Prevalence of refractory and unexplained chronic cough in adults treated in cough centre

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Shareable abstract (@ERSpublications)
Refractory chronic cough (RCC) is common in patients referred to cough clinics. Because the prevalence of RCC differs slightly depending on the diagnostic criteria, we need to define which criteria are the most appropriate in routine practice. https://bit.ly/3wpnNmc

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Abstract

Background Refractory chronic cough and unexplained chronic cough pose significant clinical challenges, impairing patients' quality of life. However, a precise definition of refractory chronic cough remains elusive. This study aimed to assess the prevalence of refractory and unexplained chronic cough among patients referred to our cough centre and to analyse the prevalence of refractory chronic cough relative to its definition.

Methods This prospective cohort study included all patients who were diagnosed at a cough clinic between 2018 and 2022. The response to therapy was measured based on reduction in cough severity (*via* a visual analogue scale) and improvement in cough-related quality of life (*via* the Leicester Cough Questionnaire). Refractory chronic cough was defined as persistent cough severity, with no or minimal improvement (change in visual analogue scale <30 mm) after two or more treatment attempts and cough severity ⩾40 out of 100 mm on the visual analogue scale.

Results Of 201 patients treated for chronic cough, only three (1.5%) were diagnosed with unexplained chronic cough. Among 166 patients monitored for therapy response, 71 (42.8%) experienced a cough severity reduction of ⩾30 mm on the visual analogue scale, while 100 (60.2%) showed an improvement of ⩾1.5 points on the Leicester Cough Questionnaire. Based on the basic refractory chronic cough definition, 51 of 166 patients (30.7%) were diagnosed with refractory chronic cough. If applying stricter criteria (persistent severe cough (⩾40 mm on the visual analogue scale), insufficient therapy response (<30 mm reduction on the visual analogue scale) and <1.5-point improvement on the Leicester Cough Questionnaire), 45 of 166 patients (27.1%) would be diagnosed with refractory chronic cough.

Conclusions Refractory chronic cough is common in patients referred to cough clinics. The prevalence of refractory chronic cough differs slightly depending on the diagnostic criteria. Therefore, the definition of refractory chronic cough used in routine practice needs to be clarified.

Introduction

Cough serves as a natural physiological defence mechanism, preventing the airways from inhaling foreign particles and clearing excess mucus. However, it also manifests as a common symptom across many diseases. Chronic cough (CC), which is defined in adults as cough lasting for >8 weeks, affects up to 10% of the adult population and is more frequent in females than in males [1–3]. There are geographical differences in the prevalence of CC, with a higher prevalence in Oceania, Europe and America and a lower prevalence in Asia and Africa [4].

CC may be a symptom of several respiratory diseases and other conditions. The prevalence of CC in active smokers is three times higher than that in nonsmokers or ex-smokers [5]. In adults, the spectrum of

CC-associated diseases involves chronic bronchitis, asthma, non-asthmatic eosinophilic bronchitis, COPD, gastro-oesophageal reflux, rhinitis, rhinosinusitis, bronchiectasis, obstructive sleep apnoea, interstitial lung diseases and chronic lung infections [6–8].

CC significantly reduces a patient's quality of life, leading to increased anxiety, exhaustion and insomnia [9]. Many patients with CC experience throat pain, headache, fatigue, voice disturbances, wheezing, nausea, chest pain and urinary incontinence [10]. The impact of CC on patients' personal relationships may cause depression, self-isolation and lower productivity at work [11]. Furthermore, prolonged treatment of CC exposes patients to the unnecessary side effects of inappropriate treatment with corticosteroids, proton pump inhibitors and antibiotics [12].

Refractory chronic cough (RCC) refers to persistent CC despite identification and treatment of its underlying cause(s), while unexplained chronic cough (UCC) denotes a CC without any identified cause [13, 14]. Both RCC and UCC can be diagnosed in up to 5–10% of adults with CC but are more prevalent in patients referred to cough clinics [14]. Cough persistence despite management is caused by hypersensitivity of the cough reflex and deterioration of central neuronal inhibition of the cough. Recent studies have investigated the relevance of cough hypersensitivity syndrome, which describes the increased response triggered by low levels of thermal, mechanical or chemical exposure to the persistence of CC [15–18].

Although the pathomechanism and treatment of RCC have been the subject of many recent studies, a detailed definition of RCC has not yet been established. According to cough experts, RCC is diagnosed if the cough persists despite optimal management of conditions associated with CC, which is convergent with the present guidelines [2, 3, 19]. Additionally, symptoms suggestive of cough hypersensitivity may be present in RCC/UCC [20]. The inclusion criteria in clinical studies of novel antitussives dedicated to patients with RCC usually include not only a CC refractory to treatment but also a minimal cough duration of over 4 months [21] or a year [22] with minimal cough severity [22] or minimal limit of cough frequency [23]. Although criteria for cough duration or subjective severity may be implemented in routine practice, the use of minimal cough frequency is difficult because cough monitors are not widely available. Considering the heterogeneity of the definition of RCC, we decided to analyse the prevalence of RCC in patients referred to our cough centre in relation to how RCC was defined.

Materials and methods

Study design

This was a prospective, single-centre cohort study that included patients diagnosed at the Cough Clinic of the Department of Internal Medicine, Pulmonary Diseases, and Allergy, Medical University of Warsaw, between 2018 and 2022. This was part of a larger study evaluating the efficacy of CC treatment that has been conducted in our clinic since 2009. The study protocol was approved by the Institutional Review Board of the Medical University of Warsaw (KB/101/2009 and KB 20/A2021). All the patients signed an informed consent form to participate in the study.

The main objective of this study was to analyse the prevalence of RCC and UCC among patients treated at our cough clinic. The secondary outcome was the comparison of the prevalence of RCC with the different diagnostic criteria for RCC.

Study subjects

We included all consecutive patients diagnosed in our Cough Clinic who agreed to take part in a study evaluating the efficacy of CC treatment. The inclusion criteria were age >18 years, cough duration >8 weeks and normal (or near-normal) chest radiography. The exclusion criteria were lack of consent, pulmonary and extrapulmonary conditions that were diagnosed as cough reasons and required specific therapeutic intervention (*e.g.* interstitial lung diseases, lung cancer, other malignant diseases, tuberculosis) and unavailability to follow up the response to treatment (lost to follow-up or discontinuation of the recommended therapy).

Methods

The causes of CC were diagnosed according to the recommendations of the European Respiratory Society (ERS), British Thoracic Society and the American College of Chest Physicians [24–27]. The diagnostic algorithm is shown in supplementary figure S1 [28]. The therapy was adjusted for cough diagnosis, but the choice of drug was left to the discretion of the treating physician (supplementary figure S2). The response to therapy was measured after 6–24 weeks based on patient-related outcomes: cough severity measured *via* a 100 mm visual analogue scale (VAS) and cough-related quality of life measured using the Leicester Cough Questionnaire (LCQ) [3, 27, 29].

A VAS is a 100 mm scale in which patients mark their cough severity from 0 mm (no cough) to 100 mm (worst cough). Recently, the minimal important difference (MID) for reducing CC severity has been established as 30 mm [30, 31].

The LCQ is a quality-of-life questionnaire designed for patients with cough. It consists of 19 questions divided into three domains addressing physical, psychological and social aspects, each rated with 7 points (total score range 3–21 points). Higher scores indicate better quality of life. It is a valid assessment tool responsive to change, and the MID for the LCQ is 1.5 points [32].

Definitions of RCC

Both basic and alternative definitions of RCC were agreed on by the research team based on definitions suggested by the recent guidelines, criteria of clinically important difference and inclusion criteria of some randomised clinical trials with novel cough drugs [3, 14, 20, 22].

The basic definition of RCC is no significant decrease in cough severity (ΔVAS <30 mm) despite at least two attempts of adherent treatment, with a minimal cough severity of 40 mm on the VAS. A significant decrease in cough severity is defined as a reduction in VAS by ⩾30 mm. Five alternative definitions of RCC were included. 1) No significant decrease in cough severity despite therapy (ΔVAS <30 mm) and no improvement in LCQ (ΔLCQ <1.5 points) after at least two attempts of adherent treatment, with a minimal initial cough severity of 40 mm on the VAS. Significant improvement defined as both a decrease in cough severity (ΔVAS ⩾30 mm) and an improvement in cough-related quality of life (ΔLCQ ⩾1.5 points). 2) No significant decrease in cough severity (ΔVAS <20 mm) despite at least two attempts of adherent treatment, regardless of change in LCQ, with a minimal initial cough severity of 40 mm on the VAS. Significant improvement defined as a decrease in cough severity measured by VAS ⩾20 mm. 3) No improvement in cough-related quality of life (ΔLCQ <1.5 points) despite at least two attempts of adherent treatment. Significant improvement defined as an increase in the LCQ ⩾1.5 points. 4) No significant decrease in cough severity (ΔVAS <20 mm) despite at least two attempts of adherent treatment regardless of ΔLCQ and initial VAS. A significant decrease in cough severity defined as a reduction in VAS ⩾20 mm. 5) No significant decrease in cough severity (ΔVAS <30 mm) despite at least two attempts of adherent treatment regardless of ΔLCQ and initial VAS. Significant improvement defined as a ⩾30 mm reduction in the VAS.

A summary of defining criteria is given in table 1.

Statistical analysis

Data on patients' characteristics are expressed as median (interquartile range (IQR)) or n (%). Differences between groups were compared using the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Statistical significance was set at $p<0.05$. Statistical analyses were performed using Statistica 13.1, a StatSoft software package.

Results

Between 2018 and 2022, our Cough Centre managed 206 patients primarily presenting with CC. Among them, 201 were included in this study (figure 1). There were 137 women (68.2%) and 64 men (31.8%), with a median age of 59 years (IQR 46–68.5 years). Detailed characteristics of the study group are presented in table 2, and the CC-associated conditions are shown in table 3. Unexplained CC was diagnosed in only three patients (1.5%).

The median initial cough severity measured *via* the VAS was 55 mm (IQR 35–75 mm) and the median cough-related quality of life measured *via* the LCQ was 11.89 points (IQR 8.98−14.93 points). The

TABLE 1 Summary of the basic and alternative criteria of defining refractory chronic cough

	VAS	↓ ΔVAS	↑ ΔLCQ
Basic definition	⩾40 mm	<30 mm	Regardless
1st alternative definition	⩾40 mm	<30 mm	<1.5 points
2nd alternative definition	⩾40 mm	<20 mm	Regardless
3rd alternative definition	Regardless	Regardless	<1.5 points
4th alternative definition	Regardless	<20 mm	Regardless
5th alternative definition	Regardless	<30 mm	Regardless

VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire.

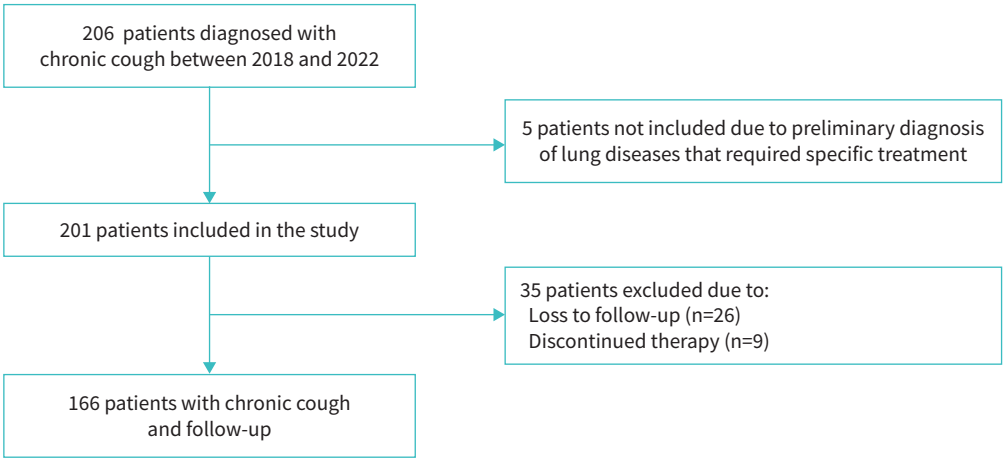

FIGURE 1 Flowchart of the included patients.

response to therapy was followed in 166 patients. The median reduction of cough severity measured using the VAS in all patients was 37 mm (IQR 30–53 mm), while the median increase in the LCQ score was 3.4 points (IQR 2.62–4.92 points).

A total of 71 out of 166 patients (42.8%) experienced a reduction in cough severity of ⩾30 mm on the VAS scale, while 82 patients (49.4%) declared a decrease of ⩾20 mm. Additionally, an improvement of ⩾1.5 points on the LCQ was noted in 100 patients (60.2%).

RCC, defined as a persistent severe cough of ⩾40 mm on the VAS scale and a response to therapy of a <30 mm VAS reduction, was diagnosed in 51 out of 166 patients (30.7%).

If a diagnosis of RCC was based on the stricter criteria (persistence of severe cough ⩾40 mm on the VAS, response to therapy <30 mm VAS reduction and improvement of LCQ score <1.5 points), it would have been diagnosed in 45 patients (27.1%). On the contrary, if the loosest criteria were used (VAS reduction <30 mm), RRC would have been diagnosed in 95 patients (57.2%). The prevalence of RCC according to the different diagnostic criteria is shown in figure 2.

TABLE 2 Characteristic of the patients

Characteristic	
Patients (n)	201
Sex	
Women	137 (68.2)
Men	64 (31.8)
Age (years)	59 (46–68)
BMI (kg·m^{-2})	27.2 (24.2–31.2)
Cough duration (months)	48 (24–120)
Smoking status	
Never-smoker	144 (71.6)
Former smoker	52 (25.8)
Current smoker	5 (2.5)
Pack-years	9 (3–20)
Years since quit smoking	19.5 (10–30)
Atopy	49 (24.4)
ACEI treatment	11 (5.4)
Improvement after ACEI discontinuation	6 (3)
F_{ENO} (ppb)	15.8 (10.3–26.3)
Blood eosinophil count (cells·µL^{-1})	85 (60–172)

Data are reported as median (interquartile range) or n (%), unless otherwise indicated. BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitor; F_{ENO}: fraction of exhaled nitric oxide.

TABLE 3 Causes of chronic cough

Cause of chronic cough	Patients
Asthma	94 (46.7)
Gastro-oesophageal reflux disease	128 (63.7)
Upper airway cough syndrome	123 (61.2)
Allergic rhinitis	36 (17.9)
Non-allergic rhinitis	54 (26.9)
Chronic rhinosinusitis	33 (16.4)
Others	
Obstructive sleep apnoea	17 (8.5)
ACEI treatment	6 (3)
MOTT infection	2 (1)
Bronchiectasis	4 (2)
COPD	3 (1.5)
Idiopathic pulmonary fibrosis	2 (1)
Hypersensitivity pneumonitis	2 (1)
Sarcoidosis	1 (0.5)
Eosinophilic bronchitis	4 (2)
Post COVID-19	2 (1)
Heart diseases	4 (2)
Unexplained chronic cough	3 (1.5)

Data presented as n (%). n=201 patients. ACEI: angiotensin-converting enzyme inhibitor; MOTT: *Mycobacterium* other than tuberculosis.

There were only a few differences between patients with RCC and those who responded to causal treatment for CC. Patients with RCC commonly experienced cough that lasted longer, exhibited greater severity and had a resulting lower quality of life. Additionally, gastro-oesophageal reflux was more common in patients with RCC than in patients who responded to cough treatment. No other significant differences were observed between the groups (table 4).

Discussion

In this study, patients with RCC comprised almost one third of all patients treated in our Cough Centre, whereas only three patients were diagnosed with UCC. We also documented that the diagnosis of RCC depends on the criterion of non-response to treatment, which in routine management is based on subjective

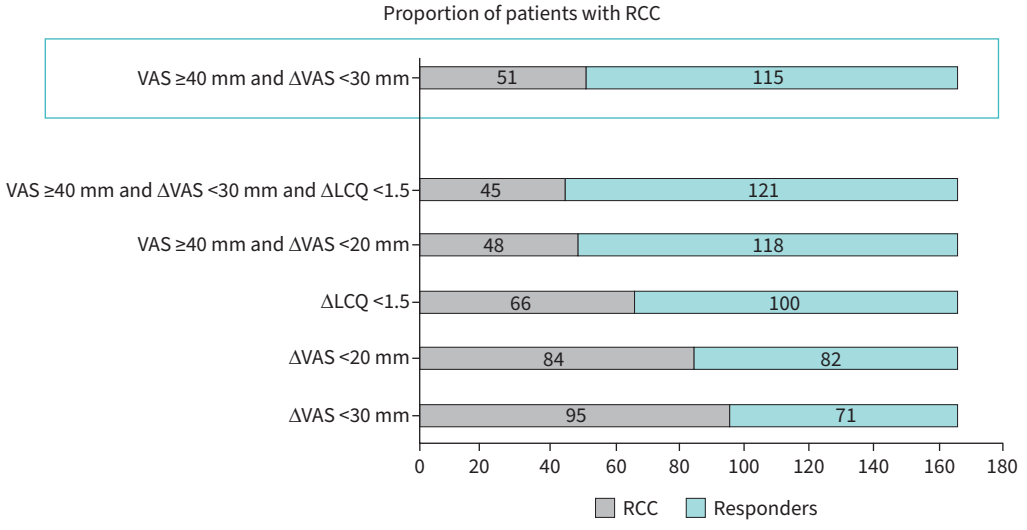

FIGURE 2 Proportion of patients with refractory chronic cough (RCC) in relation to its definition. LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale.

TABLE 4 Differences between responders and patients with refractory chronic cough (RCC) (distinguished according to the basic definition of RCC)

	Responders to treatment	RCC	p-value
Patients (n)	115	51	
Sex			0.815
Female	81	35	
Male	34	16	
Age (years)	59 (45–68)	60 (48–68)	0.608
BMI ($kg \cdot m^{-2}$)	27.1 (23.5–31.6)	26.0 (24–29.4)	0.882
Cough duration (months)	48 (24–96)	61 (48–180)	0.004
Cough characteristic			0.726
Dry	85 (74)	39 (76)	
Wet	30 (26)	12 (24)	
Cough severity (VAS, mm)	51 (30–73.5)	65 (48–80.5)	0.003
Cough-related QoL (LCQ, points)	12.42 (9.16–15.04)	10.46 (8.26–12.57)	0.018
Blood eosinophil count ($cells \cdot \mu L^{-1}$)	90 (50-220)	80 (60-130)	0.494
F_{ENO} (ppb)	13.6 (13.6–48.4)	16.14 (10.0–40.5)	0.244
Atopy	23 (20)	17 (33.3)	0.064
Number of cough-related diagnoses			0.611
1	23 (19.6)	9 (17.6)	
⩾2	89 (77.4)	42 (82.4)	
UCC	3 (2.6)	0	
Diagnosis of asthma	52 (45.2)	29 (56.8)	0.116
Diagnosis of GOR	73 (63.5)	41(80.4)	0.030
Diagnosis of UACS	72 (62.6)	31 (60.8)	0.823

Data are presented as median (interquartile range) or n (%), unless otherwise indicated. BMI: body mass index; VAS: visual analogue scale; QoL: quality of life; LCQ: Leicester Cough Questionnaire; F_{ENO}: fraction of exhaled nitric oxide; UCC: unexplained chronic cough; GOR: gastro-oesophageal reflux; UACS: upper airway cough syndrome.

patient-related outcomes. In addition, we identified only a few clinical features that distinguished patients with RCC from those who responded to treatment.

Recent progress in understanding the pathomechanism of RCC as a result of neuronal hypersensitivity has led to better treatment, with speech and language interventions, neuromodulators and novel antitussive drugs acting on peripheral cough receptors [2, 3, 14]. Therefore, the precise diagnosis of RCC is of great importance. By definition, RCC refers to CC that is refractory to guideline-based appropriate treatment, but assessing the response to antitussive treatment is not simple. Response to therapy can be measured by patient-related outcomes or by measurement of cough frequency using cough monitors. Reducing cough frequency by >30% is considered a significant reduction in cough frequency [33]. However, cough monitors are scarcely available and are usually used in clinical trials, whereas patient-related outcomes remain paramount in routine management. A significant reduction in cough severity is assessed as a reduction of >30 mm on the 100 mm VAS [31]. However, the value of the MID of 30 mm refers to patients with RCC but not to all patients with CC. Next, a distinct improvement in CC-related quality of life was established as an increase in the total LCQ score of >1.3 points [29] but >2.5 points for acute cough [34].

In clinical studies of novel antitussive drugs, RCC was defined as a persistent cough despite appropriate treatment, with a cough severity of ⩾40 mm measured using the VAS. If such criteria were used in our study, RCC would have been diagnosed in almost one third of our patients, which is similar to the results of cough clinics in other countries. In the Korean Registry, RCC was diagnosed in almost 29% of patients with CC [35]. In another recent study from Spain, the percentage of RCC was higher (64%) [11]. These results emphasise that RCC is a common clinical problem worldwide.

When analysing the criteria for RCC definition, we noticed that applying the additional criterion of the minimal initial cough severity (beyond reduction in VAS) increased the number of patients who responded to treatment and decreased the proportion of patients with RCC. The choice of additional criteria was based on our observation that mainly patients with moderate or severe CC would be willing to accept additional therapies dedicated to RCC or UCC. Thus, we believe that both elements of the definition are justified.

In this study, we showed that the percentage of RCC slightly depended on the criteria used to define it. Given the dependence of the RCC proportion on the diagnostic criteria, we would like to point out the need to determine a more precise diagnosis of RCC, especially considering the perspective of novel antitussive drugs. There is a need to establish the minimal number of cough treatment attempts required, bearing in mind the possibility of coexisting cough causes, various therapeutic methods and patient adherence to therapy, before a diagnosis of RCC is established. According to the ERS guidelines on cough, the duration of treatment trials should be limited to 2–4 weeks [3]. We suggest that it should be as many therapeutic trials as necessary to respond to all identifiable treatable traits for CC, as per the recent British Thoracic Society definition of RCC [20]. When RCC or UCC is diagnosed, additional treatments should be initiated. Such patients require either non-pharmacological or pharmacological therapies based on opiates, neuromodulators or novel cough drugs [3, 14, 20, 27]. Assuming that RCC therapy is successful and cough severity is decreased, it may be necessary to reconsider the term RCC and potentially adopt a different term to accurately describe the improved cough condition.

Taking into account the pathomechanism of neuronal peripheral and central hypersensitivity in both RCC and UCC, it seems reasonable to implement a term that unifies these two entities. Similarly to the classification of chronic pain, “primary” CC has recently been discussed as an overarching term for both RCC and UCC, as opposed to a cough that is “secondary” to underlying respiratory or other cough causes.

In contrast to the high percentage of RCC cases, we diagnosed few patients with UCC, lower than what has been reported in other studies. In a study by Arinze *et al*. [36] based on a Rotterdam Study population, 21.2% of all CC cases in the general adult population were UCC. Similarly, in previous European studies, 15–47% of adults with CC had no identifiable treatable traits or risk factors [37, 38]. Such a low percentage of UCC in our study resulted from our thorough diagnostic algorithm, which included frequent second-step investigations (chest and sinus computed tomography, polysomnography, induced sputum analysis, bronchial provocation test, nasal and video laryngoscopy, and bronchoscopy) that allowed the diagnosis of less common cough-associated diseases. Besides, we considered treatable traits such as gastro-oesophageal reflux, obstructive sleep apnoea and upper airway diseases as potential cough causes rather than independent comorbidities. However, recent ERS guidelines suggest simplifying the diagnostic process to shorten the patients’ journey to receiving a diagnosis of RCC and UCC [3]. We believe it is very important to follow stepwise intensification of therapy and to introduce add-on treatment related to all comorbid cough causes, which is usually time-consuming and related to difficulties in maintaining patient adherence. Therefore, in our routine practice we usually recommend more than two therapeutic trials before diagnosing RCC.

Our study had some limitations. First, this was a single-centre study with a limited number of patients. Second, owing to the real-life character of this study, some differences in therapy were probable. Third, the choice of the basic definition of RCC was arbitrary although based on the most frequently used criteria. Fourth, owing to the lack of cough monitors, we used only patient-reported outcomes to follow the response to therapy. Despite these limitations, we believe that the results of this study contribute to the discussion on RCC.

In conclusion, RCC is common among patients referred to cough clinics. The prevalence of RCC differs slightly depending on the diagnostic criteria. There is a need to define which criteria are the most appropriate in routine practice.

Provenance: Submitted article, peer reviewed.

Ethics statement: The study protocol was approved by the Institutional Review Board of the Medical University of Warsaw (KB/101/2009 and KB 20/A2021). All the patients signed an informed consent form to participate in the study.

Conflict of interest: All authors declare no conflict of interest related to the manuscript.

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