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Assessing quality of life and burden of disease in chronic rhinosinusitis: a review*

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Abstract

Background: Chronic rhinosinusitis has been shown to have a significant impact on patients' quality of life (QoL). We present and summarize current knowledge on assessment methods of Chronic Rhinosinusitis (CRS) burden and QoL.

Methodology: Review of the literature using the PubMed database (search of terms "chronic rhinosinusitis", "CRS", "quality of life", "QoL", "outcome measures", "assessment of CRS", "CRS burden" separately or combined) limited to articles published in the English language.

Results: Despite the plethora of objective methods available to assess and quantify burden of CRS, discrepancies are occasionally encountered when correlation with subjective measures of QoL is attempted via numerous patient self-reporting tools.

Conclusion: CRS has a detrimental effect on QoL and assessing disease severity and burden is a difficult goal. The applicability of known assessment methodologies should be re-evaluated and validated according to research findings on CRS pathophysiology, and new tools should be developed based on the emerging knowledge and the need for personalized treatment and evaluation methods.

Key words: chronic rhinosinusitis, QoL, burden of disease, outcome measures, disease-specific QoL questionnaires

Introduction

Chronic rhinosinusitis (CRS) is a disease characterized by chronic inflammation of nose and paranasal sinuses, with a high prevalence among the USA and Europe. In respect to observable characteristics, CRS is distributed in two major phenotypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [1]. Disease and its subtypes vary amongst population subgroups, depending on demographic characteristics and co-morbid conditions [2]. CRS symptoms have a debilitating effect on productivity and patients' emotional status [3,4]. This was shown to be significantly more pronounced in cases with concomitant chronic pulmonary diseases and psychiatric disorders [5,6]. Furthermore, disease-associated financial expenses and lost workdays are far from negligible [7]. The combination of socioeconomic burden and negative impact on well-being ultimately affects patients' quality of life (QoL) [8].

Diagnosis of CRS is based on a combination of symptoms and objective findings from nasal endoscopy and/or imaging examinations [1]. Disease control is defined as a state in which patients do not have symptoms or symptoms are not bothersome, accompanied with a healthy or almost healthy mucosa [1,9]. Multiple measures have been utilized to diagnose and assess burden of disease, level of control, response to treatment and, overall QoL. Beside endoscopy, computed tomography (CT) imaging of nose and paranasal sinuses is regularly used to assess disease severity and is always necessary for surgical planning [1].
Beside objective measures, a variety of patient rated outcome measures (PROM) are available. These tools can be either generic or disease-specific. The latter one is aiming to evaluate specific aspects of the disease, quantify symptoms severity, and overall to assess QoL [10]. Among different disease-specific outcome measure instruments in CRS, the Sino-Nasal Outcome Test

(SNOT)-22 is widely accepted and has been used in several studies [11]. Based on total severity visual analog scale (VAS) score, CRS can be classified into mild, moderate, and severe. A VAS>5 is considered to affect patients' QoL [1].

Herein, we present established and new knowledge on assessment tools used in the Rhinology field to evaluate CRS burden and QoL in CRS patients. We performed a review of the literature using the PubMed database (search of terms "chronic rhinosinusitis", "CRS", "quality of life", "QoL", "outcome measures", "assessment of CRS", "CRS burden" separately or combined) limited to articles published in the English language. Furthermore, we aim to describe published factors which are known to affect patients' QoL, as determined by outcome measures.

Measuring quality of life

According to the World Health Organization (WHO), health is defined as a "state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" [12]. The earliest publications addressing QoL issues appeared in the mid-twentieth century [13] and the first QoL measurement instrument was introduced in 1981 [14]. These terms are not identical and should be distinguished from each other [15], although they are frequently considered and treated as synonymous. It has been advocated that health-related QoL (HRQoL) is a subset of QoL relating only to aspects of health [16], and consists the main target of medical research and rehabilitation. Multiple types of QoL measurements exist: dimension-specific, disease- or population-specific, generic, individualized and utility measures [17]. Under this scope, CRS assessment should not be limited to health-related or disease-specific QoL measurements [18,19].

Subjective (psychometric) assessment methods of CRS: scales and questionnaires

Visual scales

As measurement instruments, visual scales can provide a means for subjective characteristics or attitudes assessment that cannot be directly measured. Respondents specify their level of agreement to a statement by indicating a position along a continuous or discrete scale between two end-points [20]. The Visual Analogue Scale (VAS) concept was first described and used in the early 20th century, and since then is widely used in questionnaires. There is evidence showing that VAS have superior metrical characteristics than discrete ones, thus a wider range of statistical methods can be performed on the acquired data [20]. Results from a validation study with 355 participants are reported and show that the scales generated with VAS Generator approximate an interval-scale level. In light of previous research on VAS versus categorical (e.g., radio button) scales in Internet-based research, we conclude that categorical scales only reach ordinal-scale level, and thus, VAS is to be preferred whenever possible. VAS is simple, easy to use, does not require training and it has been proved to be a fast and inexpensive method to describe population and group characteristics in the health science field and in clinical practice [20].

The Sino-Nasal Outcome Test (SNOT)

The SNOT questionnaire has been specifically designed to include symptoms intimately related with rhinosinusitis. The SNOT-20 and SNOT-22 variants are the most widely used and have been proved reliable tools for prediction of post-surgical improvement, as well as outcomes assessment after Endoscopic Sinus Surgery (ESS) [11,21]. The SNOT-16 variant has been successfully used to determine the effectiveness of interventions to improve disease-specific QOL in adults with acute rhinosinusitis [22]. One of the main advantages of the SNOT-22 is the distribution of symptoms into discrete domains (rhinologic, extra-nasal rhinologic, ear/facial, psychological and sleep). A recent study has demonstrated that scores in different groups of symptoms can differentially predict and guide treatment modality selection in CRS [23]. The SNOT-22 has been translated and validated in multiple languages, thus providing a "common ground" for medical cross-communication and a homogenous data pool for multi-center studies and meta-analyses [24–26].

The 36-Item Short Form Survey (SF-36)

The 36-Item Short Form Survey (SF-36) is a 36-item, patient-reported survey of patient health that came out from the Medical Outcome Study (MOS) [27–29]. While designed as a generic QoL assessment tool, it has been successfully used to evaluate post-operative outcomes after ESS [30], as well as calculate the health and socioeconomic burden of chronic CRS [4,6,31]. Known limitations of this questionnaire are that it does not take into consideration a sleep variable, and has a low response rate in older (>65 years) age groups [32].

Nasal Obstruction and Symptom Evaluation (NOSE)

The NOSE instrument was originally developed as a disease-specific tool for the assessment of nasal obstruction in patients with nasal septum deformities, as well as other related pathologies (mucosal congestion, turbinate hypertrophy, adenoid hypertrophy, nasal mass, and others) [33]. Since its initial conception, it has been used to classify nasal obstruction severity [34], its efficiency has been verified [35], and has been adapted and validated in several language and cultural settings [36]. Although its usage is continually expanded for the evaluation and treatment outcomes in diseases affecting the upper airway [37–40], it is not suitable for CRS severity and outcomes measurements [41].

EuroQol 5-Dimensional (EQ5D)

The EuroQol 5-Dimensional (EQ5D) is a standardized instrument for measuring generic health status, first introduced in 1990 by the EuroQol Group [42]. Although a generic QoL assessment

instrument, it has been successfully used for studying clinical outcomes in CRS [10,43,44]. With good validity and reliability, ease of use and wide applicability, it has become one of the most commonly used generic health status measurement tools.

Living with CRS: disease impact on quality of life

Patients with CRS report impaired QoL in both the physical and mental domains. This negative effect is more pronounced in emotional function, general health, role physical function, female gender, the elderly and subjects with high-level education [45]. In another study [46], significantly more reduced HRQoL was identified in female subjects indifferent of CRS phenotype, especially in the anxiety/depression domain, with more prominent findings in the CRSwNP subgroup. Also, worse QoL and disease-associated pain in CRS may lead to neurocognitive dysfunction, although the underlying mechanisms have still not been identified [47]. Sleep disruption prevalence is significantly higher in CRS patients, and is linked with worse QoL, impaired cognitive function and mood disturbances [48,49]. Strangely, CRS-associated smell and taste disturbances do not seem to affect eating-related QoL, while co-morbidities like aspirin-exacerbated respiratory disease (AERD) and depression appear to be independent risk factors [50]. This is compatible with the findings of a recent study [41], which identified only a limited association between nasal obstruction assessed with the NOSE instrument and CRS-related QoL. Overall, changes in the sleep and ear/facial domains are shown to be the most greatly associated with QoL [51].

Working with CRS: the hampering effect of reduced quality of life on productivity

CRS negatively affects multiple aspects of a patient's life, including work productivity, resulting in a high socioeconomic burden. This is attributable to the disease-associated depression symptoms, missed workdays and treatment needs [52,53]. Also, facial pain appears to be a significant factor resulting to presentiism [54]. The frequency of acute exacerbations of the disease has also been shown to result in reduced productivity in both asthmatic and non-asthmatic patients [55]. The overall indirect cost due to CRS-related work productivity loss in the USA has recently been estimated to be over 20 billion dollars per annum [56].

The effect of CRS treatment in quality of life

CRS is a complex disease where multiple intrinsic and extrinsic factors interact, thus forming a wide spectrum of disease variants with diverse characteristics on clinical and pathophysiologic level [57]. Medical treatment, including nasal irrigation and anti-inflammatory agents (either systematic or local), is the first-line modality indicated in all cases. Surgical treatment is reserved when maximal medical treatment fails to provide a satisfactory outcome, as evaluated by objective and subjective measures [1,9]. CRS affects multiple aspects of QoL in variable manners, and no gold standards exist for its evaluation and treatment, especially when surgical interventions are planned.

Medical treatment

First-line medical treatment with nasal irrigations and intranasal corticosteroids (INCS) usually is administered by primary health care physicians, but refractory cases should be referred to an otolaryngologist [58]. There is no evidence to support the regular administration of topical antifungals, antibiotics, antihistamines and surfactant irrigations, while nasal decongestants may be used short-term complementary to INCS in patients with CRSwNP [59]. Also, there is no proven superiority of any INCS type, form of delivery (spray, aerosol, drops) or higher dosage for CRS treatment [60]. The long-term benefit of a short-course oral corticosteroid treatment is unclear [61]. Encouraging evidence exists for the usage of monoclonal antibodies (anti-IgE, anti-IL-5, anti-IL-4, anti-IL-13) in CRSwNP treatment and their beneficial effect on QoL, although more research is required in this field [62]. A recent meta-analysis suggests that appropriate medical treatment is associated with improved QoL in cases of non-refractory disease and sustained improvement of QoL after sinus surgery [63].

Surgical treatment

ESS has been a widely adopted therapeutic modality for CRS, especially in cases refractory to medical treatment, with variable long-term results [64]. Its beneficial effect on QoL appears to be more pronounced in patients with nasal polyposis and asthma [65,66]. Approximately 75% of patients with medically refractory CRS report sleep disturbances, and sinus surgery has been shown to offer improvement in this domain [67–69]. A recent prospective study [70] showed that ESS significantly improved the HRQoL and decreased absenteeism in patients with either CRS phenotype. In select cases of CRSwNP, endoscopic polypectomy in clinic (EPIC) may offer comparable to traditional ESS QoL improvements [71]. Patients with cystic fibrosis (CF) may experience similar improvement in postoperative QoL [72]. Acetylsalicylic acid (ASA) intolerance and depression have been associated with poorer QoL outcomes after ESS, while previous sinus surgery and asthma are variably reported as either negative predictive factors or without significance on postoperative response to treatment [73]. Mucosal eosinophilia and increased IL-5 levels on nasal mucosa have been associated with greater disease severity and higher rates of revision surgery [73,74]. Likewise, patients with CRSwNP are more likely to recur and need reoperation [1]. In paediatric population, ESS is rarely performed compared to the adult population, yet is a viable option for selected cases. In CF, severe nasal polyposis, and allergic fungal sinusitis this treatment modality may offer marked benefits on patients' QoL [1].

Other parameters affecting QoL in CRS

Co-morbidities should always be identified and treated accordingly, as they pose an obstacle for optimal therapeutic outcome and improvement of QoL. Based on the concept of "the unified airway", upper and lower respiratory tracts are both anatomically and functionally tightly related entities [20]. Thus, it has been supported that treating the upper airway results in alleviation of lower airway symptoms [1,75,76]. Patients with asthma and primary ciliary dyskinesia may benefit from ESS, achieving improved lung function, and better overall QoL [77]. The same is also true for other chronic pulmonary diseases, like CF [78].
While patients with nasal polyposis and coexisting asthma may enjoy better QoL after FESS, an algorithm for optimal individualized therapy has not been defined yet, nor which outcomes and measurement scales are required to properly assess the response to treatment of such populations [79]. AERD in patients with nasal polyposis (Samter's triad) may receive an additional benefit from FESS if aspirin desensitization is administered postoperatively [80]. Furthermore, nasal septum deviation and nasal valve area deformities may contribute to CRS symptoms and treating those deformities should always be taken into consideration to alleviate burden of CRS disease [81].
Environmental factors may also have a detrimental effect on CRS severity and efficacy of sinus surgery. Small inhalant pollutants may contribute to non-allergic symptomatology in patients with and without nasal polyposis and lead to treatment failure due to undetected coexisting allergic or non-allergic rhinitis (NAR) [82]. This has been shown to be true even on the absence of rhinitis, especially in patients with CRSsNP, underlining the significant burden air pollutants pose on disease severity and progression, as well as on QoL [83].
The psychological implication of CRS is a neglected field of research, although the emotional burden of the disease is far from negligible. General health assessment may be paramount for proper diagnosis and better comprehension of patients' needs, since the clinical picture may greatly differ from the patient's estimation of the disease and its symptoms [84]. Neither depression nor anxiety may be alleviated after FESS, despite significant improvement of disease specific objective and QoL measurements [85]. On the other hand, co-morbid anxiety is associated with reduced QOL improvement following ESS [86].
For a variety of reasons, control of disease will fail in a considerable number of patients [87]. Before the final diagnosis of a difficult-to-treat CRS / uncontrolled CRS / Severe Chronic Upper Airway Disease (SCUAD) is made, disease-unrelated factors such as patient adherence, inappropriate treatment or incorrect diagnosis must be identified and addressed accordingly [9]. SCUAD results in poor QoL, affects both children and adults, poses a high socioeconomic burden, and presents a difficult treatment challenge [88–91]. Clinical markers associated with SCUAD are presence of nasal polyps, asthma co-morbidity and AERD [92].
A multitude of cellular, immunologic, genetic and molecular biomarkers are under investigation, to unravel the pathophysiologic profile of such patients and determine the optimal medical and/or surgical treatment [93,94].

Discrepancies and controversies

The value of objective and subjective outcome assessment methods cannot be underestimated. Lately, there is a growing acceptance that patients' perspective on outcome is more important than objective assessment methods [95]. Towards this direction mobile technology is contributing to further help patients deal with CRS burden [96–98]. Furthermore, discrepancies do exist between objective and subjective measures of disease burden assessment. It has been shown that the Lund-Mackay score can provide information about the expected postoperative improvement of QoL after ESS, yet confined on certain SNOT-22 domains (rhinologic and extranasal) [99]. For nasal polyposis, ESS has shown to offer significant improvement on SF-36 and VAS scores for mid-term periods (6 to 12 months) but worsened Lund-Kennedy endoscopic scores accordingly [100].
PNIF measurements tend to correlate well with QoL, especially with postoperative SNOT-22 questionnaire results, but not with the preoperative Lund-Mackay and Lund-Kennedy scales [101].
Unexpectedly low score on PROM after ESS may be attributed to existing co-morbidities and should not necessarily be seen as a failure to reflect the burden of CRS. This has been proved in cases with concomitant obstructive sleep apnea (OSA) [102].
In view of such findings, patient selection based on traditional phenotype classification and measures of disease severity may not be adequate for defining the optimal treatment modality, either medical or surgical, underlining the need for novel criteria for state-of-the-art therapeutic interventions [103].
Another issue to be addressed is that QoL is subjectively perceived, based on the unique way it is experienced by each individual. "Quantification" and "objectification" are not easy tasks; each PROM tool tries to interpret solely intrinsic procedures into measurable variables. Widely used and reliable questionnaires like SNOT-22, EQ5D and EQ5D-VAS detect otologic/facial pain and sleep-related problems as more prominent on CRS patients, underlining the differential effect of symptoms and underlying pathophysiologic mechanisms on QoL [104]. Strangely, generic QoL assessment tools, such as the General Well-Being Schedule (GWBS), may be more sensitive than disease- and symptom-specific PROMs for depicting the patient's perception of the disease and its treatment [105]. It is also prudent to acknowledge the significance of QoL assessment methodology, as shown by the response shift paradigm in sinus surgery outcomes [106,107].
Additionally, there is a trend to simplify evaluation of QoL in chronic upper airway diseases. In AR, VAS was found to correlate well with QoL measurement instruments such as RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire) [75]. Likewise, VAS

has been very recently shown to have a strong association with SNOT-22 in CRS patients [108]. Finally, the evaluation of PROM scores on QoL should be both longitudinal and cross-sectional, given the inhomogeneous profiles of patients suffering from CRS and the quite often encountered discrepancies between the statistical and clinical importance sinus surgery results [65]. Finally, as it has been clearly pointed out [109], the heterogeneity of outcome assessment methodologies poses an obstacle on treatment effectiveness evaluation and comparison. Development and endorsement of core outcomes sets will facilitate future meta-analyses and increase the value of research on disease therapeutic approaches.

Conclusion

Chronic rhinosinusitis is still an unconquered domain, despite the plethora of objective and subjective measurements of disease severity. Current basic research aims at clarifying the underlying pathophysiologic mechanisms of the disease, since its classical phenotypic classification does not meet the needs of modern and individualized medicine. The results of this effort will possibly provide new ground for adaptation of current assessment methodologies of disease burden. Meanwhile, QoL outcome tools are continually under active investigation and refinement, technological evolution provides more accurate devices for diagnostic and therapeutic purposes, and the accumulation of surgical experience and innovations increases the efficiency and efficacy of the procedures. The combined breakthrough knowledge on these fields may obviate in the future the need of the term "uncontrolled rhinosinusitis".

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DK: Writing - Original draft preparation; MD: Writing - Reviewing and Editing; AK: Writing - Reviewing and Editing; SV: Reviewing; AM: Writing - Original draft preparation; EP: Conceptualization, Methodology, Supervision, Writing - Reviewing and Editing.

Conflict of interest

None to declare.

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