BMJ Open Respiratory Research

Patient-reported outcome measures for use in patients with alpha-1-antitrypsin deficiency: results of a systematic selection process

Karolina Müller ,[1] Louisa Vogl,[1] Helge Knüttel ,[2] Timm Greulich,[3,4] Frank Lammert,[5,6] Pavel Strnad,[7] Claus, Franz Vogelmeier,[3] Marion Wilkens,[8] Robert Bals,[9] Michael Koller[1]

To cite: Müller K, Vogl L, Knüttel H, *et al*. Patient-reported outcome measures for use in patients with alpha-1-antitrypsin deficiency: results of a systematic selection process. *BMJ Open Respir Res* 2025;**12**:e003583. doi:10.1136/bmjresp-2025-003583

RB and MK are joint senior authors.

Received 25 June 2025
Accepted 2 November 2025

For numbered affiliations see end of article.

Correspondence to
Professor Michael Koller; m.koller@ukr.de

ABSTRACT

Objective Alpha-1-antitrypsin deficiency (AATD) is a hereditary condition associated with the risk of developing chronic lung and liver disease. We aimed for a patient-reported outcome measure (PROM) that addresses generic, lung-specific and liver-specific aspects of quality of life (QoL) in individuals with AATD. Rather than developing a new PROM, we evaluated existing PROMs.

Method An extensive literature search and eligibility assessment, accompanied by standardised group processes including patient representatives, were conducted in accordance with the guidelines in this research area (COnsensus-based Standards for the selection of health Measurement INstruments, COSMIN; Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Prisma; Peer Review of Electronic Search Strategies, PRESS).

Results Over 1200 records were identified and screened. In total, 427 PROMs were obtained and assessed for eligibility. 15 of the 247 PROMs fulfilled the predefined eligibility criteria. The final selection of the three PROMs—EuroQoL 5 Dimension 5 Level (generic), COPD Assessment Test (lung-specific) and Chronic Liver Disease Quality of Life (liver-specific)—was guided by factors such as brevity, ease of use, interpretability, strong content validity, availability of minimal clinically important differences, sensitivity to change, ability to differentiate disease severity and availability of reference data. A questionnaire was assembled that incorporated the three selected PROMs, as well as additional QoL issues not covered by them, to ensure a comprehensive assessment of patient-reported outcomes.

Conclusion The PROM named Assessment of Lung, Liver and Patient Health in Alpha-1 (ALPHA) was designed to address generic, lung-specific as well as liver-specific QoL issues in patients with AATD. As a next step, the validity and feasibility in clinical practice of the designed questionnaire will be evaluated.

PROSPERO registration number CRD42021265360.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Up to now, there is no accepted and validated measurement approach addressing quality of life in patients with alpha-1-antitrypsin deficiency.

WHAT THIS STUDY ADDS

⇒ We reviewed the current literature on patient-reported outcome measures for alpha-1-antitrypsin deficiency. Based on our findings, we propose a measure that covers generic, lung-specific and liver-specific aspects of quality of life in patients with this rare disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our work contributes to enhancing patient-centred assessment in alpha-1-antitrypsin deficiency and may support both clinical care and future research by promoting the standardisation in outcome measurement.

INTRODUCTION

Alpha-1-antitrypsin deficiency (AATD) is a hereditary condition that encompasses rare severe forms (such as the most common type Pi*ZZ) as well as mild genotypes (such as Pi*MZ).[1] AATD is associated with an elevated risk of developing chronic obstructive pulmonary disease (COPD), emphysema, chronic liver disease, ANCA-positive vasculitis and panniculitis.[1 2] The management of AATD primarily addresses lung and liver pathologies. Pulmonary manifestations present as an early-onset form of COPD and emphysema and are treated similarly to the non-deficient forms. Additionally, these patients may receive augmentation therapy with weekly infusions of purified AAT. At present, no specific drug has been approved for the treatment of liver disease associated with AATD.

Awareness is growing that patient-reported outcomes (PROs) are a crucial element of both effective patient care and well-designed clinical studies.[3] The umbrella term PRO

relates to all types of outcomes that are directly reported by patients, such as quality of life (QoL), satisfaction with care, preferences or somatic symptoms.[4] QoL is the most encompassing concept and is commonly defined as a multidimensional construct covering subjective well-being and behavioural capacities in the psychological, social and somatic domains.[5]

Patient-reported outcome measures (PROMs) were initially designed for clinical trials to evaluate treatment efficacy. Over time, their use has expanded into routine clinical practice, aiding clinical decision-making and treatment planning.[6] It is widely agreed that assessing PROs is particularly valuable for individuals with chronic conditions. PROs enhance communication between patients and healthcare providers by offering information about symptoms, side effects and QoL. This ensures that patients feel better heard and understood. Consequently, the selection of appropriate PROMs is essential not only for clinical studies but also for everyday clinical care, to ensure relevance and utility in both contexts.

The overall goal of this project was to survey the current state of PRO assessment in AATD patients to identify an appropriate assessment system and, subsequently, to test its feasibility and validity through a pair of studies to be conducted in specialised AATD centres across Germany.

This paper presents the results of a systematic literature review and outlines the decision-making process for selecting the most appropriate PROMs.

METHOD

Overview

The selection of PROMs requires a profound methodological approach.[6] Therefore, the current project was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement on reporting systematic review protocols,[7] the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) initiative on systematic reviews of PROMs and selection of outcome measures,[8 9] as well as additional guidelines in this research area.[3 10–12] The study protocol was registered in PROSPERO (CRD42021265360), and the corresponding protocol was published.[13]

We searched for PROMs that were specifically developed for AATD patients as well as for PROMs used in the context of AATD studies. These PROMs might assess generic QoL or address symptoms and signs connected with the sequelae of AATD, in particular COPD or chronic liver disease. All identified instruments were rated against pre-defined eligibility criteria and content-based criteria defined by clinical experts.

Our selection process focused on the content and clinical appropriateness of PROM candidates (which are the initial criteria according to COSMIN) rather than on their psychometric properties. Our project also included an empirical phase to investigate the feasibility and psychometric performance of the selected PROMs. Results will be addressed in upcoming publications.

Defining selection criteria

Basic eligibility criteria

At the start of the project, the research group specified a set of eligibility criteria that the questionnaire should fulfil[13]: The questionnaire

- Is a PROM and assesses QoL.
- Is available in German.
- Is designed for adults.
- Is either specifically developed for AATD patients and/or covers generic aspects and/or disease-specific aspects for either lung or liver symptoms of AATD patients.
- Covers a range of early and late disease symptoms seen in these patients.
- Is user-friendly, short and free of charge for academic use.

Defining contents from a clinical perspective

Relevant QoL domains for AATD patients were defined in the context of a standardised group process.[11] The group consisted of six experts (clinicians: RB, TG, CV, FL, PS, and representative of patient organisation: MW) with years of experience in treating or caring for AATD patients (range 6 years to 35 years). In preparation for the group process, two experts in QoL (KM and MK) prepared a list of 151 QoL issues that covered general QoL aspects (n=38), general symptoms (n=50), lung-specific symptoms (n=17) and liver-specific symptoms (n=46). This list was sent out to the six AATD experts, who independently rated each QoL issue on a 4-point Likert scale (0=not relevant, 1=less important, 2=important, 3=very important). Results of the survey were presented and consented to in a web-based group meeting. Table 1 summarises the outcome of the group consensus.

Systematic search for PROMs

Literature search I: PROMs specifically developed for AATD patients

In July 2021, the questionnaire databases PROQOLID, Hogrefe Testzentrale, Open Test Archive and Registry of Scales and Measures were searched for AATD-specific PROMs by a statistician with methodical expertise (KM). Only a single concept, “AATD” was used. The search was adapted for several synonyms, such as “α1-antitrypsin deficiency”, “alpha 1-antitrypsin deficiency”, “alpha-1 antitrypsin deficiency” and “alpha-1-antitrypsin deficiency”.

Literature search II: PROMs used in AATD patients

In July 2021, searches in electronic bibliographic databases (MEDLINE (Ovid), Embase (Ovid), Science Citation Index Expanded & Social Sciences Citation Index (Web of Science), APA PsycInfo (EBSCOhost), CINAHL (EBSCOhost), COSMIN Database of Systematic Reviews

Table 1 Summary of relevant quality of life domains and aspects selected by experts

General physical health	Exercising activities	Social aspects	Emotional aspects	Fear regarding liver problems	Fear regarding lung problems	Unspecific symptoms	Symptoms of fatigue	Organ specific symptoms
Physical fitness	Acting independently	Restrictions on family life	Worries/fears about the future	Concern regarding availability of an organ in case of transplantation	Fear of dyspnoea	Muscle atrophy	Loss of performance	Cough in general
Assessment of the general state of health	Performing strenuous/ moderately strenuous/ light activities	Family planning	General worries	Fear of worsening of liver disease	Fear of oxygen dependence	Susceptibility to infections	Decreased energy	Dry cough
Invalidity (permanent)	Limitation in everyday activities	Social isolation	Fear of immobility		Fear of asphyxiation	Weight loss	Exhaustion	Shortness of breath
	Limitations in the exercise of profession		Fear of death		Concern regarding availability of an organ in case of transplantation	Loss of appetite	Concentration disturbance	Phlegm
	Limitation in the practice of hobbies		Anxiety in general				Difficulties in thinking and problem solving	Sputum when coughing
	Activity limitation due to respiratory problems		Emotional problems				Sleepiness	Respiratory distress
			Depression				General fatigue	Jaundice of the eyes
							Daytime sleepiness	Jaundice of the skin

and Cochrane Library (Wiley)), the web search engine Google Scholar (first 100 results) and trial registers for ongoing and recently completed trials (ClinicalTrials.gov and EU CTR) were carried out in accordance with COSMIN and Peer Review of Electronic Search Strategies (PRESS) guidelines.[8 12] As a deviation from the protocol, WHO ICTRP was not searched as the platform was not in a fully functional state at that time.

Complete and reproducible search strategies and Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Search Extension (PRISMA-S) checklist are available.[14] An initial search strategy for MEDLINE was created by a librarian with expertise in searching for systematic reviews (HK) and peer-reviewed by an independent librarian (BD). This strategy was then adopted to the other databases. No limits regarding study design, date or language were used.

Additionally, the reference lists of included primary studies and relevant published reviews, as well as the authors' personal files, were used as sources of information by the reviewers (KM and LV).

Literature search III: PROMs used in patients with lung or liver disease

As lung and liver disease are the most common clinical sequelae of AATD,[2] the COSMIN database of systematic reviews of outcome measurement instruments was searched by KM in January 2022 for reviews of PROMs used in patients with "lung disease" and "liver disease" to identify potentially relevant PROMs for AATD patients.

Screening records

Abstract screening and preparing full texts

Two reviewers (KM and LV) independently screened the titles and abstracts of all records (including primary studies, reviews, position papers, abstracts, trials) identified by the searches, with a focus on whether the records contained the target concepts AATD patients and PROM. Next, full texts of all records that included these target concepts were obtained. Full texts were excluded if any of the exclusion criteria applied: duplicate, previous version of a record, no adequate translation by using Google Translate or DeepL Translator could be carried out, no full text of the record could be requested, no AATD topic was addressed and the record did not capture the target concept (AATD patients and PROM). Disagreement regarding the eligibility of specific records was discussed by the reviewers (KM and LV) and resolved by consensus. If consensus could not be obtained, a third reviewer was involved (MK). The number of records at each stage of the search and the reasons for excluding records were recorded. None of the reviewers was blinded to the journal titles, the study authors or the institutions.

Full text screening

The reviewers (KM and LV) independently read the full texts of the remaining records and identified the use of PROMs in the context of AATD patients. The numbers of identified generic, lung-specific and liver-specific PROMs were recorded.

Selecting PROMs

PROM eligibility assessment

KM and LV independently screened the identified PROMs and excluded PROMs that did not meet the predefined basic eligibility criteria[13] and relevant QoL domains (table 1). Disagreement regarding the eligibility of PROMs was discussed by the reviewers (KM and LV) and resolved by consensus. If consensus could not be reached, a third reviewer was involved (MK).

Study group consensus

The study group consisted of clinical AATD experts (RB, TG, CV, FL and PS), a representative of a patient organisation (MW) and methodological experts (MK and KM). Based on the findings of the literature search and the clinical perspective with regard to an adequate PROM, the group discussed various options and came to a final decision by group consensus.[11]

Data management

All records identified in database searches were compiled in Citavi. Duplicates were removed in Endnote using the method of Bramer *et al*.[15] Review documentation was compiled in the free web tool Rayyan (www.rayyan.ai) and Microsoft Excel. Review documentation in Rayyan was stored on cloud services and automatically backed up daily. Review documentation, search results studies and relevant PROMs were saved and backed up on the institute's own data server. Data were only accessed by the reviewers (KM, LV and MK).

RESULTS

Overview

Figure 1 represents an overview of the literature search and the identification and selection process. The literature search process yielded a total of N=2045 records. After removing duplicates, n=1255 records were screened for the target concepts AATD patients and PROM. In the resulting n=191 records, 427 PROMs were identified. Different versions of PROMs (eg, 36-Item Short Form Health Survey (SF-36) and 12-Item Short Form Health Survey (SF-12) or EuroQoL 5 Dimension 3 Level (EQ-5D-3L) and EuroQoL 5 Dimension 5 Level (EQ-5D-5L)) as well as usage of single or all subscales of a PROM (eg, EuroQol Visual Analogue Scale (EQ VAS) and/or EuroQol Health Utility Index (EQ Index)) in a record were combined into one hit. Eligibility assessment of the 427 PROMs resulted in a total of 15 eligible PROMs. Information about screened records and the eligibility assessment of hits is available.[14]

Literature search I: PROMs specifically developed for AATD patients

Comprehensive literature search I did not identify a single questionnaire that was specifically developed for AATD patients.

Literature search II: PROMs used in AATD patients

In total, 48 PROMs were identified that had been used for outcome assessment in patients with AATD. Of these, n=11 could be labelled 'generic', n=16 'lung-specific', n=1 'liver-specific' and n=20 'other' (eg, Oral Health Impact Profile-14). Additionally, in ten records, no standardised questions were used and in six records, a specific PROM was not named.

Literature search III: PROMs used in patients with lung or liver disease

28 of the 48 identified PROMs in literature search II were also identified in literature search III. Additionally, 379 PROMs were identified that had been used for outcome assessment in patients with lung or liver disease. Of these, n=196 could be labelled 'generic', n=60 'lung-specific', n=4 'liver-specific' and n=119 'other disease specific' (eg, Inflammatory Bowel Disease Questionnaire).

Eligibility assessment and preselection of PROMs used in AATD patients: creating a short list

The identified 427 PROMs were compared with basic eligibility criteria and content criteria specified by the experts. As a result, 412 questionnaires were omitted due to the following reasons:

- n=266 were not or partially not relevant in terms of content.
- n=53 were not available in German.
- n=74 did only address one relevant QoL dimension,
- n=19 other reasons (not for adults, interviewer administered, too many items, not standardised (single) items, fees/conflicting information on licence costs).

The exclusions were consented to by AATD experts, resulting in a short list of 15 PROMs (table 2):

- Generic=COOP/WONCA charts,[16] EQ-5D-5L,[17] Functional Assessment of Cancer Therapy-General (FACT-G),[18] Memorial Symptom Assessment Scale-Short Form (MSAS-SF),[19] Nottingham Health Profile (NHP),[20] Profil der Lebensqualität Chronisch Kranker (Profile of Quality of Life with Chronic Disease) (PLC),[21] Psychological General Well-Being Index (PGWBI).[22]
- Lung-specific=Breathlessness, Cough and Sputum Scale (BCSS),[23] Chronic Respiratory Disease Questionnaire (CRQ),[24] Clinical COPD Questionnaire (CCQ),[25] COPD Assessment Test (CAT),[26] Pulmonary-Specific Quality of Life Scale (PQLS),[27] Quality of Life

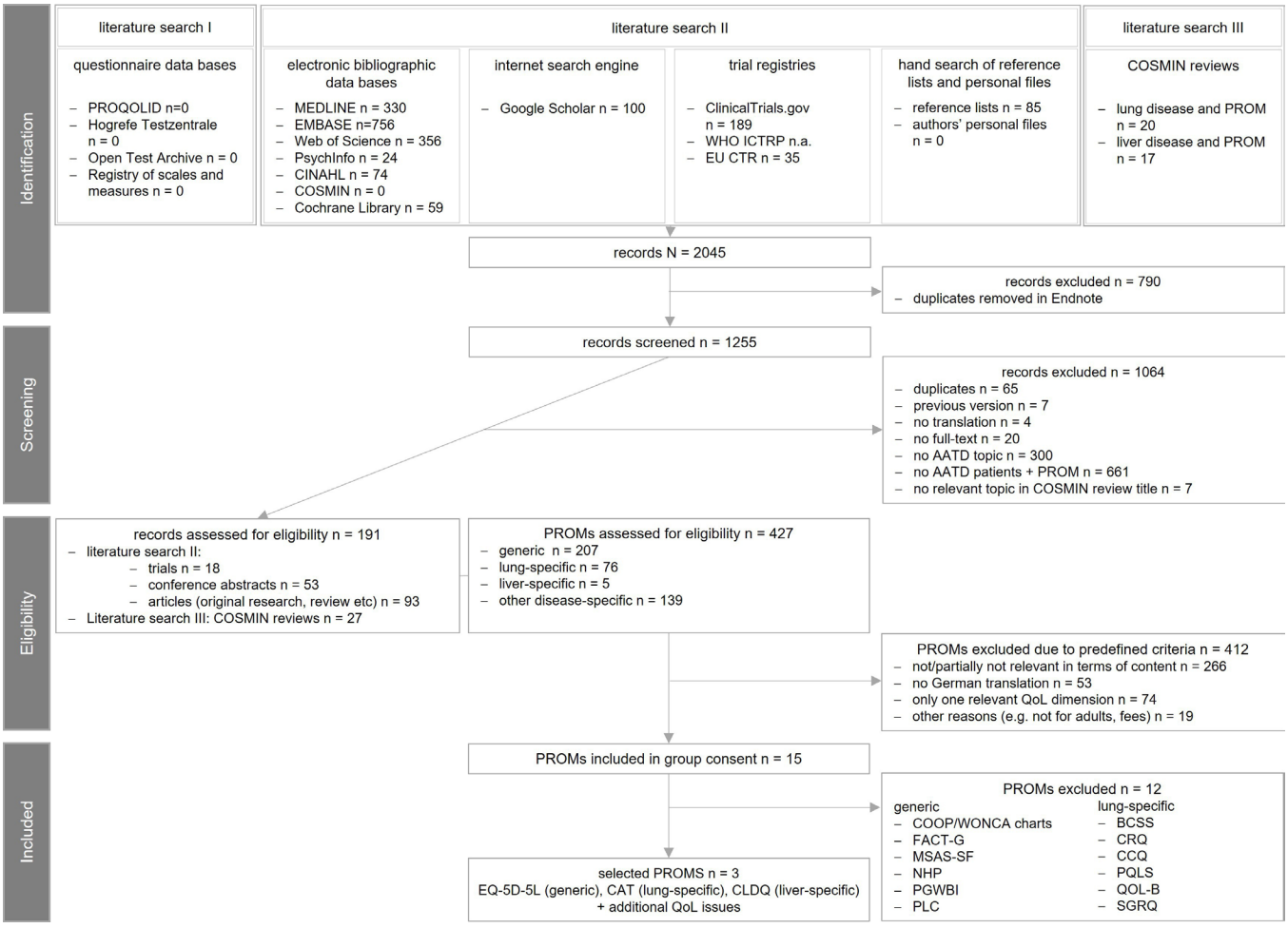

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. AATD, alpha-1-antitrypsin deficiency; BCSS, Breathlessness, Cough and Sputum Scale; CAT, COPD Assessment Test; CLDQ, Chronic Liver Disease Quality of Life; COSMIN, COsensus-based Standards for the selection of health Measurement INstruments; CRQ, Chronic Respiratory Disease Questionnaire; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; FACT-G, Functional Assessment of Cancer Therapy-General; MSAS-SF, Memorial Symptom Assessment Scale-Short Form; NHP, Nottingham Health Profile; PGWBI, Psychological General Well-Being Index; PLC, Profil der Lebensqualität Chronisch Kranker; PQLS, Pulmonary-Specific Quality of Life Scale; PROM, patient-reported outcome measure; QoL, quality of life; QOL-B, Quality of Life Questionnaire Bronchiectasis; SGRQ, St. George Respiratory Questionnaire.

Questionnaire Bronchiectasis (QOL-B),[28] St. George Respiratory Questionnaire (SGRQ).[29]

- Liver-specific=Chronic Liver Disease Quality of Life (CLDQ).[30]

Expert consensus: reasons for selecting PROMs from the short list

Generic PROM

The group agreed to select the widely used EQ-5D-5L because of its brevity, availability of normative data and suitability for health-economic evaluations.[17] PROMs measuring general QoL are less sensitive to map changes than disease-specific QoL.[31–33] The SF-12 would have been an alternative candidate that also shared these positive characteristics but was discarded at an earlier stage mainly due to conflicting information on licensing and cost issues.

The COOP-WONCA is easy to use with a short administration time, but it was rarely used in patients with COPD[34] and chronic liver disease.[35] The PGWB has been used in patients with mild asthma,[36] but there is little information on the development of the questionnaire and its factor structure. The MSAS-SF is longer than the EQ-5D-5L, and there remains uncertainty about the degree of developmental maturity of the questionnaire (unclear which version is recommended). Furthermore, it does not distinguish between moderate and severe COPD.[37] Although FACT-G was developed for cancer patients, it assesses QoL in a general manner without referencing any specific disease.[18] However, the FACT-G, NHP and PLC are longer than the EQ-5D-5L. Besides the length, the NHP is less used nowadays, and the PLC is only available in German.

Table 2 Preselected PROMs

PROM	Number of items	Domains	Scores	Completing time	Paper-based/ electronic	Recall period	Languages
Generic PROMs							
COOP/WONCA charts	6	6: physical fitness, feelings, daily activities, social activities, change in health, overall health	6: physical fitness, feelings, daily activities, social activities, change in health, overall health	<5 min	Paper-based	2 weeks	German, English+19 translations
EuroQoL 5-Dimension 5-Level (EQ-5D-5L)	6	6: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, general state of health	7: mobility score, self-care, usual activities, pain/discomfort, anxiety/ depression, EQ Index, EQ VAS	<5 min	Paper-based/ electronic	today	German, English+206 translations
Functional Assessment of Cancer Therapy-General (FACT-G)	27	4: physical, social/family, emotional, functional well-being	4: physical, social/family, emotional, functional well-being	5–10 min	Paper-based/ electronic	1 week	German, English+76 translations
Memorial Symptom Assessment Scale-Short Form (MSAS-SF)	32	2: physical symptoms, psychological symptoms	3: global distress index, physical symptom distress score, psychological symptom distress score	10–15 min	Paper-based	1 week	German, English+5 translations
Nottingham Health Profile (NHP)	45	6: sleep, physical mobility, energy, pain, emotional reactions, social isolation+life areas affected	6: sleep, physical mobility, energy, pain, emotional reactions, social isolation	>15 min	Paper-based	No specific recall period	German, English+27 translations
Profile der Lebensqualität Chronisch Kranker (Profiles of Quality of Life with Chronic Disease) (PLC)	40	6: physical, psychological and social capacity of performance and well-being	6: physical, psychological and social capacity of performance and well-being	>15 min	Paper based	1 week	German, Spanish
Psychological General Well-Being Index (PGWBI)	22	6: anxiety, depression, positive well-being, self-control, general health, vitality	7: anxiety, depression, positive well-being, self-control, general health, vitality, total score	5–10 min	Paper-based	1 week or 1 month	German, English+38 translations
Lung-specific PROMs							
Breathlessness, Cough and Sputum Scale (BCSS)	3	3: breathlessness, cough, sputum	3: breathlessness, cough, sputum	<5 min	Paper-based	Today	German, English 25 translations
Chronic Respiratory Disease Questionnaire (CRQ)	20	4: dyspnoea, fatigue, emotional function, mastery of breathlessness	5: dyspnoea, fatigue, emotional functioning, mastery of breathlessness, total score	10–15 min	Paper-based	2 weeks	German, English+19 translations
Clinical COPD Questionnaire (CCQ)	10	3: symptoms (dyspnoea, cough, phlegm), functional state (daily activities), mental state (depressed, concerns about breathing)	4: symptoms, functional, mental, total score	<5 min	Paper-based/ electronic	1 day or 1 week	German, English+70 translations
COPD Assessment Test (CAT)	8	cough, phlegm (mucus) in chest, tightness in chest, breathlessness, limited in activities, doubts, sleeping problems, energy	1: total score	<5 min	Paper-based/ electronic	No specific recall period	German, English+60 translations

Continued

Table 2 Continued

PROM	Number of items	Domains	Scores	Completing time	Paper-based/ electronic	Recall period	Languages
Pulmonary-Specific Quality of Life Scale (PQLS)	25	3: task interference, physical, psychological,	4: task interference, physical, psychological, total score	10–15 min	Paper-based	1 month	German, English
Quality of Life Questionnaire Bronchiectasis (QOL-B Version 3.1)	37	8: respiratory symptoms, physical functioning, vitality, role functioning, health perceptions, emotional functioning, social functioning, treatment burden	8: respiratory symptoms, physical functioning, vitality, role functioning, health perceptions, emotional functioning, social functioning, treatment burden	10–15 min	Paper-based	1 week	German, English+44 translations
St. George Respiratory Questionnaire (SGRQ)	50	3: symptom score, activity score, impacts score	4: symptoms, activity, impacts, total score	>15 min	Paper-based	1, 3 or 12 months	German, English+185 translations
Liver-specific PROMs							
Chronic Liver Disease Quality of Life (CLDQ)	29	6: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, worry	7: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, worry, overall score	10–15 min	Paper-based	2 weeks	German, English+97 translations

EQ Index, EuroQol Health Utility Index; EQ VAS, EuroQol Visual Analogue Scale; PROM, patient-reported outcome measure.

The EQ-5D-5L consists of six variables.[17] The five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) are assessed on a 5-point Likert scale and can be combined into an EQ Index ranging from −0.661 (worst health state) to 1.000 (best health state). Additionally, the questionnaire consists of a VAS, ranging from 0 (worst health) to 100 (best health). In the context of COPD, a minimal clinically important difference of 8 score points on the EQ VAS was determined.[38] QoL of patients with COPD without AATD and patients with COPD with AATD is comparable with or without augmentation therapy.[39 40]

Lung-specific PROM

After considering the properties of the various questionnaires and discussing them in the group, the CAT turned out to be the most adequate questionnaire for the present purposes. The CAT was developed to measure the impact of COPD on patients' health and is intended to complement clinical assessments such as forced expiratory volume.[26] The questionnaire consists of eight variables assessed on a 6-point Likert scale. The summary score ranges from 0 to 40, while higher scores indicate a higher impact of COPD on well-being: 0–9 low, 10–20 medium, 21–30 high, 31–40 very high impact.

The SGRQ is the most frequently used lung-specific PROM (table 2), but also the longest questionnaire (depending on the version 40–76 items). The CAT has similar properties to the more complex SGRQ.[26 41 42] Previous studies have shown that the CAT correlates highly with the SGRQ, while the CAT is easier and faster to complete.[42–46] In addition, patients as well as researchers rate the CAT as easier and faster to use than the SGRQ.[26]

The CCQ was developed for patients with COPD and resembles numerous features of the CAT.[25] Both the CCQ and the CAT are comparable in terms of short completion time, ease of completion and score calculation, psychometric properties, the ability to predict mortality, the high importance of information for healthcare providers in clinical routine and good acceptability by the patients.[25 47–49] The CCQ and the CAT also show a clinically relevant change between exacerbation and recovery.[50] A minimal important difference criterion is defined for the CCQ.[49 51] However, it does not distinguish between repeated measurement error at the group level and at the individual level.[52] On the other hand, the minimal important difference defined for the CAT (1–3.8 points) can be distinguished from repeated measurement error at the group level.[52] In summary, the CAT was favoured over the CCQ as the CAT has been used in AATD patients and is more suitable for measuring changes in respiratory symptoms.

The PQLS was developed for patients with end-stage lung disease who are awaiting a lung transplant. However, the questionnaire has been rarely used and never in patients with AATD. Besides the rare usage and sometimes lack of tests of psychometric properties, the PQLS has more items than the favoured CAT.

The QoL-B was developed for patients with bronchiectasis and has shown sufficient content validity of high quality and good psychometric data.[28 38 53] The CRQ was developed for patients with chronic airflow limitations.[54 55] Due to their rare usage in AATD patients and a higher number of items, QoL-B and CRQ are less favoured than CAT.

The BCSS was developed for patients with COPD[23] and was never used in patients with AATD. It is a 3-item short PROM assessing the severity of breathlessness, cough and sputum. Although BCSS is shorter than CAT, CAT incorporates more relevant QoL aspects.

Liver-specific PROM

For liver-specific PROM, only one questionnaire with good psychometric properties was available: CLDQ,[56] and more specifically the validated and linguistically adapted German version CLDQ-D.[30] The CLDQ was developed for patients with chronic liver diseases and consists of 29 items assessed on a seven-point Likert scale. The CLDQ covers six sub-scores (fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, worry) and an overall score.[56] The criteria for content validity were rated as sufficient and the quality of the evidence as high, although the CLDQ was not developed for AATD patients and not all methodical details were clearly addressed in the original manuscript.[56]

Each CLDQ score ranges from 1 to 7 with higher scores indicating better QoL.[30] A difference of 0.5 in CLDQ scores is considered a minimal clinically important difference.[56] According to the German scoring information regarding repeated measures, differences of 0.8 are clinically relevant for individual analyses and deviations of ≥0.5 SD for group analyses. CLDQ scores are responsive to change, as shown in studies on liver transplantation.[56 57]

Summary of the selection process and additional questions

In a standardised group process including information about preliminary psychometric properties, three PROMs with high content validity and feasibility in clinical routine as well as clinical studies (eg, shortness, comprehensibility) were selected for a modular approach assessing QoL in AATD patients: EQ-5D-5L (generic), CAT (lung-specific) and CLDQ (liver-specific). These questionnaires cover predefined relevant QoL domains (table 1). This group decision was unanimous (100% group consensus).

In addition, relevant QoL issues/aspects that were not addressed by the three selected PROMs were included: concerns regarding the availability of a suitable organ in the event of a lung transplant, feeling joy of life, going to lung sports, receiving psychological treatment, need for psychological support and feeling informed about AATD. Moreover, sociodemographic and health-related questions were added to the designed questionnaire: sex, age, height, weight, highest education, current employment status, year of AATD diagnosis, AATD type, AATD organ manifestation, laboratory parameters, substitution, need for oxygen treatment, transplantation, comorbidities, current health status (modified Karnofsky performance status scale) and degree of disability. This objective supplementary information is necessary to complement subjective data. Figure 2 illustrates the final PROM that we consider for further use in AATD patients

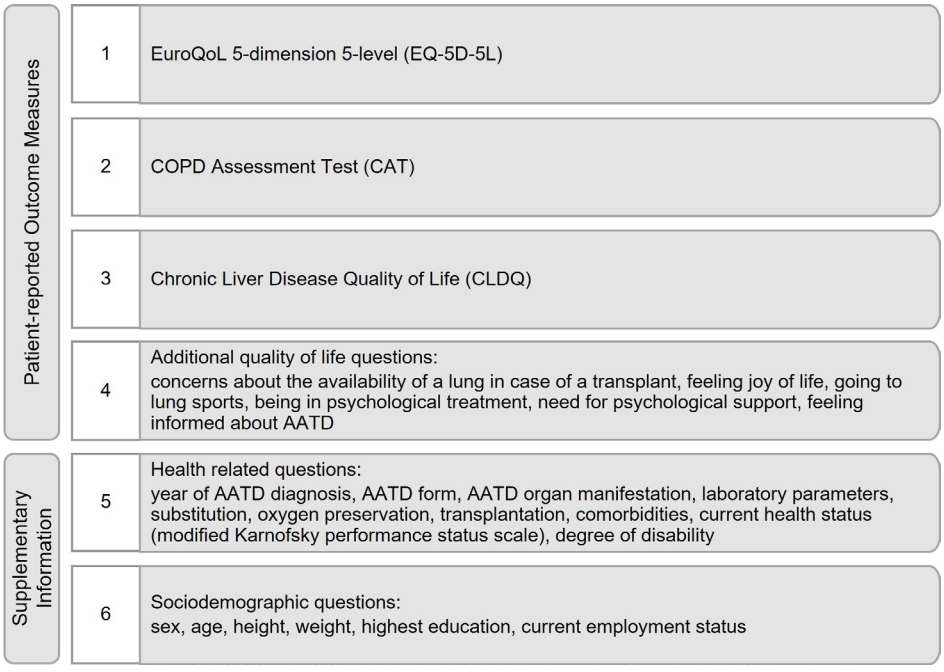

Figure 2 ALPHA (Assessment of Lung, Liver and Patient Health in Alpha-1): the patient-reported outcome measure designed for patients with alpha-1 antitrypsin deficiency.

and propose to name ALPHA (***A***ssessment of ***L***ung, Liver and ***P***atient ***H***ealth in ***A***lpha-1).

DISCUSSION

The past two decades have witnessed an ever-growing literature on PROMs.[6] The database PROQOLID (https://eprovide.mapi-trust.org) compiles more than 6000 PROMs, and the number continues to grow. Therefore, instead of developing and validating a new questionnaire for the research project of interest, one should take advantage of one or more of the existing validated PROMs.[6] If necessary, appropriate candidates may be amended to fit the target population and setting. Care must be taken to ensure that any modifications do not violate the content and psychometric criteria of the original questionnaire. Whereas PROMs are designed to assess patients' subject health perception, the documentation of objective clinical data will provide a comprehensive view of a patient's health status.

Up to now, no accepted and validated measurement approach has existed that addresses QoL issues of patients with AATD. To select appropriate PROMs for use in patients with AATD, a step-by-step process was applied. In literature searches, over 1200 records were identified and screened. Within standardised group processes, crucial eligibility criteria were defined, and a modular approach to assessing generic, lung-specific and liver-specific QoL was agreed on. In total, 247 PROMs were identified and assessed for eligibility. 15 out of 247 PROMs fulfilled predefined eligibility criteria. Most PROMs had satisfactory psychometric properties. The selection of the final three PROMs was based on the following aspects: content and clinical appropriateness, brevity, easy usage and interpretation, availability of minimal clinically important differences, sensitivity to change, possibility to distinguish between disease severity and availability of reference data. The three selected PROMS assess generic (EQ-5D-5L), lung-specific (CAT) and liver-specific (CLDQ) aspects of QoL. A short set of self-developed items at the very end of the questionnaire examines treatment-related aspects of QoL as well as basic sociodemographic and objective health criteria.

AATD may affect different organ systems, most commonly the lungs and liver. Depending on genotype, comorbidity, lifestyle and age, there are also cases with lung and liver symptoms presenting simultaneously. To address these major disease manifestations, the ALPHA instrument was designed as a modular tool that allows the assessment of QoL domains relevant to the individual patient's clinical presentation. This flexible structure enables the use of generic and organ-specific components according to disease involvement and will be further examined in the forthcoming validation study.

Based on this conceptual framework, the selected PROMs were combined to form the ALPHA instrument while maintaining the scoring of each questionnaire. No summary score or weighted scores will be calculated, as the instruments address distinct dimensions of QoL. This approach preserves conceptual clarity and allows for comparability with published reference values.

The questionnaire assembled through this combined systematic review and consensus-based approach holds potential value for both clinical practice and research in patients with AATD. In clinical settings, the modular approach combining generic (EQ-5D-5L), lung-specific (CAT) and liver-specific (CLDQ) measures allows for a comprehensive assessment of QoL across multiple domains relevant to AATD patients, which helps monitor PRO over time, guide treatment decisions and identify areas requiring medical attention.

For research purposes, the standardised and validated nature of the selected instruments allows for consistent data collection across studies, facilitating comparisons and meta-analyses. While we recognise that the sole use of the EQ-5D-5L is unlikely to fully capture treatment-related changes in QoL,[33] the lung- and liver-specific questionnaires address the very symptoms at the core of healthcare.

A potential limitation of the present manuscript may be the lack of a fully flagged presentation of the evaluation of preselected questionnaires according to the COSMIN checklist. Because our initial review of the literature suggested that comprehensive psychometric evaluations of the questionnaires for AATD patients were not to be expected due to the rarity of the disease, we used a pragmatic two-step research approach. First, we searched for potential questionnaire candidates that assessed QoL contents of clinical interest, and second, we determined the psychometric properties of these candidates in a subsequent set of prospective studies. According to this project plan, follow-up papers will report on these studies and the psychometric findings.

Another limitation concerns the exclusion of questionnaires without an available German translation. While this may restrict generalisability, focusing on German-language instruments ensured linguistic and cultural applicability within the intended clinical context. Automated translations were not considered appropriate, as the use of PROMs requires standardised forward–backward translation and cross-cultural validation procedures according to established guidelines.[58] All identified instruments, including reasons for exclusion, are provided in the open-access dataset.[14] The selected PROMs (EQ-5D-5L, CAT and CLDQ) are internationally established instruments available in major languages, including English, German, Spanish and Chinese, ensuring broad applicability and comparability across studies.

CONCLUSIONS

The research group agreed on a modular approach that covered relevant generic, lung-specific and liver-specific

QOL aspects. Three appropriate PROMs (EQ-5D-5L, CAT, CLDQ) were selected. These PROMs were supplemented by relevant QoL issues not addressed otherwise. An additional pair of studies will provide information on the psychometric properties of the selected questionnaires in AATD patients and their feasibility in clinical routine.

Author affiliations
[1]Center for Clinical Studies, University Hospital Regensburg, Regensburg, Germany
[2]University Library, University of Regensburg, Regensburg, Germany
[3]Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Marburg, Germany
[4]German Center for Lung Research, Marburg, Germany
[5]Department of Medicine II, Saarland University Medical Center, Homburg, Germany
[6]Health Sciences, Hannover Medical School, Hanover, Germany
[7]Department of Internal Medicine III, University Hospital Rheinisch-Westfälisch Technische Hochschule, Aachen, Germany
[8]Gesellschaft für Alpha-1-Antitrypsin-Mangel Erkrankte e.V, Gernsheim, Germany
[9]Department of Pulmonary, Allergology and Critical Care Medicine, University Hospital of Saarland, Homburg, Germany

Acknowledgements We thank Brigitte Doß, University Library, University of Regensburg, for the peer review of the search strategy for the systematic review and Monika Schöll, Center for Clinical Studies, University Hospital Regensburg, for the linguistic revision of the manuscript.

Contributors MK is the guarantor of this review. KM and MK drafted the manuscript, and RB commented on the draft. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. HK developed the search strategy in cooperation with KM and MK. KM and MK provided statistical expertise. RB, TG, FL, PS, CV and MW provided expertise on AATD. KM and LV screened records independently and evaluated the identified PROMs. Disagreements were solved by MK. All authors read, provided feedback and approved the final manuscript.

Funding The systematic review and selecting of adequate PROM for assessing QoL in patients with AATD is part of a larger project. The project was financially supported by CSL Behring GmbH. The funder had no role in the design and conduct of the study.

Competing interests PS is supported by the DFG grant STR1095/6-1. PS reports receiving grants and honouraria from Arrowhead Pharmaceuticals, CSL Behring, Grifols Inc, consulting fees or honouraria from Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, BioMarin Pharmaceutical, Dicerna Pharmaceuticals, GSK, Intellia Pharmaceuticals, Takeda Pharmaceuticals, Novo Nordisk and Ono Pharmaceuticals, participating in leadership or fiduciary roles in Alpha1-Deutschland, Alpha1 Global, and material transfer support for Vertex Pharmaceuticals and Dicerna Pharmaceuticals. The other authors declare no conflicts of interest related to this study.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. Data supporting this study is available via open-access publication server of the University of Regensburg (Müller K, Vogl L, Knüttel H, Greulich T, Lammert F, Strnad P et al. Supporting Data for the Manuscript "Patient-related outcome measures for use in patients with alpha-1-antitrypsin deficiency: Results of a systematic selection process"; 2025. doi: 10.5283/epub.76669).

ORCID iDs
Karolina Müller https://orcid.org/0000-0001-5241-2945
Helge Knüttel https://orcid.org/0000-0002-2654-6517

REFERENCES

1 Strnad P, McElvaney NG, Lomas DA. Alpha1-Antitrypsin Deficiency. *N Engl J Med* 2020;382:1443–55.
2 Greulich T, Nell C, Hohmann D, *et al*. The prevalence of diagnosed α1-antitrypsin deficiency and its comorbidities: results from a large population-based database. *Eur Respir J* 2017;49:1600154.
3 Calvert M, Kyte D, Mercieca-Bebber R, *et al*. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA* 2018;319:483–94.
4 Food and Drug Association. Guidance for industry: patient-reported outcome measures. use in medicinal product development to support labelling claims 2009. Available: https://www.fda.gov/media/77832/download [Accessed 18 Sep 2020].
5 Fayers P, Machin D. *Quality of Life: The Assessment, Analysis and Interpretation of Patient-Reported Outcomes*. 2nd edn. New York, NY: John Wiley & Sons, 2013.
6 Churruca K, Pomare C, Ellis LA, *et al*. Patient-reported outcome measures (PROMs): A review of generic and condition-specific measures and a discussion of trends and issues. *Health Expect* 2021;24:1015–24.
7 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
8 Prinsen CAC, Mokkink LB, Bouter LM, *et al*. COSMIN guideline for systematic reviews of patient-reported outcome measures. *Qual Life Res* 2018;27:1147–57.
9 Prinsen CAC, Vohra S, Rose MR, *et al*. Guideline for selecting outcome measurement instruments for outcomes included in a core outcome set 2016. Available: https://cosmin.nl/wp-content/uploads/COSMIN-guideline-selecting-outcome-measurement-COS.pdf [Accessed 31 May 2021].
10 Johnson C, Aaronson N, Blazeby JM, *et al*. Guidelines for developing questionnaire modules 2011. Available: https://www.eortc.org/app/uploads/sites/2/2018/02/guidelines_for_developing_questionnaire-_final.pdf [Accessed 27 May 2021].
11 Van de Ven AH, Delbecq AL. The nominal group as a research instrument for exploratory health studies. *Am J Public Health* 1972;62:337–42.
12 McGowan J, Sampson M, Salzwedel DM, *et al*. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40–6.
13 Müller K, Knüttel H, Greulich T, *et al*. Patient-related outcome measure (PROM) for assessing quality of life (QoL) in patients with alpha-1-antitrypsin deficiency (AATD): a systematic review protocol. 2021
14 Müller K, Vogl L, Knüttel H, *et al*. Supporting Data for the Manuscript "Patient-related outcome measures for use in patients with alpha-1-antitrypsin deficiency: Results of a systematic selection process": Universität Regensburg. 2025.
15 Bramer WM, Giustini D, de Jonge GB, *et al*. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc* 2016;104:240–3.
16 Van Weel C. *Measuring Functional Health Status with the COOP/WONCA Charts: A Manual*. Groningen: Noordelijke Centrum voor Gezondheidsvraagstukken, 1995.
17 EuroQol Research Foundation. EQ-5d-5l user guide 2019. Available: https://euroqol.org/wp-content/uploads/2023/11/EQ-5D-5LUserguide-23-07.pdf [Accessed 28 Sep 2023].
18 Cella DF, Tulsky DS, Gray G, *et al*. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–9.
19 Chang VT, Hwang SS, Feuerman M, *et al*. The Memorial Symptom Assessment Scale Short Form (MSAS-SF). *Cancer* 2000;89:1162–71.
20 Kohlmann T, Bullinger M, Kirchberger-Blumstein I. Die deutsche Version des Nottingham Health Profile (NHP): Übersetzungsmethodik und psychometrische Validierung. *Soz Praventivmed* 1997;42:175–85.
21 Siegrist J, Broer M, Junge A. *Profile der Lebensqualität Chronisch Kranker: Manual*. Göttingen: Beltz Test, 1996.
22 Chassany O, Dimenäs E, Dubois D, *et al*. *The Psychological General Well-Being Index (Pgwbi) User Manual*. Lyon, France: Mapi Research Institute, 2004.
23 Leidy NK, Rennard SI, Schmier J, *et al*. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. *Chest* 2003;124:2182–91.

24 Puhan MA, Behnke M, Laschke M, *et al*. Self-administration and standardisation of the chronic respiratory questionnaire: a randomised trial in three German-speaking countries. *Respir Med* 2004;98:342–50.
25 van der Molen T, Willemse BWM, Schokker S, *et al*. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003;1:13.
26 PolkeyM, Vogelmeier C, Dransfield, Mark on behalf of CAT Governance Board. CAT copd assessment test: user guide. expert guidance on frequently asked questions 2022. Available: https://www.catestonline.org/content/dam/global/catestonline/documents/CAT_HCP%20User%20Guide.pdf [Accessed 28 Sep 2023].
27 Nöhre M, Albayrak Ö, Brederecke J, *et al*. Psychometric Properties of the German Version of the Pulmonary-Specific Quality-of-Life Scale in Lung Transplant Patients. *Front Psychiatry* 2019;10:374.
28 Quittner AL, O'Donnell AE, Salathe MA, *et al*. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax* 2015;70:12–20.
29 Jones PW. St george's respiratory questionnaire: manual 2022. Available: https://www.sgul.ac.uk/research/research-operations/research-administration/st-georges-respiratory-questionnaire/docs/SGRQ-Manual-March-2022.pdf [Accessed 9 Oct 2023].
30 Häuser W, Schnur M, Steder-Neukamm U, *et al*. Validation of the German version of the Chronic Liver Disease Questionnaire. *Eur J Gastroenterol Hepatol* 2004;16:599–606.
31 Carone M, Bruletti G, Bertella E, *et al*. Quality of life evaluation in patients with alpha1-antitripsin deficiency: A 3-year prospectic study. *Eur Respir J* 2011;38. Available: http://erj.ersjournals.com/content/erj/38/Suppl_55/p3632
32 Ringbaek T, Brøndum E, Martinez G, *et al*. EuroQoL in assessment of the effect of pulmonary rehabilitation COPD patients. *Respir Med* 2008;102:1563–7.
33 Gnanasakthy A, DeMuro CR. The Limitations of EQ-5D as a Clinical Outcome Assessment Tool. *Patient* 2024;17:215–7.
34 Stavem K, Jodalen H. Reliability and validity of the COOP/WONCA health status measure in patients with chronic obstructive pulmonary disease. *Qual Life Res* 2002;11:527–33.
35 Unal G, de Boer JB, Borsboom GJ, *et al*. A psychometric comparison of health-related quality of life measures in chronic liver disease. *J Clin Epidemiol* 2001;54:587–96.
36 van der Molen T, Postma DS, Schreurs AJ, *et al*. Discriminative aspects of two generic and two asthma-specific instruments: relation with symptoms, bronchodilator use and lung function in patients with mild asthma. *Qual Life Res* 1997;6:353–61.
37 Eckerblad J, Tödt K, Jakobsson P, *et al*. Symptom burden in stable COPD patients with moderate or severe airflow limitation. *Heart Lung* 2014;43:351–7.
38 McLeese RH, Spinou A, Alfahl Z, *et al*. Psychometrics of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. *Eur Respir J* 2021;58.
39 Karl FM, Holle R, Bals R, *et al*. Costs and health-related quality of life in Alpha-1-Antitrypsin Deficient COPD patients. *Respir Res* 2017;18:60.
40 Fähndrich S, Biertz F, Karch A, *et al*. Cardiovascular risk in patients with alpha-1-antitrypsin deficiency. *Respir Res* 2017;18:171.
41 Jones PW, Harding G, Berry P, *et al*. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–54.
42 Folch Ayora A, Macia-Soler L, Orts-Cortés MI, *et al*. Comparative analysis of the psychometric parameters of two quality-of-life questionnaires, the SGRQ and CAT, in the assessment of patients with COPD exacerbations during hospitalization: A multicenter study. *Chron Respir Dis* 2018;15:374–83.
43 Ringbaek T, Martinez G, Lange P. A comparison of the assessment of quality of life with CAT, CCQ, and SGRQ in COPD patients participating in pulmonary rehabilitation. *COPD* 2012;9:12–5.
44 Morishita-Katsu M, Nishimura K, Taniguchi H, *et al*. The COPD assessment test and St George's Respiratory Questionnaire: are they equivalent in subjects with COPD? *Int J Chron Obstruct Pulmon Dis* 2016;11:1543–51.
45 Dodd JW, Hogg L, Nolan J, *et al*. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. *Thorax* 2011;66:425–9.
46 Edgar RG, Griffiths D, Stockley RA. P149 Validation of the COPD assessment test (CAT) within -1 antitrypsin deficiency (A1ATD). *Thorax* 2010;65:A141.
47 Kocks JWH, Blom CMG, Kasteleyn MJ, *et al*. Feasibility and applicability of the paper and electronic COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ) in primary care: a clinimetric study. *NPJ Prim Care Respir Med* 2017;27:20.
48 Casanova C, Marin JM, Martinez-Gonzalez C, *et al*. Differential Effect of Modified Medical Research Council Dyspnea, COPD Assessment Test, and Clinical COPD Questionnaire for Symptoms Evaluation Within the New GOLD Staging and Mortality in COPD. *Chest* 2015;148:159–68.
49 Tsiligianni IG, van der Molen T, Moraitaki D, *et al*. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulm Med* 2012;12:20.
50 Miravitlles M, García-Sidro P, Fernández-Nistal A, *et al*. Course of COPD assessment test (CAT) and clinical COPD questionnaire (CCQ) scores during recovery from exacerbations of chronic obstructive pulmonary disease. *Health Qual Life Outcomes* 2013;11:147.
51 Kocks JWH, Tuinenga MG, Uil SM, *et al*. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006;7:62.
52 Hansen H, Beyer N, Frølich A, *et al*. Inter-Day Test-Retest Reproducibility of the CAT, CCQ, HADS and EQ-5D-3L in Patients with Severe and Very Severe COPD. *Patient Relat Outcome Meas* 2021;12:117–28.
53 Quittner AL, Marciel KK, Salathe MA, *et al*. A preliminary quality of life questionnaire-bronchiectasis: a patient-reported outcome measure for bronchiectasis. *Chest* 2014;146:437–48.
54 Guyatt GH, Berman LB, Townsend M, *et al*. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–8.
55 Knebel AR, Leidy NK, Sherman S. Health related quality of life and disease severity in patients with alpha-1 antitrypsin deficiency. *Qual Life Res* 1999;8:385–91.
56 Younossi ZM, Guyatt G, Kiwi M, *et al*. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 1999;45:295–300.
57 Younossi ZM, McCormick M, Price LL, *et al*. Impact of liver transplantation on health-related quality of life. *Liver Transpl* 2000;6:779–83.
58 Koller M, Aaronson NK, Blazeby J, *et al*. Translation procedures for standardised quality of life questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach. *Eur J Cancer* 2007;43:1810–20.