0.43 and r=0.52 respectively); but both tools had only weak to moderate associations with nutritional status and were not related to lung function [42].

Details of the correlations between muscle function and other outcomes for all the ULM and LLM tests are reported in Table 4.

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Table 1
Characteristics of the 37 studies included.

Study details			Population								Outcomes		
First Author (reference)	Year	Country	N	Age (group)	M/F	Age (years)	Weight (kg)	BMI(kg.m^{-2})	PA status (%)	FEV1 (% predicted value)	Muscle groups assessed	Clinimetric properties reported?	Related outcomes reported?
Sheppard [26]	2018	Canada	15	Adults (18+)	9/6	32±13	66.3 ±15.1	25.9±9.7	87%	73±19	LLM	√	X
Radtke [27]	2016	Switzerland	14	Adults (18+)	6/8	29 (25.5-36)	53.9 (49-65.9)	19.7 (18.8-21)	100%	53 (43-56.5)	LLM	√	√
Gruet [28]	2010	France	16	Adults (18+)	11/5	29.9±8	59.1±5	21.1±2	-	55.1±8	LLM	√	X
Enright [29]	2006	UK	20	Adults (18+)	10/10	22.7±3.4	58.8±7.5	20.1±4.4	-	62.4±9.7	RM	√	X
Rovedder[30]	2019	Brazil	41	Adults (16+)	14/27	24.6±7.6	-	20.6±2.3	-	57.9±25.1	ULM, LLM	X	√
Sovtic [31]	2018	Serbia	69	Children (8+) and adults	36/33	16.8±6.5	-	18.4±3.3	-	76.5±27.1	RM	X	√
Papalexopoulou [32]	2018	UK	29	Children (12-19)	11/18	15 [12-19]	-	*−0.09 [−2.73–1.19]*	-	*−1.87 [−5.70–0.82]*	RM	X	√
Gambazza [33]	2018	Italy	25	Adults (18+)	9/16	22.2±3.5	-	20.5±2.2	44%	79.7±19.9	RM	X	√
Radtke [34]	2017	Switzerland	15	Adults (18+)	8/7	31 (25-33)	-	20 (18-22)	73%	49 (34-55)	LLM	X	√
Stein [35]	2016	Germany	10	Children(-18)	10/0	16.7±0.8	61.9±8.3	20.3±2.1	-	93.5±20.5	LLM	X	√
Vendrusculo [36]	2016	Brazil	34	Children (6-18)	20/14	14.0±2.7	46.2±14.3	18.8±3.3	26%	80.1±27.7	RM	X	√
Gruet [37]	2016	France	15	Adults (18+)	12/3	28±6	-	21±3	-	72 (SD not reported	LLM	X	√
Gruet [38]	2016	France	25	Adults (18+)	17/8	30±9	55.6±6.2	20.4±1.9	92%	59.5 [22-112]	LLM	X	√
Dekerlegand [39]	2015	USA	58	Adults (18+)	28/30	32.3±9.3	58.6±10.2	21.6±2.7	76%	59.6±26.9	RM	X	√
Dassios [40]	2015	Greece	53	Children (7-18) and adults	29/24	14 (11-19.5)	48 (35-59)	*0.14 (-0.63 to 0.72)*	-	88 (61-101)	RM	X	√
Wells [41]	2014	Canada	82	Children (7-18)	42/40	13.8±2.3	49.2±13	19.7±3.1	-	87.8±14.1	ULM, LLM	X	√
Dassios [42]	2013	Greece	123	Children (from 6) and adults	66/57	14 (10-17)	49 (36-59)	*0.22 (-0.42 to 0.87)*	-	100.3 (74.0–117.4)	RM	X	√
Burtin [43]	2013	Belgium	19	Adults (18+)	13/6	25±6	-	20.9±2.9	74%	55±19	LLM	X	√
Dassios [44]	2013	Greece	140	Children (from 6) and adults	68/72	14 (10-17)	49 (36-59)	*0.22 (-0.51-0.87)*	-	100.3 (74.4-117)	RM	X	√
Wieboldt [45]	2012	UK	38	Adults (18+)	24/14	32.3±10.7	-	21.7±2.2	-	60.6±22.1	LLM	X	√
Leroy [46]	2011	France	18	Adults (18+)	4/18	32±12.6	-	19.8±1.9	-	44.1±18.8	RM	X	√
Dunnink [47]	2009	Netherlands	27	Adults (18+)	13/14	26±7	61±11	21±3	-	63±25	RM	X	√
Troosters [48]	2009	Belgium	64	Adults (18+)	35/29	25.1±7.5	60.4±12.4	-	-	64.9±19.3	ULM, LLM	X	√
Hahn [49]	2008	Germany	47	Children (9-18) and adults	26/21	14 (12–21)	46 (33–55)	-	-	59 (50–83)	RM	X	√
Barry [50]	2008	UK	15	Adults (18+)	15/0	23.9 [19-40]	60.3±7.4	21.3±1.9	-	68.3±22.2	RM, ULM, LLM	X	√
Ziegler [51]	2008	Brazil	39	Adults (16+)	16/23	23.7±6.4	-	20.3±1.8	-	53.2±26.9	RM	X	√
Enright [52]	2007	UK	40	Adults (18+)	22/18	22.4±0.6	60.2±0.9	22±0.5	-	46.5±0.3	RM	X	√
Sahlberg [53]	2005	Sweden	33	Adults (16+)	17/16	24.3±5.6	66.6±9.4	22.5±2.7	-	91.9±21.1	LLM	X	√
Barry [54]	2003	UK	23	Adults (18+)	13/10	23.3±5.1	-	20.6±2.5	-	48.7±24.0	RM, ULM, LLM	X	√
Hussey [55]	2002	UK	13	Children(-18)	13/0	13.0±4.7	45.3±15.4	18.3±2.9	-	82.5±20.1	ULM, LLM	X	√
De Jong [56]	2001	Netherlands	22	Children (12-18) and adults (18+)	12/10	19±5	57.7±11	19.5±2.8	-	62±28	RM, ULM, LLM	X	√
Elkin [57]	2000	UK	25	Adults (18+)	20/5	28±8	61.6±9.4	20.9±2.2	-	[20-101]	LLM	X	√
Ionescu [58]	1998	UK	25	Adults (18+)	15/10	22.9±3.8	-	21.3±3.8	-	61.1±26.3	RM, ULM	X	√
Hayot [59]	1997	France	16	Children (-18)	13/3	11±2	33±6	-	-	81±16	RM	X	√
Lands [60]	1993	Canada	14	Children and adults	6/8	21±8.4	52.8±9.6	-	-	72.5±24.8	RM, LLM	X	√
Mier [61]	1990	UK	25	Adults (16+)	18/7	21 [16- 28]	52 [35-63]	-	-	46±21	RM, LLM	X	√
O'Neill [62]	1983	Canada	25	Children (7-18) and adults	14/11	14.5±5.0	38.4±17.9	15.3±3.9	-	34.7±11.2	RM	X	√

Values are presented as means ± standard deviations (SD), mean [minima-maxima], [minima-maxima] alone or medians (Q1 – Q3) according to the results expressed within the study. Values expressed as "z-scores" are presented in italics inside the table. Values not reported are represented as "-". For studies that reported several muscle strength tests but did not evaluate the clinimetric properties or related outcomes for all of them, only the muscle groups assessed are presented in this table.
Abbreviations: FEV1: forced expiratory volume in 1 second, LLM: lower limb muscles, PA: Pseudomonas aeruginosa, RM: respiratory muscles, ULM: upper limb muscles.

Table 2
Clinimetric properties of the muscle function tests and the measurement procedures used.

Measurement tool		Reference	Clinimetric properties								Measurement procedures
			Validity			Learning effect	Reliability			Responsiveness	
			Construct	Content	Criterion		Intra-rater	Inter-rater	Test-retest		
RM	MIP	[29]	-	-	NA	Not analysed	√	-	√	-	Electronic manometer, 3 attempts from RV to TLC (performed according to ATS/ERS guidelines), maximal pressure developed in the first 1'' recorded
	IWC	[29]	-	-	-	Free from learning effect	√	-	√	-	Electronic manometer, 3 "sustained maximal efforts" from RV to TLC, area under the inspiratory pressure curve over time recorded and transformed to IWC through mathematical conversion
Pressure-time product of the inspiratory muscles (PTImus), MRPD-MIP and MEP, MRR-MIP and MEP, and MEP were not assessed for clinimetric properties											
LLM	STST1'	[27]	-	-	-	Learning effect	√	-	√	Large (ES 0.965)	Chair 40 or 46 cm, from 1 to "a few" practice trials, from 1 to 3 attempts performed, from no rest to 3' rest before the test, demonstrated by the operator, standardized verbal encouragements, self-chosen speed, stop allowed, mean of the 3 last attempts or single test number of sit-to stand movements recorded
	STST30''	[26]	-	-	√	-	-	-	-	-	Chair 46 cm, 3 attempts (no practice trial), demonstrated by the operator, mean of the 3 attempts, number of sit-to-stand movements recorded
	Vertical Jump Test	[26]	-	-	√	-	-	-	-	-	3 attempts, demonstrated by the operator, highest jump from a standing position, arm stretched vertically and mark the wall at the top of the jump, mean value of the 3 distances between standing height and top jump height recorded
	Stair Climb Power test	[26]	-	-	√	-	-	-	-	-	3 attempts, demonstrated by the operator, climb 10 stairs and time recorded (converted with Bean equation), mean value of the 3 attempts recorded
	Triple Hop Distance	[26]	-	-	√	-	-	-	-	-	3 attempts, demonstrated by the operator, hop 3 times consecutively on dominant leg, mean of the 3 attempts recorded
	Maximal voluntary isometric contraction (quadriceps)	[28]	-	-	NA	Free from learning effect	-	-	√ (verified and low variability)	-	Isometric ergometer, subjects seated (110° hip angle, 90° knee flexion), dominant leg measured for peak torque using a torque transducer, straps across the chest and pelvis, 3 maximal isometric contractions (5-s duration) separated by 2-minrest period, standardized verbal encouragement and best performance definedas MVC.
	Endurance time (quadriceps)	[28]	-	-	-	Free from learning effect	-	-	X (high variability)	-	Isometric submaximal contraction (50% MVC) maintained until exhaustion (designated target force on a computer screen), stop if the force decreased +5%, designated as time limit (Tlim), standardized verbal encouragement
Quadriceps isometric (D or SG) strength using handheld dynamometry, quadriceps 1RM strength, quadriceps isokinetic strength, leg strength (cycloergometer), potentiated twitch force, absolute endurance-index, STST derived measures and hamstrings isometric or isokinetic strength were not assessed for clinimetric properties											
ULM	*Biceps isometric strength, biceps 1RM strength, handgrip, shoulder flexor isokinetic strength and shoulder extensor isokinetic strength were not assessed for psychometric properties*										

Clinimetric properties that have not been addressed within the identified studies are represented as "-"
Abbreviations: D: dynamometric, ES: effect size, IWC: inspiratory work capacity, LLM: lower limb muscle, MEP: maximal expiratory pressure, MIP: maximal inspiratory pressure, MRPD-MEP: maximal rate of pressure development of the expiratory muscles, MRPD-MIP: maximal rate of pressure development of the inspiratory muscles, MRR-MEP: maximal relaxation rate of the expiratory muscles, MRR-MIP: maximal relaxation rate of the inspiratory muscles, MVC: maximal voluntary contraction, RM: respiratory muscles, RV: residual volume, SG: strain gauge, STST1': one minute sit-to-stand test, STST30'': 30 seconds sit-to-stand test, TLC: total lung capacity, ULM: upper limb muscle, 1RM: 1-repetition maximal strength

Table 3
Relationships between respiratory muscle function and other outcomes.

Muscle Tool	Measurement procedure	Reference	Related outcomes Significant correlations	Lack of correlation
MIP	Handheld manometer [1]	[32]	FFM [m]; LBM UL [m] LL [w] Trunk [w]; Shuttle runs [w]	BMI
	Digital manuvacuometer, subjects seated/nose clip, 5 attempts from RV (40'' rest), best value recorded[α]	[36]	FEV1(%) [m]; FVC (%) [m]; BMI (z-score) [w]	-
	Handheld manometer [1]; 2 practice trials and at least 5 manoeuvres (within 10% variability) with a 2' rest, best value recorded[β]	[39]	FEV1(%) [m]; RV/TLC [m−]; BMI [w]; %IBW [w]; LBM [w]; Dyspnoea [m−]	-
	Measurement from RV [1]; 5 "reproducible" attempts, best value reported [β]	[44]	UAMA [m]	BMI
	Manometer, subjects seated; 5 to 7 trials at FRC until 10% variation max, best value recorded [γ]	[46]	Dyspnoea at peak exercise [m]	FEV1, FVC, RV/TLC; FRC; age, BMI, LBM and BG
	Manometer, nose clip/mouthpiece, 4 to 8 attempts from RV, best value recorded [δ]	[47]	HG left [m]; HG right [s]; Quadriceps [m]; MST [m]; CFQ-R social limitation [s]	Dyspnoea
	Pneumotachograph; at least five attempts at FRC (within 10% variability); best value recorded [δ]	[49]	FEV1(%) [w]; FRC/TLC [w−]	-
	Pressure transducer [2], subjects seated, nose clip, attempts repeated until 10% variation at FRC [ε]	[50]	-	Testosterone level, free testosterone level
	Manometer, subjects seated, nose clip, 5 attempts from RV, "suitable rest" until plateau, best of 2 manoeuvres within 10% variation recorded [ζ]	[51]	-	FEV1 and FVC (%); BMI; Brasfield and Schwachman scores; triceps skinfold
	Electronic manometer, maximal sustained effort from RV, maximal pressure in the first 1'' recorded	[52]	Diaphragm thickness [w]	-
	Manometer [2], attempts until 2 reproducible values (within 10%) with "several" rests at FRC [ε]	[54]	FEV1(%) [s]; BMI [m]; CSI [s−]; KE% [s]; KF% [s]; EF% [vs]; HG% [m]; MEP [vs]	Age, days of hospitalisation
	Attempts from RV until plateau, highest pressure maintained for 1'' recorded [δ]	[56]	FEV1 (%) [m]; EF% [m]	BMI
	Electronic manometer; manoeuvre from RV, maximal pressure in the first 1'' recorded [β]	[58]	Lean body mass (%IBW) [m]	-
	Repeated static maximal attempts until maximum (3 to 5 attempts) at FRC, 5'' efforts (at least 1'') [η]	[60]	-	RV/TLC; LBM, leg strength
	4 to 10 attempts from RV "until no further learning effect", nose clip/mouthpiece, "suitable rest" [δ]	[61]	QS [s]; MEP [m]	-
	Diaphragm pressure gauge and transducer, subjects sited, nose clips, repeated measures from RV until 3 "technically satisfactory measurements", best value recorded [β]	[62]	-	RV/TLC; RV; Weight; BMP
IWC	Electronic manometer, measured from RV, area under the inspiratory pressure curve over time recorded	[52]	Height [m]; FFM [w]; BMI [w]; Diaphragm thickness [m]	-
	Electronic manometer, measured from RV, area under the pressure-time curve recorded [θ]	[58]	LBM (%IBW) [s]; HG [vs]; MUMC [s]	-
IME	Incremental loading test (throughout load device), 2' at 30% of MIP and increase by 10% every 2', maximal load reported as the highest percentage of MIP achieved and maintained 1', stop in case of intense fatigue or 3 consecutive failure to open the valve	[36]	Total airway resistance [w]; central airway resistance [m]	BMI
	Incremental loading test, beginning 20% of MIP and increase by 10% every 2', maximal inspiratory pressure sustained for 2' recorded, highest percentage of MIP achieved reported	[46]	Dyspnoea at peak exercise [−s]	Anthropometric data; lung function; BG; VO2 peak
PTImus	Pneumotachograph, derived from MIP, 5 trials, best value recorded, PTImus= (Pimean/MIP) x (Ti/Ttot) (Pimean=average inspiration airway pressure with Pimean = 5 x P0.1 x Ti considering Ti: inspiration time, Ttot: total time for each breath and P0.1: pressure generated during the first 100msec of the manoeuvre)	[44]	FEV1 (%) [vw−]; UAMA [vw−]	BMI
	Pneumotachograph, derived from MIP, PTImus=PImean/MIP x Ti/Ttot and PImean=5 x P0.1 x Ti	[49]	Raw (%) [m]; Sgaw (%) [m−]; FEV1 (%) [m]; FEV1/VC% [w]; FRC/TLC% [m]; VC (%) [m]; SaO2% [m]	-
	At least 5 attempts at FRC until 3 reproducible measurements (within 10% variation) to measure MIP; PImean measured through 10 occlusions (2-3/minute) and PImean= 5 x P0.1 x Ti (P0.1=pressure generated during the first 100msec of the manoeuvre) [β]	[59]	FRC Box (%) [s]; FRC Box He [s]; Lean body mass [s−]; UAMA [s−]; Age [s−]	Height/weight; body fat mass; UAFA
MRPD-MIP	Pneumotachograph, 5 trials derived from MIP from RV, best value recorded, "positive peak of the pressure derivative as a function of time during the initial incline of the maximal respiratory pressure curve"	[42]	Weight [m]; Height [m]; BMI [w]; MAMC [w]; UAMA [m]; MIP [s]; MEP [m]	FEV1 and FVC (%); MEF (25-75); TST
MRR-MIP	Pneumotachograph, 5 trials derived from MIP from RV, best value recorded, "first derivative of pressure with respect to time over the first half of the relaxation curve and expressed as a percentage of the pressure fall in 10ms"	[42]	FEV1(%) [w]; FVC (%) [w]; Weight [m−]; Height [m−]; BMI [w−]; MAMC [m]; TST [w]; UAMA [w]	MIP; MEP

(continued on next page)

Table 3 (*continued*)

Muscle Tool	Measurement procedure	Reference	Related outcomes Significant correlations	Lack of correlation
Time constant of inspiratory muscle relaxation	Handheld manometer, "at least" 3 reproducible MIP (from RV), followed by normal quiet expiration, using, measured as the reciprocal of the slope of the pressure decline as a function of time (lower 60% of the curve), mean value of at least 3 maximal MIP recorded	[40]	FEV1 $^{-w}$; FVC $^{-w}$	BMI, UAMA, MEF (25-75), RR, TV
MEP	5 or more attempts (2' rest) until 2 "reproducible values" from TLC $^{\delta}$	[31]	Wmax ^{m}	-
	Handheld manometer [1]	[32]	FFM ^{m}; LBM UL ^{m}; LL ^{m}; Trunk ^{m}	BMI; shuttle runs
	Handheld manometer [1]; 5 "reproducible" attempts, best value recorded $^{\iota}$	[33]	6MWW ^{s}	FEV1 and FVC (z-score); BMI; age; MUMA; 6MWD
	5 "reproducible" attempts from TLC, best value recorded $^{\beta}$	[44]	UAMA ^{w}	-
	Manometer, nose clip/mouthpiece, 4 to 8 attempts from TLC, best value recorded $^{\delta}$	[47]	HG left ^{s}; HG right ^{s}; QS ^{m}	Dyspnoea
	Pressure transducer [2], subjects seated, nose clip, attempts repeated at FRC until 10% variation, best value recorded $^{\varepsilon}$	[50]	HG % ^{m}; QS ^{m}; SF ^{s}	Testosterone and free testosterone
	Manometer, subjects seated, nose clip, 5 attempts from TLC, "suitable rest" until plateau, best of 2 manoeuvres within 10% variation recorded $^{\zeta}$	[51]	-	FEV1 and FVC (%); BMI; Brasfield and Schwachman scores; triceps skinfold
	Manometer [2], attempts until 2 reproducible values (within 10%) with "several" rests at FRC $^{\varepsilon}$	[54]	FEV1(%) ^{s}; BMI ^{m}; CSI $^{s-}$; KE% ^{s}; KF% ^{s}; EF% ^{vs}; HG% ^{m}; MIP ^{vs}	Age; days of hospitalisation
	Repeated static maximal attempts until maximum (3 to 5 attempts) at FRC, 5" efforts (at least 1") $^{\eta}$	[60]	LBM ^{s}; Leg strength ^{s}	-
	4 to 10 attempts from TLC, "until no further learning effect", nose clip/mouthpiece, "suitable rest" $^{\delta}$	[61]	MIP ^{m}; QS ^{s}	-
	Diaphragm pressure gauge and transducer, subjects seated, nose clips, repeated measures from TLC until 3 "technically satisfactory measurements", best value recorded $^{\beta}$	[62]	Weight ^{s}	BMP
MRPD-MEP	Pneumotachograph, 5 trials derived from MEP from TLC, best value recorded, "positive peak of the pressure derivative as a function of time during the initial incline of the maximal respiratory pressure curve"	[42]	Height ^{w}; Weight ^{m}; BMI ^{w}; MAMC ^{w}; UAMA ^{m}; MIP ^{s}; MEP ^{m}	FEV1 and FVC (%); MEF (25-75); TST
MRR-MEP	Pneumotachograph, 5 trials derived from MEP from TLC, best value recorded, "first derivative of pressure with respect to time over the first half of the relaxation curve and expressed as a percentage of the pressure fall in 10ms"	[42]	Height $^{w-}$	FEV1 and FVC (%); MEF (25-75); weight; BMI; MAMC; UAMA; TST; MIP; MEP

Studies that reported multiple muscle measurements are reported repeatedly in this table; significant correlations were reported as indices within the table and correlation strength are reported as follows: 0–0.19 was regarded as very weak and reported as ^{vw}, 0.20–0.39 weak reported as ^{w}, 0.4– 0.59 moderate reported as ^{m}, 0.60–0.79 strong reported as ^{s} and 0.80–1.0 as very strong and reported as ^{vs} (negative correlations were preceded by the "-" sign)

Abbreviations:BG: blood gas parameters, BMI: body mass index, BMP: body mass percentile, CSI: corticosteroid inhalation, CFQ-R: cystic fibrosis questionnaire revised, EF: elbow flexors, FEV1: forced expiratory volume in 1 second, FFM: fat free mass, FRC: functional residual capacity, FVC: forced vital capacity, HG: handgrip, IBW: ideal body weight, IME: inspiratory muscle endurance, IWC: inspiratory work capacity, KE: knee extensors, KF: knee flexors, LBM: lean body mass, LL: lower limb, MAMC: mid arm muscle circumference, MEF: mean expiratory flow, MEP: maximal expiratory pressure, MIP: maximal inspiratory pressure, MRPD-MEP: maximal rate of pressure development of the expiratory muscles, MRPD-MIP: maximal rate of pressure development of the inspiratory muscles, MRR-MEP: maximal relaxation rate of the expiratory muscles, MRR-MIP: maximal relaxation rate of the inspiratory muscles, MST: modified shuttle test, MUMC: mid-upper arm circumference, PTImus: pressure-time product of the inspiratory muscles, QS: quadriceps strength, Raw: airway resistance, RR: respiratory rate, RV: residual volume, SaO2: arterial oxygen saturation, Sgaw: airway conductance, TLC: total lung capacity, TST: triceps skinfold thickness, TV: tidal volume, UAFA: upper arm fat area, UAMA: upper arm muscle area, UL: upper limb, VC: vital capacity, WMax: maximal work, 6MWD: 6-minutes walking distance, 6MWW: 6-minutes walking work.

[1] study that followed the American Thoracic Society and European Respiratory Society guidelines for respiratory muscle testing

[2] study that followed the method described in the following study: McParland C, Resch EF, Krishnan B, et al. Inspiratory muscle weakness in chronic heart failure: role of nutrition and electrolyte status and systemic myopathy. Am J Respir Crit Care Med 1995; 151:1101-1107

$^{\alpha}$ Reference equation: Heinzmann-Filho JP, Vidal PCV, Jones MH, Donadio MVF. Normal values for respiratory muscle strength in healthy pre-schoolers and school children. Respir Med 2012;106(12):1639-1646.

$^{\beta}$ Reference equation: Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis May. 1969;99(5):696–702.

$^{\gamma}$ Reference equation: Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. Thorax 1995;50(4):371–5.

$^{\delta}$ Reference equation: Wilson SH, Cooke NT, Edwards RHT, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults. Thorax 1984; 39:535–8.

$^{\varepsilon}$ Reference equation: McParland C, Krishnan B, Wang Y, et al. Inspiratory muscle weakness and dyspnea in chronic heart failure. Am Rev Respir Dis 1992; 146:467-472

$^{\zeta}$ Reference equation: Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. Braz J Med Biol Res 1999;32(6):719–727.

$^{\eta}$ Reference equation: Cook CD, Mead J, Orzalesi MM. Static volume-pressure characteristics of the respiratory system during maximal efforts. J Appl Physiol 1964; 19:1016-22.

$^{\theta}$ Reference equation: Chatham K, Berrow S, Beeson C, Griffiths L, Brough D, Musa I. 1994. Inspiratory pressures in adult cystic fibrosis. Physiotherapy. 80:748–752.

$^{\iota}$ Reference equation: Evans JA, Whitelaw WA. The assessment of maximal respiratory mouth pressures in adults. Respiratory Care, 2009; 54(10), 1348–1359.

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Table 4
Relationships between peripheral muscle (lower and upper limb) function tests and other outcomes.

Muscle tool		Measurement procedure	Reference	Related outcomes	
				Significant correlations	Lack of correlation
LLM Quadriceps	Isometric strength (dynamometry)	Computerized dynamometer, subjects seated, 3 attempts at 80° knee flexion (1' rest), best value recorded, verbal encouragements	[35]	FEV1(L) ^{vs}; FEV1(%) ^{s}	FFM, BCM
		Computerized dynamometer back straight, 90° hip flexion, 60° knee flexion $^{\alpha}$	[48]	Moderate PA ^{m}; hard PA ^{m}	FEV1, FVC
		Computerized dynamometer, 2 practice trials and "numerous" attempts until 3 within 10% variation, dominant limb tested, 8'' contraction, hip flexion 90°, knee flexion 60°, best value recorded	[50]	MEP ^{m}; Weight ^{m}	Testosterone level, free testosterone level
		Computerized dynamometer, 2 practice trials and 3 attempts (within 10% variation), 8'' contraction, both limbs assessed, best value recorded	[54]	FEV1(%) ^{m}; CSI $^{s-}$; MIP ^{s}; MEP ^{s}	BMI
		Handheld dynamometer, patient seated, knee flexion 90°, break method (gradually overcame patient's force), 3 attempts (2' rest), non-dominant limb tested and compensations accepted $^{\beta\gamma}$	[56]	FEV1(%) ^{s}	BMI
	Isometric strength (strain gauge)	Recumbent chair connected to an analogue force transducer, hips extended 120°, knee flexion 90°, arms crossed over the chest, 5 attempts (3'' contraction), rest period 30'' minimum, mean of thetwo highest peak force values reported.	[43]	Testosterone level ^{vs}	Inflammatory markers
		Knee extension against inextensible strap connected to strain gauge, attempts repeated until no progression (30'' rest), verbal encouragements	[45]	Weight $^{s;}$ FFM ^{m}; SNIP ^{vw}; MIP ^{w};MEP ^{w}; HG ^{m}	Step count
		Strain gauge chair, subjects seated, hip and knee flexion 90°, 3 attempts	[57]	Muscle mass $^{s;}$ Leg bone density ^{m}	-
	Isometric strength (undefined)	Adjustable chair, knee flexion 90°, 4 to 10 attempts until no further learning effect, "suitable rest pauses"	[61]	MIP ^{s}; MEP ^{s}	-
	1RM	Full knee extension movement, increase of 0.5 to 1kg until 1 repetition and exhaustion	[30]	FEV1(L) ^{m}; FEV1(%) ^{m}; FVC(L) ^{m} and FVC (%) ^{w}; BMI $^{w;}$ 6MWD ^{w}; SpO2 rest ^{m}; SpO2 exercise $^{m;}$ Borg exercise $^{m-}$	-
	Isokinetic strength (dynamometry)	Computerized dynamometer, hip flexion 120°, arms crossed, 3 practices trials followed by 3 attempts (concentric contraction) at 60°/s, both sides tested (randomized order), best value recorded	[53]	Lean body mass ^{vs}	-
		Computerized dynamometer, 5 alternate measures KE (alternate with KF) at 30°/s from 90° knee flexion to full extension followed by 1' rest and 5 measures at 90°/s, 10' rest before other side testing, average of both sides recorded	[55]	30°/s: FEV1(%) ^{s}; 90°/s: FEV1 (%) ^{s}30°/s: BMI ^{m}	90°/s BMI
	Potentiated twitch force	Recumbent chair connected to an analogue force transducer, hips extended 120°, knee flexion 90°, arms crossed over the chest, measured 3'' after theend of each volitional manoeuvre, transcutaneous magnetictwitch on the femoral nerve at 100% of power output, the mean of the twohighest values (5 attempts)reported.	[43]	Testosterone level ^{vs}	Inflammatory markers
	Absolute endurance index (total force-time product)	Fatiguing task: sets of 10 isometric contractions(5'' on-5'' off) starting at 10% MVC and increasing by 10% at each set until task failure, ended when subject unable to maintain the target force for +2.5'', real-time visual feedback and soundtrack for contraction–relaxation rhythm, product of the total number of contractions and the total force produced	[37]	VO2 peak ^{m}	-
LLM (global)	STST1'	40 cm chair, 1 practice test (patients familiar with test), 3' rest seated before STST1', self-chosen speed, stop allowed, number of STS recorded	[34]	VO2 peak (%) ^{s}; Pmax (%) ^{s}; VO2 peak absolute ^{w}; Pmax absolute $^{m;}$ Desaturations <90% during CPET $^{s-}$	Height, Weight
		46 cm chair, demonstrated by the operator, "a few" practice tests, self-chosen speed, number of STS recorded	[38]	-	FEV1, Pmax, VO2 peak absolute, AQAP, CFQ-R
		46 cm chair, 1' rest before the test, 5 STST1' conducted, at least 15' recovery if 2 STST the same day, mean of 3 last attempts recorded	[27]	VO2 peak (%) ^{s}; Pmax (%) ^{s};FEV1 (%) ^{w}; FVC (%) ^{vw}; BMI ^{w}; Physical functioning CFQ-R ^{s}	-
	Power STST	40 cm chair, 1 practice test (patients familiar with test), 3' rest seating before STST1', self-chosen speed, stop allowed, PowerSTST = [(Leg length – 0.4) x body mass x g x STS reps] / Time STS	[34]	Height ^{vs}; Weight ^{vs}; VO2 peak (%) ^{w}; Pmax (%) ^{w}; VO2 peak absolute ^{vs}; Pmax absolute ^{vs}	-

(*continued on next page*)

Table 4 (*continued*)

Muscle tool		Measurement procedure	Reference	Related outcomes	
				Significant correlations	Lack of correlation
	STST x body weight	46 cm chair, demonstrated by the operator, "a few" practice tests, self-chosen speed, number of STS x Body weight (kg)	[38]	Pmax [m]; VO2 peak [m]; AQAP [m]	FEV1, CFQ-R
	Vertical Jump test	Vertical measuring device, subjects standing feet together and 1 arm fullyextended above their head, 3 attempts, countermovement jump technique: drop into a crouch from the standing position and,jump vertically as high as possible, best value of vertical jump height reported(difference between the highest pointof their jump and standard reach)	[41]	VO2 peak [w]	FEV1
	"Leg strength"	Cycle ergometer, all-out effort at pre-set speed, maximal peak power (peak torque during a pedal revolution multiplied by the rotational velocity) developed over a 10'' sprint at 60rpm recorded	[60]	LBM [vs]; MEP [s]	-
LLM HS	Isometric strength (dynamometry)	Computerized dynamometer, 2 practice trials and then 3 attempts with 8'' contractions (within 10% variation), both sides tested and best value recorded	[54]	CSI [s−]; MIP [s]; MEP [s]	FEV1 (%), BMI
	Isokinetic strength (dynamometry)	Computerized dynamometer, 5 alternate measures KF (alternate with KE) at 30°/s from 90° knee flexion to full extension followed by 1' rest and 5 measures at 90°/s, 10' rest before other side testing, average of both sides recorded	[52]	30°/s BMI [m], 90°/s FEV1 [s]	30°/s FEV1 (%), 90°/s BMI
ULM biceps	Isometric strength (dynamometry)	Computerized dynamometer, 2 practice trials and then 3 attempts with 8'' contractions (within 10% variation), both sides tested and best value recorded.	[54]	CSI [s-;] MEP [vs;] MIP [vs]	FEV1, BMI
		Handheld dynamometer, subjects in supine position, elbow flexion 90°, break method (gradually overcame patient's force), 3 attempts (2' rest), non-dominant limb tested and compensations accepted [βγ]	[56]	FEV1 (%) [s]; BMI [m]; MIP [m]	-
	1 RM	Full elbow flexion movement, increase of 0.5 to 1kg until 1 repetition and exhaustion	[30]	FEV1(L) [m]; FVC (L) [m]; HR rest [m−]	FEV1 (%), FVC (%); BMI, 6MWD, SpO2, Borg exercise
ULM forearm muscles	Handgrip	Handgrip dynamometer, 3 attempts, participants standing, arms at their side with a small distanceof the body (<20 cm), dominant hand, maximal isometric effort for 5'', best value recorded	[41]	FEV1 [vw]; VO2 peak [vw]	-
		Hydraulic hand dynamometer, arm in neutral position, elbow flexion 90° [δ]	[48]	FEV1 (%) [w]; FVC (%) [w]	-
		Handgrip dynamometer, 3 attempts, 1' rest, best value recorded.	[50]	Weight [s;] Height [m]; MEP [m]	Testosterone level, free testosterone level
		Handgrip dynamometer, subjects standing, shoulder adducted, elbow flexion 90°, repeated attempts until 10% variation maximum, both sides tested, best value recorded	[54]	MIP [m]; MEP [m]	FEV1 (%), BMI, CSI
		Handgrip dynamometer, "sustained handgrip force" recorded	[58]	Lean body mass (%IBW) [m]	-
ULM shoulder flexors	Isokinetic strength (dynamometry)	Computerized dynamometer, 3 attempts, elbow extended, shoulder flexion movement from shoulder flexion 90° to full elevation and back to the original position	[50]	Height [s]; MEP [s]	Testosterone level, free testosterone level
	Isokinetic strength (dynamometry)	Computerized dynamometer, 5 alternate measures SF (alternate with SE) at 30°/s from 90° knee flexion to full extension followed by 1' rest and 5 measures at 90°/s, 10' rest before other side testing, average of both sides recorded	[55]	-	FEV1, BMI
ULM shoulder extensors	Isokinetic strength (dynamometry)	Computerized dynamometer, 5 alternate measures SE (alternate with SF) at 30°/s from 90° knee flexion to full extension followed by 1' rest and 5 measures at 90°/s, 10' rest before other side testing, average of both sides recorded	[55]	-	FEV1, BMI

Studies that reported multiple muscle tests are reported repeatedly in this table; significant correlations are reported as indices within the table and correlation strengths are reported as follows: 0–0.19 = very weak,: reported as [vw], 0.20–0.39 = weak: reported as [w], 0.4– 0.59 = moderate: reported as [m], 0.60–0.79 = strong: reported as [s] and 0.80–1.0 = very strong: reported as [vs] (negative correlations were preceded by the "-" sign)

Abbreviations: AQAP: physical activity self-questionnaire ("auto-questionnaire activité physique"), BCM: body cell mass, BMI: body mass index, CFQ-R: cystic fibrosis questionnaire revised, CPET: cardio-pulmonary exercise testing, CSI: corticosteroid inhalation, D: dynamometric measurement, FAM: forearm muscles, FEV1: forced expiratory volume in 1 second, FFM: fat free mass, FVC: forced vital capacity, HG: handgrip, HR: heart rate, HS: hamstrings, IBW: ideal body weight, KE: knee extensors, KF: knee flexors, LBM: lean body mass, LLM: lower limb muscles, MEP: maximal expiratory pressure, MIP: maximal inspiratory pressure, PA: physical activity, Pmax: maximal power, SE: shoulder extensors, SF: shoulder flexors, SG: strain gauge, SNIP: maximum sniff nasal, SpO2: pulsed oxygen saturation, STST: sit-to stand test, ULM: upper limb muscles, VO2: oxygen consumption, 6MWD: 6-minute walking distance

[α] Reference equation: Decramer M, de Bock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996; 153: 1958–1964.

[β] Reference equation: Backman E, Johansson V, Hager B, Sjoblom P, Henriksson KG 1995 Isometric muscle strength and muscular endurance in normal persons aged between 17 and 70 years. Scandinavian Journal of Rehabilitation Medicine 27: 109–117

[γ] Reference equation: Backman E, Odenrick P, Henriksson KG, Ledin T 1989 Isometric muscle force and anthropometric values in normal children aged between 3.5 and 15 years. Scandinavian Journal of Rehabilitation Medicine 1989 21: 105 –114

[δ] Reference equation: Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil 1985; 66: 69–74.

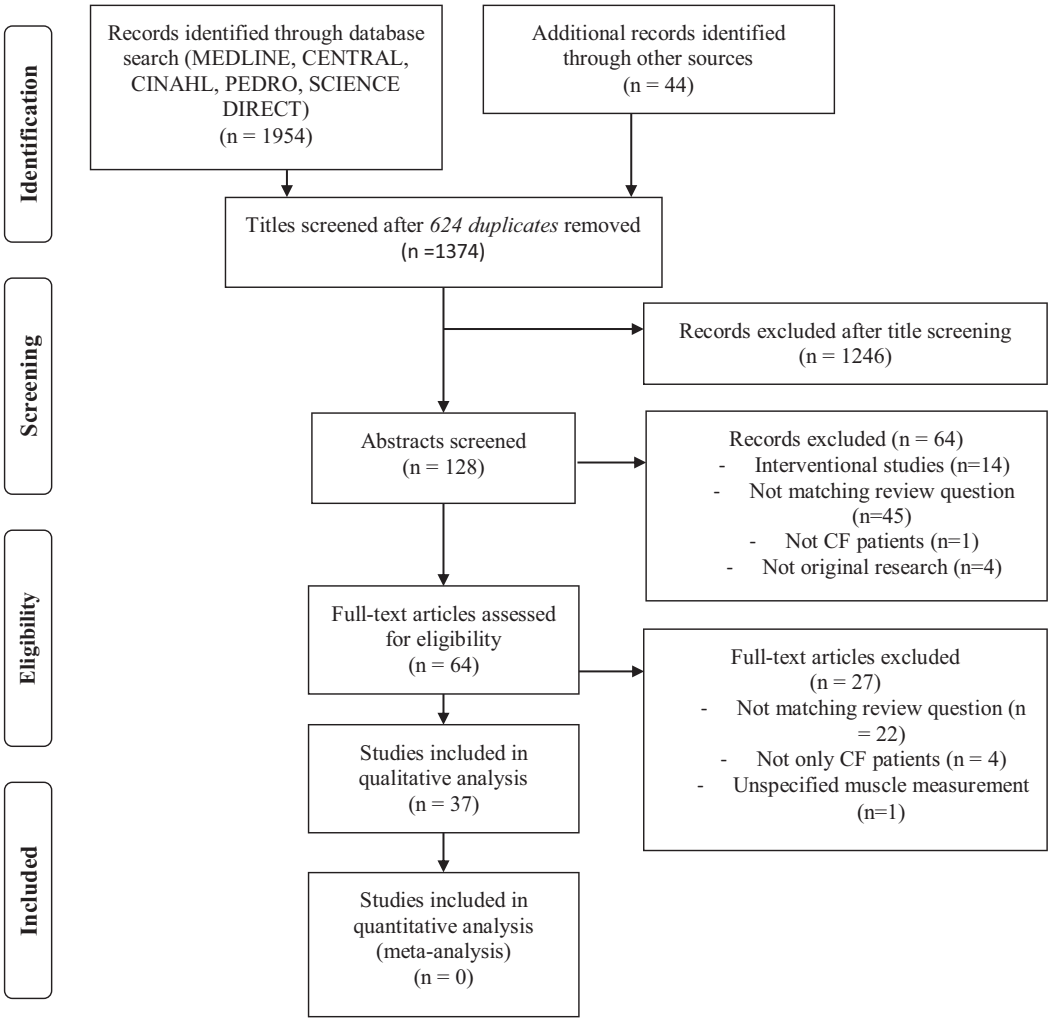

Fig. 1. PRISMA flow diagram of the studies included

Two studies reported strong to very strong correlations between quadriceps strength and forced expiratory volume in 1 second (FEV1) in children with CF (correlation coefficients ranging from r=0.72 to 0.82) [35,55]. Three studies of adults with CF reported non-significant or moderate correlations between quadriceps strength and lung function [30,48,54]. Three studies evaluated STST1' in adults with CF and reported moderate correlations with lung function and nutritional status [27,34,38]. Moreover, significant strong correlations were reported between STST1' and peak oxygen uptake (peak VO2 expressed as the percentage of predicted value) in two studies (r=0.63 and r=0.66 respectively) [27,34]. Another study contradicted these results and reported a lack of correlation between STST1' and peak VO2 (absolute value) and with quadriceps strength measured using handheld dynamometry [38]. Finally, derived measures of STST1' (linked with body weight) revealed stronger associations with peak VO2 and a moderate relationship with quadriceps strength measured using handheld dynamometry [34,38]. One study reported a very strong correlation between quadriceps strength measured with or without magnetic twitch stimulation of the femoral nerve and testosterone levels in adults with CF [43].

3.4. Risk of bias assessment

Details of the risk of bias assessment are reported in the Table 5. The three studies that evaluated the reliability of MIP, IWC, STST1' and both MVC and endurance time of the quadriceps muscle all lacked investigator blinding to prior findings or other information relative to clinical status of the individuals included [27–29]. Only one study evaluated criterion validity and reported similar limitations regarding the applicability of the 4 tests evaluated for routine practice and the selection of the individuals included, but the reference standard test was well-conducted [26].

4. Discussion

The main findings of this systematic review were that:

1) although few studies have evaluated the clinimetric properties of muscle function tests in individuals with CF, the data indicated that a) MIP and IWC are reliable measurements of inspiratory muscle function in adults with CF, b) quadriceps MVC (measured with computerised dynamometry) is reliable; but quadriceps endurance-time evaluated by sustained contractions is highly variable despite satisfactory relative reliability; c) STST1' is a reliable and responsive test of functional exercise capacity in adults with CF but its validity for the measurement of quadriceps strength is unknown and d) other field tests (STST30", vertical jump test, triple hop distance, stair climbing power test) have verified criterion validity for the measurement of quadriceps strength in adults with CF, however their reliability as well as the other components of validity still need to be evaluated.

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Table 5
Risk of bias of the studies that evaluated the reliability (QAREL) and the validity (QUADAS-2) of the different muscle function tests.

References		Tool	QAREL											
			Sample of subject's representative?	Raters representative?	Raters blinded to other raters' findings?	Raters blinded to their prior findings?	Raters blinded to the results of the reference standard?	Raters blinded to other clinical information?	Raters blinded to additional cues?	Order of the examination varied?	Time interval between repeated measures suitable?	Test applied and interpreted correctly?	Appropriate measures of agreement?	Global score /11
Reliability studies	[29]	MIP	Yes	Yes	N/A	No	No	No	No	No	Yes	Yes	Yes	5/10
	[29]	IWC	Yes	Yes	N/A	No	No	No	No	No	Yes	Yes	Yes	5/10
	[27]	STST1'	No	Unclear	No	No	No	No	No	No	Yes	Yes	Yes	3/11
	(28)	MVC quadriceps	Yes	Unclear	No	No	No	No	No	No	Yes	Yes	Yes	4/11
	[28]	Endurance time	Yes	Unclear	No	No	No	No	No	No	Yes	Yes	Yes	4/11
Total agreement between the raters = 97%														

References		Tool	QUADAS-2						
			Risk of bias				Concerns about applicability		
			Patient selection	Index Test	Reference standard	Flow and timing	Patient selection	Index Test	Reference standard
Validity studies	[26]	STST30''	Low	Low	Low	High	Low	Low	Low
	[26]	Vertical Jump Test	Low	High	Low	High	Low	Low	Low
	[26]	Stair climb power test	Low	Unclear	Low	High	Low	High	Low
	[26]	Triple hop distance	Low	Unclear	Low	High	Low	Unclear	Low
Total agreement between the raters = 89%									

Abbreviations: IWC: inspiratory work capacity, MIP: maximal inspiratory pressure, MVC: maximal voluntary contraction, STST1': one-minute sit-to-stand test, STST30'': 30 seconds sit-to-stand test

2) the clinimetric properties of measures of isometric quadriceps strength using a strain gauge or handheld dynamometry and isokinetic quadriceps strength tests have not been evaluated in either adults or children with CF.
3) RM strength, ULM strength and LLM strength are moderately to strongly positively correlated with each other.
4) RM strength is not correlated with lung function; however, quadriceps strength is, especially in children with CF.

This systematic review identified a single study that addressed the reliability of tests of RM function [31]. In this study, MIP increased by 163% following a habituation protocol. This level of difference could be considered as a clinically important, while it is in fact merely a learning effect. This calls into question the accuracy of first-time MIP measurements in people with CF. Unfortunately, the differences between the two last MIP measurements (after the habituation protocol) were not analysed statistically, therefore we could not determine if, following a habituation protocol, one further MIP measurement is sufficient or if several more measurements are required to eliminate the learning effect [29]. Surprisingly, there was no mention of the use of a habituation protocol in the recently published recommendations for RM testing [10]. However, one study reported that a warm-up session prior to testing (two sets of 30 repetitions in an inspiratory muscle training device with a load set at 40% of personal MIP) significantly reduced MIP variability in healthy subjects [63]. This evidence suggests that several MIP measurements should be taken to control for any learning effect when testing MIP, especially in individuals for whom the test is new. Although in clinical practice, this will increase the test duration but it will improve reliability.

None of the other studies that evaluated the correlation between RM strength (measured by MIP) and other outcomes used any sort of habituation protocol. This could explain the disparity of results across the studies. Moreover, it was not specified if the individuals were familiar with MIP measurements before the study. Another explanation could be that because CF respiratory symptoms vary from day-to-day, this may have affected the relationship between RM strength and other outcomes [64]. However, most of the individuals included in the studies targeted were clinically stable (defined as not having had an acute exacerbation for several weeks). It is also important to note that the studies also used different methodologies and testing procedures. For example, the numbers of trials conducted varied across studies, with some not even reporting the number. Laveneziana et al. recently recommended conducting 3 MIP trials (with a maximal variability of 10%) and report the best value [10]. Furthermore, RM strength was expressed according to different reference equations that have led to different results regarding the degree of weakness (Table 3) as has been previously shown in various chronic respiratory conditions [14]. Recently published guidelines have also stated that MIP measurements conducted at residual volume (RV) or at functional residual capacity (FRC) should be compared with caution, since the measurement at FRC depends on lung hyperinflation and the severity of the restriction [10].

The STST1' was found to have high intra-observer reliability, test-retest reliability and responsiveness in this systematic review, but we did not find any studies that addressed its validity for the measurement of quadriceps strength [27]. Gruet et al. reported that the STST1' was not correlated with quadriceps strength measured with handheld dynamometry, however handheld dynamometry cannot be considered as a reference test for the measurement of quadriceps strength, and their finding was only based on the results of one performance of the test [38]. In contrast, a recent study found that the STST1' had significant criterion validity for the measurement of quadriceps strength in individuals with COPD when five iterations were performed [65]. This difference might be due to the greater number of trials performed in the study by Crook et al. [52]. Further research is needed to assess the different aspects of validity of the STST1' for the measurement of quadriceps strength using the results from multiple trials of the test, to ensure maximal effort. Another explanation is that COPD patients in that study had a large functional impairment (mean STST1': 16 to 24 repetitions) compared to age-adjusted reference values (35 to 41 for men and 33 to 36 for women), and a large inter-individual variability on the STST1' results that could have led to a stronger correlation between STST1' and quadriceps strength [65,66]. On the other hand, individuals with CF had almost normal STST1' results in the studies included in the present review suggesting a potential ceiling effect with a lower inter-individual variability that could be responsible for the absence of strong association between the STST1' results and other outcomes [27,38,66]. The other field tests for LLM function described in this systematic review (STST30'', vertical jump test, triple hop distance, stair climbing power test) had significant criterion validity for the measurement of quadriceps strength [26]. However, the complete validation of a measurement tool requires evaluation of all the components of validity (construct validity through hypothesis testing or agreement or content validity using cross-sectional validation). Moreover, further studies should be conducted to identify other factors associated with performance on such tests since relationships with other factors have not yet been explored. For instance, the vertical jump test was only weakly correlated with VO2 peak [41]. We therefore suggest that these tests cannot currently be used to replace specific quadriceps strength measurements and further studies to evaluate their clinimetric properties (such as test-retest or inter-rater reliability and complete validation) are needed.

The function of the quadriceps muscle is of extreme importance for the performance of functional tasks and activities of daily living in individuals with CF. One of the studies included in this systematic review reported high test-retest reliability and low variability for the measurement of quadriceps strength [28]. In that study, quadriceps strength was measured using an experimental isometric computerised dynamometer connected to a torque transducer. This experimental device showed robust clinimetric properties but may be difficult to implement in routine clinical practice [67]. We did not find any studies that reported the clinimetric properties of other specific quadriceps strength measurements (handheld dynamometry, 1-rep max or strain gauge testing) in this particular population. Computerized dynamometry is generally considered as the gold standard for the assessment of isometric quadriceps strength, however its use in clinical practice is limited by the high equipment costs [16]. Although it has been considered as reliable in COPD patients, methodological issues between studies such as limb position or number of attempts have been reported [68]. Similarly, the procedures used in the studies included in the present systematic review that report outcomes associated with quadriceps (or other LLM) strength are very varied which limits the comparison of results. Gruet et al. recently stated that if computerized dynamometry is unavailable due to technical limitations, strain gauge measurements should be considered [67]. Strain gauge testing has been found to have high validity and reliability in individuals with COPD [16]. It has also been shown to be feasible in people with CF, however the clinimetric properties of this test have not yet been evaluated in the CF population [37]. In the present work, a few studies have used handheld dynamometry to evaluate quadriceps muscle strength [38,54,57]. Handheld dynamometry is easily implementable in clinical practice due to its low cost and ease of use; nevertheless, its reliability also depends on the strength of the tester even in frail individuals [69]. Handheld dynamometry measurements in active individuals with CF with higher quadriceps strength could therefore be highly variable. Recent studies have suggested the use of fixed handheld

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dynamometry to enhance measurement accuracy in patients with COPD [70,71]. That procedure was used once in people with CF but the clinimetric properties of the measure were not reported, except for the absence of a correlation with both the STST and 6-minute walking test results [38].

The measurement of quadriceps muscle endurance was also reported to have high relative test-retest reliability for individuals with CF [28]. However, the time to exhaustion of the quadriceps muscle (time limit) was highly variable across repeated measurements in individuals with CF compared to healthy controls [28]. One explanation for this is that the protocol used in that study was based on a sustained contraction of the quadriceps muscle (at 50% of the MVC), which is highly dependent on subject motivation and could have led to early discomfort in the CF population due to rapid muscle ischemia [72]. Protocols including incremental loading and both voluntary and evoked contractions of the quadriceps muscle (e.g. the QIF: quadriceps intermittent fatigue test) published later have shown high reliability in healthy subjects, and have the advantage of being less affected by motivation or discomfort [73]. One study by Gruet et al., described in this review, used such a protocol to compare quadriceps endurance in individuals with CF and healthy peers, but its reliability for use in CF has not yet been addressed [37]. Another study reported a lower number of knee-bends performed by young girls with CF compared to healthy peers, suggesting impaired quadriceps endurance [53]. The clinimetric properties of the knee-bend endurance test were not assessed and were therefore not reported in this systematic review. Endurance testing of the quadriceps muscle could be of great interest for individuals with CF. Future studies should evaluate the performance of both individuals with and without CF matched for physical activity level during a specific quadriceps muscle test with progressive incremental loading (including evoked contractions) and minimal cardio-respiratory demand to avoid confounding factors [2,72].

This systematic review aimed to report the validity of different muscle function measurements in individuals with CF. However, criterion validity was the only component of validity reported for 4 different tools to measure quadriceps strength, and furthermore it was only assessed using simple correlations with the reference test (i.e. computerised dynamometry) in a single study [26]. These tools cannot be confirmed as valid based only on criterion validity. Further research is therefore required to complete the few available data. To note, one study reported correlations between MRPD during MIP and MEP measurements, and MIP and MEP; however, these measures were taken during the same manoeuvre and cannot be considered as the assessment of criterion validity [42]. Future studies should take potential confounding factors into account by performing multivariate analyses of the correlations between the different methods used to measure muscle function rather than single correlations only [48]. Furthermore, all components of the validity of a measurement tool need to be evaluated; future studies should explore agreements between muscle function measurement tools and the corresponding reference tests through the Bland-Altman approach [74]. This approach indicates if a measurement has an acceptable level of error when measuring the same construct as the reference test. Evaluation of the construct validity of these tools by testing hypothesis is necessary to determine the extent to which a measurement tool relates to the outcome addressed (the specificity to detect muscle weakness, positive predicted value, the predictive or discriminative capacity through receiver-operating curves etc.) [12,75]. Cross-sectional validation is also essential to determine if similar changes occur in both the tool being evaluated and the gold standard following an intervention [75]. The evaluation of criterion validity based on single linear correlations is important but insufficient. Evaluation of all the components of validity is fundamental to determine the validity of a tool for the measurement of a particular variable in a particular population.

5. Limitations

This systematic review has several limitations. Firstly, only 4 of the 37 studies included actually addressed the primary outcome of this review. Secondly, the studies included used different measures of muscle function and those that used similar tests employed different measurement procedures, thus comparisons were limited. Moreover, some of the samples of individuals with CF included in the retrieved studies were heterogenous. This may have strengthened the correlations between different outcomes as several individuals presented heterogenous levels of lung function, functional exercise capacity or muscle function. Furthermore, the studies included in this systematic review included children, adults or both. Numerous factors including oxidative stress, inflammation or frequent exacerbation and CF-related comorbidities (e.g. CF-related diabetes) that could contribute to muscle function impairment tend to be increased through the lifespan of individuals with CF leading to greater muscle dysfunction in adults compared to children [76–78]. It is also important to note that maximal exercise testing measurements were not included within this systematic review and only specific measurements of muscle function were identified. Finally, the exclusion of interventional studies that did not evaluate clinimetric properties meant that the analysis of relationships between muscle function and other outcomes was not exhaustive, since observational studies that evaluated relationships with other outcomes were included whilst interventional studies that only reported relationships with other outcomes were not.

Despite these limitations, however, this study reported the results from 1310 individuals with CF which we consider to be a large, representative sample. This systematic review is the first to address the question of clinimetric properties of the muscle function tests in individuals with CF and highlights areas of future research to improve the accuracy of muscle testing and rehabilitation.

6. Conclusion

Several muscle function tests for use in people with CF are described in the literature. Of these, MIP and IWC were shown to be reliable in adults if used after a short period of training or habituation for the patient to measure RM strength and endurance. For LLM, the measurement of quadriceps MVC using an experimental isometric dynamometer was shown to be reliable, with little variability across repeated measurements. Different field tests (mostly the STST1') have also been evaluated, but none of these tests can be considered as valid to measure muscle function and there are insufficient data to enable evidence-based practice recommendations to be made.

Future studies, therefore, are needed to identify, evaluate and validate tests that can be readily used in routine clinical practice for the assessment of muscle function in individuals with CF. At the time of writing, for example, no papers exist on the clinimetric properties of tests of expiratory muscle or ULM function, or for the specific (isometric or isokinetic handheld dynamometry) measurement of quadriceps muscle strength in this population. High-quality, original research is thus needed in this area. Moreover, the responsiveness of the different measures of muscle function to evaluate change following different treatments, as well as the minimal clinically important difference for individuals with CF are yet to be determined.

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Declaration of Competing Interest

None.

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Supplementary materials

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