MUNI

COMMENTARY TO HABILITATION THESIS[1]

Chronic obstructive pulmonary disease (COPD) is one of the most frequent chronic diseases, affecting ca 330 million persons worldwide. Since the disease affects one of the vital organs, it is associated with significant risk of mortality. Currently, COPD ranks as the 3rd leading cause of death worldwide among the non-communicable diseases. In the Czech Republic, COPD is one of the most frequent causes of death, claiming ca 3,500 lives annually. Mortality in COPD patients is mainly related to cardiovascular and pulmonary factors. Unfortunately, most of the available pharmacological and non-pharmacological treatments have no effect on long-term survival rate. A few exceptions include early smoking quitting in early COPD, alpha-1 antitrypsin (A1AT) substitution treatment in patients with severe A1AT deficiency, lung transplant in patients with very severe bronchial obstruction [forced expiratory volume in one second (FEV_1) <15% of predicted values], lung volume reduction surgery (LVRS) in patients with upper-lobe predominant emphysema and with low upper-lobe perfusion, and long-term domiciliary oxygen treatment in patients with severe chronic hypoxemia. Identification of high risk patients may be important for timely optimization of treatments and for an overall more assertive treatment approach.

Prognosis assessment is one of the key measures to be taken by the physician at initial assessment of a patient with COPD, as well as periodically during follow-up. Prognosis assessment should be done in order to identify patients at high risk of long-term mortality, stressing the need for a more assertive treatment approach. Traditionally, the parameter of FEV_1 % of predicted value has been used for basic prognostic evaluation. In the long-term, this parameter reflects progressive decline in lung function that is directly associated with increasing risk of mortality. FEV_1 (% of predicted value) also served for classification into The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I-IV. In 2011, a new classification model has been introduced, based on symptoms severity and exacerbations. This model categorizes patients into groups A-D. In 2004, a new composite tool for long-term prognosis assessment has been introduced, the BODE index. Subsequently, several other prognostic instruments have been constructed or derived from BODE index, including ADO, BODEx, BODEXS90 or CODEX. The scoring systems of the most widely used BODE and ADO indices have specific weaknesses. For ADO index, the main criticism is that the index has extensive linkage to the age factor that is a strong factor of mortality risk per se. On the other hand, the BODE index includes 6-minute walk test (6-MWT) that may not be feasible if the patient experiences disability / immobility or if the physician has no spaces or instrumentation to perform 6-MWT.

In most cases, prognosis of COPD patients cannot be improved. In these patients, at least improvement of respiratory symptoms is desired, along with a decrease in exacerbation rates, using with various treatment strategies.

In this habilitation thesis, I present six scientific articles. Three articles focus on long-term mortality risk in COPD patients. Two studies focus on issues related to quality of life improvement and treatment outcomes in COPD patients. The last article presents current recommendations for diagnosis, management and treatment of COPD in the Czech Republic.

The three articles dedicated to mortality risk in COPD patients were based upon prospective data from the Czech Multicenter Research Database of COPD, a network of 14 tertiary care centers in the Czech Republic. In the first study (**chapter 2.2.**), we learned that the GOLD classification scheme into stages I-IV had better prognostic power than the newer classification into groups A-D. We demonstrated that group C had lower mortality risk compared to group B and concluded that this may be confusing to the clinicians in the daily

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[1] The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

practice. In the second study (**chapter 2.1.**), we analyzed associations between respiratory parameters (blood gases and peripheral oxygen saturation) and mortality risk in patients with COPD according to GOLD groups. We found that chronic hypoxemia was by far the strongest predictor of mortality risk; in particular for patients in group B. This is an important finding since group B patients constitute the largest subcategory of patients with COPD in the real-life settings and identification of high-risk patients is essential. We concluded that group B patients with chronic hypoxemia <7.3 kPa had high risk of 2-year mortality. We suggest that blood gas examination should be performed in those patients with detected peripheral oxygen saturation <90%. This work was awarded 1st place in Publication of the Year 2018 by the Czech Pneumological and Phthisiological Society. In the third study (**chapter 2.3.**), we report construction of a new prognostic tool for mortality risk assessment in COPD patients. The prognostic index was named CADOT and points to the final score are assigned for each of these five clinical parameters: patient history of **C**hronic heart failure, **A**ge, the degree of **D**yspnea measured by mMRC score, bronchial **O**bstruction measured by FEV_1 % of predicted value and **T**Lco (diffusion capacity of the lungs for carbon monoxide). This new prognostic index prevents certain shortcomings of the BODE and ADO indices and can be useful unless 6-MWT cannot be performed. In a head-to-head comparison, the CADOT performed better than the BODE and ADO indices both on the derivation (Czech CMRD cohort) and validation (Dutch CIROCO+ cohort) cohorts.

Another part of this habilitation thesis is the Position paper of the Czech Pneumological and Phthisiological Society on diagnosis, management and treatment of stable COPD (**chapter 2.4.**). In this comprehensive work, we present current knowledge on COPD epidemiology, risk factors, pathophysiology, recommended diagnostic procedures, classification and treatment strategy. In order to establish a balanced and practical set of recommendations, the authors of this document considered not only reports from randomized controlled trials but also data from real-life studies. Unlike other national guidelines for COPD management, this document uses a stratified approach to disease classification, based on both GOLD stages and groups and six pre-defined clinical phenotypes. This classification translates also into a stratified treatment strategy with certain mandatory treatments recommended with guidance of GOLD stage and group and of individualized therapy based on presence of specific phenotypes of COPD. In global, this is a very progressive and unique approach tailored to the scope and needs of the Czech healthcare system regarding care for patients with COPD.

In the last two articles we report a newly designed protocol for a randomized controlled trial (**chapter 2.5.**) and the formulation of the "Five Steps Assessment" – a universal and a practical tool for assessment of the patient´s inhalation technique (**chapter 2.6.**). The new protocol describes the design of a randomized trial aiming to compare the efficacy of two types of inspiratory muscles training (IMT) methods. The first method is the conventional IMT with the use of IMT Threshold device and the second is the test of incremental respiratory endurance (TIRE), both compared with sham. The study will begin in May 2021 and will be supported by Ministry of Health research grant No NU21J-09-00004 (Principal Investigator: Filip Dosbaba). We expect inclusion of 12 subjects with COPD in each of the three arms. We believe the TIRE method may have additional benefits over the traditional IMT method and we expect improvement in inspiratory muscle strength and endurance, quality of life measures, functional and exercise capacity and COPD-related symptoms. In the last article (**chapter 2.6.**), we introduced and tested the use of a universal easy-to-use method of inhalation / application technique. This method was named "Five Steps Assessment". Compared to other often very complicated and unintuitive inhalation technique assessment tools, the "Five Steps Assessment" is very simple and universal tool usable for all types of inhaler devices. We evaluated its function on a large cohort of patients with COPD and we demonstrated that the two most problematic steps regarding inhalation / application technique, were breathing out completely before inhalation and the actual dose inhalation. Only 30% of patients performed all five steps correctly. The "Five Steps

Assessment" can be used both for patient as well as for medical staff (re-)education. Correct inhalation technique is the key to maximal therapeutic response and optimal disease control.

My contribution to the six articles constituting this habilitation thesis is summarized in the tables below. Each table presents my contribution to the related scientific article with special emphasis on experimental work, supervision, manuscript writing and research direction.

[1] Brat K, Plutinsky M, Hejduk K, Svoboda M, Popelkova P, Zatloukal J, Volakova E, Fecaninova M, Heribanova L, Koblizek V. Respiratory parameters predict poor outcome in COPD patients, category GOLD 2017 B. *Int J Chron Obstruct Pulmon Dis.* 2018;13:1037-52.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	70	80	80

[2] Plutinsky M, **Brat K**, Svoboda M, Zatloukal J, Popelkova P, Koblizek V. Prognostic Accuracy of Three COPD Classification Systems in Relation to Long-Term Mortality of COPD Patients: A Prospective Multicenter Study. *Lung.* 2019;197(2):173-9.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	80	50	80

[3] Brat K, Svoboda M, Hejduk K, Plutinsky M, Zatloukal J, Volakova E, Popelkova P, Novotna B, Engova D, Franssen FME, Vanfleteren LEGW, Spruit MA, Koblizek V. Introducing a new prognostic instrument for long-term mortality prediction in COPD patients: the CADOT index. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2021;165(2):139-145.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	40	45	40

[4] Zatloukal J, **Brat K**, Neumannova K, Volakova E, Hejduk K, Kudela O, Kopecky M, Plutinsky M, Koblizek V. Chronic obstructive pulmonary disease - diagnosis and management of stable disease; a personalized approach to care, using the treatable traits concept based on clinical phenotypes. Position paper of the Czech Pneumological and Phthisiological Society. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2020; 164(4):325-56.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
NA	70	40	40

[5] Formiga MF, Dosbaba F, Hartman M, Batalik L, Plutinsky M, **Brat K**, Ludka O, Cahalin LP. Novel versus traditional inspiratory muscle training regimens as home-based, stand-alone therapies in COPD: protocol for a randomized controlled trial. *Int J Chron Obstruct Pulmon Dis.* 2020;15:2147-55.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
NA	30	20	20

[6] Vytrisalova M, Hendrychova T, Touskova T, Zimcikova E, Vlcek J, Nevoranek L, Svoboda M, Hejduk K, **Brat K**, Plutinsky M, Novotna B, Musilova P, Cernohorsky M, Koblizek V. Breathing Out Completely Before Inhalation: The Most Problematic Step in Application Technique in Patients With Non-Mild Chronic Obstructive Pulmonary Disease. *Front Pharmacol.* 2019;10:241.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	15	15