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Stanovení prognózy pacienta s chronickou obstrukční plicní nemocí – výstupy pro klinickou praxi.

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Poděkování

Ze všeho nejvíc děkuji své rodině a blízkým za jejich podporu a pochopení. Dále děkuji všem svým kolegům, spoluautorům prací a své předchůdkyni ve funkci přednostky kliniky prof. MUDr. Janě Skřičkové, CSc. za pomoc a odborné rady. V neposlední řadě děkuji všem pacientům, kteří se ochotně účastnili našich výzkumů a pomohli tak posunout hranice vědeckého poznání.

Obsah

1. ÚVOD

Na úvod této habilitační práce (formou komentovaného souboru šesti časopiseckých prací) bych chtěl čtenáře uvést v adekvátní teoretický rámec aktuálních znalostí a klinické problematiky týkající se morbidity a rizika mortality pacientů s chronickou obstrukční plicní nemocí (CHOPN).

1.1. Definice základních pojmů

CHOPN je dle definice GOLD „preventabilní a léčitelná nemoc charakterizovaná přítomností perzistentních respiračních symptomů, obstrukce dýchacích cest a/nebo abnormit plicních alveolů, která vznikla v důsledku expozice škodlivým částicím a plynům působením na vnímavého jedince (faktor hostitele). Závažné komorbidity mohou mít vliv na morbiditu a mortalitu pacienta“ (1).

Oproti staršímu paradigmatu prostého dělení CHOPN na složky plicního emfyzému a chronické bronchitidy je nemoc odbornou a vědeckou komunitou v současnosti vnímána jako komplexní a heterogenní syndrom postihující nejen plíce, ale také různé další orgánové systémy lidského organizmu (2, 3).

Základním patofyziologickým momentem zůstává inhalace různých druhů škodlivého kouře, par, plynů, prachů či jiných částic. Na prvním místě se ale jedná o kouření tabáku - aktivní či pasivní formou (4). Dalšími faktory, které jsou asociovány s vyšším rizikem rozvoje CHOPN, jsou nižší porodní váha (5, 6), astma v dětství (7, 8), časté respirační infekce v dětství (6, 7), prodělaná tuberkulóza či HIV infekce (9-11). Uplatňují se i genetické a epigenetické vlivy, nejznámějšími jsou deficit A1AT (12) a genetické polymorfizmy pro glutation S-transferázu (13), matrix-metaloproteinázy (14) a superoxid-dismutázu (15).

Chronická expozice výše uvedeným noxám vede u vnímavých osob k oxidativnímu stresu, aktivaci leukocytů, nerovnováze proteázo-antiproteázového systému a iniciaci non-

infekčních zánětlivých dějů (16, 17). Dominantním typem je neutrofilní typ zánětu, ale u cca 20% pacientů jsou detekovatelné i rysy eozinofilního zánětu (18). Chronický zánět vede k hyperfunkci hlenotvorného aparátu průdušek, ztrátě elastických vláken v plicním parenchymu, destrukci stěn drobných průdušek, mikrovaskulatury a plicních sklípků, remodelaci dýchacích cest (19, 20). Tyto mechanizmy pak vedou k dynamické a statické hyperinflaci plic, air trappingu, rozvoji emfyzému, poruchám výměny plynů v alveolech. Následkem pak je snížená tolerance fyzické zátěže, rozvoj námahové dušnosti a sekundární pokles fyzické aktivity, což problém dál umocňuje (20, 21). Neustále přibývají důkazy o tom, že dalším důležitým mechanizmem patogeneze CHOPN je senescence, akcelerované stárnutí plic (22, 23). Význam tohoto objevu je umocněn tím, že proces senescence u pacientů s CHOPN není limitován jen na plíce, ale postihuje i jiné orgány / orgánové systémy na základě společného patofyziologického procesu zprostředkovaného extracelulárními partikulemi. Hypoteticky by tak léčba cílená na mechanizmus senescence („senoterapie“) mohla zprostředkovat terapeutický efekt nejen na CHOPN jako takovou, ale i na významné komorbidity, které nemoc CHOPN provázejí (chronické srdeční selhání, akcelerovaná ateroskleróza, osteoporóza, sarkopenie, deprese, zvýšené riziko rozvoje nádorových onemocnění) (22, 23).

1.2. Epidemiologická situace ve světě a v České republice

Prevalence CHOPN ve světě je za rok 2010 odhadována na 11,7% populace starší 30 let věku (24). Znamená to nárůst prevalence o 68,9% oproti roku 1990, kdy činila 10,7% dospělých osob nad 30 let věku (24). Přeneseno do absolutních čísel se jedná o cca 328 miliónů osob ve světě (25). Lze tak říci, že CHOPN je jedna z nejčastějších chronických nemocí vůbec. Co je však alarmující, je nízké procento diagnostikovaných a léčených osob na celkové odhadované prevalenci v daném regionu (26). Prediktivní modely přitom

předpovídají další nárůst prevalence CHOPN v následujících letech (27) nebo nárůst celkového počtu pacientů s CHOPN při stabilní míře prevalence daný celkovým růstem počtu obyvatel naší planety (28). Příznivý trend poklesu prevalence kouření zejména v ekonomicky vyspělých zemích je totiž balancován stárnutím populace (28). Spolu s nárůstem počtu pacientů s CHOPN tak předpokládáme i nárůst počtu hospitalizací a celkový objem výdajů na tuto nemoc (28).

Podle posledního kvalifikovaného odhadu je prevalence CHOPN v České republice odhadována na 6,7% celkové populace, tedy na přibližně 710 tisíc osob (29). Pravidelně léčených a sledovaných je ale v České republice jen kolem 235 tisíc pacientů s CHOPN, což znamená, že u většiny osob nemoc dosud nebyla rozpoznána (29). Časná diagnóza a odvykání kouření je přitom jediná účinná intervence, která dokáže snížit riziko mortality pacientů s CHOPN na populační úrovni (30).

Úmrtnost na CHOPN je velmi závažným celosvětovým problémem. CHOPN je po ischemické chorobě srdeční a cévním onemocnění mozku aktuálně třetí nejčastější příčinou úmrtí na neinfekční nemoci (tzv. non-communicable diseases) (30, 31). Roční počet úmrtí na CHOPN ve světě převyšuje 3 miliony osob (31). Kvůli pokračující epidemii kouření v rozvojových regionech světa a stárnutí populace v rozvinutých zemích nelze v nejbližších letech očekávat zlepšení trendů v rámci této statistiky (30).

Globálně ve státech Evropské unie byl v období mezi lety 1994 a 2010 pozorován lineární trend poklesu mortality na CHOPN (32), v některých státech ale úmrtnost na tuto nemoc stoupala (33). Počet úmrtí na CHOPN v České republice klesal do roku 1996, kdy dosáhl nejnižší hodnoty 1062 úmrtí (34), od té doby však lineárně stoupá, s jistým skokovým nárůstem mezi léty 2012 a 2013 (34). V posledních letech počet úmrtí na CHOPN v České republice osciluje kolem hodnoty 3500 zemřelých ročně (33, 34).

1.3. Klinický kontext

V České republice je kolem 90% pacientů s CHOPN léčeno pneumology, pouze menšina pacientů je léčena cestou praktických lékařů nebo alergologů (pacienti s překryvem astmatu a CHOPN s dominující astmatickou složkou) (3). Tato organizace péče a dobrá dostupnost komplementárních vyšetření umožňuje poměrně sofistikovanou diagnostiku, klasifikaci nemoci i organizaci komplexu terapeutických opatření. Základním principem je snaha o individualizovaný přístup k pacientovi založený na co nejpřesnějším popisu nemoci u každého jednotlivce. U každého pacienta s CHOPN je popsáno stadium nemoci dle GOLD – v závislosti na predikované hodnotě FEV_1 (1), skupina nemoci dle GOLD – v závislosti na míře klinických symptomů (mMRC a CAT skóre) a na počtu exacerbací v posledních 12 měsících (1) a tzv. fenotyp nemoci – v závislosti na přítomnosti klinických (kašel s expektorací, nízké BMI, exacerbace), radiologických (bronchiektázie, emfyzém), laboratorních (eozinofilie) či funkčních (bronchiální hyperreaktivita) patologií (3). Jeden pacient přitom může mít přítomných i několik fenotypů zároveň (3) (blíže viz v Kapitole 2.4.). Princip fenotypizace vychází z konceptu CHOPN jako nehomogenního syndromu, u něhož konkrétní projevy u jednotlivců vykazují značnou interindividuální variabilitu (35, 36). Fenotyp CHOPN představuje charakteristický projev nebo soubor znaků, který definuje podskupinu pacientů s tímto společným rysem. Pokud je fenotyp podmíněn konkrétním patofyziologickým procesem, mluvíme o endotypu (35). Nejznámějším endotypem u CHOPN je geneticky podmíněný vrozený deficit A1AT (37). Některé fenotypy mohou být současně tzv. léčitelnými rysy („treatable traits“) a můžeme tak pro ně definovat některé druhy cílené, individualizované terapie (35). Jako příklad léčitelného rysu uvedu opět deficit A1AT – pacient s CHOPN vzniklou na podkladě jeho vrozeného deficitu může být léčen substituční léčbou A1AT po splnění indikačních kritérií. V tomto případě se jedná se o vysoce specializovanou a přísně individuální léčbu (35).

V každodenní klinické praxi vykazuje přibližně 50-70% pacientů s CHOPN stabilitu své nemoci v čase, a to díky užívání adekvátní bronchodilatační léčby (38, 39). Třetina až polovina pacientů je ale z dlouhodobého časového hlediska nestabilní, což je způsobeno zejména třemi klíčovými faktory – výskytem exacerbací CHOPN, rychlým poklesem plicních funkcí v čase (tzv. „fast decliners“) a přítomností komorbidit, především kardiovaskulárních (40). Tyto definované jevy jsou zodpovědné nejen za zvýšenou morbiditu a mortalitu pacientů s CHOPN, ale jsou spojeny i s vysokou ekonomickou zátěží na zdravotnický systém, zejména z důvodu vyššího výskytu exacerbací a nutnosti hospitalizací (38, 41). Pochopení těchto základních principů a včasná identifikace přítomnosti výše zmíněných jevů u pacienta jsou klíčem k zavedení adekvátních protiopatření, kterými se snažíme o redukci rizika a zlepšení kvality života na straně pacienta a o redukci nákladů na straně zdravotnického systému. Je známo, že dle aktuálně platné klasifikace CHOPN dle GOLD (systém skupin A-D), je skupina B největší kategorií pacientů (42-45), která ale evidentně zahrnuje subpopulaci pacientů s komorbiditami a častými exacerbacemi (3, 42, 43) ohrožených deteriorací do skupiny D v krátkém čase (např. do roka) a zvýšenou mortalitou (38). Stěžejním úkolem klinika u této skupiny pacientů (GOLD B) je tak pečlivost, a to nejen ve vztahu k přesnému popisu charakteru CHOPN u daného pacienta, ale také k vývoji jeho celkového stavu a charakteru nemoci v průběhu času.

Exacerbace CHOPN jsou epizody s akutním zhoršením respiračních symptomů ústící v potřebu změny medikace (46). Většina exacerbací CHOPN je spuštěna virovým či bakteriálním infektem dolních cest dýchacích, případně znečištěným ovzduším, smogem (1, 47, 48), ale až třetina je idiopatického původu (1). Exacerbace CHOPN vede k amplifikaci zánětu v dýchacích cestách, zvýšené mukoprodukci, dynamické plicní hyperinflaci, air trappingu, zhoršení již existující ventilačně-perfuzní nerovnováhy a k respiračnímu selhání (1, 49, 50). Těžké exacerbace s respiračním selháním jsou provázeny vysokým rizikem

hospitalizační (cca 20%) i dlouhodobé post-hospitalizační mortality (cca 63% do 3 let od dimise) (51). Rekonvalescence po exacerbaci CHOPN může trvat týdny až měsíce a u části pacientů už nikdy nedojde k restituci původní úrovně plicních funkcí (52). Exacerbace se mohou v krátkém čase kumulovat a vytvářet klastry (53) a pacient, který exacerboval jednou, je náchylnější k dalším exacerbacím i v budoucnu (54). Opakované epizody zánětlivého vzplanutí ve stěně průdušek, kortikosteroidní léčebné kúra, zvýšená pravděpodobnost bakteriální kolonizace dolních cest dýchacích vedou ke vzniku bronchiektázií a postupně se tak vytváří a fixuje začarovaný kruh, který vede k rychlé deterioraci stavu pacienta (1). Exacerbace CHOPN je proto potřeba vnímat jako velmi nežádoucí jev, který pacienta ohrožuje na životě aktuálně v danou chvíli, ale i v budoucnu. Entita frekventního exacerbátora jako samostatného fenotypu CHOPN vyžadujícího pozornost klinika je zakotvena i v recentně publikovaném Pozičním dokumentu ČPFS k léčbě stabilní fáze CHOPN – viz též Kapitola 2.4. této práce (3). Fenotyp frekventního exacerbátora rozeznávají i jiné dokumenty upravující národní doporučení k léčbě stabilní fáze CHOPN, např. španělská doporučení (55), ale také francouzská, ruská, finská, portugalská či švédská (56).

Klinickým korelátem rychlého poklesu plicních funkcí v čase je ve většině případů vznik plicního emfyzému (57, 58). Emfyzém znamená ztrátu efektivní plochy pro výměnu plynů mezi organizmem a vnějším prostředím. Obecně je pokles plicních funkcí rychlejší zejména v nižších stádiích CHOPN (59, 60), existuje ale podskupina pacientů, u kterých je deklinace plicních funkcí výrazně akcelerována (61-63). Rychlý pokles plicních funkci je přitom asociován s vyšší mírou dlouhodobého rizika zejména kardiovaskulární mortality (61, 64, 65). Emfyzém je asociován s vyšším rizikem mortality, obzvlášť pokud pacient zažívá exacerbace (66).

1.4. Morbidita a mortalita pacientů s CHOPN

Jak je uvedeno v předchozí kapitole, komorbidity - zejména kardiovaskulární - jsou vedle častých exacerbací a rychlé deteriorace plicních funkcí v čase třetím klíčovým faktorem podílejícím se na vysoké míře nemocnosti, utilizace zdravotní péče, ekonomické zátěži a mortalitnímu riziku pacientů s CHOPN (67, 68). Nejčastěji u CHOPN pozorujeme kardiovaskulární komorbidity, dále osteoporózu, malnutrici a sarkopenii nebo obezitu, metabolický syndrom a diabetes, anxiózně-depresivní syndrom, zvýšené riziko rozvoje nádorových onemocnění (zejména karcinomu plic), anémii, poruchy spánku i současnou fibrózu plic (69, 70). Některé komorbidity (např. plicní hypertenze, bronchiektazie nebo malnutrice a sarkopenie) jsou vnímány více jako důsledek CHOPN samotné, jiné sdílejí stejné patofyziologické dráhy s plicním postižením a jsou většinou důsledkem systémového zánětu, dysfunkce cévního endotelu, aktivace koagulačního systému a poruch výměny plynů a acidobazické rovnováhy (69). Tato skupina komorbidit pak CHOPN spíše provází na principu zvýšené pravděpodobnosti, a má tendenci k výskytu v klastrech (69, 71). Platí i vzájemná provázanost, a to že komorbidity dokáží zhoršovat průběh exacerbací CHOPN a naopak, exacerbace CHOPN obvykle zhoršují stav komorbidit (69). Variabilita výskytu komorbidit v subpopulacích dle jednotlivých fenotypů CHOPN se jeví být spíše menší (72). Komorbidity lze detekovat již od časných stádií CHOPN, a to poměrně s vysokou prevalencí (72), jejich výskyt a distribuce pak stoupá s pokročilejším stadiem CHOPN dle GOLD (I-IV), přičemž prevalence kardiovaskulárních komorbidit může být ve stadiu IV paradoxně relativně nižší, pravděpodobně důsledkem vysoké mortality tohoto stadia nemoci (73). Distribuce komorbidit se může lišit i v závislosti na pohlaví pacientů – u žen je častější CHSS, depresivní syndrom, u mužů pak arytmie, cor pulmonale a kognitivní a degenerativní poruchy mozku (73).

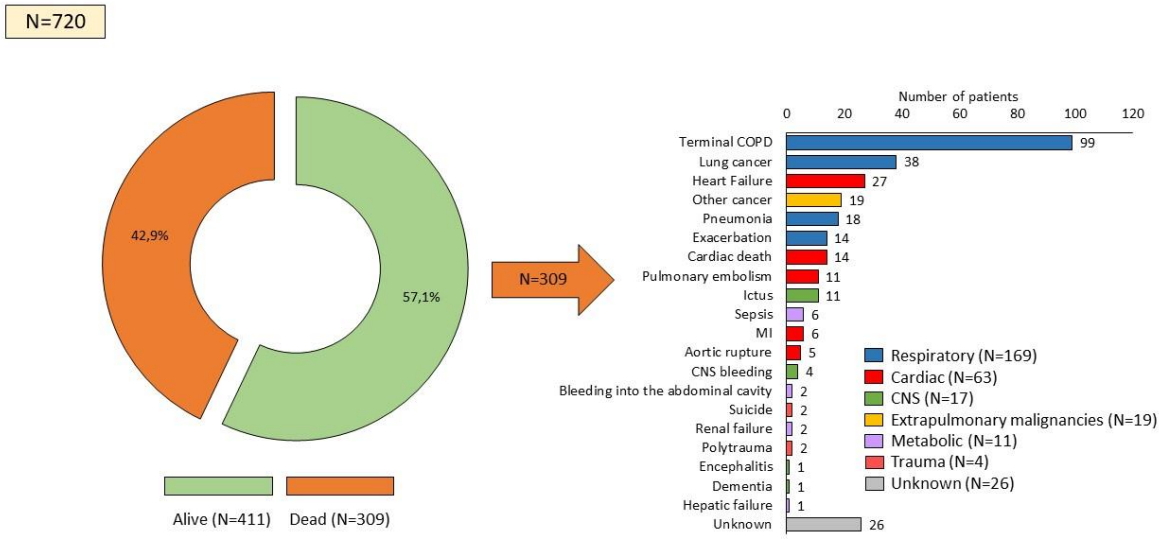
Fascinující jsou novější vědecké zprávy o společné patogenenezi CHOPN a jejích komorbidit na bázi systémového zánětu a mechanizmu senescence (22, 23, 73). Senescentní

buňky se vyznačují výraznou sekretorickou aktivitou, která udržuje v chodu chronické zánětlivé děje, mluvíme o tzv. „senescence-associated secretory phenotype“ (22, 23). Tyto děje vedou k poklesu hladin sirtuinů 1 a 6, což jsou klíčové molekuly bránící stárnutí buněk, tkání a organizmu (22, 23). Teoretické důsledky pochopení těchto mechanizmů jsem již zmiňoval výše – otevírají možnost hypotetické společné léčby CHOPN i komorbidit jedním univerzálním typem medikamentózní léčby („senoterapie“ – např. látky quercetin, dasatinib, navitoclax) (23, 75, 76). Souběh CHOPN s četnými asociovanými komorbiditami je některými autory nazýván jako komorbidní fenotyp (3, 77).

Vědeckých důkazů pro to, že komorbidity mají u CHOPN významný vliv na mortalitu pacientů, je dostatek. Mezi tři nejčastější příčiny úmrtí pacientů s CHOPN patří malignity, kardiovaskulární příčiny a respirační selhání (78, 79). I jiné práce poukazují na kardiovaskulární události a respirační selhání jako na hlavní příčiny úmrtnosti pacientů s CHOPN (80, 81). Jasná souvislost mezi přítomností CHSS a zvýšeným rizikem hospitalizací i mortality pacientů s CHOPN byla prokázána i v nedávno publikované metaanalýze britských autorů (82).

Dosud nepublikovaná data z českého Registru CHOPN (popis registru blíže viz Kapitola 1.7.) z data exportu ze druhé poloviny roku 2020 uvedená na obrázku níže (Graf X) prokazují, že velká část pacientů (cca 42%) v této prospektivně sledované kohortě zemřela z respiračních příčin (respirační selhání, pneumonie, exacerbace CHOPN), ale za podstatnou část úmrtí jsou zodpovědné komorbidity (kardiovaskulární příčiny 20%, karcinom plic 12%, extrapulmonální malignity 6%, cévní mozkové příhody cca 5%).

Graph X Number of dead patients and reasons of deaths



Pro zhodnocení efektu přítomnosti komorbidit na riziko mortality byl zkonstruován i index COTE, který je specifický pro CHOPN pacienty a který pracuje s deseti nejfrekventnějšími položkami komorbidit u pacientů s CHOPN (83).

1.5. Odhad prognózy pacienta s CHOPN

Prognózu pacientů s CHOPN ve vztahu k riziku mortality lze stanovit na základě přítomnosti různých znaků nebo hodnot některých parametrů (84). Tradičně používaným parametrem je % náležité hodnoty postbronchodilatačního FEV_1 (84-86), který byl a je používán v rámci klasifikace CHOPN do stádií GOLD I-IV (87). Plicní funkce reprezentované % náležité hodnoty postbronchodilatačního FEV_1 u pacientů s CHOPN v rámci evoluce nemoci klesají a dosahují postupně hodnot, při kterých se objeví první klinické symptomy, posléze značné omezení základních životních funkcí a na závěr dosáhnou letálních hranic (FEV_1 kolem 15% náležité hodnoty) (59, 60, 88). Stoupající riziko mortality u pacientů s CHOPN je přímo úměrné poklesu FEV_1 v čase (85), někteří autoři ale prognostickou roli FEV_1 zpochybňují (89).

Dalšími známými faktory asociovanými se zvýšeným rizikem mortality pacientů s CHOPN jsou chronická hypoxémie (90) (viz též Kapitola 2.1. této práce), vzdálenost ušlá během 6-MWT (91), nízké BMI (86, 92) a vysoká míra dušnosti (89). Poněkud složitější jsou vztahy mezi rizikem mortality a hyperkapnií. Některé práce chronickou hyperkapnii jako jasný rizikový faktor mortality prokazují (93), jiné vzájemnou asociaci vylučují (94). Ani novější verze klasifikace GOLD nepřinesly zlepšení prognostických vlastností oproti klasisifikaci GOLD založené na hodnotě postbronchodilatačního FEV_1 (95-97). V naší práci jsme zjistili, že se zvýšeným rizikem mortality jsou asociovány příslušnost pacienta do skupiny D dle GOLD nebo přítomnost hypoxémie (PaO_2 <7.3 kPa) u pacienta s CHOPN skupiny B dle GOLD. Blíže viz původní práce v Kapitole 2.1.

Jednotlivé výše zmíněné parametry ale z prognostického hlediska neposkytují dostatečně široký pohled na komplexnost nemoci CHOPN a jejích komorbidit. Pro stratifikaci rizika u pacientů s CHOPN proto byly vytvořeny kompozitní prognostické nástroje. Ve světě je pro odhad rizika dlouhodobé mortality v klinické praxi nejčastěji používán prognostický index BODE (84). Tento nástroj má čtyři komponenty: BMI, hodnotu postbronchodilatačního FEV_1, zhodnocení dušnosti pomocí mMRC skóre a výsledek 6-MWT (počet ušlých metrů). Tento nástroj tak inkorporuje řadu charakteristik s prokázaným vztahem k riziku mortality. Slabším místem indexu je parametr 6-MWT. Vzdálenost ušlá během 6-MWT může být ovlivněna celou řadou faktorů, které mohou výsledek testu zkreslovat. Zejména problematické jsou artróza kolenních či kyčelních kloubů, polyneuropatie dolních končetin a samozřejmě stavy po amputaci dolní končetiny nebo imobilita jiného původu. I drobný rozdíl v ušlé vzdálenosti může vést k horšímu bodovému skóre (např. 150 vs 149 metrů) (84). Dalším problémem u 6-MWT je potřeba adekvátních prostor k jeho provedení (např. chodba délky 20 až 30 metrů), což může být v řadě lékařských ordinací problém. V roce 2009 byla provedena reevaluace BODE indexu, při které autoři zjistili jeho subideální funkčnost na dvou

nezávislých pacientských kohortách (98). Autoři této práce navrhli aktualizaci verze BODE indexu s rozšířením jeho bodové škály na 15 bodů (98). Tato úprava indexu ale jen dále zvyšuje potenciální dopad problému se 6-MWT (např. při ušlých vzdálenostech 350 vs 349 metrů má pacient přiřazeno 0 vs 4 body) (98). Zajímavé výsledky ve vztahu k predikci mortality u pacientů s CHOPN publikoval autorský kolektiv kolem de Torrese, který zkombinoval použití indexů BODE a COTE, čímž se zvýšil prediktivní potenciál obou těchto indexů s finální hodnotu AUC 0,81 (99). Nevýhodou tohoto přístupu je potřeba vypracovat 2 indexy zároveň.

Výsledkem práce španělských autorů byla konstrukce ADO indexu jakožto jednoduchého prognostického nástroje navrhovaného pro používání mimo pneumologické ordinace (např. pro ordinace praktických lékařů) (98). Index ADO se skládá ze třech parametrů: věku, hodnoty postbronchodilatačního FEV_1 a mMRC skóre (98). Značnou nevýhodou tohoto indexu je faktor věku, kterému je alokováno až 50% bodové hodnoty. Věk není specifickým znakem ve vztahu k CHOPN, ale má vlastní a velmi úzký vztah k riziku úmrtí, tzv. Gompertz-Makehamův zákon mortality (100). Ani mMRC skóre není zcela specifické pro CHOPN, jelikož jeho výsledek může být ovlivněn celou řadou mimoplicních příčin dušnosti.

Z indexu BODE byly ještě vyvinuty jeho další modifikace: indexy BODEx (prvky BODE indexu, kde 6-MWT je nahrazen těžkými exacerbacemi) (101), BODEXS90 (index BODEX s hodnotou saturace hemoglobinu kyslíkem) (102). Pro úplnost ještě uvedeme index CODEX, který je určen k predikci rizika rehospitalizace, ale také 12-měsíčního rizika mortality (103). Všechny tyto novější nástroje buď nedosáhly většího rozšíření mezi kliniky nebo mají své specifické nedostatky. V nedávno publikované baskické práci autoři v závěru práce konstatují, že komorbidity by měly být zvažovány jako prognostický ukazatel, nejlépe v kombinaci s již existujícími kompozitními indexy / skórovacími systémy (104).

Stanovení prognózy pacientů s CHOPN se i s kolektivem spolupracovníků věnuji již řadu let. V prvních třech kapitolách komentované části této habilitační práce prezentuji originální práce, které se zabývají stanovením rizika dlouhodobé mortality u pacientů s CHOPN. Za významnou považuji konstrukci prognostického nástroje / indexu CADOT, který předchází některým nevýhodným vlastnostem indexů ADO a BODE (viz výše) a který inkorporuje důležitou komorbiditu (CHSS) jako integrální součást skórovacího systému (blíže viz Kapitola 2.3. této práce). Index CADOT je díky snadné dostupnosti vyšetření difuzní kapacity plic dobře uzpůsoben k použití v podmínkách zdravotnického systému České republiky a jako takový byl doporučen k rutinnímu používání i v rámci Pozičního dokumentu ČPFS k léčbě stabilní fáze CHOPN – viz Kapitola 2.4. této práce.

1.6. Terapeutické cíle farmakologické a nefarmakologické léčby

Základními cíli farmakologických i nefarmakologických modalit léčby CHOPN jsou snížení úrovně symptomů a prevence vzniku či snížení počtu exacerbací nemoci. Dalšími cíli jsou obecné zlepšení kvality života pacientů, zlepšení tolerance fyzické zátěže a zpomalení poklesu plicních funkcí (= zpomalení progrese nemoci v čase) (1). „Svatým grálem“ terapie CHOPN zůstává ovlivnění mortality pacientů. Tohoto cíle – s několika málo výjimkami u specifických podskupin pacientů – nebylo dosud plošně dosaženo prakticky u žádného typu léčby.

Existuje celá řada léčebných přístupů, farmakologických i nefarmakologických, které sledují různé cíle. Tyto cíle jsou navíc definovány různě pro jednotlivé národní zdravotnické systémy. České doporučení bylo formulováno v nedávno publikovaném Pozičním dokumentu ČPFS k léčbě stabilní fáze CHOPN. Základním východiskem tohoto dokumentu je snaha o individualizovanou léčbu CHOPN dle aktuálních potřeb a prezentace znaků nemoci u daného pacienta. Léčba je stratifikována do pěti základních okruhů / kroků, které zahrnují: 1/

eliminaci (nebo omezení vlivu) rizik, 2/ základní léčbu, 3/ fenotypicky-vázanou léčbu, 4/ paliativní léčbu a terapii respiračního selhání a 5/ léčbu přítomných komorbidit. Větší podrobnosti na toto téma jsou prezentovány v Kapitola 2.4. této práce. Zde bych chtěl zmínit pouze ty léčebné postupy nebo opatření, u kterých je zdokumentován efekt na snížení rizika mortality.

Nejzásadnějším opatřením v rámci snahy o snížení rizika mortality pacientů s CHOPN se jeví časná diagnóza nemoci a časné odvykání kouření. Kouření je zodpovědné až za cca 90% úmrtí pacientů s CHOPN, tedy jakákoli intervence snižující tabákovou nálož se projeví jako snížení dlouhodobého rizika úmrtí (105). Ve velké americké longitudinální prospektivní studii (Lung Health Study) bylo prokázáno, že zanechání kouření vede ke zlepšení plicních funkcí a následně k výraznému zpomalení jejich poklesu v čase ve srovnání s aktivními kuřáky (60, 88, 106). Zároveň byl pozorován signifikantní vliv odvykání kouření na snížení mortality pacientů (107). Efekt bronchodilatační léčby na mortalitu zatím nebyl jednoznačně prokázán, byť je intenzivně diskutován (108).

Další specifickou podskupinou pacientů jsou pacienti s plicním emfyzémem na podkladě deficitu A1AT. U těchto pacientů je prokázáno, že čím nižší je denzita jejích plicní tkáně na CT snímcích, tím vyšší je riziko mortality (109). Do procesu akcelerovaného poklesu plicních funkcí a ztráty denzity plicní tkáně u těchto pacientů lze aktivně vstoupit zahájením substituční léčby A1AT (109). Z analýzy dat z velkého amerického registru pacientů s deficitem A1AT jasně vyplývá, že pacienti léčení substitucí A1AT měli signifikantně nižší riziko mortality (110). Tato data nicméně nepocházejí z randomizované studie, proto je potřeba brát s jistou rezervou (110).

U pacientů s velmi pokročilým stadiem CHOPN (s hodnotami FEV_1 blížícími se k letálním limitům = cca 15% predikované hodnoty) (88), je velmi pravděpodobné, že na jejich přežití bude mít pozitivní efekt transplantace plic (111). Při vyšších hodnotách FEV_1 se

tento benefit může vytrácet, což je jasným imperativem ke zpřesnění indikačních kritérií pro transplantaci plic u pacientů s CHOPN (111, 112). Jiní autoři zdůrazňují, že pro defitinivní průkaz efektu transplantace plic na sníženou mortalitu je potřeba dalších prací a jasnější vědecké důkazy (113).

Další chirurgickou metodou, která může snížit riziko mortality, je chirurgická volumredukce (lung volume reduction surgery – LVRS). LVRS je ale účinná pouze u pacientů s emfyzémem dominujícím v horních lalocích a musí být současně přítomna snížená perfuze (dle perfuzní scintigrafie) v těchto partiích plic (114). Jiní autoři zdůrazňují, že LVRS je zatížena vysokým rizikem mortality v časném pooperačním období a měla by být proto indikována s velkou opatrností a po dostatečné úvaze (115).

Zřejmě posledním typem léčby, u které byl prokázán vliv na snížení rizika mortality pacientů s CHOPN, je DDOT. Efekt dlouhodobé kontinuální kyslíkové terapie na snížení mortality u pacientů s těžkou CHOPN a těžkou chronickou hypoxemickou respirační insuficiencí prokázaly dvě studie provedené začátkem osmdesátých let 20. století (90, 116). Naproti tomu, u pacientů s mírnější hypoxémií efekt oxygenoterapie na mortalitu nebyl prokázán (117).

Co se týče medikamentózní léčby, efekt některých léků na snížení mortality je diskutován, zejména inhalačních kortikosteroidů, nicméně dosud žádná práce neprokázala jednoznačný a neoddiskutovatelný efekt (118).

Z výše uvedeného vyplývá, že provedení kvalifikovaného odhadu rizika mortality pacienta s CHOPN má velký klinický význam.

V časné fázi nemoci může pomoct identifikovat rizikovější pacienty a zavést komplex opatření, pomocí kterých by se nemoc dala zpomalit. Včasné odvykání kouření může křivku poklesu plicních funkcí v čase navrátit blíže k normální křivce zdravého člověka (59). Kromě zanechání kouření lze provést celou řadu opatření za účelem zabránění deteriorace stavu a

zamezení exacerbacím nemoci, např. edukaci a zahájení dispenzární péče o pacienta, eliminaci inhalačních rizik, zahájení bronchodilatační (a doplňkové farmakologické) léčby (pokud je indikována), pečlivou léčbu případných komorbidit, cílenou fyzioterapii, očkování proti závažným respiračním patogenům, pravidelné monitorování vývoje plicních a respiračních funkcí v čase a pravidelné přehodnocení stavu nemoci a rizika u daného nemocného (3). Nutným předpokladem k časné intervenci je také časná diagnóza CHOPN. Autor této práce je členem pracovní skupiny a sám aktivně pracuje v rámci projektu ÚZIS „Časný záchyt chronické obstrukční plicní nemoci“ (3). Průběžně je záchyt CHOPN u screenovaných osob s identifikovanými rizikovými faktory až na úrovni kolem 25%, což je mimořádná míra výkonu screeningového programu.

U pacientů se středně závažnými formami nemoci (zajména stadia GOLD II nebo skupiny GOLD B) pomáhá zhodnocení rizika dlouhodobé mortality identifikovat ty pacienty, kteří jsou ohroženi rychlou deteriorací stavu a výskytem exacerbací. Toto je důležité zejména z důvodu, že GOLD stadium II a skupina B jsou nejpočetnější kategorie pacientů a identifikace rizikových pacientů nemusí být jednoduchá. U rizikových pacientů je potřeba maximalizovat léčebnou a preventivní snahu celého ošetřujícího týmu a zamezit exacerbacím a rychlé deterioraci plicních funkcí, která je nejrychlejší především ve stádiích II a III dle GOLD (1, 59).

Pacienti v pokročilých stádiích CHOPN (GOLD stádia III-IV a skupina D) jsou obecně ohroženi vysokým rizikem mortality, identifikace jedinců s vyšším rizikem v rámci těchto subpopulací má ale význam zejména z důvodu možnosti zavedení DDOT (u indikovaných jedinců) (90, 116) a adekvátní přípravy pacienta k transplantaci plic (u indikovaných jedinců) po stránce psychologické, celkové výkonnosti, stavu výživy a imunity a optimalizaci léčby (111).

Snaha o snížení rizika mortality patří mezi základní úkoly pneumologa v rámci péče o pacienta s CHOPN, byť jsou reálné možnosti takových intervencí omezené jen na některé konkrétní podskupiny pacientů a za pomoci velmi specifických léčebných opatření (diskutováno výše). Jen důsledná identifikace rizikových pacientů ale umožní optimalizovat veškeré léčebné, diagnostické i preventivní kroky a případně zavést ta opatření, která mají na mortalitu vliv.

V rámci této habilitační práce prezentuji a komentuji šest časopiseckých prací, které získanými poznatky pomáhají identifikovat vysoce rizikové pacienty za pomoci krevních plynů a pulzní oxymetrie ve skupině GOLD B (kapitola 2.1.), v celé populaci pacientů s CHOPN za pomoci nového prognostického nástroje (kapitola 2.3.). V jedné práci poukazujeme na nedokonalost a neintuitivnost klasifikačního systému GOLD A-D ve vztahu k riziku mortality (kapitola 2.2.). Poziční dokument ČPFS k léčbě stabilní fáze CHOPN (kapitola 2.4.) je velmi moderním dílem s novým konceptem managementu stavu a léčby pacienta s CHOPN; v dokumentu je věnován prostor i stanovení prognózy pacienta s CHOPN v rámci samostatné kapitoly. Další dvě práce pojednávají o námi vyvinutých metodách optimalizace inhalační resp. aplikační techniky inhalačních preparátů (kapitola 2.6.) a o návrhu randomizované studie k posouzení nejeefektivnější metody posílení inspiračního svalstva pacientů s CHOPN, kterou zahájíme v květnu 2021 s podporou výzkumného grantu AZV MZ ČR č. NU21J-09-00004 s názvem „*Srovnání nových a tradičních metod tréninku inspiračního svalstva u pacientů s CHOPN založených na vzdáleném monitorování*“.

1.7. Registr CHOPN v České republice

Několik prací z tohoto komentovaného souboru vzniklo na platformě multicentrické spolupráce pneumologických pracovišť v České republice v rámci Registru CHOPN. Registr CHOPN byl založen v roce 2013, participuje na něm 14 pneumologických center terciárního

nebo univerzitního typu v České republice a je administrován Institutem Biostatistiky a Analýz, s.r.o. Cílem tohoto unikátního neintervenčního projektu je prospektivní sledování pacientů s CHOPN po dobu 5 let od zařazení, sledování přirozené i léčbou modifikované evoluce jejich nemoci, výskytu exacerbací, průběhu léčby, morbidity a mortality. Do registru byli zařazováni pouze pacienti s jistou diagnózou CHOPN, s FEV_1 pod 60% predikované hodnoty, stabilní po dobu posledních 2 měsíců a kteří souhlasili se zařazením do projektu. Vyřazeni byli pacienti s předpokládanou délkou života méně než 6 měsíců a s dominujícím jiným zdravotním problémem než CHOPN (např. karcinom plic, vícečetné bronchiektázie) (119). Hlavními sledovanými parametry jsou: demografická a anamnestická data, úroveň symptomů (mMRC skóre, CAT skóre), kvalita života (SGRQ skóre), farmakologická i nefarmakologická léčba, plicní funkce (spirometrie, bodypletyzmografie, difuzní kapacita plic pro oxid uhelnatý, FeNO) a jiné klinické údaje (CT plic, EKG, krevní plyny) (119). Nábor celkem 784 pacientů byl ukončen v prosinci 2016 a sledování pacientů bude pokračovat do konce roku 2021.

Z technických parametrů: projekt Registru CHOPN byl registrován na ÚZIS pod identifikačním číslem 1301100001 a na ClinicalTrials.gov s identifikátorem NCT01923051. Projekt probíhá v souladu s právním rámcem České republiky i Evropské Unie a s etickým rámcem vymezeným Helsinskou deklarací. Projekt Registru CHOPN (včetně jeho protokolu) byl schválen Multicentrickou etickou komisí Masarykovy univerzity dne 16.1.2013 (kód schválení: CHOPN) a regionálními etickými komisemi jednotlivých participujících center (119).

Autor této habilitační práce je členem steering committee Registru CHOPN, také zadával data do registru, je jedním z publikačně nejaktivnějších členů pracovní skupiny a přednostou Kliniky nemocí plicních a tuberkulózy LF MU a FN Brno, která je jedním z největších přispěvatelů dat do Registru CHOPN.

2. KOMENTOVANÉ PRÁCE

2.1. Respiratory parameters predict poor outcome in COPD patients, category GOLD 2017 B.

Citace: 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.

Komentář:

V této prospektivní multicentrické práci jsme analyzovali prognostickou hodnotu arteriálních krevních plynů a dalších respiračních parametrů u pacientů s CHOPN skupin GOLD A-D ve vztahu k dlouhodobé mortalitě. Krevní plyny a 6-MWT s měřením periferní saturace hemoglobinu kyslíkem patří mezi jednoduché a snadno dostupné metody posouzení aktuální respirační funkce plic.

Racionálním základem pro tuto práci byla změna klasifikace CHOPN, která byla ustanovena novým dokumentem GOLD na konci roku 2016 a která vedla k velkým přesunům pacientů z jedné kategorie do jiné. Touto změnou došlo k velkému přesunu pacientů zejména ze skupiny D do skupiny B, což mělo dvě zásadní konsekvence: 1/ skupina B se stala nejpočetnější kategorií CHOPN čítající dle různých autorů až 50% počtu pacientů v různých kohortách (42, 44, 45) a 2/ pacienti překlasifikováni ze skupiny D na B teoreticky měli podstoupit redukci léčby, zejména o inhalační kortikosteroidy, které v léčbě pacientů skupiny B nebyly doporučovány (97). Kategorie B je přitom skupina pacientů s vyšším výskytem komorbidit, u kterých lze reálně očekávat deterioraci CHOPN, výskyt exacerbací a zvýšenou mortalitu (3, 42, 43).

Pacienti s těžkou plicní arteriální hypertenzí (>60mm Hg) a/nebo se syndromem spánkové apnoe byli z této analýzy vyřazeni. Ze zbývajícího počtu 725 pacientů splňovalo kritéria potřebná k provedení mortalitních analýz 391 pacientů pro krevní plyny a 552 pacientů pro periferní saturaci hemoglobinu kyslíkem. Ostatní pacienti v kohortě Registru CHOPN neměli provedeny odběry krevních plynů nebo 6-MWT (tyto položky nejsou v Registru CHOPN mandatorní).

V rámci popisu základních charakteristik souboru byly kategoriální parametry prezentovány jako absolutní hodnoty a relativní četnosti z celkového n, kontinuální proměnné jako průměr (± SD) nebo medián (5. a 95. percentil). Byly konstruovány Kaplan-Meierovy křivky 3-letého přežití pro skupiny GOLD A-D dle starší i novější GOLD klasifikace, a to pro tyto respirační parametry: PaO_2, $PaCO_2$, pH krve, bazální SpO_2, minimální SpO_2 při 6-MWT, desaturace během 6-MWT. Pro kontinuální proměnné (např. PaO_2) byly pomocí ROC analýzy identifikovány ideální cut-off hodnoty, v případě $PaCO_2$ byly použity klinicky relevantní kategorie. V případě signifikantních rozdílů v riziku mortality byly pro dané parametry doplněny uni- a multivariantní regresní analýzy k identifikaci faktorů asociovaných s rizikem mortality.

Kohorta byla složena převážně z mužů průměrného věku 66,7 let, téměř 90% aktivních či bývalých kuřáků, s průměrnou hodnotou FEV_1 na úrovni 44,9% predikované hodnoty a průměrnou vzdáleností 335 metrů ušlou během 6-MWT. Dle starší klasifikace GOLD platné v letech 2011-2016 (96) patřila většina pacientů do skupiny D (69.6%), dle novější verze GOLD (97) s překlasifikováním stadia nemoci byla nejpočetnější skupina B s 53%.

Co se týče predikční schopnosti respiračních parametrů, v rámci ROC analýzy měly všechny studované parametry podobnou hodnotu AUC (0,59 – 0,631). Pozorovali jsme významnou korelaci mezi hodnotami PaO_2 a bazální i minimální SpO_2. Signifikantní rozdíly

v pravděpodobnosti mortality byly pro PaO_2 <7,3 kPa pozorovány zejména ve skupině GOLD B (p=0,001), ale i v celé kohortě (p<0,001), pro různé kategorie hodnoty kapnémie ($PaCO_2$ <5 kPa, 5-7 kPa a >7 kPa) ve skupině GOLD B (p<0,001) a pro desaturaci během 6-MWT ve skupině GOLD B (p=0,022) a v celé kohortě (p=0,004). V logistických regresních modelech byla testována asociace zmíněných parametrů s rizikem mortality, přičemž jediným relevantním faktorem nezávisle asociovaným s mortalitou byla hodnota arteriální oxémie (PaO_2) <7,3 kPa.

Nejvýznamnějším výsledkem naší práce bylo, že jsme v rámci největší skupiny GOLD B pacientů s CHOPN identifikovali podskupinu s vysokým rizikem dlouhodobé mortality – pacienty s hypoxémií <7,3 kPa (HR 2,398; 95% CI 1,245-4,63; p=0,009). Přítomnost chronické hypoxémie byla identifikována jako rizikový faktor mortality pacientů s CHOPN i v jiných pracích, kde ale nebyl zkoumán vztah ke stadiu či skupině nemoci (120, 121). Je důležité zmínit, že dlouhodobá domácí oxygenoterapie nemá vliv na mortalitu pacientů s lehkou až středně těžkou chronickou hypoxémií (116, 122). V rámci doporučení pro klinickou praxi tedy spíše navrhujeme soustředit se na snahu o optimalizaci terapie pro tyto vysoce rizikové pacienty, nejen ve smyslu medikamentózní léčby, ale i ostatních modalit, jakými jsou odvykání kouření (pokud do té doby neproběhlo), fyzioterapie, případně doplněna o nutriční podporu (u pacientů s rozvíjející se kachexií), vakcinace proti *Streptococcus pneumoniae*, virům chřipky a SARS-CoV-2, indikace domácí oxygenoterapie, asertivnější management akutních exacerbací (3). Cílem takových opatření je snaha o zmírnění symptomů, minimalizaci počtu a dopadu exacerbací, zpomalení deteriorace stavu pacienta v delším časovém horizontu a zachování co nejlepšího celkového stavu pacienta před indikací případné transplantace plic.

V naší práci jsme neprokázali, že by kapnémie >7 kPa byla nezávislým rizikovým faktorem dlouhodobé mortality u pacientů s CHOPN. Tento výsledek potvrzuje předchozí

vědecké poznatky, že vztah chronické hyperkapnémie a rizika mortality není tak jednoznačný jako u hypoxémie (93, 94). Mechanizmy vzniku hypoxémie a hyperkapnémie u pacientů s CHOPN nejsou zcela totožné. Hyperkapnémie u CHOPN je spíše vyjádřením alveolární hypoventilace způsobené bronchiální obstrukcí a hyperinflací, ale i metabolických důsledků respirační acidózy na funkci respiračních svalů (indukcí mitochondriální dysfunkce) (123). Naproti tomu, hlavními mechanizmy vzniku hypoxémie jsou ventilačně-perfuzní nerovnováha, pravolevý zkrat, snížená difuze a alveolární hypoventilace (124). Hypoxémie pak zvyšuje ventilační drive, regionálně klesá $PaCO_2$, což indukuje plicní vazokonstrikci a periferní vazodilataci, stimuluje erytropoézu, zvyšuje se viskozita krve. Důsledkem je náročnější ventilace, zvýšení srdeční frekvence, srdečního výdeje a srdeční práce (125). Z výše uvedeného - zejména s ohledem na rozvoj sekundárního srdečního postižení - vyplývají i rozdíly v riziku mortality, které je u chronické hypoxémie výraznější i konzistentnější napříč literaturou.

Vyšetření arteriálních krevných plynů je jednoduché a objektivní vyšetření, které snadno odhalí vysoce rizikové pacienty v rámci největší skupiny GOLD B. Jistým problémem může být dostupnost tohoto vyšetření, avšak v naší práci jsme také prokázali významnou pozitivní korelaci mezi PaO_2 a klidovou SpO_2, kterou tímto navrhujeme používat jako jednoduchou screeningovou metodu. Při zjištění SpO_2 <90% je vhodné pacienta nasměrovat na vyšetření krevních plynů (126).

Závěrečné shrnutí jednou větou: V této práci jsme prokázali, že přítomnost hypoxémie <7,3 kPa u pacientů s CHOPN skupiny B je asociována s vysokým rizikem dlouhodobé mortality a lze ji tak použít pro identifikaci pacientů vyžadujících asertivnější terapeutický přístup.

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ORIGINAL RESEARCH

Respiratory parameters predict poor outcome in COPD patients, category GOLD 2017 B

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Background: Respiratory parameters are important predictors of prognosis in the COPD population. Global Initiative for Obstructive Lung Disease (GOLD) 2017 Update resulted in a vertical shift of patients across COPD categories, with category B being the most populous and clinically heterogeneous. The aim of our study was to investigate whether respiratory parameters might be associated with increased all-cause mortality within GOLD category B patients.

Methods: The data were extracted from the Czech Multicentre Research Database, a prospective, noninterventional multicenter study of COPD patients. Kaplan–Meier survival analyses were performed at different levels of respiratory parameters (partial pressure of oxygen in arterial blood [PaO_2], partial pressure of arterial carbon dioxide [$PaCO_2$] and greatest decrease of basal peripheral capillary oxygen saturation during 6-minute walking test [6-MWT]). Univariate analyses using the Cox proportional hazard model and multivariate analyses were used to identify risk factors for mortality in hypoxemic and hypercapnic individuals with COPD.

Results: All-cause mortality in the cohort at 3 years of prospective follow-up reached 18.4%. Chronic hypoxemia (PaO_2 <7.3 kPa), hypercapnia ($PaCO_2$ >7.0 kPa) and oxygen desaturation during the 6-MWT were predictors of long-term mortality in COPD patients with forced expiratory volume in 1 second ≤60% for the overall cohort and for GOLD B category patients. Univariate analyses confirmed the association among decreased oxemia (<7.3 kPa), increased capnemia (>7.0 kPa), oxygen desaturation during 6-MWT and mortality in the studied groups of COPD subjects. Multivariate analysis identified PaO_2 <7.3 kPa as a strong independent risk factor for mortality.

Conclusion: Survival analyses showed significantly increased all-cause mortality in hypoxemic and hypercapnic GOLD B subjects. More important, PaO_2 <7.3 kPa was the strongest risk factor, especially in category B patients. In contrast, the majority of the tested respiratory parameters did not show a difference in mortality in the GOLD category D cohort.

Keywords: mortality, hypoxemia, hypercapnia, COPD, GOLD 2017 update

Introduction

COPD is a major health problem affecting 11.7% of the global population and causing the death of about 3 million persons annually.[1] Currently, the Global Initiative for Obstructive Lung Disease (GOLD) introduced a new approach in COPD classification by using separate evaluations of spirometric values (stages 1–4) and the presence of symptoms and exacerbations (categories A–D).[1] Application of the new GOLD 2017 recommendations profoundly affected the distribution of patients in the A–D groups. An obvious consequence of the new classification is a vertical shift of a large portion of COPD patients from the C to the A group and from the D to the

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B group. Thus, more than half of the real-life COPD population represents substantially heterogeneous B category.[2]

Several risk factors predictive of poor outcome have been identified for stratification of stable COPD patients. Lung function, represented by forced expiratory volume in 1 second (FEV_1), has been the most widely used prognostic factor and still has an important role in the assessment of COPD patients.[1,3–6] Other prognostic factors associated with an increased risk of death include low exercise tolerance, a high degree of functional breathlessness and a low body mass index (BMI).[5] In 2004, Celli et al published an integrative, multidimensional prognostic model for COPD patients named the BODE index (BMI, Obstruction, Dyspnea and Exercise).[5] Subsequently, the COTE (COPD-specific comorbidity test) index, involving the BODE index and comorbidities assessment, has been introduced.[4] Other scoring instruments may also be predictive of poor outcomes. In a Swedish multicenter study, a Clinical COPD Questionnaire score higher than 2 was associated with a prognosis of higher mortality.[7] Since 2011, GOLD recommends stratification of COPD patients into A–D categories;[8] however, prognostic values of BODE and COTE indices have been found superior to GOLD 2011 A–D categories.[4] Two important studies revealed the shortcomings of GOLD 2011 classification. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study as well as in the Copenhagen City Heart Study, no advantages over GOLD 1–4 classification were demonstrated with the introduction of GOLD A–D categories in better predicting long-term mortality.[9,10]

The latest GOLD 2017 Update does not recommend the use of elementary respiratory parameters for disease classification or for mortality risk assessment or treatment strategy improvement.[1] However, chronic respiratory failure is a frequent feature (or rather consequence) of the disease, and the presence of chronic hypoxemia and/or hypercapnia is associated with remarkably higher mortality and morbidity.[3] Hypoxemia is a state in which partial pressure of oxygen in arterial blood (PaO_2) is decreased below the reference values adjusted for age. Limits between normal and abnormal PaO_2 decrease with age. Hypercapnia is defined by partial pressure of arterial carbon dioxide ($PaCO_2$) >6 kPa.[11,12]

Various respiratory parameters have been assessed as potential risk factors for mortality by a large number of studies. However, there is limited evidence of how respiratory parameters affect outcome in specific subgroups of COPD subjects. The general purpose of the Czech Multicentre Research Database (CMRD) of the COPD project was to analyze the association among respiratory parameters, clinical phenotypes, GOLD categories and all-cause mortality in COPD individuals. The primary aim of the presented study was to assess selected respiratory parameters as potential predictors of death in COPD patients, classified according to the new GOLD 2017 strategy with emphasis on the largest population of COPD individuals: GOLD 2017 category B patients.

Methods

Study design

All patients for the study were recruited from the CMRD of COPD. This project (registered by the State Institute for Drug Control under the identifier 1301100001 and at ClinicalTrials.gov as NCT01923051) was initiated in August 2013.[13] The prospective CMRD study is being conducted in full accordance with Czech and European Union laws. The CMRD study and its protocol were approved by The Multicentre Ethical Committee of Masaryk University, Brno, Czech Republic (approval date: JAN-16-2013, protocol code: CHOPN) as well as ethics and regional review boards of all individual participating centers.[13] All COPD participants signed a written consent form before study enrolment.

Basic criteria for patient enrolment were respiratory physician's diagnosis of COPD at least 12 months before enrolment, post-bronchodilator $FEV_1 \leq 60\%$, exacerbation-free period for at least 8 weeks and patient's written consent. We used the GOLD definition of COPD case, that is, a patient with confirmed post-bronchodilator airflow limitation (FEV_1/forced vital capacity <0.70). Patient recruitment finished in December 2016. Longitudinal and prospective follow-up (in regular 6-month periods) of patients is planned for 5 consecutive years and will be finished in 2021.[13] At each control, the patients completed pulmonary function tests, an elementary physical examination, measurement of respiratory and nonrespiratory symptoms and systematic assessment of the patient's history. Completing a 6-minute walking test (6-MWT) and/or an arterial blood gas (ABG) analysis was optional (not mandatory).[13] If done, ABG analysis and/or a 6-MWT were performed without oxygen supplementation in all cases. Any changes in medication, onset of new comorbidities or number of exacerbations were recorded. The prospective nature of the project enabled assessment of various outcomes, including long-term mortality and exacerbation rates, to follow the development of multiple comorbidities as well as to understand the natural evolution of the disease and its manifestations (represented by various clinical phenotypes and GOLD categories).[13]

In this particular study, the following respiratory parameters were selected for mortality analyses: PaO_2, $PaCO_2$, arterial potential of hydrogen (pH), basal peripheral capillary oxygen saturation (SpO_2), minimal SpO_2 during a 6-MWT, greatest decrease in SpO_2 during a 6-MWT and the presence of desaturation (ie, at least 4% drop and/or decrease of SpO_2 <90% during 6-MWT).

Study population

Inclusion criteria for our analyses were regular follow-up in the CMRD. Exclusion criteria were the presence of sleep apnea syndrome or systolic pulmonary arterial hypertension (PAH) >60 mmHg (in patient history and/or echocardiographic finding of PAH >60 mmHg during the study enrolment).

Statistical analyses

For a basic description of the study population, categorical parameters are presented as absolute (relative) frequencies. Relative frequencies are calculated from valid *N*. Continuous variables are described by valid *N*, using mean with SD and median supplemented by 5th and 95th percentiles.

Kaplan–Meier curves illustrating 3-year survival were calculated for survival analysis of patients in the complete cohort along with groups A–D according to the GOLD 2016 and GOLD 2017 guidelines for these parameters: PaO_2 (oxemia), $PaCO_2$ (capnemia), arterial pH, basal SpO_2, minimal SpO_2 during (after) 6-MWT, greatest decrease of SpO_2 during 6-MWT and the presence of desaturation during 6-MWT. The figures are supplemented by numerical data showing proportion of survival at 6, 12, 24 and 36 months of follow-up. Differences in survival between groups were tested by log-rank test.

Correlations of blood gases (PaO_2, $PaCO_2$, basal SpO_2, minimal SpO_2 during (after) 6-MWT and greatest decrease of SpO_2 during 6-MWT) were analyzed by Spearman's coefficient of correlation. In addition, the best calculated cutoff values of oxemia, capnemia, blood pH, basal SpO_2, minimal SpO_2 during (after) 6-MWT and greatest decrease of SpO_2 during 6-MWT were calculated for prediction for mortality.

A Cox proportional hazard model was used to assess risk factors for mortality. Multivariate models analyzed other potential predictors of all-cause mortality for patient groups with hypoxemia, three levels of capnemia and desaturation during a 6-MWT.

Analyses were performed using SPSS Statistics 24.0 software with the level of significance at α=0.05.

Results

Of the 784 patients included in the CMRD (by December 2016), 53 patients were excluded because of the presence of sleep apnea syndrome and six patients because of severe PAH (Figure 1). Of the remaining 725 patients, the inclusion criteria for the proposed analyses of ABGs were met in 391 patients and for SpO_2 in 552 patients.

Patients' characteristics

Basic demographic characteristics included sex, age at inclusion, age at COPD diagnosis, BMI and smoking status (Table 1). Seventy-two percent of the study population were men, 89% were past or current smokers, median age was 67.1 years and median BMI was 26.5. The most frequently reported symptoms were cough (72%), expectoration (58%) and fatigue (47%). Mean exacerbation rate was 1.2 events per year, one-third (0.4 event per year) of these requiring hospitalization. Lung function tests showed that the median FEV_1 was 46% of predicted value (pred), and median transfer factor for carbon monoxide was 51% pred, whereas median distance covered during a 6-MWT was 359.5 m (Table 1).

Respiratory parameters

Table 2 summarizes the results of ABG analyses and the results of pulse oximetry performed at rest and during a 6-MWT. Correlation analyses of respiratory parameters showed significant and strong correlation between PaO_2 and basal and minimal SpO_2 and a significant negative correlation between PaO_2 and $PaCO_2$ for the complete study cohort and for GOLD 2017 group B (Table 3).

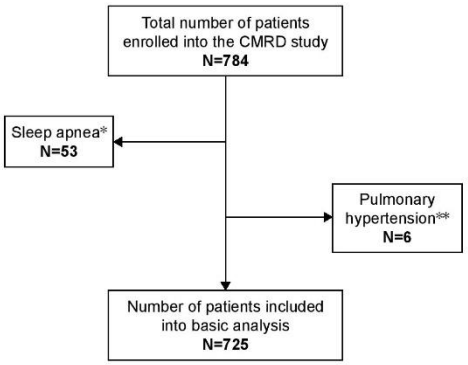


Figure 1 Flow chart of patients.
Notes: *Self-reported history of sleep apnea. **Self-reported history of pulmonary hypertension.
Abbreviation: CMRD, Czech Multicentre Research Database.

Table 1 Basic characteristics of the study cohort – COPD patients (n=725)

Demography	
Sex – men	520 (71.7%)
Age at inclusion	n=725; 66.7 (9.4)
BMI	n=725; 26.9 (5.8)
Smoking status	
Ex-smoker	491 (67.7%)
Nonsmoker	79 (10.9%)
Current smoker	155 (21.4%)
Symptoms	
Dyspnea – mMRC	
0	36 (5.0%)
1	141 (19.4%)
2	289 (39.9%)
3	150 (20.7%)
4	109 (15.0%)
CAT	n=715; 16.0 (7.8)
Fatigue	331 (46.8%)
Cough	521 (71.9%)
Expectoration	423 (58.3%)
Atopy	86 (11.9%)
Asthma	75 (10.3%)
Exacerbations in the last 12 months	
Treated at home	n=725; 0.8 (1.3)
Requiring hospitalization	n=725; 0.4 (0.8)
Total	n=725; 1.2 (1.6)
Lung functions	
FEV_1 (% pred)	n=725; 44.9 (11.6)
FVC (% pred)	n=725; 69.2 (17.7)
FEV_1/FVC (%)	n=725; 0.5 (0.1)
RV (% pred)	n=587; 189.0 (58.7)
TLC (% pred)	n=583; 112.1 (25.8)
IC/TLC (%)	n=422; 42.1 (24.6)
TL_{CO} (% pred)	n=473; 52.5 (22.1)
FeNO (ppb)	n=267; 18.6 (19.4)
6-MWD (m)	n=552; 334.9 (131.7)
Phenotypes	
Czech approach (one COPD subject = one or more "phenotypical labels – treatable traits")	
Bronchitic	423 (58.3%)
Emphysematous	263 (78.0%)
BCOS	105 (31.9%)
ACOS*	23 (4.1%)
Frequent exacerbators	225 (31.0%)
Cachexia	111 (15.3%)
Spanish approach (one COPD subject = one "clinical phenotype")	
ACOS**	85 (11.7%)
Non-AE	451 (62.2%)
AE CB	126 (17.4%)
AE non-CB	63 (8.7%)
GOLD	
GOLD 2016 (A–D)	
A	34 (4.9%)
B	140 (20.2%)
C	37 (5.3%)
D	483 (69.6%)
GOLD 2017 (A–D)	
A	60 (8.3%)
B	383 (53.0%)
C	14 (1.9%)
D	265 (36.7%)

Notes: Categorical parameters are described by absolute (relative) frequencies. Relative frequencies are calculated from valid data. Continuous parameters are described by valid N, mean (SD). *Czech approach has used more restrictive criteria[13] than simplified. **Spanish approach.[15]

Abbreviations: 6-MWD, 6 minute walking distance; ACOS (ACO), asthma COPD overlap syndrome; AE CB, frequent exacerbators with chronic bronchitis; AE non-CB, frequent exacerbators without chronic bronchitis; BCOS, bronchiectases COPD overlap syndrome; BMI, body mass index; CAT, COPD Assessment Test; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; IC/TLC, inspiratory capacity to total lung capacity ratio; mMRC, modified Medical Research Council dyspnea scale; ppb, part per billion; pred, predicted value; RV, residual volume; TLC, total lung capacity; TL_{CO}, transfer factor for carbon monoxide.

Survival analyses

Of the tested respiratory parameters, minimal SpO_2 during the 6-MWT yielded the highest ability to predict mortality (area under curve 0.631; $p<0.001$; Table 4). Survival analyses showed significant differences in long-term all-cause mortality in relation to the selected respiratory parameters (PaO_2, $PaCO_2$ and desaturation during a 6-MWT; Figures 2A–C, 3A–C and 4A–C).

PaO_2

Significant association has been found between severe hypoxemia (PaO_2 <7.3 kPa) and all-cause mortality in the complete COPD cohort ($p<0.001$; Figure 2A) as well as in the GOLD 2017 B category ($p=0.001$; Figure 2B). In contrast, severe hypoxemia (PaO_2 <7.3 kPa) did not result in a significant difference in all-cause mortality in the COPD 2017 D category ($p=0.061$; Figure 2C).

$PaCO_2$

In GOLD 2017 category B patients, the highest survival rate was observed if the level of $PaCO_2$ was 5–7 kPa.

Table 2 Respiratory parameters (n=725)

Respiratory parameters	
PaO_2 (kPa)	n=391; 8.8 (1.6)
$PaCO_2$ (kPa)	n=391; 5.2 (0.9)
pH	n=391; 7.42 (0.43)
Basal SpO_2 (%)	n=552; 94.5 (3.6)
Minimal SpO_2 during (after) 6-MWT (%)	n=552; 89.6 (7.0)
Greatest decrease of SpO_2 during 6-MWT (%)	n=552; 4.8 (4.7)

Note: Continuous parameters are described by valid N, mean (SD).

Abbreviations: 6-MWT, 6-minute walking test; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; pH, arterial potential of hydrogen; SpO_2, peripheral capillary oxygen saturation.

Table 3 Correlation of respiratory parameters (all patients and GOLD 2017 B patients)

All patients	PaO_2 (kPa)	$PaCO_2$ (kPa)	Basal SpO_2 (%)	Minimal SpO_2 (%)	Greatest decrease of SpO_2 (%)
PaO_2 (kPa)	–	n=391 −0.306 (<**0.001**)	n=351 0.552 (<**0.001**)	n=351 0.535 (<**0.001**)	n=351 −0.367 (<**0.001**)
$PaCO_2$ (kPa)	n=391 −0.306 (<**0.001**)	–	n=351 −0.274 (<**0.001**)	n=351 −0.298 (<**0.001**)	n=351 0.219 (<**0.001**)
Basal SpO_2 (%)	n=351 0.552 (<**0.001**)	n=351 −0.274 (<**0.001**)	–	n=552 0.742 (<**0.001**)	n=552 −0.350 (<**0.001**)
Minimal SpO_2 (%)	n=351 0.535 (<**0.001**)	n=351 −0.298 (<**0.001**)	n=552 0.742 (<**0.001**)	–	n=552 −0.860 (<**0.001**)
Greatest decrease of SpO_2 (%)	n=351 −0.367 (<**0.001**)	n=351 0.219 (<**0.001**)	n=552 −0.350 (<**0.001**)	n=552 −0.860 (<**0.001**)	–
GOLD 2017 B patients					
PaO_2 (kPa)	–	n=181 −0.345 (<**0.001**)	n=168 0.462 (<**0.001**)	n=168 0.477 (<**0.001**)	n=168 −0.338 (<**0.001**)
$PaCO_2$ (kPa)	n=181 −0.345 (<**0.001**)	–	n=168 −0.303 (<**0.001**)	n=168 −0.279 (<**0.001**)	n=168 0.167 (**0.030**)
Basal SpO_2 (%)	n=168 0.462 (<**0.001**)	n=168 −0.303 (<**0.001**)	–	n=287 0.738 (<**0.001**)	n=287 −0.351 (<**0.001**)
Minimal SpO_2 (%)	n=168 0.477 (<**0.001**)	n=168 −0.279 (<**0.001**)	n=287 0.738 (<**0.001**)	–	n=287 −0.853 (<**0.001**)
Greatest decrease of SpO_2 (%)	n=168 −0.338 (<**0.001**)	n=168 0.167 (**0.030**)	n=287 −0.351 (<**0.001**)	n=287 −0.853 (<**0.001**)	–

Notes: Spearman's coefficient of correlation. Significant differences are indicated in bold.
Abbreviations: $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, peripheral capillary oxygen saturation.

The presence of hypercapnia ($PaCO_2$ >7 kPa) significantly increased (p<0.001) the mortality rate in this group. Interestingly, there was no effect of capnemia on all-cause mortality in the complete cohort (p=0.290) or in the GOLD 2017 category D group (p=0.409) (Figure 3A–C).

pH

pH was not found to be associated with increased risk for mortality in any of the tested patient groups.

Desaturation during 6-MWT

Desaturation was present in 46.4% of the study cohort (Table S1). The presence of desaturation was associated with increased mortality in the complete cohort (p=0.004) and in the GOLD 2017 B category (p=0.022). Desaturation was not associated with higher mortality in the GOLD 2017 D category (p=0.175; Figure 4A–C).

Table 4 Prediction of all-cause mortality by respiratory parameters

Respiratory parameters	AUC (95% CI)	*p*-value
PaO_2 (kPa)	0.590 (0.507; 0.673)	**0.020**
$PaCO_2$ (kPa)	0.600 (0.521; 0.679)	**0.010**
Basal SpO_2 (%)	0.607 (0.537; 0.676)	**0.002**
Minimal SpO_2 during 6-MWT (%)	0.631 (0.569; 0.693)	<**0.001**
Greatest decrease of SpO_2 (%)	0.610 (0.548; 0.671)	**0.001**

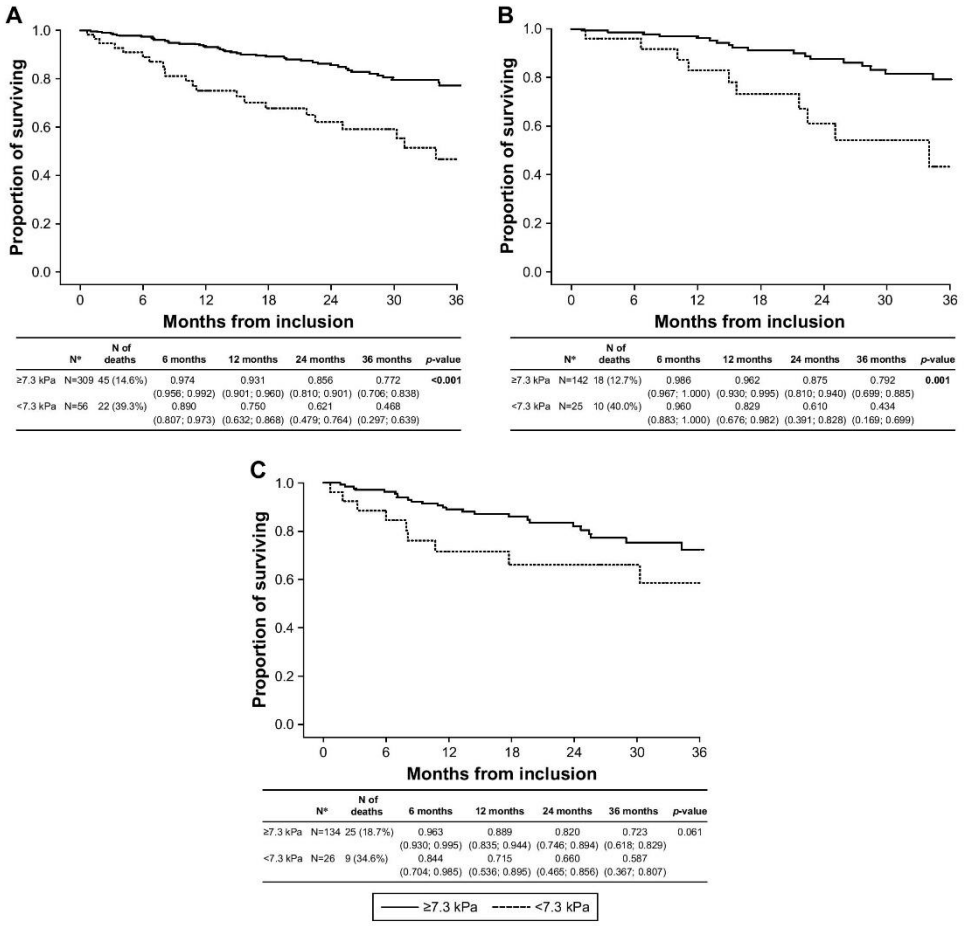
Notes: Receiver operating characteristic analysis was used to determine parameter ability to predict mortality of COPD patients. AUC with *p*-value illustrated the power of this ability. Significant differences are indicated in bold.
Abbreviations: 6-MWT, 6-minute walking test; AUC, area under curve; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, peripheral capillary oxygen saturation.

Univariate analyses

Univariate analyses using the Cox model of proportional risk showed that different levels of oxemia and capnemia along with desaturation during a 6-MWT were risk factors for mortality in the complete cohort (Table 5A) as well as in the GOLD 2017 group B (Table 5B). In contrast, we found no relationship between the tested parameters and mortality risk in the GOLD 2017 D category. Severe hypoxemia (PaO_2 <7.3 kPa) has been identified as a strong predictor of all-cause mortality in the complete cohort (hazard ratio [HR] 3.064; p<0.001) as well as in the GOLD 2017 B category (HR 3.532; p=0.001). Similarly, severe hypercapnia ($PaCO_2$ >7 kPa) has been identified as a strong predictor of all-cause mortality in the GOLD B category (HR 10.185; p=0.001). Blood pH was not associated with increased risk of death in any of the tested patient groups.

Multivariate analyses

A multivariate analysis containing patients with PaO_2 ≤7.3 kPa identified PaO_2 ≤7.3 kPa as a single and very strong independent risk factor for all-cause, long-term mortality



	N°	N of deaths	6 months	12 months	24 months	36 months	*p*-value
≥7.3 kPa	N=309	45 (14.6%)	0.974 (0.956; 0.992)	0.931 (0.901; 0.960)	0.856 (0.810; 0.901)	0.772 (0.706; 0.838)	**<0.001**
<7.3 kPa	N=56	22 (39.3%)	0.890 (0.807; 0.973)	0.750 (0.632; 0.868)	0.621 (0.479; 0.764)	0.468 (0.297; 0.639)	

	N°	N of deaths	6 months	12 months	24 months	36 months	*p*-value
≥7.3 kPa	N=142	18 (12.7%)	0.986 (0.967; 1.000)	0.962 (0.930; 0.995)	0.875 (0.810; 0.940)	0.792 (0.699; 0.885)	**0.001**
<7.3 kPa	N=25	10 (40.0%)	0.960 (0.883; 1.000)	0.829 (0.676; 0.982)	0.610 (0.391; 0.828)	0.434 (0.169; 0.699)	

	N°	N of deaths	6 months	12 months	24 months	36 months	*p*-value
≥7.3 kPa	N=134	25 (18.7%)	0.963 (0.930; 0.995)	0.889 (0.835; 0.944)	0.820 (0.746; 0.894)	0.723 (0.618; 0.829)	0.061
<7.3 kPa	N=26	9 (34.6%)	0.844 (0.704; 0.985)	0.715 (0.536; 0.895)	0.660 (0.465; 0.856)	0.587 (0.367; 0.807)	

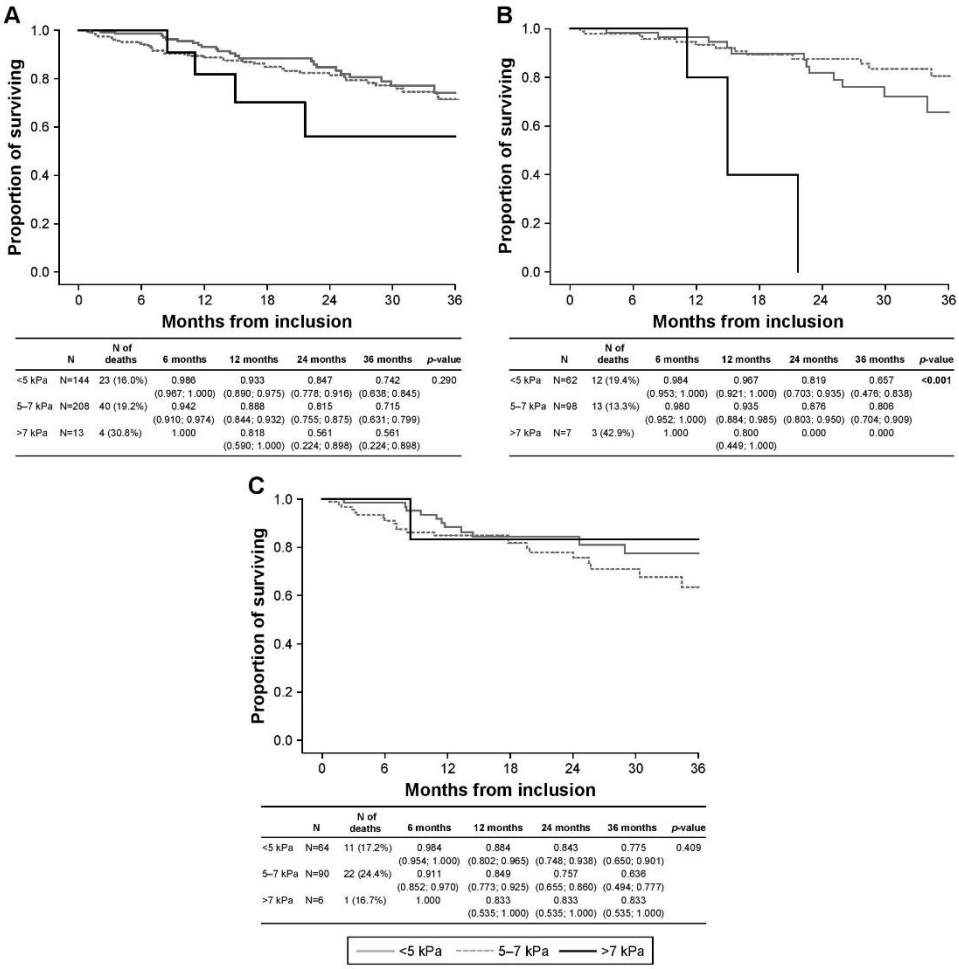
Figure 2 (**A**) Long-term survival according to PaO_2 (all patients); (**B**) long-term survival according to PaO_2 (GOLD 2017 group B COPD subjects); (**C**) long-term survival according to PaO_2 (GOLD 2017 group D COPD subjects).
Notes: *Number of patients with known follow-up. *p*-values <0.001, 0.001 respectively in bold represent significant survival difference between presence of severe hypoxemia and absence of severe hypoxemia in total COPD cohort, and in GOLD 2017 B category.
Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; $PaCO_2$, partial pressure of arterial carbon dioxide.

(HR 2.398; 95% CI: 1.245–4.630) (Table 6). In an analysis containing three $PaCO_2$ categories (<5, 5–7 and >7 kPa), none of the tested parameters showed as a significant, independent predictor of death (Table S2A). In a multivariate analysis containing desaturation during 6-MWT, only the BODE index was identified as an independent risk factor for all-cause mortality with HR 1.310 (95% CI: 1.168–1.470) (Table S2B).

Additional note: When ideal cutoff values for each of the studied parameter were calculated, PaO_2 level <7.1 kPa yielded the highest sensitivity and specificity. By using the PaO_2 level <7.1 kPa for a multivariate analysis, the HR of this independent risk factor was as high as 5.135 (95% CI: 2.415–10.917) (Table S2C and D). However, oxemia levels of 7.3 and 8.0 kPa are more relevant for clinicians; therefore, only these are further discussed in the paper.

Additional analyses: assessment of the role of comorbidities

The relationships between comorbidities and respiratory parameters in the CMRD study were also assessed



	N	N of deaths	6 months	12 months	24 months	36 months	*p*-value
<5 kPa	N=144	23 (16.0%)	0.986 (0.967; 1.000)	0.933 (0.890; 0.975)	0.847 (0.778; 0.916)	0.742 (0.638; 0.845)	0.290
5–7 kPa	N=208	40 (19.2%)	0.942 (0.910; 0.974)	0.888 (0.844; 0.932)	0.815 (0.755; 0.875)	0.715 (0.631; 0.799)	
>7 kPa	N=13	4 (30.8%)	1.000	0.818 (0.590; 1.000)	0.561 (0.224; 0.898)	0.561 (0.224; 0.898)	

	N	N of deaths	6 months	12 months	24 months	36 months	*p*-value
<5 kPa	N=62	12 (19.4%)	0.984 (0.953; 1.000)	0.967 (0.921; 1.000)	0.819 (0.703; 0.935)	0.657 (0.476; 0.838)	**<0.001**
5–7 kPa	N=98	13 (13.3%)	0.980 (0.952; 1.000)	0.935 (0.884; 0.985)	0.876 (0.803; 0.950)	0.806 (0.704; 0.909)	
>7 kPa	N=7	3 (42.9%)	1.000	0.800 (0.449; 1.000)	0.000	0.000	

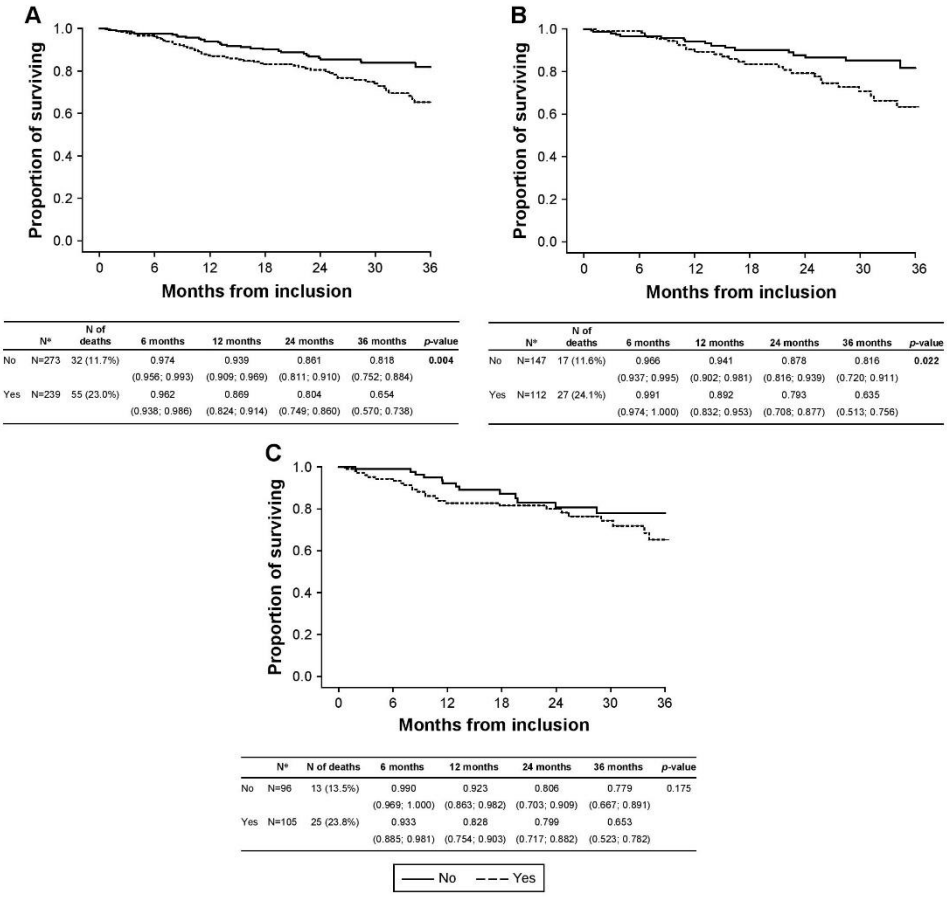
	N	N of deaths	6 months	12 months	24 months	36 months	*p*-value
<5 kPa	N=64	11 (17.2%)	0.984 (0.954; 1.000)	0.884 (0.802; 0.965)	0.843 (0.748; 0.938)	0.775 (0.650; 0.901)	0.409
5–7 kPa	N=90	22 (24.4%)	0.911 (0.852; 0.970)	0.849 (0.773; 0.925)	0.757 (0.655; 0.860)	0.636 (0.494; 0.777)	
>7 kPa	N=6	1 (16.7%)	1.000	0.833 (0.535; 1.000)	0.833 (0.535; 1.000)	0.833 (0.535; 1.000)	

Figure 3 (**A**) Long-term survival according to $PaCO_2$ (all patients); (**B**) long-term survival according to $PaCO_2$ (GOLD 2017 group B COPD subjects); (**C**) long-term survival according to $PaCO_2$ (GOLD 2017 group D COPD subjects).
Note: *p*-value <0.001 in bold represents significant survival difference between hypocapnic, normocapnic, and hypercapnic patients in GOLD 2017 B category only.
Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; $PaCO_2$, partial pressure of arterial carbon dioxide.

(as complementary analyses). The self-reported history of heart failure, tumor and depression was associated with a greater probability of death during 3 years of follow-up (Table S3A). The presence of atopy was associated with higher levels of PaO_2 (Table S3B). Personal history of heart failure, coronary artery disease and diabetes was associated with significantly lower PaO_2 levels. Finally, levels of $PaCO_2$ > or <5–7 kPa were associated with atopy and/or bronchial asthma, heart failure and/or diabetes (Table S3C).

Discussion

The most important finding of our study was that chronic hypoxemia (PaO_2 <7.3 kPa) was a distinctive and very strong prognosis-modifying pattern associated with increased risk of long-term mortality in COPD group B patients. We observed significant differences in all-cause long-term mortality supported by results from univariate and multivariate analyses in the complete cohort and in groups B and D (GOLD 2017). However, the association was the strongest for



	N*	N of deaths	6 months	12 months	24 months	36 months	*p*-value
No	N=273	32 (11.7%)	0.974 (0.956; 0.993)	0.939 (0.909; 0.969)	0.861 (0.811; 0.910)	0.818 (0.752; 0.884)	**0.004**
Yes	N=239	55 (23.0%)	0.962 (0.938; 0.986)	0.869 (0.824; 0.914)	0.804 (0.749; 0.860)	0.654 (0.570; 0.738)	

	N*	N of deaths	6 months	12 months	24 months	36 months	*p*-value
No	N=147	17 (11.6%)	0.966 (0.937; 0.995)	0.941 (0.902; 0.981)	0.878 (0.816; 0.939)	0.816 (0.720; 0.911)	**0.022**
Yes	N=112	27 (24.1%)	0.991 (0.974; 1.000)	0.892 (0.832; 0.953)	0.793 (0.708; 0.877)	0.635 (0.513; 0.756)	

	N*	N of deaths	6 months	12 months	24 months	36 months	*p*-value
No	N=96	13 (13.5%)	0.990 (0.969; 1.000)	0.923 (0.863; 0.982)	0.806 (0.703; 0.909)	0.779 (0.667; 0.891)	0.175
Yes	N=105	25 (23.8%)	0.933 (0.885; 0.981)	0.828 (0.754; 0.903)	0.799 (0.717; 0.882)	0.653 (0.523; 0.782)	

Figure 4 (**A**) Long-term survival according to desaturation (all patients); (**B**) long-term survival according to desaturation (GOLD 2017 group B COPD subjects); (**C**) long-term survival according to desaturation (GOLD 2017 group D COPD subjects).
Notes: *Number of patients with known follow-up. *p*-values 0.004, 0.022 respectively in bold represent significant survival difference between presence of desaturation and absence of desaturation in total COPD cohort, and in GOLD 2017 B category.
Abbreviation: GOLD, Global Initiative for Obstructive Lung Disease.

COPD group B. This finding is very important for clinicians because group B currently represents the largest portion of COPD patients in real-life studies.[2] For this group, novel and easy-to-obtain parameters predictive of poor outcome are warranted. In our study, oxemia <7.3 kPa was the strongest independent predictor of mortality in COPD group B patients (using the GOLD 2017 Update). Where arterial blood gasometry is not available, desaturation during a 6-MWT – as an easier-to-obtain parameter (or a simple screening method) – may be used instead of ABG analysis, according to our results. This finding might be important in emergency cases or within areas where ABG analyzers are unavailable.

Our study cohort comprised 71.7% men; median age was 67.1 years, median FEV_1 was 46% pred and median PaO_2 was 8.8 kPa. Compared to other large cohorts (ECLIPSE, POPE, COPDGene, COCOMICS), the main differences were lower FEV_1 and lower proportion of group A patients in favor of groups B and D.[14,15] Moreover, a greater proportion of men were enrolled in our study cohort. The differences in rates of COPD groups A–D along with lower median FEV_1 are consequences of different inclusion criteria for enrolment in the CMRD study; only patients with FEV_1 ≤60% pred were included.[13] The CMRD study is focused on all-cause long-term mortality of COPD patients. Patients with a more

Table 5A Prediction of all-cause mortality by respiratory parameters – all patients

Respiratory parameter	Cox model of proportional risk	
	HR (95% CI)	*p*-value
PaO_2 (kPa)		
Continuously*	1.304 (1.108–1.534)	**0.001**
<7.3	3.064 (1.840–5.103)	**<0.001**
<8.0	1.700 (1.040–2.779)	**0.034**
$PaCO_2$ (kPa)		
Continuously**	1.484 (1.177–1.870)	**0.001**
5.0–7.0	Reference category	
<5.0	0.805 (0.482–1.345)	0.407
>7.0	1.813 (0.648–5.071)	0.257
Desaturation		
Yes	1.883 (1.217–2.911)	**0.004**

Notes: *HR represents change of risk of mortality, if parameter decreases by unit (lower values are risk). **HR represents change of risk of mortality, if parameter increases by unit (higher values are risk). Desaturation, greatest decrease of SpO_2 during 6-MWT (%) >4% and/or minimal SpO_2 during (after) 6-MWT (%) <90%. *p*-values in bold represent significant change of mortality risk (expressed as hazard ratio).
Abbreviations: 6-MWT, 6-minute walking test; HR, hazard ratio; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, peripheral capillary oxygen saturation.

pronounced impairment of lung function (FEV_1 ≤60% pred) are at higher risk of death compared to patients with mild COPD. All 14 centers of the CMRD project represent university or tertiary-type hospitals taking care of nonmild COPD patients.[13] In addition, the absence of COPD patients with FEV_1 >60% reduces the chance of mistaken enrolment of patients with transient, mild bronchial obstruction (eg, smoking asthmatics who can normalize lung function within a few months). Moreover, globally, milder COPD patients are often underdiagnosed.[2,13] On the other hand, the FEV_1 threshold in the CMRD study set at 60% pred

Table 5B Prediction of all-cause mortality by respiratory parameters – GOLD 2017 B patients

	Cox model of proportional risk	
	HR (95% CI)	*p*-value
PaO_2 (kPa)		
Continuously*	1.282 (0.997–1.647)	0.052
<7.3	3.532 (1.628–7.662)	**0.001**
<8.0	1.462 (0.675–3.169)	0.336
$PaCO_2$ (kPa)		
Continuously**	1.723 (1.085–2.734)	**0.021**
5.0–7.0	Reference category	
<5.0	1.564 (0.712–3.438)	0.265
>7.0	10.185 (2.719–38.158)	**0.001**
Desaturation		
Yes	2.001 (1.090–3.672)	**0.025**

Notes: *HR represents change of risk of mortality, if parameter decreases by unit (lower values are risk). **HR represents change of risk of mortality, if parameter increases by unit (higher values are risk). Desaturation, greatest decrease of SpO_2 during 6-MWT (%) >4% and/or minimal SpO_2 during (after) 6-MWT (%) <90%. *p*-values in bold represent significant change of mortality risk (expressed as hazard ratio).
Abbreviations: 6-MWT, 6-minute walking test; HR, hazard ratio; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, peripheral capillary oxygen saturation.

Table 6 Prediction of all-cause mortality – multivariate analysis containing PaO_2 (kPa) ≤7.3

Prognostic parameter	Cox model of proportional risk	
	HR (95% CI)	*p*-value
6-MWD (m)*	0.996 (0.993–0.999)	**0.003**
PaO_2 (kPa) ≤**7.3**	2.398 (1.245–4.630)	**0.009**

Notes: *HR represents change of risk of mortality, if parameter increases by unit. *p*-values in bold represent significant change of mortality risk (expressed as hazard ratio).
Abbreviations: 6-MWD, 6-minute walking distance; HR, hazard ratio; PaO_2, partial pressure of arterial oxygen.

allowed us to analyze also a substantial portion of GOLD stage 2 patients, not just GOLD stage 3 and 4 subjects. Thus, we believe that the CMRD study cohort (including GOLD stage 2–4 individuals) is representative of a real-life setting. The low number of patients and of deaths in groups A and C (resulting from the abovementioned facts) did not allow us to perform mortality analyses for these groups.

The proportions of GOLD categories (groups) in our study cohort were represented as follows: groups A+C 10.2%, group B 20.2% and group D 69.6% when GOLD 2016 classification was used. Application of the GOLD 2017 Update resulted in major shifts in the distribution of patients across A–D groups, that is, groups A+C 10.2% and group D 36.7%, whereas group B, at 53.0%, represented the most numerous disease category in our cohort. Similar results were published recently by Tudoric et al and Koblizek et al, who demonstrated the consequences of application of the GOLD 2017 Update on the POPE study population, comprising 3,361 COPD patients.[2,15] The authors observed major shifts in the distribution of COPD groups A–D, resulting in making group B the most abundant. According to the GOLD 2016 guideline, group B was represented in 30.5% and group D in 57.3%.[2,15] When applying the classification approach presented in the GOLD 2017 Update, 50.8% of patients were classified in B and 36.9% in group D.[2,15] Importantly, the authors pointed out that 71.5% of the patients who shifted from group D to B used inhaled corticosteroids (ICS), and 18.4% of these group D-to-B shifters had severe airflow limitation (GOLD 4). In consequence, the shift to stage B in these patients may result in discontinuation of ICS treatment and/or in reduction of dual bronchodilator therapy to single bronchodilator use with potentially harmful consequences (ie, unstable COPD and risk of disease progression).[2] The authors concluded that the GOLD 2017 Update is relatively closer to the phenotypic approach in the disease management.[2] However, the abovementioned shortcomings of the GOLD 2017 Update stress the need for identifying group B patients at higher risk of rapid disease progression and poor outcome.

Our data showed that a negative correlation exists among PaO_2, basal SpO_2 and minimal SpO_2 on the one hand and

$PaCO_2$ on the other hand. This finding is in accordance with the differences in pathophysiology of both types of respiratory failure. Interestingly, some patients with the same disease develop only hypoxemia, whereas others also develop hypercapnia. Hypercapnia alone is rather a rare condition in the COPD population. Although both types of respiratory failure may coexist in a single patient (with increased probability in certain diseases, eg, in COPD patients), the underlying mechanisms of development of hypoxemia and hypercapnia exhibit differences. Hypercapnia is the respiratory expression of alveolar hypoventilation, and in COPD, it results dominantly from severe airflow limitation and hyperinflation.[16] Hypercapnia and respiratory acidosis may augment the decrease in respiratory muscle function because of the deleterious effect on mitochondrial function.[16] The most important mechanisms underlying the development of chronic hypoxemia include ventilatory/respiratory mismatch, right-to-left shunt, decreased/impaired diffusion, alveolar hypoventilation and hypoxia due to low oxygen intake.[11,17] Hypoxemia increases ventilatory drive to increase PaO_2 (thus decreasing $PaCO_2$), induces regional pulmonary vasoconstriction and peripheral vasodilation (thus increasing heart rate and cardiac output) and stimulates erythropoiesis, resulting in enhanced oxygen-transporting capacity, although the hematologic viscosity rises.[18] In consequence, breathing becomes more difficult, and the cardiac workload increases.[18]

In COPD patients, by far the most important determinant of hypoxemia is ventilatory/respiratory mismatch (V/Q mismatch).[11,18] V/Q mismatch is the consequence of hypoxic pulmonary vasoconstriction that develops in areas with reduced ventilation (eg, emphysema).[11] In the COPDGene study, female sex, higher BMI and reduced FEV_1 were associated with the development of chronic hypoxemia in COPD patients.[19]

As demonstrated in our study, chronic hypoxemia is a major risk factor for mortality in COPD patients. Several other studies showed similar results.[20–22] The severity of chronic hypoxemia is strengthened by the fact that long-term oxygen treatment (LTOT) may not decrease mortality in mild-to-moderate hypoxemic COPD patients.[23,24] In the CMRD study, almost 11% of the included COPD individuals (78 out of 725) were treated with LTOT. The evidence for indication of LTOT is traditionally based on the results of three studies conducted in the 1970s.[25–27] Recent research confirms that LTOT in stable COPD patients with moderate desaturation (ie, with mild-to-moderate chronic respiratory failure) does not provide any substantial benefit in relation to mortality, time to first hospitalization or any other followed endpoint.[24] However, for COPD patients with severe chronic hypoxemia, LTOT significantly reduces long-term mortality and remains one of the most important treatment options.[20] In a systematic review of randomized trials, no mortality benefit was observed if hypoxemia was present because of cause other than COPD or cardiogenic pulmonary edema.[28] Our results showed positive correlation between basal SpO_2, minimal SpO_2 and hypoxemia. The relationships between PaO_2 and SpO_2 were assessed in a Spanish study published in 2015.[29] The authors demonstrated that in patients with acute exacerbation of COPD (AE-COPD), SpO_2 had a high correlation coefficient with PaO_2 (0.89), and the optimal cutoff value for the detection of hypoxemia was SpO_2 90%.[29]

In our study, hypercapnia >7 kPa was predictive of poor outcome in Kaplan–Meier survival analyses and in univariate analyses. However, in multivariate analyses, $PaCO_2$ failed to be an independent risk factor. These findings are in accordance with previous research. The prognostic value of carbon dioxide in the blood and hypercapnia were much weaker than that of hypoxemia in relation to mortality. Jones et al reported $PaCO_2$ to be a significant predictor of long-term mortality in COPD patients.[30] Foucher et al reported 30%–40% two-year mortality of COPD patients with chronic hypercapnia.[31] Chailleux et al found hypercapnia associated with higher mortality in COPD patients receiving LTOT at the 3-year follow-up.[32] Ahmadi et al referred to the U-shaped association between capnemia and mortality, with values >7.0 and <5.0 kPa at increased risk of death.[27] However, Aida et al found no association between capnemia and mortality.[33]

Research data supporting the prognostic value of capnemia are more consistent for acute hypercapnia.[12,34–36] Lun et al reported association between hypercapnia and respiratory acidosis during AE-COPD with higher risk of future life-threatening events and mortality.[12] Acute hypercapnia during AE-COPD has been found as a significant prognostic factor of long-term mortality in a number of studies.[34–36]

In COPD patients with chronic respiratory failure, acute respiratory failure is the most common cause of death, followed by cardiovascular causes, respiratory infection and cancer.[3,37,38] Acute respiratory failure is frequently associated with exacerbations (and vice versa).[38] In-hospital mortality of patients with AE-COPD and acute respiratory failure was only 2.5% in a cohort examined by Patil et al,[39] but 20.3% in a study by Breen et al.[40] In the same study, postdischarge mortality at 3 years was 63.5%.[40] In-hospital mortality of mechanically ventilated patients with acute respiratory failure ranges between 21% and 82%, according to the results of various studies.[41] The association between acute/

chronic respiratory failure and mortality applies despite the discovery of several prognosis-modifying treatments and strategies for COPD in the last decades, including ICS,[42] their combination with long-acting bronchodilators[43] or noninvasive ventilation.[44] Considering the data obtained from the ECLAIR study, extracorporeal carbon dioxide removal for acute hypercapnic respiratory failure has been found to be neither an effective nor a safe procedure.[45]

Our study has several limitations. The first one is the preselection bias caused by inclusion of patients with post-bronchodilator $FEV_1 \leq 60\%$ only. Seventy-two percent of the study population were men, which might introduce another bias (gender). In the study cohort, only a minimum (ca. 10% in total) of group A and group C patients were present. In consequence, the number of deaths for these groups was so low that it did not allow us to perform mortality analyses. Another important limitation is related to relatively lower availability of ABG (54% of patients) and 6-MWT data (76% of patients) from the CMRD study cohort. The primary aim of the CMRD study was to observe the rate of all-cause mortality in a real-life COPD population. Monitoring of respiratory parameters (ABG and SpO_2 during 6-MWT) was considered an additional and a nonmandatory component only. This might bias the composition of the current study cohort because more expressed impairment of lung function and more frequent hospitalization because of COPD exacerbation (before enrolment) might slightly increase the patient's chance of having ABG analysis. In contrast, better lung functions were associated with a gently higher frequency of 6-MWT being performed. According to our ex-post analysis, the differences between these groups were minimal (Table S4). Moreover, of the 725 enrolled subjects, SpO_2 was measured during a mandatory physical exam and the results strongly correlated with SpO_2 assessed during a 6-MWT (Table S5A and B).

Despite these limitations, we believe that we demonstrated the importance and the prognostic role of respiratory parameters, particularly of $PaO_2 < 7.3$ kPa in COPD category B patients (GOLD 2017 Update).

Conclusion

Our results show that certain respiratory parameters are associated with increased risk of death among patients in different COPD categories. Of the tested parameters, severe hypoxemia ($PaO_2 < 7.3$ kPa) was identified as the strongest risk factor for long-term, all-cause mortality in the complete cohort as well as in group B (using the GOLD 2017 Update). The importance of this finding is underlined by the fact that group B seems to be the largest group of COPD individuals in real practice.[2] In emergency cases, SpO_2 may be used to determine the presence of hypoxemia. Undoubtedly, for exact PaO_2 measures, arterial blood gasometry should be performed.

Another important observation is that COPD category D (GOLD 2017 Update) now seems to be a well-defined group with the highest rate of long-term mortality and a minimum of risk-modifying signs and factors.

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Supplementary materials

Table S1 Frequency of desaturation (n=552)

Desaturation	n=552
No	296 (53.6%)
Yes	256 (46.4%)

Note: Desaturation means greatest decrease of SpO_2 during 6-MWT (%) >4% and/or minimal SpO_2 during (after) 6-MWT (%) <90%.
Abbreviations: 6-MWT, 6-minute walking test; SpO_2, basal peripheral capillary oxygen saturation.

Table S2 (**A**) Prediction of all-cause mortality – multivariate analysis containing $PaCO_2$ (kPa) – categories (<5; 5–7 – reference; >7). (**B**) Prediction of all-cause mortality – multivariate analysis containing desaturation. (**C**) Prediction of mortality by parameters of blood gases – ideal cutoff values. (**D**) Prediction of mortality – multivariate analysis containing PaO_2 (kPa) ≤7.1.

Prognostic parameter	Cox model of proportional risk	
	HR (95% CI)	*p*-value
A		
TL_{CO} (%)*	0.979 (0.961–0.998)	**0.032**
6-MWD (m)*	0.996 (0.993–0.998)	**0.001**
$PaCO_2$ (kPa)	–	–
B		
BODE*	1.310 (1.168–1.470)	**<0.001**
TLC (%)*	0.985 (0.975–0.995)	**0.004**
Desaturation	–	–

	AUC (95% CI)	*p*-value	Cutoff	Sensitivity	Specificity
C					
PaO_2 (kPa)	0.590 (0.507; 0.673)	**0.020**	≤7.1	0.313	0.914
$PaCO_2$ (kPa)	0.600 (0.521; 0.679)	**0.010**	≥0.54	0.537	0.654
Basal SpO_2 (%)	0.607 (0.537; 0.676)	**0.002**	≤95.5	0.701	0.473
Minimal SpO_2 during 6-MWT (%)	0.631 (0.569; 0.693)	**<0.001**	≤93.5	0.851	0.366
Greatest decrease in SpO_2 (%)	0.610 (0.548; 0.671)	**0.001**	≥4.5	0.552	0.626

	Cox model of proportional risk	
	HR (95% CI)	*p*-value
D		
BMI*	0.921 (0.865–0.982)	**0.012**
RV (%)*	0.993 (0.987–1.000)	**0.038**
6-MWD*	0.994 (0.991–0.998)	**<0.001**
PaO_2 (kPa) ≤7.1	5.135 (2.415–10.917)	**<0.001**

Notes: *HR represents change of risk of mortality, if parameter increases by unit. Desaturation, greatest decrease of SpO_2 during 6-MWT (%) >4% and/or minimal SpO_2 during (after) 6-MWT (%) <90%. Bold *p*-values represent statistically significant differences in mortality between tested end-points.
Abbreviations: AUC, area under curve; 6-MWT, 6-minute walking test; BMI, body mass index; BODE, body-mass index, airflow obstruction, dyspnea, and exercise; HR, hazard ratio; TLC, total lung capacity; SpO_2, basal peripheral capillary oxygen saturation; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of arterial carbon dioxide; TL_{CO}, transfer factor for carbon monoxide; RV, residual volume.

Table S3 Relationship between comorbidities and all-cause mortality (**A**); relationship between comorbidity and PaO_2 (**B**); relationship between comorbidity and $PaCO_2$ (**C**)

Comorbidity	Death		*p*-value
	No	Yes	
A			
Atopy	75 (12.4%)	11 (9.2%)	0.357
Asthma	66 (10.9%)	9 (7.5%)	0.325
Coronary artery disease	149 (24.6%)	39 (32.5%)	0.087
Heart failure	88 (14.5%)	27 (22.5%)	**0.039**
Atrial fibrillation	74 (12.2%)	16 (13.3%)	0.762
Hypertension	341 (56.4%)	72 (60.0%)	0.481
Syncope	29 (4.8%)	7 (5.8%)	0.645
Tumor	79 (13.1%)	27 (22.5%)	**0.011**
Osteoporosis	85 (14.0%)	15 (12.6%)	0.772
Diabetes mellitus	129 (21.3%)	26 (21.7%)	0.904
Anemia	68 (11.2%)	21 (17.5%)	0.067
Depression	109 (18.0%)	35 (29.2%)	**0.008**
Ulcer disease	118 (19.5%)	22 (18.3%)	0.899
	Comorbidity		***p*-value**
	No	**Yes**	
B			
Atopy	8.8 (1.6); 8.7 (6.3–11.7)	9.4 (1.7); 9.4 (7.1–11.8)	**0.020**
Asthma	8.8 (1.6); 8.8 (6.3–11.8)	9.1 (1.5); 9.3 (6.3–11.7)	0.262
Coronary artery disease	8.9 (1.6); 8.9 (6.3–11.8)	8.6 (1.7); 8.4 (6.1–11.2)	**0.036**
Heart failure	9.0 (1.6); 8.9 (6.6–11.8)	8.0 (1.7); 7.8 (5.3–10.9)	**<0.001**
Atrial fibrillation	8.8 (1.6); 8.8 (6.3–11.8)	8.9 (1.6); 8.9 (6.1–11.2)	0.644
Hypertension	8.9 (1.6); 9.0 (6.4–11.3)	8.8 (1.7); 8.7 (6.1–11.9)	0.339
Syncope	8.8 (1.6); 8.8 (6.3–11.7)	9.4 (1.9); 9.0 (6.5–12.5)	0.201
Tumor	8.8 (1.6); 8.8 (6.4–11.7)	8.9 (1.8); 9.0 (5.9–12.2)	0.708
Osteoporosis	8.8 (1.6); 8.9 (6.4–11.7)	8.8 (1.9); 8.6 (6.0–12.0)	0.808
Diabetes mellitus	8.9 (1.7); 8.9 (6.3–11.9)	8.6 (1.5); 8.6 (6.4–11.3)	**0.038**
Anemia	8.9 (1.6); 8.9 (6.4–11.7)	8.6 (1.9); 8.4 (5.5–12.2)	0.307
Depression	8.8 (1.6); 8.8 (6.3–11.7)	9.1 (1.8); 9.1 (6.4–12.2)	0.197
Ulcer disease	8.8 (1.6); 8.7 (6.4–11.7)	9.1 (1.7); 9.3 (6.0–11.9)	0.067
C			
Atopy	5.3 (0.9); 5.2 (4.0–6.8)	5.0 (0.6); 5.0 (4.1–6.2)	**0.046**
Asthma	5.3 (0.9); 5.2 (4.0–6.8)	5.0 (0.8); 4.9 (3.8–5.7)	**0.025**
Coronary artery disease	5.2 (0.9); 5.2 (4.0–6.8)	5.3 (0.9); 5.2 (4.2–6.8)	0.918
Heart failure	5.2 (0.8); 5.1 (3.9–6.4)	5.6 (0.9); 5.4 (4.4–7.2)	**<0.001**
Atrial fibrillation	5.2 (0.9); 5.1 (4.0–6.8)	5.3 (0.8); 5.2 (3.9–6.7)	0.089
Hypertension	5.2 (0.8); 5.2 (3.9–6.8)	5.2 (0.9); 5.2 (4.2–6.7)	0.871
Syncope	5.2 (0.9); 5.2 (4.0–6.8)	5.2 (0.9); 5.1 (3.9–6.9)	0.614
Presyncope	5.2 (0.9); 5.2 (4.0–6.8)	5.2 (0.7); 5.2 (3.9–6.2)	0.974
Tumor	5.3 (0.8); 5.2 (4.2–6.8)	5.1 (1.0); 5.2 (3.9–6.8)	0.538
Osteoporosis	5.3 (0.8); 5.2 (4.2–6.8)	5.1 (0.9); 5.1 (3.7–6.8)	0.153
Diabetes mellitus	5.2 (0.9); 5.1 (3.9–6.8)	5.4 (0.8); 5.3 (4.3–6.8)	**0.010**
Anemia	5.2 (0.8); 5.1 (4.0–6.8)	5.4 (0.9); 5.4 (3.9–6.9)	0.122
Depression	5.2 (0.8); 5.2 (4.0–6.7)	5.4 (1.1); 5.2 (3.9–7.0)	0.302
Ulcer disease	5.3 (0.8); 5.2 (4.1–6.8)	5.2 (1.1); 5.0 (3.9–6.8)	0.102

Notes: Parameters are described by absolute (relative) frequencies and tested by Fisher's exact test (**A**). Parameters are described by mean (SD); median (5th and 95th percentiles) and tested by Mann–Whitney test (**B**, **C**). Bold *p*-values represent statistically significant differences in mortality between tested end-points.
Abbreviation: $PaCO_2$, partial pressure of arterial carbon dioxide.

Table S4 Comparison of parameters between groups according to valid data (n=725)

Tested parameter	Without 6-MWT and ABG (n=133)	Only with 6-MWT (n=201)	Only with ABG (n=40)	With 6-MWT and ABG (n=351)	*p*-value
Demography					
Sex – men	97 (72.9%)	146 (72.6%)	25 (62.5%)	252 (71.8%)	0.597
Age at inclusion	67.4 (10.3)	65.3 (10.0)	69.4 (9.3)	67.0 (8.5)	0.078
BMI	26.7 (5.6)	27.1 (5.4)	25.9 (4.7)	26.9 (6.1)	0.553
Symptoms					
mMRC	2.0 (1.1)	2.3 (0.9)	2.5 (1.1)	2.2 (1.2)	**0.007**
CAT	17.3 (8.2)	15.5 (7.2)	17.5 (8.0)	15.5 (7.9)	0.067
Exacerbations					
Treated at home (moderate)	0.6 (1.1)	0.8 (1.2)	0.9 (1.1)	0.9 (1.5)	0.223
Requiring hospitalization (severe)	0.2 (0.6)	0.2 (0.5)	0.7 (0.8)	0.5 (0.9)	**<0.001**
Total	0.8 (1.4)	1.0 (1.4)	1.6 (1.4)	1.4 (1.9)	**<0.001**
Lung function					
FEV_1 (%)	45.3 (11.2)	47.7 (11.6)	44.8 (12.9)	43.2 (11.4)	**<0.001**
FVC (%)	71.8 (16.8)	69.1 (15.2)	71.3 (15.5)	68.0 (19.5)	0.057
TL_{CO} (% pred)	52.1 (21.9)	62.1 (24.1)	48.6 (16.2)	49.4 (21.0)	**<0.001**

Notes: Categorical parameters are described by absolute (relative) frequency. Differences are tested by Fisher's exact test. Continuous parameters are described by mean (SD). Differences are tested by Kruskal–Wallis test. Significant differences are indicated in bold.
Abbreviations: 6-MWT, 6-minute walking test; ABG, arterial blood gas; BMI, body mass index; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale; pred, predicted value; TL_{co}, transfer factor for carbon monoxide.

Table S5 SpO_2 according to physical examination (n=725) (**A**), correlation between SpO_2 (physical examination*) and SpO_2 (6-MWT°) (n=552) (**B**)

	Valid N, mean (SD), median (5th and 95th percentile)
A	
SpO_2 (physical examination*)	n=725; 93.8 (4.6); 95.0 (87.0; 98.0)
SpO_2 (6-MWT°)	n=552; 94.5 (3.6); 95.0 (88.0; 98.0)
	Spearman's coefficient of correlation (*p*-value)
B	
SpO_2	n=552; 0.779 (**<0.001**)

Note: *Mandatory parameter available in all COPD subjects, °optional (nonmandatory) parameter used in our analysis.
Abbreviations: 6-MWT, 6-minute walking test; SpO_2, peripheral capillary oxygen saturation.

2.2. Prognostic Accuracy of Three COPD Classification Systems in Relation to Long-Term Mortality of COPD Patients: A Prospective Multicenter Study.

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Komentář:

V této multicentrické práci se zaměřujeme na srovnání prognostických vlastností 3 klasifikačních systémů GOLD ve vztahu k riziku mortality a k době do akutní exacerbace. Racionálním podkladem pro tuto práci byly dvě změny klasifikačního systému CHOPN definované dokumenty GOLD, která byly uvedeny do praxe v letech 2011 a pak 2017. Do roku 2011 byla CHOPN klasifikována do 4 stádií (I-IV) dle míry bronchiální obstrukce (FEV_1 % predikované hodnoty) (87). Stádia GOLD I-IV jsou asociována s progresivně narůstajícím rizikem dlouhodobé mortality (stadium I – nejnižší riziko, stadium IV – nejvyšší riziko), obdobně jako je tomu u klasifikace NYHA u CHSS (127) nebo u 8. verze TNM klasifikace karcinomu plic (128). Některé práce prokázaly, že novější verze GOLD klasifikace tuto jednoduchou intuitivnost postrádají (129, 130), což u kliniků může vést k jisté míře nepochopení či dezinterpretace ve vztahu k očekávaným výstupům. Dostupná data ale byla poměrně omezená co do rozsahu, proto jsme se rozhodli využít možnosti analýzy prospektivních multicentrických dat z Registru CHOPN a srovnat prognostický význam posledních 3 klasifikací GOLD, tedy: verze 2007-2011 (stadia I-IV), verze 2011-2016 (skupiny A-D), verze 2017- (skupiny A-D s překlasifikováním pacientů po vyjmutí spirometrické hodntoty FEV_1) ve vztahu k riziku dlouhodobé mortality a doby do první exacerbace.

Ze 784 pacientů Registru CHOPN (119) bylo 64 vyřazeno pro nekompletnost dat a dále byla analyzována data zbylých 720 pacientů. Pro analýzu mortality byly zkonstruovány Kaplan-Meierovy křivky 4-letého přežití pro všechny 3 klasifikační systémy GOLD. Rozdíly v riziku mortality jednotlivých CHOPN stádií/skupin byly testovány pomocí log-rank testu. Jelikož poslední 2 verze klasifikace GOLD nebyly primárně koncipovány pro odhad rizika mortality, ale charakterizují úroveň symptomů a počet exacerbací, srovnali jsme také dobu do první exacerbace ve vztahu ke všem 3 klasifikacím CHOPN dle GOLD.

Z demografického pohledu tvořilo kohortu 73% mužů průměrného věku 58,7 let, s průměrnou BMI 27,1, současných nebo bývalých kuřáků bylo 90%. Průměrná hodnota FEV_1 byla 45,6% náležité hodnoty a pacienti měli průměrně 1,2 exacerbace za rok. V rámci klasifikace nemoci bylo 50% pacientů ve stadiu III (dle GOLD 2007-2011), 69% pacientů skupiny D (dle GOLD 2011-2016) a 53% skupiny B po překlasifikování nemoci (dle GOLD 2017). Co se týče mortality, klasifikace GOLD 2007-2011 vykazovala logickou stupňovitost – čím vyšší stadium, tím vyšší bylo riziko mortality. Rozdíly byly statisticky významné ($p=0,001$). U dalších 2 systémů (2011-2016 a 2017-) byla stupňovitost porušena – riziko mortality bylo vyšší ve skupině B než C (GOLD 2011-2016; $p=0,009$) a dle poslední verze (2017-) ve skupině C než D ($p=0,05$). Dle ROC analýzy se přitom hodnoty AUC výrazněji nelišily (0,727 pro GOLD 2007-2011; 0,728 pro GOLD 2011-2016 a 0,747 pro GOLD 2017), výsledek je ale ovlivněn absencí pacientů nejlehčích stádií CHOPN. Doba do exacerbace byla nejintuitivněji předpovídatelná pomocí systému GOLD 2007-2011 (nejkratší doba ve stadiu IV, nejdelší ve stadiu II), u obou verzí klasifikace A-D byla doba do exacerbace kratší ve skupině C než B (vše $p<0,001$).

Výsledky naší práce poukazují na poměrně zmatečný charakter novějších verzí klasifikace nemoci CHOPN. Od těchto verzí nelze očekávat adekvátní prognostické vlastnosti, proto by k tomuto účelu ani neměly být používány. Prognóza pacienta s CHOPN

by tak měla být stanovena adekvátními a k tomu účelu určenými nástroji, nejlépe pomocí kompozitních skórovacích systémů (indexů), které jsou vystavěny na několika nezávislých ukazatelích s prognostickou hodnotou (83, 98). Viz také kapitolu 2.3. této práce, kde pojednáváme o konstrukci nového prognostického nástroje CADOT.

Závěrečné shrnutí jednou větou: Klasifikace GOLD z let 2007-2011 (stadia I-IV) má nejlepší prediktivní schopnosti pro rámcový odhad rizika dlouhodobé mortality pacientů s CHOPN; naproti tomu, klasifikační systémy A-D by k účelu stanovení prognózy pacienta neměly být používány.

2.3. Introducing a new prognostic instrument for long-term mortality prediction in COPD patients: the CADOT index.

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Komentář:

V této práci jsme zkonstruovali nový prediktivní nástroj ke stanovení dlouhodobé prognózy pacienta s CHOPN. Nový prognostický index byl nazván CADOT a dle přímého srovnání s jinými indexy vykazoval vyšší prognostickou sílu. Jeho další výhodou je možnost použití v situacích, kdy hodnotu jiného prognostického indexu nelze kalkulovat.

O důležitosti stanovení prognózy pacienta s CHOPN již bylo pojednáno výše. Ke stanovení prognózy lze použít jednoduchých parametrů (např. FEV_1, vzdálenost ušlá během 6-MWT, mMRC, hypoxémie či hyperkapnie, BMI) (83), ale mnohem přesnějších prediktivních vlastností dosahují kompozitní prognostické nástroje / indexy. Ve světě jsou nejvíce používány 2 indexy – BODE a ADO (83, 98). Tyto nástroje však mají některé nevýhody, které činí jejich použití v klinické praxi méně výhodnými. Index ADO je až z 50% bodového skóre vystavěn na bodech za věk, což je faktor, který pro CHOPN není nijak specifický. Mezi věkem a rizikem mortality existuje silná závislost, tzv. Gompertz-Makehamův zákon mortality (100). V případě indexu BODE je jeho limitací 6-MWT, který vyžaduje jak prostorovou kapacitu pracoviště k jeho provedení (30-metrová chodba), tak pacientovu spolupráci a schopnost 6-MWT podstoupit, což je problém u pacientů s

neurologickými nemocemi, artrózou kolen či kyčlí, po amputacích či těžkých úrazech dolní končetiny a podobně. Subideální vyšetřitelnost z objektivních důvodů či z důvodu nižší spolupráce totiž může být významným zdrojem falešně horších výsledků 6-MWT, kterému je v rámci BODE indexu přisuzován nezanedbatelný počet bodů (83). V novější verzi BODE indexu je výsledku 6-MWT přiřazen ještě významnější podíl na bodovém skóre a jen malá změna v ušlé vzdálenosti během 6-MWT může způsobit velký rozdíl v celkovém bodovém skóre pacienta (98). Cílem naší práce bylo identifikovat nezávislé faktory se vztahem k riziku mortality u pacientů s CHOPN a zkonstruovat nový prognostický nástroj, který by byl méně závislý na faktoru věku a který by byl použitelný i v situacích, kdy nelze 6-MWT validně provést.

Pro samotnou konstrukci a první testování prognostické síly nového predikčního nástroje CADOT jsme použili data 699 pacientů z Registru CHOPN (derivační kohorta). Pro ověření prognostické síly nového nástroje jsme použili data 187 pacientů s CHOPN z externí, nezávislé kohorty pacientů CIROCO+ z Nizozemí (71).

Pro účely identifikace faktorů se vztahem k riziku mortality jsme derivační kohortu rozdělili na živé a mrtvé pacienty. Ke srovnání rozdílů mezi oběma skupinami jsme použili Mann-Whitneyův U test a Fisherův exaktní test. Diskriminační síla identifikovaných faktorů byla testována pomocí ROC analýzy, a to na bázi jednotlivých faktorů i přidáním faktorů k již existujícím platformám indexů BODE a ADO. Plocha pod ROC křivkou byla testována pomocí c-statistiky a rozdíly mezi ROC křivkami pomocí DeLongova testu (131). Následovaly reklasifikační analýzy, které identifikovaly ty parametry, které signifikantně zvyšovaly hodnotu c-statistiky (132, 133). Získané parametry byly zakomponovány do finálního predikčního nástroje. Bodové ohodnocení nových faktorů bylo provedeno na základě hodnot odds ratio získaných z výsledků logistické regresní analýzy. Byly konstruovány křivky přežití pro 4 vytvořené kategorie nového indexu s použitím dat derivační

i validační kohorty. Na závěr bylo provedeno přímé srovnání prognostické hodnoty indexu CADOT s indexy ADO a BODE na datech obou kohort separátně.

Derivační kohorta zahrnovala 616 žijících a 83 zemřelých pacientů. Ve skupině zemřelých byly signifikantně nižší hodnoty FEV_1, FVC, TL_{CO}, K_{CO}, BMI, vyšší věk, kratší vzdálenost ušlá během 6-MWT a častější výskyt CHSS. Z uvedeného vyplynulo, že se jednalo o parametry konstituující indexy ADO a BODE a navíc o faktory difuzní kapacity plic pro CO a CHSS. V další práci jsme tedy nový prognostický nástroj budovali na bázi platformy indexů ADO a BODE s cílem vylepšit jejich prognostické vlastnosti. Jako ideální faktory pro vylepšení prediktivních vlastností se ukázaly TL_{CO} a CHSS, a to na bázi indexu ADO. Výsledný index CADOT tedy zahrnuje: CHSS, věk, mMRC skóre, hodnotu FEV_1 (% predikované hodnoty) a TL_{CO}. Na základě výsledků regresní analýzy bylo absenci nebo přítomnosti CHSS přiřazeno 0 resp. 3 body, bodové skóre za TL_{CO} bylo ohodnoceno 0, 1 a 2 body za ≥45%, 30-44% a <30% predikované hodnoty. Výsledné skóre CADOT indexu tedy může dosahovat hodnot 0-15 bodů, hodnoty skóre s podobnou prediktivní hodnotou byly začleněny do společné kategorie, čímž vznikají 4 kategorie rizika (nízké, střední, vysoké a velmi vysoké riziko) s hodnotami bodového skóre 0-2, 3-5, 6-9 a 10-15. Přímé srovnání prognostické síly CADOT indexu s indexy ADO a BODE (pomocí ROC analýzy) ukázalo nejvyšší hodnoty c-statistiky CADOT indexu ze všech 3 srovnávaných indexů, a to jak pro derivační kohortu (0,701 vs 0,644 vs 0,677; $p<0,001$), tak i pro nezávislou validační kohortu (0,842 vs 0,825 vs 0,799; $p<0,001$). CADOT jsme ještě jedenkrát revalidovali s odstupem 22 měsíců – na stejné kohortě, ale s delší periodou follow-up – a index potvrdil svou vysokou prediktivní hodnotu (hodnota c-statistiky: 0,685).

Hlavním přínosem této práce je konstrukce nového prognostického indexu CADOT, který nejenže vykazuje vyšší míru prognostické přesnosti, ale také odstraňuje nebo minimalizuje nevýhody indexů BODE a ADO. Oproti indexu BODE odpadá potřeba provádět

6-MWT, oproti indexu ADO je celkové skóre CADOT méně ovlivněno faktorem věku a opírá se o dva nové parametry s úzkým vztahem k riziku mortality, tedy přítomnost CHSS a hodnotu TL_{CO}. Je známo, že CHSS je jednou z nejčastějších a nejzávažnějších komorbidit a příčin úmrtí u pacientů s CHOPN (123, 134). Snížená hodnota TL_{CO} je výrazem/projevem plicního emfyzému (= efektivní ztráty plicního parenchymu), plicní hypertenze a/nebo CHSS, což jsou všechno faktory asociované s rizikem mortality pacientů s CHOPN (123, 134). Důležitým aspektem našich výsledků je také to, že CADOT prokázal vynikající predikční schopnost (hodnota c-statistiky: 0,842) na kohortě pacientů s průměrně „lehčí“ CHOPN, tedy s mírnější úrovní obstrukce dýchacích cest a nižší mírou výskytu komorbidit. Na základě tohoto poznatku lze CADOT s úspěchem používat v klinické praxi i pro zhodnocení prognózy pacientů s CHOPN lehkých stádií (GOLD I-II, GOLD A-C), čímž umožní zachytit rizikové pacienty zavčas.

Jistou limitací CADOT indexu může být dostupnost vyšetření TL_{CO} (vyšetření difuzní kapacity plic). Podle dotazníkových šetření v minulosti ale cca 80% pneumologů v České republice udává snadnou dostupnost vyšetření difuzní kapacity plic do několika dnů. Dalšími limitacemi práce je menší počet pacientů s lehkou bronchiální obstrukcí a možné problémy s dostupností echokardiografie.

CADOT index byl zapracován i do Pozičního dokumentu ČPFS – Diagnóza a management stabilní fáze CHOPN (viz kapitola 2.4.).

Závěrečný souhrn jednou větou: Zkonstruovali jsme nový kompozitní prognostický index nazvaný CADOT, který má lepší prediktivní schopnosti než indexy BODE a ADO, zároveň minimalizuje či zcela obchází jejich objektivní nevýhody.

Introducing a new prognostic instrument for long-term mortality prediction in COPD patients: the CADOT index

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Objectives. The BODE (BMI, Obstruction - FEV_1, Dyspnoea – mMRC, Exercise – 6-MWT) and the ADO (Age, Dyspnoea – mMRC, Obstruction – FEV_1) indices are widely used prognosis assessment tools for long-term mortality prediction in COPD patients but subject to limitations for use in daily clinical practice. The aim of this research was to construct a prognostic instrument that prevents these limitations and which would serve as a complementary prognostic tool for clinical use in these patients.
Methods and Participants. The data of 699 COPD subjects were extracted from the Czech Multicentre Research Database (CMRD) of COPD patients (the derivation cohort) and analysed to identify factors associated with the long-term risk of mortality. These were entered into the ROC analysis and reclassification analysis. Those with the strongest discriminative power were used to construct the new index (CADOT). The new index was validated on 187 patients of the CIROCO+ cohort (Netherlands; the validation cohort).
Results. The CADOT was constructed by adding two newly identified prognosis-determining factors, chronic heart failure (CHF) and TL_{CO}, to the ADO index. In a head-to-head comparison, the CADOT index showed highest c-statistic values compared to the BODE and ADO indices (0.701 vs 0.677 vs 0.644, respectively). The prognostic power was more definitive when applied to the Dutch validation (CIROCO+) cohort (0.842 vs 0.799 vs 0.825, respectively).
Conclusions. The CADOT index has comparable prognostic power to the BODE and ADO indices. The CADOT is complementary/an alternative to the BODE (if 6-MWT is not feasible) and ADO (with less dependence on the age factor) indices.
Trial registration: ClinicalTrials.gov (NCT01923051).

Key words: COPD, prognostic index, pulmonary function, mortality

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INTRODUCTION

According to the latest World Health Organization data, chronic obstructive pulmonary disease (COPD) was the third leading cause of death worldwide, claiming approximately 3 million lives in 2016 (ref.[1]). In the Czech Republic, the annual COPD-related death rate is around 3,500 events per 10.6 million population[2]. According to an epidemiological prediction model, COPD prevalence is expected to rise in the coming years[3].

COPD is considered a heterogeneous syndrome with inter-individual differences in disease manifestation, comorbidity and long-term mortality risk[4,5]. For this reason, accurate tools for estimating the life expectancy of COPD patients are warranted[6,7]. The BODE (Body mass index, airflow Obstruction, Dyspnoea and Exercise) and the ADO (Age, Dyspnoea and Obstruction) indices are globally the most widely used instruments for long-term mortality assessment[8,9]. A number of other prediction tools have been constructed, e.g. the e-BODE, BODEx and

COTE (ref.[10,11]). Use of the BODE (and derived indices) may be difficult in some patients (e.g. with a disability) or in some outpatient settings where the 6-minute walk test (6-MWT) cannot be performed (e.g. lack of a ~30-meter corridor). Two of the 3 parameters determining the ADO score may be associated with other confounders – the specificity of the mMRC score (alternative causes of dyspnoea – pulmonary "other-than-COPD", cardiogenic, extrathoracic, neuromuscular, systemic, etc.) and the age factor (mortality risk/rate is strongly determined by age – the "Gompertz-Makeham Law of Mortality") (ref.[9,12,13]).

The Czech Multicenter Research Database of COPD (CMRD) comprises a large number of regularly monitored COPD patients[14]. Based on an analysis of all-cause mortality in CMRD COPD subjects, the aim of the present research was to construct an alternative long-term prognostic instrument for use in situations where the BODE score cannot be calculated and that would improve the ADO index by augmenting the role of COPD-specific conditions predictive of poorer prognosis.

METHODS

The derivation cohort (Czech Republic)

The data for development of the new scale were extracted from the CMRD Registry[14], an observational prospective study with a primary objective to monitor and assess morbidity and all-cause mortality in patients with moderate to very severe COPD (Global Initiative for Obstructive Lung Disease (GOLD) grades II to IV) in the Czech Republic (ClinicalTrials.gov Identifier: NCT01923051). Patients were recruited in 14 centers providing specialised respiratory care between February 2013 and December 2016. Follow-up of patients within the CMRD Registry is still ongoing. Detailed description was published elsewhere[14].

At the time of the new prognostic instrument construction (July 2016), the registry included 699 COPD patients. Parameters assessed at enrolment included demographics, patient history data [general practitioners' (GPs') and specialists' records], symptoms [dyspnoea – mMRC score[15], COPD Assessment Test (CAT) (ref.[16])], quality of life measures [St George's Respiratory Questionnaire (SGRQ) (ref.[17])], treatment, pulmonary functions and other clinical examinations (chest CT, ECG, blood gases, echocardiography etc.). GPs' and specialists' records were also used to identify chronic heart failure (CHF).

The validation cohort (Netherlands)

To validate the new prognostic index, data from the CIROCO+ cohort, an observational single-center study, were used[18]. Patients with moderate to very severe COPD (GOLD grades II to IV) (ref.[19]), aged 40 to 80 years and in a clinically stable condition were prospectively recruited between November 2007 and November 2010 during initial evaluation of a comprehensive pulmonary rehabilitation program at CIRO+ (ref.[20]). CHF was identified from patient history (Charlson comorbidity index); FEV_1 and TL_{CO} values were measured at inclusion[20].

Development of the new index

The steps to develop the new index included identification of parameters discriminating between patients who died and those who were alive (Step 1), testing of the discriminatory power of these parameters (Step 2) and refinement with a reclassification analysis (Step 3).

The derivation cohort was separated into patients who died and those who were alive at the time of analysis. Clinical characteristics of these two subgroups were compared using the Mann-Whitney U-test and the Fisher exact test to identify parameters discriminating between the two subgroups (Step 1).

The discriminatory power of the identified parameters (Step 2) was tested with the receiver operating characteristic (ROC) analysis. The ROC analysis included the existing ADO and BODE indices alone and ADO and BODE indices with addition of the risk parameters identified during Step 1. The quality of fit was assessed with the c-statistic that equals the area under the ROC curve. The significance of the differences between the ROC curves was tested with the DeLong test[21].

Reclassification analyses (Step 3), namely the NRI and IDI methods[22,23], were used for parameters that significantly increased the c-statistics (the ROC analysis) of the ADO/BODE to further refine selection of components for the new prognostic index; only the parameters with significant results in the reclassification analysis were included in the final index.

Logistic regression was used to calculate the risk of death for the newly added parameters and, based on this, patients were divided into risk groups. Each group was assigned risk points that these parameters added to the new scale. The risk points were determined by rounding the ORs from the logistic regression. The new index was then divided into risk categories with similar prognostic power.

To validate the new scale, we calculated long-term survival estimates for the derivation (July 2016) and validation (April 2017) cohorts to assess differences in mortality risk between subgroups assigned to the risk categories. The CMRD Registry is still an ongoing project and the prospective nature of the study enabled us to reassess the prognostic utility of the CADOT twice more in March 2018 and in January 2020, in order to confirm its unique prognostic properties.

All presented analyses were performed using the IBM SPSS Statistics 24.0 (ref.[24]) and R-studio software (ref.[25]). All statistical tests used α=0.05 as the level of significance.

RESULTS

Step 1: The derivation cohort (median follow-up 18.5 months) was split into subgroups of 616 alive and 83 dead patients. The two subgroups differed in the total ADO and BODE scores as well as the individual parameters within the two indices. Concurrently, we observed lower values of pulmonary function tests (FEV_1/FVC, TL_{CO}, K_{CO}) in the subgroup of dead vs living patients (P<0.001 for all). CHF was significantly more frequent in the dead vs alive subgroup (33.7% vs 15.0%). Detailed characteristics of

Table 1. Descriptive statistics of the derivation (CZ) cohort (n=699).

	Total	Death		*P*
		No	Yes	
Sex - men (n, %)	517 (74.0%)	454 (73.7%)	63 (75.9%)	0.790
Age at inclusion (median, 5th; 95th percentile)	67.0 (51.4; 81.1)	66.7 (50.2; 79.8)	68.9 (60.9; 85.0)	**<0.001**
Age at diagnosis (median, 5th; 95th percentile)	58.9 (38.7; 74.4)	58.4 (37.7; 73.2)	63.9 (50.5; 80.7)	**<0.001**
BMI (median, 5th; 95th percentile)	26.8 (18.6; 38.0)	27.2 (18.8; 38.1)	23.9 (17.5; 37.0)	**<0.001**
Atopy (n, %)	90 (12.9%)	77 (12.5%)	13 (15.7%)	0.388
Asthma (n, %)	71 (10.2%)	66 (10.7%)	5 (6.0%)	0.245
Heart failure (n, %)	120 (17.2%)	92 (15.0%)	28 (33.7%)	**<0.001**
Atrial fibrillation (n, %)	89 (12.8%)	73 (11.9%)	16 (19.3%)	0.078
Diabetes mellitus (n, %)	162 (23.2%)	143 (23.3%)	19 (22.9%)	0.999
Depression (n, %)	136 (19.5%)	109 (17.7%)	27 (32.5%)	**0.003**
Apnoea (n, %)	51 (7.3%)	47 (7.6%)	4 (4.8%)	0.500
FEV_1 (%) (median, 5th; 95th percentile)	45.6 (25.1; 60.4)	46.7 (25.2; 60.6)	39.5 (18.5; 58.6)	**<0.001**
FVC (%) (median, 5th; 95th percentile)	67.7 (39.7; 99.0)	68.5 (41.6; 99.0)	62.6 (33.2; 93.3)	0.057
FEV_1/FVC (median, 5th; 95th percentile)	0.53 (0.33; 0.73)	0.53 (0.34; 0.72)	0.48 (0.31; 0.73)	**0.014**
TL_{CO} (%) (median, 5th; 95th percentile)	50.0 (22.0; 96.0)	52.0 (22.0; 97.0)	37.0 (18.0; 61.0)	**<0.001**
K_{CO} (%) (median, 5th; 95th percentile)	67.0 (31.0; 115.0)	68.0 (32.0; 116.0)	55.0 (24.0; 93.0)	**<0.001**
6-MWD (m) (median, 5th; 95th percentile)	350.5 (110.0; 528.0)	360.0 (120.0; 530.0)	243.0 (60.0; 460.0)	**<0.001**
BODE index (median, 5th; 95th percentile, mean, SD)	4.0 (1.0; 8.0) 4.2 (2.1)	4.0 (1.0; 8.0) 4.0 (2.1)	5.0 (2.0; 9.0) 5.3 (2.0)	**<0.001**
ADO index (median, 5th; 95th percentile, mean, SD)	5.0 (2.0; 7.0) 4.8 (1.6)	5.0 (2.0; 7.0) 4.6 (1.5)	5.0 (3.0; 8.0) 5.5 (1.6)	<0.001

6-MWD = Six Minute Walking Distance; ADO = Age, Dyspnoea and airflow Obstruction; BMI = Body Mass Index; BODE = Body-mass index, airflow Obstruction, Dyspnoea, and Exercise; FEV_1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity; K_{CO} = Transfer Coefficient for Carbon Monoxide; TL_{CO} = diffusing capacity (Transfer Factor) for Carbon Monoxide

Table 2. Assignment of points for the CADOT index.

	0 points	1 point	2 points	3 points	4 points	5 points
CHF	No			Yes		
Age	40–49	50–59	60–69	70–79	80–89	≥ 90
mMRC	0–1	2	3	4	-	-
FEV_1	≥ 65	64–36	≤ 35	-	-	-
TL_{CO}	≥ 45	30–44	< 30	-	-	-

CHF = Chronic Heart Failure; FEV_1 = Forced Expiratory Volume in 1 Second; mMRC = modified Medical Research Council dyspnoea scale; TL_{CO} = diffusing capacity (Transfer Factor) for Carbon Monoxide

the derivation cohort and its subgroups are presented in Table 1.

Step 2: Since total ADO/BODE and their individual items discriminated between the two subgroups, the ADO and BODE indices were used as platforms for the development of a new index.

The potential of the newly identified parameters, i.e. CHF, FEV_1/FVC, TL_{CO} and K_{CO} to increase the discriminative power for all-cause mortality prediction of the existing risk indices (ADO/BODE) is presented in the Table A1. The DeLong test showed that adding CHF, TL_{CO} and K_{CO} to the ADO platform provided statistically significant differences in mortality prediction. No significant result was identified for any combination of the new parameters and the BODE.

Consequently, CHF, TL_{CO} and K_{CO} were entered in the reclassification analysis (Step 3) using the ADO platform as the cornerstone. The reclassification analysis showed CHF and TL_{CO} to be appropriate for definitive use as additional factors for mortality prediction (Table A2).

Table 3. Prediction of 2-year mortality (95% CI) according to the CADOT total score.

Category	Score	Derivation cohort	Validation cohort
CADOT 1	0–2	0.0%	0.0%
CADOT 2	3–5	7.9% (3.2% – 12.5%)	4.3% (0.2% – 8.5%)
CADOT 3	6–9	15.2% (9.0% – 21.5%)	20.5% (6.9% – 34.1%)
CADOT 4	10–15	45.4% (21.0% – 69.9%)	–

CADOT = Chronic heart failure, Age, Dyspnoea, airflow Obstruction, TL_{CO} - diffusion capacity (Transfer factor) for Carbon Monoxide; CI = Confidence Interval

Therefore, the development process resulted in a new prognostic index with 5 components, i.e. **C**HF, **A**ge, **D**yspnoea (mMRC score), **O**bstruction (FEV_1 - % of predicted value) and TL_{CO} (% of predicted value) (CADOT). CHF was assigned 0 points (absent) and 3 points (present; rounded OR = 3). TL_{CO} values were categorized into three categories and assigned 0 points (≥45%), 1 point (30-44%) and 2 points (<30%). The rating of the individual items of the CADOT index is described in Table 2. The CADOT scores can range between 0 and 15 points. Detailed characteristics of the CMRD cohort with complete CADOT data are presented in Table A3. Like the BODE index, the individual scores were split into 4 prognostic categories (low risk, intermediate risk, high risk, very high risk of death) with similar prognostic power (Table A3 and Table 3).

Table 4. ROC analysis – index capacity to separate patients according to mortality.

Index	Cohort	C-statistics (95% CI)	*P*
BODE	Derivation cohort	0.677 (0.610–0.744)	**<0.001**
	Validation cohort – NL	0.799 (0.681–0.917)	**<0.001**
ADO	Derivation cohort	0.644 (0.581–0.706)	**<0.001**
	Validation cohort – NL	0.825 (0.735–0.914)	**<0.001**
CADOT	Derivation cohort	0.701 (0.625–0.776)	**<0.001**
	Validation cohort – NL	0.842 (0.755–0.930)	<0.001

ADO = Age, Dyspnoea and airflow Obstruction; BODE = Body-mass index, airflow Obstruction, Dyspnoea, and Exercise; CADOT = Chronic heart failure, Age, Dyspnoea, airflow Obstruction, TL_{CO} – diffusion capacity (Transfer factor) for Carbon Monoxide

Validation

Characteristics of the validation cohort (median follow-up 26.2 months) are presented in Table A4. The outcomes of the validation are presented in Table 3 (the CADOT index performance), Table 4 (prognostic power of the BODE, ADO and CADOT) and in Fig. 1 (long-term survival estimates).

Estimated two-year survival rates for the low, intermediate, high and very high risk groups were 100%, 92.1%, 84.8% and 54.6%, respectively (P<0.001) in the derivation cohort, 100%, 95.7%, 79.5% and N/A, respectively (P<0.001) in the validation cohort.

Confirmation of prognostic utility of the CADOT from a long-term perspective

The c-statistic of the CADOT in the March 2018 reassessment was 0.685 (P<0.001). In the last reassessment in January 2020, estimated five-year survival rates for the low, intermediate, high and very high risk groups were 88.9%, 66.7%, 42.6% and 22.9%, respectively (P<0.001). (Fig. A1).

DISCUSSION

The BODE index is the most widely used and globally accepted instrument for COPD prognosis assessment. We present a complementary/ alternative prognostic tool, the CADOT index. Having comparable prognostic power to the BODE and ADO indices, the CADOT has features that may be of special benefit in selected settings, in particular, if the 6-MWT is not practicable. The CADOT index also functioned well in subjects with milder airway obstruction (Table 4) and its properties were confirmed on an independent validation cohort.

The CADOT addresses some specific weaknesses of the ADO and BODE, such as 6-MWT in BODE or the impact of age on ADO.

Disabled or unfit COPD patients (e.g. severe arthrosis, polyneuropathy, lower limb amputees) may be unable (or unwilling) to undergo the 6-MWT or complete a shorter distance and fall into a BODE poorer prognosis. In addition, not all medical offices are equipped to perform the 6-MWT (e.g. lack of a ~30-meter corridor). Consequently, the BODE may be of limited use in COPD populations with disability/immobility. In 2009, Puhan et al. attempted to increase the prognostic accuracy of the BODE and ADO indices[9]. For BODE ("updated BODE index"), the main difference was the 6-MWT scoring where the different walking distances were assigned 0 (>350 m), 4 (250-349 m), 7 (150-249 m) or 9 points (<150 m), respectively[9]. However, this modification reinforced the reliance of the BODE on the 6-MWT, since a single one meter difference in walking distance (e.g. 350 vs 349 m) may result in a total score change of up to 4 points[9]. Since the CADOT does not include the 6-MWT, the issues associated with the 6-MWT are completely avoided.

The ADO index is based on age, FEV_1 and mMRC score assessments[9]. Up to 50% of the total score is determined by age alone (5 points of the 10-point scale assigned to age >90 years) (ref.[9]). The 2012 ADO update

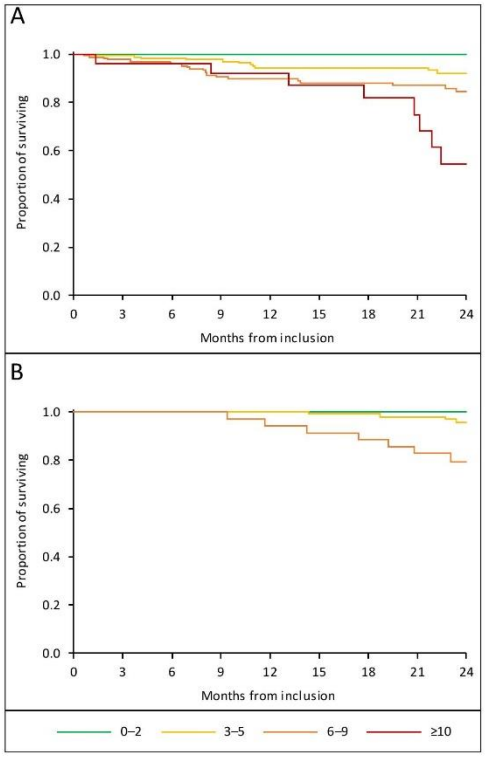

Fig. 1. Long-term survival according to the CADOT index (comparison of the derivation - CZ (A) and validation - NL (B) cohorts). CZ – Czech Republic; NL – Netherlands

maintains the prominence of the age factor (up to 7 of 14 points assigned for age >80 years) (ref.[26]).

Addition of CHF and TL_{CO} to the ADO index enabled us to develop a prognostic tool based on a well-established platform but reducing its dependence on age.

Evidence shows that CHF is a frequent comorbidity and one of the most important causes of death among COPD patients[27-29]. Our derivation cohort included 17.2% of patients with concurrent CHF and this comorbidity was shown to be one of the main drivers of mortality in our cohort. CHF was also frequent in other cohorts, e.g. in the POPE study, the prevalence of CHF ranged between 10.8% and 19.4% according to disease phenotype; for the frequent-exacerbator phenotypes (with obviously higher mortality risk) it was 16.6% and 19.4%, respectively[30].

In COPD patients, reduced TL_{CO} usually reflects the presence of emphysema, pulmonary arterial hypertension or CHF that are all associated with increased risk of long-term mortality[27,31,32]. In Central Europe, COPD patients are cared for mainly by pulmonary physicians, unlike Western Europe, where GPs are the prevailing caregivers[33]. In the Czech Republic, around 80% of outpatient non-hospital respiratory practices are equipped with (or have access to) a diffusion capacity assessment device. The situation is similar in Germany (personal communication with the Lemon Medical GmBH). Recent analysis of the POPE cohort illustrated that TLco vs 6-MWT data were available in 90% vs 11% of Croatians and 63% vs 20% of Czechs with COPD (ref.[30,34]). This means that in some regions or countries, TLco assessment may be more accessible than a ~30-meter corridor, i.e. the 6-MWT.

The CADOT index performed equally well in various populations of patients (CMRD and CIROCO). CMRD represents a population of moderate-to-very severe COPD subjects with higher (> 17%) prevalence of CHF, while the CIROCO cohort included more patients with milder airway obstruction (mean FEV_1 was 50%). In addition, the CIROCO patients were younger, had higher mean TL_{CO} (56%) and CHF was less prevalent (3%). This was consequent to the CIROCO study exclusion criteria (unstable COPD, myocardial infarction in the previous 6 months, asthma history, alpha-1 antitrypsine deficiency, previous lung surgery, malignancy in the previous 5 years) (ref.[18]). Importantly, the prognostic power (c-value) of the CADOT was higher in the "milder" COPD population of the CIROCO cohort. Since the long-term mortality risk among GOLD I subjects is very low, a large cohort of these subjects and a year-long follow-up would be needed to learn the prognostic properties of CADOT in this category of patients. An easy way for assessing risk among GOLD I patients using CADOT is a periodical (e.g., annual) calculation of the CADOT score where the disease progression/deterioration can be captured.

Our study has limitations. First, the derivation cohort included patients from tertiary and university hospital-based centers and thus, further external validation on larger cohorts with higher proportions of mild COPD patients are desirable. Second, the TL_{CO} test may be less available in primary care settings. However, this is strongly region/country-dependent and the availability of TL_{CO} in some regions or countries may exceed that of 6-MWT. For example, in Czechia, the availability of TL_{CO} for respiratory physicians is more than 80%. Third, the presence of CHF has not been re-assessed at patient inclusion. However, of the 120 CMRD subjects with a history of CHF, 29 had an echocardiographic (ECHO) examination of the heart within the CMRD study protocol (ECHO was a non-mandatory test). Of these, 26 patients (93%) had ECHO signs compatible with left- or right-sided CHF. Of the remaining 94 subjects with a CHF history, 87 (93%) were treated with 1 or more CHF treatments (ACE inhibitors, angiotensin II receptor antagonists, betablockers, diuretics). These data suggest reliability of the patient history data from the CMRD database. Fourth, our cohorts included a lower portion of patients with COPD, GOLD grade I. Though the CADOT performed well on a cohort with milder airway obstruction, further studies are needed to assess the utility of the CADOT in GOLD grade I subjects. Finally, the majority of both cohorts was composed of men (74% of the derivation cohort and 58% of the validation cohort, respectively) and the applicability to

women may be somewhat limited. However, in the the BODE and ADO construction studies, the proportion of men and women was unequal as well – in the 2012 study of Puhan et al, the proportion of men was 60%, while in the Puhan study of 2009, men accounted for a 60% (Swiss cohort) and 93% (Spanish cohort) (ref.[9,12]).

CONCLUSIONS AND IMPLICATIONS

We constructed and validated a new prognostic index (CADOT) that has slightly higher prognostic power than the BODE and ADO indices. The CADOT is complementary (or alternative) to the BODE in situations where 6-MWT is not feasible. The CADOT index improves the ability of respiratory physicians to determine risk for patients with COPD and severe comorbidities.

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2.4. 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.

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Komentář:

Poziční dokument ČPFS "Chronická obstrukční plicní nemoc – diagnóza a management stabilní faze nemoci – personalizovaný léčebný přístup s použitím léčitelných rysů založených na klinických fenotypech." je aktualizovanou, přepracovanou a doplněnou verzí původního dokumentu z roku 2013. Dokument upravuje a vymezuje obecná i konkrétní doporučení pro diagnostiku, management péče a léčbu CHOPN. Aktuální dokument staví nejen na bazi poslední verze z roku 2013 (135), ale také dokumentu GOLD 2020 (136) a čerpá inspiraci i v jiných národních doporučeních pro léčbu CHOPN (např. ve španělském GesEPOC) (55). Pro formulaci jednotlivých léčebných doporučení nebyly použity jen literární zdroje z velkých randomizovaných studií, ale i data získaná ze studií z reálné klinické praxe (real-life studies). Dokument a doporučení v něm obsažená se tak snaží o maximální míru přiblížení k realitě klinické praxe v kontextu a rámci zdravotnického systému České republiky. Systém klasifikace i léčby CHOPN použitý v tomto dokumentu je ve světě unikátní

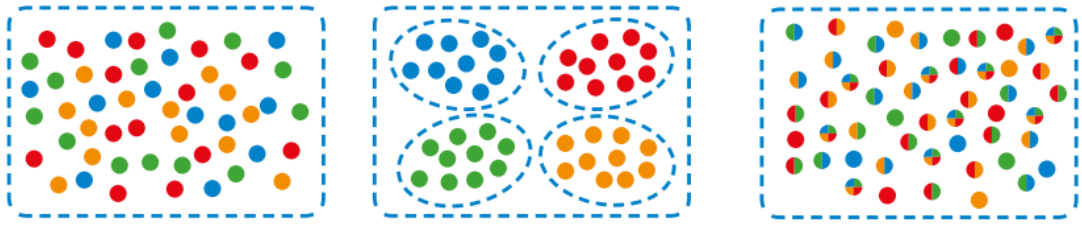
a je založen na stratifikovaném principu popisu diagnózy i vedení léčby. Poziční dokument je výsledkem několikaleté systematické práce expertního týmu ČPFS.

V úvodních kapitolách pozičního dokumentu pojednáváme o základním rámci jeho platnosti, o jeho cílech a záměrech autorů prezentovat nejnovější vedecké poznatky formou, která je reálně použitelná v každodenní klinické praxi v intencích zdravotnického systému České republiky. Je prezentována aktuálně platná definice nemoci, základní epidemiologický přehled a je pojednáno o známých i novějších patofyziologických principech a rizikových faktorech vzniku CHOPN. Zde zmíním, že kouření tabáku nadále zůstává hlavním rizikovým faktorem, mohou se uplatnit ale i jiné mechanizmy (frekventní infekce dolních cest dýchacích v dětském věku, nízká porodní váha, dětské astma, znečištění ovzduší, nižší sociální status), které v budoucnu - s ohledem na očekávaný pokles prevalence tabákizmu - zřejmě budou nabývat na významu. Z patofyziologických procesů je pro budoucnost velmi slibný zejména mechanizmus senescence, který se dle vědeckých poznatků z posledních letech jeví hrát klíčovou roli v patogenezi CHOPN a jejích komorbidit (22, 23). Potenciál společného ovlivnění průběhu CHOPN i přidružených závažných komorbidit jedním lékem (mono- nebo multi-komponentním) činí z mechanizmů senescence atraktivní terapeutický cíl pro výzkumníky, lékaře i farmaceutický průmysl (23).

Novou kapitolou v dokumentu je stanovení prognózy pacienta s CHOPN. Pro stratifikaci rizika doporučujeme použití indexu BODE (83), který je ve světě používán již 15 let. Pokud není BODE kalkulovatelný (nejčastěji z důvodu nemožnosti provést 6-MWT při nedostatku prostorových kapacit nebo pohybovém omezení na straně pacienta), navrhujeme jako alternativu použít index CADOT (původní práce viz kapitola 2.3.). Hrubou informaci o vyšším riziku u pacienta může při nedostupnosti kalkulace zmíněných indexů přinést i nízká hodnota FEV_1 (83), klasifikace pacienta do skupiny D dle GOLD nebo přítomnost hypoxémie (PaO2 <7.3 kPa) u pacienta s CHOPN skupiny B dle GOLD (viz původní práce kapitola 2.1.).

V rámci pátrání po případné hypoxémii lze (screeningově) vyšetření krevních plynů nahradit měřením SpO_2; hodnoty pod 90% jsou imperativem k následnému vyšetření krevních plynů.

Diagnózu CHOPN doporučujeme stanovit na základě klasických kritérií – přítomnosti symptomů (dušnost, kašel, expektorace), ireverzibilní (nebo jen částečně reverzibilní) bronchiální obstrukce pomocí spirometrie a vyloučení alternativních diagnóz. Důležitým aspektem, kterému v pozičním dokumentu věnujeme velký prostor, je iniciální klasifikace nemoci. Od správné klasifikace případu CHOPN se totiž odvíjí i komplex léčebného doporučení s vizí maximální míry jeho individualizace pro každého pacienta. Doporučujeme vícevrstevnou klasifikaci nemoci. Za prvé, dle hodnoty postbronchodilatační FEV_1 stanovujeme stádium CHOPN dle GOLD (I-IV) a získáváme základní obraz o míře limitace plicních funkcí (1). Za druhé, stanovujeme skupinu CHOPN dle GOLD (A-D), která odráží úroveň symptomů pacienta a počet i závažnost exacerbací (1). Za třetí, stanovujeme fenotypické projevy CHOPN. Tento přístup je používán i v jiných zemích, např. ve Španělsku, kde je jednomu pacientovi přiřazen jeden dominantní klinický fenotyp nemoci (55). Český přístup k fenotypizaci rozeznává celkem 6 klinických fenotypů (emfyzematický, bronchitický, překryv CHOPN s astmatem, překryv CHOPN s bronchiektaziemi, plicní kachexie a frekventní exacerbace) a je inspirován konceptem profesora Agustího z Barcelony; u jednoho pacienta je popsána přítomnost jednoho (vzácně žádného) nebo více klinických fenotypů - viz níže obrázek č. 5 z Pozičního dokumentu (35).



Každý z těchto fenotypů je přesně charakterizován přítomností nebo absencí předem definovaných znaků. Tento ve světě unikátní přístup umožňuje popsat nemoc pacienta více

fenotypickými “nálepkami” zároveň a lékař-klinik tak nesoustřeďuje svou pozornost pouze na dominanntí fenotyp, nýbrž se mu otevírá prostor pro léčbu všech přítomných fenotypů zaráz. Všechny výše definované fenotypy zároveň považujeme za léčitelné rysy CHOPN (treatable traits), pro které jsou v další kapitole definovány konkrétní léčebné postupy a doporučení.

Kapitola věnovaná strategii léčby CHOPN definuje celou paletu léčebných opatření a postupů na medikamentózní bázi i nemedikamentózního charakteru. Léčba je – obdobně jako klasifikace nemoci – stratifikována do několika (zde pěti) okruhů resp. kroků.

Prvním krokem je eliminace (či alespoň minimalizace) rizik, zejména kouření tabáku (i “pasivního” kouření) (137) a inhalačních expozic profesního původu či v domácnosti. Druhým krokem je základní (mandatorní) léčba. Tato zahrnuje bronchodilatancia (dlouhodobě či krátkodobě působící parasympatolytika, β2-sympatomimetika nebo jejich kombinace), respirační fyzioterapii (138, 139) i s případnou nutriční podporou, nácvik správné inhalační techniky (140) a vakcinaci proti viru influenzy, nemoci COVID-19 a *Streptococcus pneumoniae* (1). Třetím krokem je fenotypicky-vázaná léčba. Z praktických důvodů nebudu detailně pojednávat o každém typu léčby zvlášť, pouze pro přehled vyjmenuji jednotlivé léčebné modality doporučené pro konkrétní fenotypy. U fenotypu frekventních exacerbací (≥2 exacerbace/rok) doporučujeme inhalační kortikosteroidy [zejména u pacientů s počtem eozinofilů v periferní krvi ≥300/μL (141)], inhibitory fosfodiesterázy-4, mukoaktivní látky (erdostein nebo N-acetylcystein), vybraná antibiotika (azitromycin, moxifloxacin) nebo kombinaci těchto léků. U bronchitického fenotypu doporučujeme inhibitory fosfodiesterázy-4, mukoaktivní látky a expektorační techniky v rámci respirační fyzioterapie; u fenotypu kachexie doporučujeme nutriční intervenci, psychosociální podporu, intenzivní respirační fyzioterapii a trénink kosterního svalstva. Pro pacienty s fenotypem ACO doporučujeme léčbu IKS/LABA nebo fixní trojkombinaci IKS/LAMA/LABA, lze zkusit antileukotrieny; pro pacienty s BCO inhibitory fosfodiesterázy-4, mukoaktivní látky,

antibiotika (azitromycin, moxifloxacin), fyzioterapii, imunomodulancia nebo kombinaci těchto přístupů. U pacientů s emfyzémem zvažujeme metylxantiny a doporučujeme plicní fyzioterapii, při deficitu A1AT jeho substituci, u lokalizovaného emfyzematického postižení BLVR endobronchiálními chlopněmi nebo coily, případně chirurgickou LVRS. Při kombinaci (souběhu) více fenotypů u jednoho pacienta léčíme všechny přítomné rysy. Čtvrtým pilířem léčby je léčba velmi pokročilé CHOPN a přidružených problémů. Zahrnuje domácí oxygenoterapii, domácí NIV, transplantaci plic a srdce nebo jen plic a paliativní léčbu. Posledním, pátým, krokem je léčba komorbidit. Zejména se soustředíme na léčbu kardiovaskulárních komorbidit a deprese, které mají významný vztah k mortalitě.

Poziční dokument dále představuje probíhající projekt MZČR Časného záchytu CHOPN, který cílí na předem definované rizikové skupiny dospělých obyvatel. Cílem projektu je záchyt CHOPN v časném stadiu, kdy je největší pravděpodobnost snížení mortality při adekvátní a včasné terapeutické intervenci.

Závěrem představujeme možné směry dalšího vývoje v oblasti CHOPN. Nové třídy léků budou zahrnovat inhalační inhibitory PDE3/4, molekuly s kombinovanou LAMA i LABA aktivitou, protizánětlivé léky z řad monoklonálních protilátek a další. Důraz by měl být kladen i na časný záchyt nemoci a na výraznější celospolečenskou debatu o účincích kouření tabáku.

Poziční dokument "CHOPN – diagnóza a management stabilní faze nemoci – personalizovaný léčebný přístup s použitím léčitelných rysů založených na klinických fenotypech." je jedním z nejpropracovanějších a nejmodernějších dokumentů na toto téma.

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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

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This position paper has been drafted by experts from the Czech national board of diseases with bronchial obstruction, of the Czech Pneumological and Phthisiological Society. The statements and recommendations are based on both the results of randomized controlled trials and data from cross-sectional and prospective real-life studies to ensure they are as close as possible to the context of daily clinical practice and the current health care system of the Czech Republic. Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable heterogeneous syndrome with a number of pulmonary and extrapulmonary clinical features and concomitant chronic diseases. The disease is associated with significant mortality, morbidity and reduced quality of life.

The main characteristics include persistent respiratory symptoms and only partially reversible airflow obstruction developing due to an abnormal inflammatory response of the lungs to noxious particles and gases. Oxidative stress, protease-antiprotease imbalance and increased numbers of pro-inflammatory cells (mainly neutrophils) are the main drivers of primarily non-infectious inflammation in COPD. Besides smoking, household air pollution, occupational exposure, low birth weight, frequent respiratory infections during childhood and also genetic factors are important risk factors of COPD development. Progressive airflow limitation and airway remodelling leads to air trapping, static and dynamic hyperinflation, gas exchange abnormalities and decreased exercise capacity. Various features of the disease are expressed unequally in individual patients, resulting in various types of disease presentation, emerging as the "clinical phenotypes" (for specific clinical characteristics) and "treatable traits" (for treatable characteristics) concept. The estimated prevalence of COPD in Czechia is around 6.7% with 3,200–3,500 deaths reported annually.

The elementary requirements for diagnosis of COPD are spirometric confirmation of post-bronchodilator airflow obstruction (post-BD FEV_1/VCmax <70%) and respiratory symptoms assessement (dyspnoea, exercise limitation, cough and/or sputum production. In order to establish definite COPD diagnosis, a five-step evaluation should be performed, including: 1/ inhalation risk assessment, 2/ symptoms evaluation, 3/ lung function tests, 4/ laboratory tests and 5/ imaging. At the same time, all alternative diagnoses should be excluded. For disease classification, this position paper uses both GOLD stages (1 to 4), GOLD groups (A to D) and evaluation of clinical phenotype(s). Prognosis assessment should be done in each patient. For this purpose, we recommend the use of the BODE or the CADOT index.

Six elementary clinical phenotypes are recognized, including chronic bronchitis, frequent exacerbator, emphysematous, asthma/COPD overlap (ACO), bronchiectases with COPD overlap (BCO) and pulmonary cachexia. In our concept, all of these clinical phenotypes are also considered independent treatable traits. For each treatable trait, specific pharmacological and non-pharmacological therapies are defined in this document. The coincidence of two or more clinical phenotypes (i.e., treatable traits) may occur in a single individual, giving the opportunity of fully individualized, phenotype-specific treatment.

Treatment of COPD should reflect the complexity and heterogeneity of the disease and be tailored to individual patients. Major goals of COPD treatment are symptom reduction and decreased exacerbation risk. Treatment strategy is divided into five strata: risk elimination, basic treatment, phenotype-specific treatment, treatment of respiratory failure and palliative care, and treatment of comorbidities.

Risk elimination includes interventions against tobacco smoking and environmental/occupational exposures. Basic treatment is based on bronchodilator therapy, pulmonary rehabilitation, vaccination, care for appropriate nutrition, inhalation training, education and psychosocial support. Adequate phenotype-specific treatment varies phenotype by phenotype, including more than ten different pharmacological and non-pharmacological strategies. If more than one clinical phenotype is present, treatment strategy should follow the expression of each phenotypic label separately. In such patients, multicomponental therapeutic regimens are needed, resulting in fully individualized care.

In the future, stronger measures against smoking, improvements in occupational and environmental health, early diagnosis strategies, as well as biomarker identification for patients responsive to specific treatments are warranted. New classes of treatment (inhaled PDE3/4 inhibitors, single molecule dual bronchodilators, anti-inflammatory drugs, gene editing molecules or new bronchoscopic procedures) are expected to enter the clinical practice in a very few years.

Key words: COPD; position paper; clinical phenotypes; treatable traits; bronchodilators; individualized care; personalized medicine

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CONTENTS

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) represents a serious disease or, more precisely, a heterogeneous syndrome, affecting hundreds of millions of people worldwide[1]. The disease is associated with significant mortality, morbidity and reduced quality of life.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) regularly (on a yearly basis) publishes a report dedicated to strategy of COPD management. This report is used by physicians worldwide as a basic strategy document, defining basic terms and concepts. However, several national or international COPD management guidelines or recommendations have been developed and published previously, that more precisely respect the scope, structure and individual characteristics of local healthcare systems[1-10]. In contrast to other guidelines, this position paper is based on clinical phenotypes of COPD and employs the treatable traits concept for COPD treatment.

Experts from the Czech national board of diseases with bronchial obstruction have been commisioned by the Czech Pneumological and Phthisiological Society (CPPS) in order to draft an update on previous (2013) recommendations for diagnosis, management and treatment of stable COPD (ref.[11]). The updated document has been discussed and revised at the Czech National Consensus Conferences in November 2018 (Hradec Kralove), April 2019 (Hradec Kralove), and June 2019 (Prague). After incorporation of the comments, the prefinal version of the document has been established. Final polishing of this official position paper has been perfomed by members of CPPS from January to August 2020 (during three expert meetings and several web based session).

The intention of the authors was to set this evidence-based position paper into the context of daily clinical practice and the current health care system of the Czech Republic. Currently, all treatment components are available in the Czech Republic; mandatory health insurance of all residents covers most of the treatment expenses including rehabilitation program, alpha-1 antitrypsin augmentation, lung transplantation, long-term oxygen treatment, and high-intensity non-invasive ventilation support. Above that, more than 90 % of care for patients with COPD is concentrated in the hands of respiratory specialists. This means, that literally almost every patient with COPD has unlimited access to lung CT scanning, advanced lung function assessment and full-scale phar-

macological and non-pharmacological treatment available in the Czech Republic[11]. Special emphasis is placed on complex management of COPD and related comorbidities, personalized approach to care and on new scientific knowledge published since the previous Czech COPD management document[11].

2. DEFINITION AND PATHOPHYSIOLOGY

COPD is a preventable and treatable disorder that is characterized by persistent respiratory symptoms and airflow limitation that is due to lower airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles and/or gases. Besides these risk exposures, host factors (genetic factors, altered childhood lung growth, and accelerated premature aging) predispose individuals to develop COPD. The most common respiratory symptoms include breathlessnes and chronic cough with or without sputum production. The above mentioned symptoms may be under-reported by COPD patients[1,12-15].

COPD is a heterogeous condition with a number of pulmonary and extrapulmonary clinical features and concomitant chronic diseases. The pulmonary component of COPD is characterized by a partially reversible airflow limitation developing gradually due to prolonged abnormal inflammatory response and/or tissue abnormalities of the airways and lung parenchyma to noxious particles and gases[1,16]. Oxidative stress, protease-antiprotease imbalance and increased numbers of pro-inflammatory cells (neutrophils, alveolar macrophages, T-lymphocytes and innate lymphoid cells) are the main drivers of primarily non-infectious inflammation in COPD (ref.[17]). A majority of patients with COPD have a predominantly neutrophilic type of inflammation, however, approximately every one of four/five patients presents with concurrent eosinophilic inflammation[18,19].

The chronic inflammation leads to accelerated and progressive breakdown of elastic fibers, peribronchial fibrosis, destruction of alveolar walls, microvessels and small airways, airway remodelling and mechanisms of chronic mucus hypersecretion[17,21,22]. Progressive airflow limitation and airway remodelling leads to air trapping, static and dynamic hyperinflation, gas exchange abnormalities and to decreased exercise capacity and physical activity[22,23]. The above listed mechanisms are expressed unequally and variably in individual patients, resulting in various types of clinical presentation. Nowadays, the "clinical phenotypes" concept is emerging, meaning "a single or combination of disease attributes that describe differences between individuals as they relate to clinically meaningful outcomes" to differentiate between various disease patterns and their clusters in specific subpopulations of COPD individuals[3,11,24-26].

Multiple systemic effects have been described in patients with COPD. Increased levels of circulating inflammatory mediators and acute-phase proteins are drivers or at least contributors to the development of comorbidities, including cardiovascular diseases, skeletal muscle dysfunction, osteoporosis, depression, cachexia, diabetes mellitus or sleep apnoea syndrome[27-32]. In consequence, persistent systemic inflammation is associated with higher risk of exacerbation and mortality[33]. COPD is also considered a proven pre-cancerous condition[27,34].

Besides the already understood mechanisms, pulmonary cellular senescence is now considered a potent driver mechanism of COPD pathogenesis. Senescent cells secrete pro-inflammatory proteins and molecules, leading to chronic inflammation. Understanding the process of pulmonary cellular senescence may allow us to identify new therapeutic targets in the future[35].

3. RISK FACTORS

Tobacco smoking – including second-hand smoke and passive exposure – is considered the main cause of COPD. Besides smoking, other environmental exposures such as household air pollution, occupational particulates, ozone and ambient particulate matter were found important risk factors of COPD development[36].

There are also studies showing association between airflow limitation in childhood and greater risk of COPD and asthma-COPD overlap syndrome (ACOS) development in adulthood[37]. The higher likelihood of developing COPD was also observed in low birth weight infants[38,39], childhood asthma[40,41] and patients with frequent respiratory infections during childhood[38,40]. Evidence also supports that tuberculosis[42,43] and HIV patients are at higher risk of COPD development[44].

However, these factors are unlikely to be the only reason of developing COPD. In a small proportion of non-smokers, a genetic component to the disease or specific interactions between genetic and epigenetic factors and effects of the environment may play an important role[45]. The most documented genetic risk factor of COPD is alpha-1 antitrypsin deficiency (AATD) (ref.[46,47]). However, other genetic polymorphisms, including single genes encoding glutathione S-transferase, matrix metalloproteinases or superoxide dismutase, may also be associated with the pathogenesis of the disease[48-50].

4. EPIDEMIOLOGY

Smoking epidemics in the developing countries, general aging of populations, and increased environmental exposure to air pollution are responsible for the increasing global incidence and prevalence of the disease[51,52]. The latest worldwide prevalence was estimated at 11.7% (ref.[52]). An estimated 12.4% of the EU population suffer from COPD (ref.[53]). In the Czech Republic, the recently estimated prevalence is around 6.7%, i.e., around 710,000 patients per the 10,65 million population of the country[54].

According to the latest epidemiological data, COPD currently ranks fourth, however, by 2020, it was projected to become the third worldwide leading cause of death from non-communicable diseases[1,51]. Current mortality data (for the year 2020) are yet not available. The disease claims around 3 million lives in the world annually[55]. In

the EU, the mortality trend was linearly decreasing during the period between 1994 and 2010 (ref.[56]). Following a period of notable increase since the 2000-10 decade, mortality from COPD in the Czech Republic was about stable between the years 2015 and 2018, with 3,200-3,500 deaths reported annually[54,57].

5. RISK ASSESSMENT

Prognostic assessment is one of the key issues regarding the disease management, offering the opportunity to identify high-risk patients requiring more assertive treatment approach. Traditionally, FEV_1 was the most widely used parameter for basic prognostic evaluation, reflecting the association between progressive lung function decline and increasing mortality risk[58].

In the last two decades, composite tools for long-term prognosis assessment have been constructed, including the ADO, BODE and related indices[58,59]. The scoring system of the BODE and the score-specific four-year mortality risk are described in the article by Celli et al.[58]. Recently, a new-generation multidimensional prognostic instrument, the CADOT index, has been introduced. The CADOT showed slightly better prognostic properties compared to ADO and BODE indices and prevented the specific problems associated with the use of BODE (ref.[60]). The CADOT incorporates also chronic heart failure that has strong linkage to mortality risk and also to functional impairment of the lungs[61]. As such, the CADOT instrument offers an alternative to the BODE index, if the 6-MWT (or an other component of the BODE) is not feasible. If calculation of BODE or CADOT score is not possible, a significantly higher risk of long-term mortality should be expected in group B patients with chronic hypoxemia (PaO_2 <7.3 kPa) and in group D patients, irrespective of hypoxemia[62].

6. DIAGNOSIS OF COPD

The elementary requirements for diagnosis of COPD consist of spirometric confirmation of post-bronchodilator (post-BD) expiratory airflow limitation (bronchial obstruction) (Fig. 1). Spirometry should be done in all individuals with chronic respiratory symptoms (dyspnoea

Fig. 1. GOLD stages (according to post-BD spirometry of COPD patients)

Table 1. Alternative diagnoses to COPD.

Alternative diagnosis	Clinical presentation similar to COPD (dominant symptom(s) **in the bold**)	Confirmation of alternative diagnosis (the most important options in the real-life practice)
Bronchial asthma#	**Cough, dyspnoea, wheezing,** sputum production	Normal TLco, periods without bronchial obstruction, normal chest HRCT
Bronchiolitis	Cough, **dyspnoea**	Chest HRCT inspiratory/expiratory (with mosaic pattern)
Bronchiectases##	Cough, **sputum production**, exacerbation	Chest HRCT (bronchiectases signs) (ref. [66, 67])
Cystic fibrosis	Cough, **sputum production, dyspnoea**	Sweat test (> 60 mmol/l) (ref. [68])
Primary ciliary dyskinesia	**Cough, sputum production**, exacerbation	Nasal Nitric Oxide (< 105 ppb) (ref. [69, 70])
Extraesophageal reflux	**Cough,** especially after lying **in supine position,** sputum production, aspiration attack	Laryngoscopy/Gastroscopy, pH metry, esophageal impedance
Tracheobronchomalacia (intrathoracic collapse)	Cough, wheezing, dyspnoea	Bronchoscopy, dynamic chest HRCT during spirometry
Tracheal stenosis (fixed)	Cough, wheezing, dyspnoea	Bronchoscopy
Sarcoidosis	Cough, wheezing	Chest HRCT
Pulmonary embolism	**Dyspnoea**	Chest CT with contrast, D-dimers
Heart failure	**Dyspnoea**, cough	Heart ultrasound, chest X-ray, NTpro-BNP*

Except for patients who have simultaneously present and balanced features of both diseases (asthma and COPD overlap - ACO)
Except for patients who have simultaneously present and balanced features of both diseases (bronchiectasis and COPD overlap - BCO)
* NTpro-BNP = N-terminal prohormone of brain natriuretic peptide

with exercise limitation and/or cough and/or sputum production), particularly in case of long-term risk exposure – see above[63]. Expiratory airflow limitation was clearly defined by the European Respiratory Society as a decrease in FEV_1/VC below the lower limit of normal values (LLN) (ref.[64,65]). Global Initiative for Chronic Obstructive Lung Disease (GOLD) simplifies the view on spirometric diagnosis of COPD to fit to the health care based on general practitioners. From the GOLD perspective, any person with post-BD FEV_1/FVC <0.7 is considered a COPD case. In order to establish the definite COPD diagnosis, all alternative diagnoses associated with bronchial obstruction should be excluded – Table 1 (ref.[1]).

COPD individuals exhibit gas trapping and increased lung hyperinflation from early stages of the disease. These important features can be documented by bodyplethysmography. Measurement of transferfactor (TL_{CO}) for carbon monoxide provides additional information on the functional impact of emphysema and cardiovascular comorbidities in COPD subjects[1,64].

Worse lung function, more dyspnoea, higher comorbidity burden, and non-stable (exacerbated) course of COPD are associated with elevated overall health risks among COPD population. The above mentioned risk factors are useful for assessing the appropriate depth of the initial examination of a newly diagnosed case (Fig. 2).

7. INITIAL CLASSIFICATION OF A COPD CASE

This position paper uses combined classification including COPD stages (1 to 4), COPD groups (A to D) according to GOLD (ref.[1]) and assessment of one or more clinical phenotype(s), if it is (they are) present.

At initial examination of COPD individuals, a comprehensive assessment of the patient using a history of worsening episodes called exacerbations and evaluation of respiratory symptoms (using the CAT questionnaire and/or the modified MRC dyspnoea scale) is recommended (Fig. 3).

The current GOLD 2020 strategy recommends that each patient be marked with the letter A-B-C-D, indicating a specific disease group. Health systems based on general practitioners propose initial pharmacological treatment according to A-D groups[1]. In the conditions of different health care system in the Czech Republic, this is not necessary, however, we still find the A-D groups useful since they describe the extent of symptoms and exacerbations (Fig. 4).

Group A represents asymptomatic subjects in early stage of the disease, these patients can be successfully treated by general practitioners (GPs). In contrast, group B deserves particular attention as it consists of comorbidity-burdened patients with a less pronounced deterioration in lung function, though with a substantial mortality

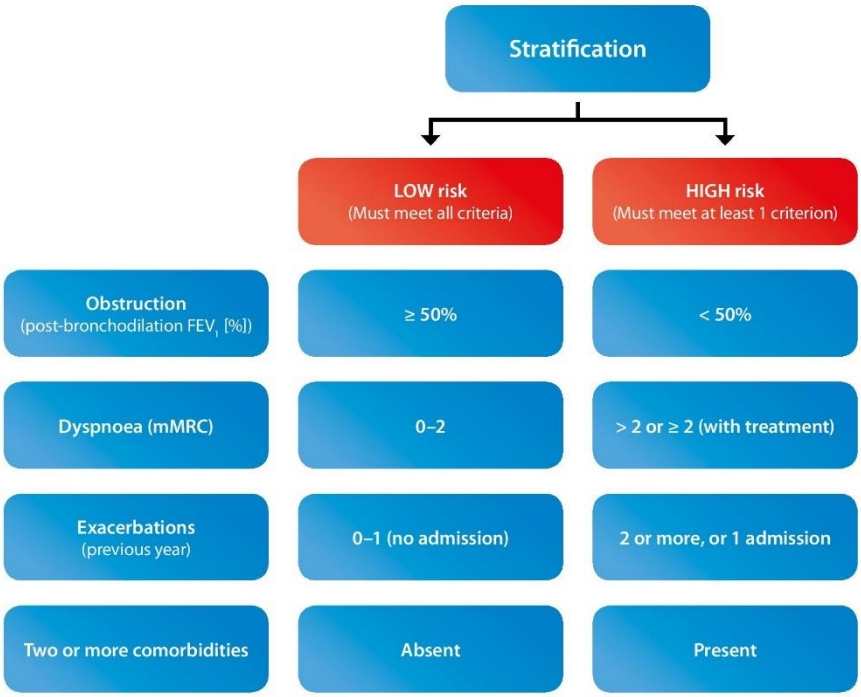
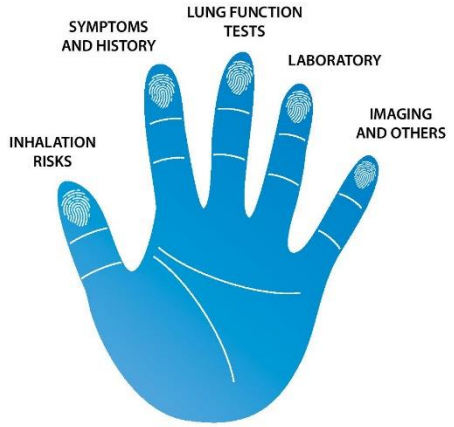


Fig. 2. Health risk assessment modified according to Miravitlles et al. (ref. [3]).



1st finger: INHALATION RISKS
Smoking and/or occupational risks and/or air pollution

2nd finger: SYMPTOMS AND HISTORY
CAT (or mMRC dyspnoea scale)
PATIENT HISTORY related to COPD and other diseases

3rd finger: LUNG FUNCTION TESTS
SPIROMETRY (before and after salbutamol) in low risk patients
SPIROMETRY + LUNG VOLUMES + DIFFUSION (in high risk patients)
6-MINUTE WALKING TEST (alternatives: CPET, 1-MINUTE SIT TO STAND TEST)

4th finger: LABORATORY
BIOCHEMISTRY (A1AT, …) + HAEMATOLOGY (EOSINOPHILS, …)
SPUTUM (culture)

5th finger: IMAGING AND OTHERS
CHEST X-RAY (or CHEST CT in high risk patients)
ECG (and HEART ULTRASOUND in high risk patients)
ABDOMINAL SONOGRAPHY (in cases of cachexia)
POLYSOMNOGRAPHY (in cases of non-mild obesity)

Fig. 3. Initial diagnostic procedures in new COPD cases.

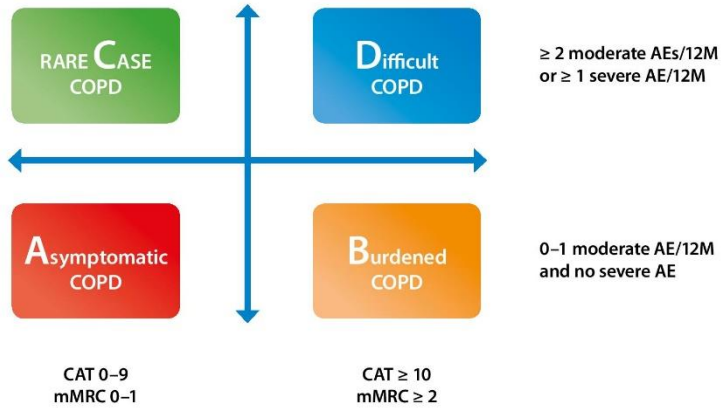


Fig. 4. GOLD groups according respiratory symptoms and number of exacerbations in the past 12 months.

risk[62]. Rare cases of oligo-symptomatic patients, comprising the small group C, can be usually found in the general population, but rarely in the pulmonologist's care. The highest mortality risk is associated with group D (difficult). Subjects of this category are extremely threatened by high respiratory and cardiovascular morbidity and mortality rates. Hence the monitoring and treatment of such individuals has to be thorough and comprehensive in every aspect.

A simple assessment of COPD severity with post-bronchodilator spirometry (stages 1 to 4) reflects the deterioration of lung function and the extent of bronchial obstruction. Despite the severity of bronchial obstruction has only weak correlation with symptoms and course of the disease, FEV_1 has a significant role in prognosis prediction and in some therapeutic decisions[1].

8. CLINICAL PHENOTYPES OF COPD

COPD is not a rigid and uniform condition, it likely represents a continuum of different sub-diseases that may share biological mechanisms (i.e., endotypes), and present with similar clinical, functional, imaging and/or biological features (i.e., phenotypes or phenotypical labels) which may require specific treatment (i.e., constituting specific treatable traits) (ref.[25,71,72]). In our concept, the six pre-defined clinical phenotypes are also considered independent treatable traits. For each treatable trait, specific pharmacological and non-pharmacological therapies are defined within this document.

Currently, there are two ways to delineate phenotypical features in each particular COPD case: the "Spanish approach" means that one COPD patient is described by one "clinical phenotype". The Czech approach is that the COPD patient may be characterized by one or more phe-

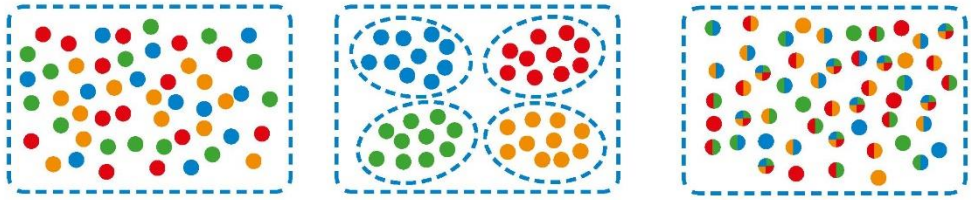


Fig. 5. Elementary concepts of COPD heterogeneity proposed by Agusti (ref. [71]).

Table 2. Phenotypical labels in COPD – characteristics.

Methods / phenotypical labels or treatable traits	CB	EMPH	AE's w. INF	AE's w. eo	ACO	BCO	CACHEXIA
Subnormal BMI (and FFMI)		+					++
Daily sputum production	++					+	
Repeated infections of lower airways	+		++	+		+	
Repeated AE's			++	++			
History of AB < 40 years					++		
History of haemoptysis (any time)			+			+	
Bodyplethysmography		++					
Transferfactor (diffusion)		++					
Exercise and daily activity		+					+
↓ A1AT (blood)		++					
↑ Eosinophils (blood)				++	++		
Sputum culture is positive	+		+			+	
HRCT emphysema signs		++					
HRCT bronchiectases signs						++	
HRCT airway disease signs	+						

A1AT – alpha-1 antitrypsin
AB – bronchial asthma
ACO – asthma/COPD overlap
AE's w. eo – acute exacerbation (with eosinophilia)
AE's w. INF – acute exacerbation (with infection)
BCO – bronchiectases and COPD overlap
BMI – body mass index
CB – chronic bronchitis
HRCT – high resolution computed tomography
EMPH – emphysema
FFMI – fat free mass index
++ Essential meaning
+ Auxiliary meaning

notypes/phenotypical labels – one patient=one or more phenotypes[3,11,62,73-75] (Fig. 5, Table 2).

Clinical phenotypes in individual patient may change over time, for example symptoms of chronic bronchitis or exacerbation rate can be improved after treatment. In these cases we prefer not to use the term "change of phenotype" but rather "achievement of clinical control" or "stabilisation of phenotype". In case of new phenotype development (e.g., new bronchiectases or frequent exacerbations), treatment should be adjusted to the actual clinical disease presentation to maintain maximal control of COPD.

All patients with COPD independently of the presence of clinical phenotype(s):

The most common clinical presentation of COPD is limitation of daily living activites due to breathlessness sensation. Dyspnoea first occurs during high-intensity physical exercise, later during milder effort, finally at rest, eventually resulting in physical inactivity, lifestyle change and social isolation[1,76-78]. Chronic fatigue is a highly prevalent sign in the COPD population. Fatigue poorly correlates with the degree of airflow limitation, but perceived fatigue seems to be a key factor in the decreasing quality of life[79,80].

8.1. FREQUENT EXACERBATOR PHENOTYPE

The long-term stable course of COPD can be intermittently interrupted in some patients by sustained worsening which exceed the normal day-to-day symptom variations. These attacks of symptoms worsening that last ≥2 days and require change in medication and/or hospitalization are called acute exacerbations (AEs) (ref.[81,82]). AEs have a significant and prolonged impact on health status and outcomes, and negative effects on pulmonary functions.

AEs with the need of antibiotic treatment and/or systemic corticosteroids' use are called moderate AEs. Those AEs resulting in hospitalization are considered severe AEs. The best threshold to distinguish "frequent exacerbators" and non-frequent exacerbators are two moderate-to-severe exacerbations per year. Therefore, the "frequent exacerbator" phenotype should be defined by at least two AEs treated in the past year. Frequent exacerbators have more pronounced airflow limitation, higher degree of symptoms and health-related quality of life impairment[83]. A significant proportion of AEs are unreported and therefore left untreated, leading to a poorer prognosis compared to those treated adequately. COPD exacerbations are heterogeneous, and various phenotypes have been proposed which differ in biologic basis, prognosis, and response to therapy. Frequent exacerbations are the strongest predictor of future exacerbation frequency, suggesting a consistent phenotype[84-87]. Therefore, reduction of AEs has beneficial impact on patient outcomes and prognosis[81,88].

8.2. BRONCHITIC PHENOTYPE

COPD patients with the bronchitic phenotype commonly experience cough, which is productive (with long-term presence of phlegm) in about 60% of cases[89,90]. CB subjects report worse respiratory symptoms (diurnal + nocturnal cough and phlegm) and experience higher risk of COPD exacerbations[91,92].

8.3. EMPHYSEMATOUS PHENOTYPE

Patients with pulmonary emphysema usually experience dyspnoea and have no chronic sputum expectoration (if there's no coincidence with bronchitic phenotype).

Emphysematous patients are clinically characterized by a more prevalent dyspnoea than any other COPD patients: A) early-morning and daytime dyspnoea in cases of mild emphysema, and B) diurnal + nocturnal dyspnoea in cases of severe emphysema. In most cases, chest high resolution computed tomography (HRCT) is necessary to confirm the presence of pulmonary emphysema. In addition, CT scans uncover the type of emphysema, its distribution and extent. Above that, CT scans help to exclude other lung diseases (tumours, lung fibrosis) and are also beneficial for bronchiectases detection[92-95].

The Fleischner Society of radiologists proposed a statement that describes and defines the phenotypic abnormalities identifiable on visual and quantitative HRCT images in subjects with COPD. Emphysema is classified as centrilobular (subclassified as trace, mild, moderate, confluent, and advanced destructive emphysema), panlobular, and paraseptal (subclassified as mild or substantial). Additional important visual features include airway wall thickening, inflammatory small airways disease, tracheal abnormalities, interstitial lung abnormalities, pulmonary arterial enlargement, and bronchiectases[96-98]. Prior to CT scanning, clinical suspicion on emphysema should be made in patients with a "barrel chest", with radiological signs of emphysema on a chest X-ray and/or with lung hyperinflation at pulmonary function tests.

8.4. ASTHMA-COPD OVERLAP (ACO)

ACO is characterized by persistent airflow limitation with several clinical features of bronchial asthma and several features typical for COPD. ACO may be a special phenotype of chronic obstructive airway diseases, in which asthma and COPD are located at the two opposite ends. The prevalence of ACO varies considerably due to variability of criteria for its diagnosis. Patients with ACO utilize a large proportion of medical resources because they experience more symptoms and AEs compared to those with asthma or COPD alone[99,100]. Although definitions of ACO vary, a most typical presentation of ACO includes persistent bronchial obstruction in a COPD patient older than 40 years with either a previous history of asthma or large bronchodilator reversibility[101]. ACO includes two different conditions such as: a) asthma of smokers with airway remodeling and incomplete airflow reversibility, b) eosinophilic phenotype of COPD (ref.[102]). Compared to their counterparts with asthma or COPD alone, patients with ACO have significantly worse respiratory symptoms, poorer respiratory quality of life, and increased exacerbations' and hospital admissions' risk[103].

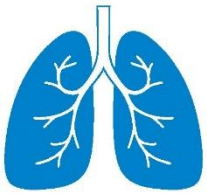
The simplified current Spanish Respiratory Society consensus defines ACO as: (a) the presence of chronic airflow limitation in a smoker or ex-smoker (more than 10 pack-years) patient ≥35 years old; (b) with current diagnosis of asthma; and/or (c) the presence of a strongly positive bronchodilator test (≥15% and ≥400 mL) or the presence of eosinophilia in peripheral blood (≥300 eosinophils/μL) (ref.[103-105]).

The Czech Pneumological and Phthiseological Society proposed the persistent presence of either two major criteria, or one major and two minor criteria that are typical for coexistence of both conditions in ACO. These approach is slightly more restrictive than the Spanish one, in order to increased specificity of ACO phenotypical label (Fig. 6) (ref.[75,106]).

8.5. BRONCHIECTASES WITH COPD OVERLAP

Parallel to COPD, a minority of patients suffer from bronchiectases (defined as an abnormal dilatation of the bronchi, usually in two or more pulmonary lobes, without any other known cause). Above that, bronchiectases may also develop during long-term course of COPD. The prevalence of bronchiectases in COPD patients increases with higher stage of the disease (highest prevalence is present in COPD stage 4).

BCO is associated with increased lung inflammation and worse lung function[107,108]. Bronchiectases should be considered in patients with COPD with greater severity of symptoms who often suffer from exacerbation or



Major criteria:
a) strongly positive bronchodilator test (change FEV_1 ≥ 15% and ≥ 400 ml)
b) history of bronchial asthma before 40 years established by physician
c) presence of eosinophilia in peripheral blood (≥ 300 eosinophils/μl)
d) sputum eosinophil count ≥ 3%
e) positivity of metacholine bronchial challenge test
f) increased FeNO (> 45–50 ppb) in the stable phase of COPD

Minor criteria:
a) mild positivity of bronchodilator test (change FEV_1 ≥ 12% and ≥ 200 ml)
b) history of atopy established by physician

Fig. 6. Asthma and COPD overlap (ACO) criteria.

repeated respiratory infections, especially in those who isolate *Pseudomonas aeruginosa* in sputum[109-112].

8.6. PHENOTYPE OF PULMONARY CACHEXIA

Approximately 5-10% of COPD patients (especially those with severe bronchial obstruction) display a tendency towards gradual, slow, and unintentional decrease in body weight and altered body composition (simplified criterion BMI <21), particularly in fat-free mass i.e. muscle tissue (decrease in fat-free mass index (FFMI) <16 kg/m^2 in men, <15 kg/m^2 in women) (ref.[62,113-118]). Pulmonary cachexia is associated with increased mortality risk among COPD patients[119].

8.7. COINCIDENCE/CO-PRESENCE OF MORE PHENOTYPES

Coincidence of two specific phenotypes: chronic bronchitis + frequent excerbator or BCO + frequent exacerbator are associated with a more negative influence of disease on patients quality of life and the course of the disease[77,87]. The most severe COPD patients with clinically balanced triple mixture of emphysematous + chronic bronchitic + frequent exacerbation phenotypes suffer from severe symptoms, poorer quality of life, sleep disturbances, and highest levels of depression and anxiety[92]. Co-presence of emphysema, cachexia and frequent exacerbations is associated with poorest patients' prognosis[120].

Table 2 gives an overview of those six elementary COPD phenotypical labels/treatable traits, which occasionally might occur simultaneously in real-life practice (e.g., emphysematous COPD + pulmonary cachexia, or bronchitic COPD and frequent exacerbator). All the above mentioned forms of COPD can move, usually after many years, towards the development of chronic respiratory failure (hypoxemic, and/or hypercapnic) which is often associated with pulmonary hypertension leading towards an overload or failure of the right ventricle. Individuals in an advanced stage of the disease are referred to as having terminal COPD.

COPD is often accompanied by other diseases or comorbidities: lung cancer, ischemic heart disease, lung fibrosis, pneumoconiosis, chronic heart failure, anxiety, depression, osteoporosis, anemia, peptic ulcer, gastroesophageal reflux disease and obstructive sleep apnoea[1,121,122].

9. COPD SCREENING IN THE CZECH REPUBLIC

Targeted early detection of still undiagnosed COPD subjects in the high risk (smokers or exsmokers) and symptomatic (at least one respiratory symptom) population is extremely effective[63,123-125].

Early detection programmes of various diseases are part of the Czech national general health priorities previously declared in the strategy "Health 2020 - the national strategy for health support and protection and for disease prevention". The National council for implementation and steering of programmes for early detection of diseases is the consultation authority of the Ministry of Health of the Czech Republic in this field. The programme for early detection of chronic obstructive pulmonary disease (COPD) was among others nominated by the National council for realization and received the necessary financial support.

The target population for this pilot project are "healthy persons" with pre-defined risk of COPD development, that means: history of cigarettes smoking (10 and more pack/years) and/or other inhaled risks, aged 40 - 69 years and with symptoms of breathlessness during common daily physical activities (faster walking, stairs climbing). Basic detection of persons at risk are provided by general practitions. Persons/smokers aged 40 - 69 years are actively contacted by their GP at any suitable occasion and are instructed and asked about their breathlessness. In case the patient fulfills the criteria of entering the program, he/she is referred to the cooperating pulmonologist. In the second step the pulmonologist instructs

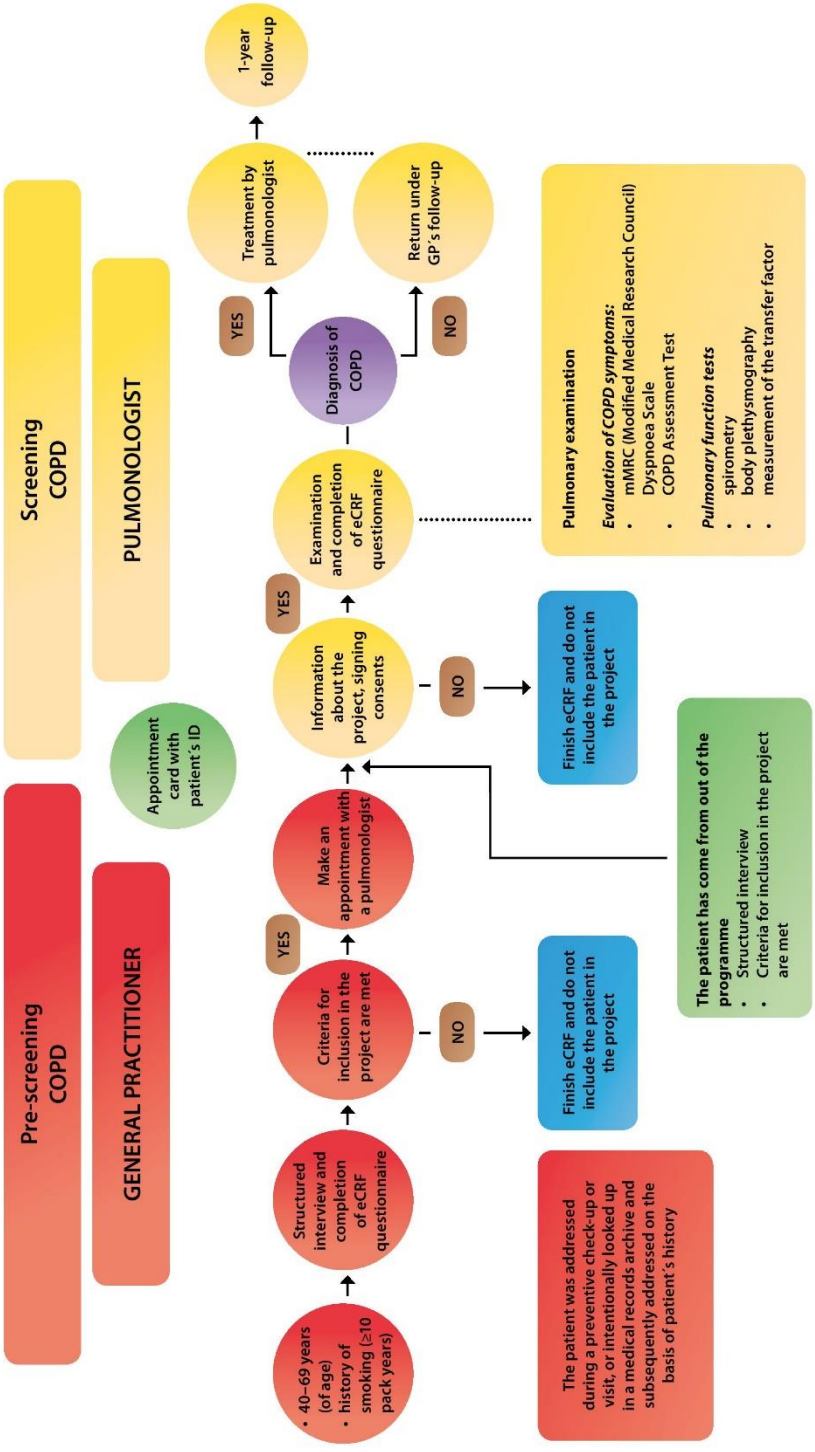


Fig. 7. The Czechia COPD screening programme in the high risk population – National Screening Centre.

Fig. 8. COPD management strategy.

the patient in detail, asks the patient for his/her written consent and evaluates the mMRC dyspnea scale and CAT questionnaire. Lung function tests are performed: post-bronchodilatory spirometry, bodyplethysmography and TL_{CO} assessement. As a result, a diagnosis of COPD can be established, together with deeper assessment of its impact on symptoms and lung function (Fig. 7).

10. TREATMENT

10.1. TREATMENT STRATEGY

Treatment of COPD should reflect the complexity and heterogeneity of the disease and be tailored to each individual patient[25]. The aim of COPD treatment is to reduce symptoms, frequency and severity of exacerbations and improve exercise tolerance, prognosis and both short-term (disease control) and long-term outcomes (reduction in risk).

Treatment of COPD includes pharmacological and non-pharmacological therapy. According to the "five-finger concept", the treatment strategy is divided into five areas/strata: (1) risk elimination, (2) basic treatment, (3) phenotype-specific treatment, (4) treatment of respiratory insufficiency and supportive care/end-of-life care, and (5) treatment of comorbidities (Fig. 8).

10.2. RISK ELIMINATION

Identification of risk factors and elimination/reduction of exposure is a fundamental part of COPD treatment. It is necessary for all patients with COPD, regardless of other therapy.

Smoking cessation

Current opinions: Smoking cessation remains the most effective intervention that reduces lung function decline, improves responses to bronchodilators and inhaled corticosteroids and reduces the incidence of acute exacerbations and bronchopulmonary infections. Therefore, effort toward smoking cessation or at least reduction of smoking exposure should be made as a first intervention in all patients with COPD. Importantly, smokers with COPD are more nicotine dependent than smokers without COPD and also depression in smokers with COPD is more frequent when compared to smokers without COPD. Smokers with COPD usually experience low degree of smoking cessation self-efficacy and also are less motivated to quit than smokers without COPD; both factors are associated with low quitting rates[126]. In a systematic review, average 12-months continuous abstinence rates for smokers with moderate-to-severe COPD were estimated at 1.4% after usual care, 2.6% after minimal counselling, 6.0% after intensive counselling and 12.3% after intensive counselling supported by pharmacotherapy[127]. Individual counselling should be offered by each pulmologist, intensive counselling plus pharmacotherapy can be provided by a pulmologist or by experts in Nicotine Treatment Centres, constituting a network across Czech Republic. Pharmacotherapy available in the Czech Republic includes nicotine replacement therapy, bupropion and varenicline. The use of E-cigarettes to aid smoking cessation remains controversial[1]. Further recommendations regarding smoking cessation are described in special guidelines[126].

Treatment recommendations of the expert group:

- Smoking cessation should be attempted in each patient.
- Psychosocial intervention should be supported by pharmacotherapy.

Environmental air pollution, occupational exposures

Current opinions: Urban air pollution contributes to the overall risk of COPD. Even more important is the role of urban air pollution as a trigger of exacerbations, particularly during seasonal worsening of urban and industrial air pollution. A specific case of environmental air pollution is passive exposure to tobacco smoke ("second hand smoking"), that may bring about respiratory symptoms and COPD exacerbation[128]. Occupational exposures, including organic and anorganic dusts, chemical agents and fumes are associated with increased risk of COPD development[1]. Elimination or reduction of exposure to occupational dusts and fumes, tobacco smoke and urban air pollutions are one of the first requirements of treatment regarding successful COPD treatment.

Treatment recommendation of the expert group:

- Elimination of all risk factors should be attempted in each COPD individual.

10.3. BASIC TREATMENT

Basic treatment of COPD is assigned for each patient with COPD as a fundamental treatment, regardless of their phenotype. Basic treatment should be started immediately after COPD is diagnosed. Basic treatment includes regular therapy by long-acting bronchodilators, symptoms-relieving treatment by short-acting bronchodilators, pulmonary rehabilitation, inhalation training, vaccination, appropriate nutrition and psychological and social support.

Long-acting bronchodilators

Current opinions: Long-acting bronchodilators should be used as the first pharmacologic step in the treatment of all patients with COPD with persistent symptoms and who require regular treatment. Long-acting bronchodilators can be divided in two groups: Long-Acting $Beta_2$-Agonists (LABA), i.e.drugs with $beta_2$ adrenergic effect (salmeterol, formoterol, olodaterol, vilanterol and indacaterol) and Long-Acting Muscarinic Antagonists (LAMA), i.e.drugs with anti-cholinergic effect (tiotropium, aclidinium, glycopyrronium, umeclidinium).

Most bronchodilators have a 12-hour duration of action and are administered twice daily, some have a 24-hour effect and can be administered once daily. Long-acting bronchodilators enable better control of symptoms, improve the quality of life, lung function and mortality and reduce the number of exacerbations and/or hospitalisations[129-133].

Pharmacological intervention with bronchodilator therapy is beneficial from early stages of COPD (ref.[131,132,134,135]). LAMA showed greater reduction of exacerbation rates than LABA (ref.[136,137]). LAMA improve the effect of pulmonary rehabilitation on exercise tolerance[138]. Combined treatment with LABA and LAMA has better effect on lung function, dyspnea and quality of life compared to monotherapy. Dual LABA and LAMA treatment can reduce number of exacerbations sligtly better that LAMA alone[134,135,139-141]. A number of different inhaler devices exist and the choice of inhaler device and dosage should be tailored to individual patient's needs and abilities. There are limited data regarding de-escalation from dual bronchodilators to monotherapy. The latest GOLD document suggested that if addition of a second long-acting bronchodilator does not improve symptoms, the treatment could be stepped down back to a single bronchodilator[1]. Similarly, a step down to monotherapy can be considered if the new component of dual bronchodilators is poorly tolerated or if serious new side effects occur.

Treatment recommendations of the expert group:

- Monotherapy with only LAMA or only LABA should be used in patients with lower degree of dyspnoea with mMRC 0-1 and less impaired lung function with FEV_1 >50%. If monoterapy is used, LAMA is preferred due to greater effect on reduction of exacerbation rates compared to LABA. One exception comes in patients with ACO where LABA is the preferable bronchodilator, usually combined with an inhaled corticosteroid (see below in Phenotype-specific treatment).
- Patients with more impaired lung function (FEV_1 ≤50%) and/or more symptomatic with mMRC ≥2 should be treated by dual bronchodilator therapy (LAMA and LABA). Combined treatment with LABA and LAMA can be administered using separate inhalers or by a single inhaler (fixed-dose LAMA/LABA). The choice of the optimal dual bronchodilator should depend on individual patient's needs and abilities.
- Patient on a LAMA or LABA monotherapy, with persistent dyspnoea or decline of lung function despite treatment, should step up to dual therapy. In case of dual therapy intolerance or if serious side effects occur, de-escalation to LAMA or LABA monotherapy can be considered. In such cases, a strict monitoring of patient is necessary and de-escalation is possible only if no worsening of symptoms, lung function decline and/or exacerbations occur.

Short-acting bronchodilators

Current opinions: Similarly to LABA and LAMA, short-acting bronchodilators include Short-Acting-Muscarinic Antagonists (SAMA) with an anti-cholinergic effect (ipratropium bromide), and Short-Acting $Beta_2$-Agonists (SABA): salbutamol, fenoterol and terbutaline. Both SAMA and SABA improve FEV_1, symptoms and exercise tolerance. Combined (fixed-dose) SAMA/SABA treatment is more effective in improving FEV_1 and symptoms compared to each monocomponent alone.

Treatment recommendations of the expert group:

- Short-acting bronchodilators should be used as an 'as-needed' treatment for occasional symptoms' relief. In most cases, they should not be used as regular treatment. SABA or/and SAMA can be added to basic treatment regardless of disease severity or COPD phenotype.
- Short-acting bronchodilators can be used as single therapy in patients without persistent symptoms, i.e., with FEV_1 ≥80%, mMRC 0 and CAT<10, who do not require regular treatment by long-acting bronchodilators.

Pulmonary rehabilitation

Current opinions: Pulmonary rehabilitation is an important part of standard non-pharmacological treatment, which includes patient education, physiotherapy, occupational therapy (focused on activities of daily living - ADL), nutritional and psychosocial support (Fig. 9) (ref.[142,143]). Physiotherapy consists of exercise training (endurance and strength) and techniques of respiratory physiotherapy. It is recommended that all patients with COPD

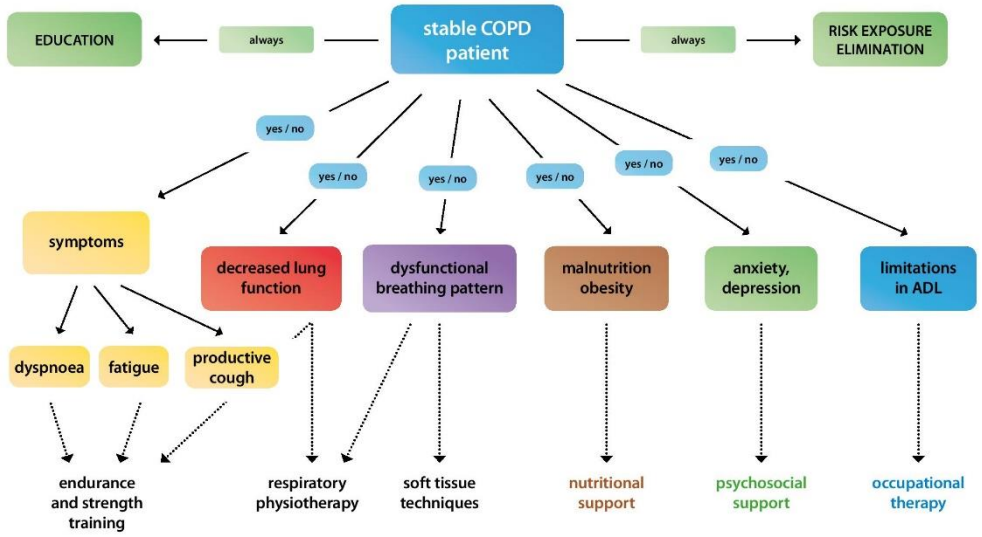


Fig. 9. Components of pulmonary rehabilitation in stable COPD.

who are symptomatic are involved in exercise training (3-5 times per week, 20-60 min, 6-8 weeks) regardless of lung function[144,145]. Training sessions should be supervised by a physiotherapist at least twice a week and the training sessions (1-3 times per week) can be performed either at the patient's home or at a community rehabilitation centre[63]. The respiratory physiotherapy techniques include reeducation of the breathing pattern, techniques of enhancing chest expansion, airway clearance techniques and ventilatory muscle training. It is very important to add other physiotherapeutic techniques to pulmonary rehabilitation treatment, if balance disorders, low back pain or stress incontinence is present (Fig. 10). These problems are more often present in patients with COPD compared to those who do not have this disease[146-149].

Treatment recommendation of the expert group:

- Pulmonary rehabilitation should be considered in each patient with symptomatic COPD regardless of disease severity or COPD phenotype.

Inhalation training

Current opinions: Inhaled medications are the cornerstone of COPD pharmacotherapy. Several types of inhalers are currently authorized and used in the treatment of COPD in the Czech Republic. The group of pressurized metered dose inhalers (pMDI group) included three types of inhalers: traditional pMDIs (aerosol), Easi-Breathe and Respimat (soft mist inhaler, SMI). They require slow and deep breathing in for at least 4 seconds and they are the method of choice for patients with low inspiratory flow. The dry powder inhalers (DPI group) comprise several types of inhalers: Handihaler, Aerolizer, Breezhaler, Diskus, Turbuhaler, Ellipta, Genuair, Twisthaler, Easyhaler or Spiromax[150-152].

Inhalator misuse is frequently observed among COPD individuals. The majority of COPD patients make mistakes, especially in the case of multiple inhalators in one patient. The inhaler technique should be checked (at least) annually by a pulmonary physician, physiotherapist, and/or respiratory nurse specialist.

Personalized training focused on all detected errors should be done subsequently by the same staff using the same instrument (Five Steps Assessment). Five Steps Assessment is available for free use at https://www.fnhk.cz/plic/aplikace-inhalacnich-leku-edukacni-videa/english-versions (animated version for patients) and the version for health-care professionals in an article by Vytrisalova et al. (Table 3) (ref.[150]).

Treatment recommendations of the expert group:

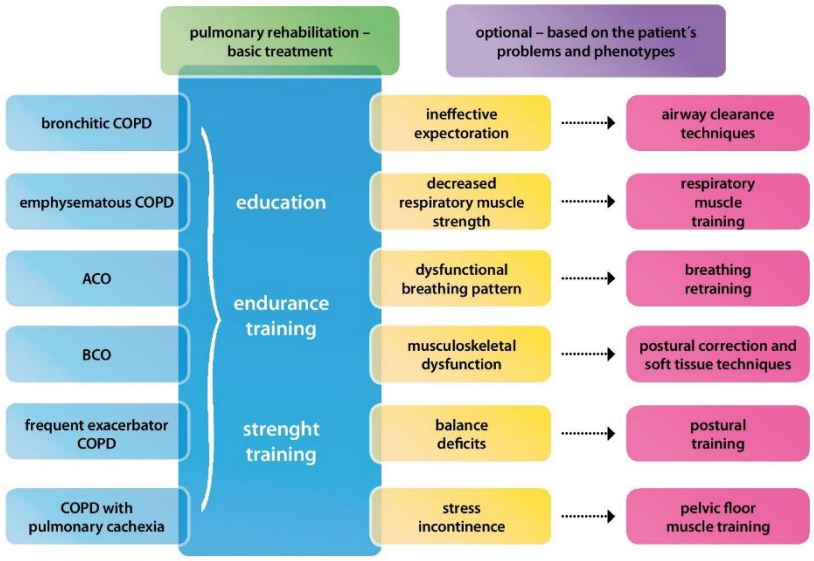
- We propose the use of a previously validated and published unique novel scoring instrument - Five Steps Assessment[150].

Vaccination

Current opinions: Influenza vaccination prevents influenza and reduces the risk of exacerbation and death in COPD patients. Pneumococcal vaccination is effective for prevention of community acquired pneumonia and invasive pneumococcal disease. Pertussis and diphtheria vaccine can also be considered.[1]

Treatment recommendations of the expert group:

- Influenza and COVID-19 vaccination is recommended in patients with COPD, particularly in the elderly.



Legend: COPD – chronic obstructive pulmonary disease; ACO – asthma/COPD overlap; BCO – bronchiectases and COPD overlap

Fig. 10. Phenotypically targeted physiotherapy.

- Pneumococcal vaccination is recommended for all patients older than 65 years and for younger COPD patients with more impaired lung function and/or with comorbidities, especially cardiovascular diseases[1,153].

Appropriate nutrition

Current opinions: Malnutrition is an important and complex problem associated with COPD. The exact causal links between malnutrition and COPD are difficult to establish. Malnutrition can be the consequence of COPD severity, systemic inflammation, hypoxia and alterations of metabolism. On the other hand, malnutrition can result in respiratory muscle wasting and other features of COPD. Risk of malnutrition is estimated at 30-60% in hospitalized patients[154]. Basic assessment of nutritional status can be provided by Body Mass Index (BMI) and Fat-Free Mass Index (FFMI) assessment. FFMI can be measured by skinfold calipers, densitometry or with the use of bioelectric impedance. Dual-energy X-ray absorptiometry (DEXA) is appropriate for combined screening of osteoporosis, fat-free mass (FFM) and fat mass. Patients with COPD and lower BMI have higher mortality risk than patients with slightly higher BMI. The prevalence of underweight in COPD increases with disease severity and is associated with the presence of emphysema. Low FFMI (less than 10%), irrespective of BMI and fat mass, is associated with higher mortality[155]. Sarcopenia is characterised by low Skeletal Muscle Index (SMI) and leads to skeletal muscle weakness, particularly in older and/or overweight patients. Skeletal muscle index can be assessed by DEXA, magnetic resonance imaging and can be estimated by anthropometry including skinfold calipers measurement[156,157].

Patients with COPD express various nutritional phenotypes associated with different clinical outcomes. Patients with obesity (BMI 30-35 kg/m^2) have increased cardiovascular risk, patients with morbid obesity (BMI >35 kg/m^2) and with sarcopenic obesity (BMI 30-35 kg/m^2 and SMI <2) furthermore have impaired physical performance. Patients with sarcopenia (SMI <2), cachexia (FFMI <16 kg/m^2 in males or FFMI <15 kg/m^2 in females) have impaired physical performance and increased mortality risk. Furthermore, malnutrition is associated with loss of mineral density, fat loss, muscle loss, or conversely with adiposity and obesity[155].

This position paper defines the specific „pulmonary cachexia phenotype" of COPD, defined as cachexia in patients with advanced COPD inexplicable by other causes. Pulmonary cachexia phenotype incorporates patients with COPD and body mass loss, fat loss, muscle loss and/or loss of mineral density. Pulmonary cachexia phenotype is considered an independent risk factor of mortality in COPD patients[158].

Dietary management includes several therapeutic interventions. Patients with pulmonary cachexia should have nutritional supplementation. The diet should contain sufficient energetic value, be rich in proteins and be eaten in several small portions split throughout the whole day. The quality of fats should be considered. Oral nutritional supplements can be used if normal food and drink is insufficient for nutritional requirements. Counselling with a dietary specialist can be beneficial. Nutritional supple-

Table 3. Correct application technique (Five Steps Assessment system) used to initial education and regular check-up (ref. [150]).

5 easy universal steps to correct application technique include:
1st step: remove the mouthpiece cover from inhaler (aerosol), turn the clear base until it clicks (soft mist inhaler) or another type of initial inhaler activation (more in video – see bellow)
2nd step: prepare dose of drug (for example insert a capsule into chamber, press the button, etc.) and hold device in the correct position (some of new inhalers have associated 1st step and 2nd step together)
3rd step: breath in and out and finally full and slow exhalation (exhale slowly all the air from the chest)
4th step: inhale the drug (slowly + smoothly during 4–5 seconds in case of pressurized metered dose inhaler or soft mist inhaler, quickly in dry powder inhalers)
5th step: take your inhaler device out of your mouth and hold your breath for several seconds and then breathe out slowly

Educational video available at: https://www.fnhk.cz/plic/aplikace-inhalacnich-leku-edukacni-videa/english-versions

mentation should be complemented by pulmonary rehabilitation programme including exercise training. Because of reported vitamin D deficiency and insufficient intake of vitamins with antioxidant capacity (vitamins A, C and E) in COPD, supplementation of vitamin D and other vitamins should be considered[155]. A three-month intervention combining nutritional support, pulmonary rehabilitation and oral administration of testosterone in malnourished patients with chronic respiratory failure on LTOT has been reported previously[159]. This multimodal intervention resulted in increased BMI and FFMI and was associated with better muscle functioning, higher quality of life and increased rate of 15-month survival[159].

Treatment recommendations of the expert group:
- Not only lower BMI, but also sarcopenia and other features of malnutrition should be sought after.
- Nutritional supplementation combined with pulmonary rehabilitation and further modalities should be used in cachectic COPD patients.
- On the other hand, adiposity should be managed by controlled weight reduction, particularly if the adiposity has clinical relevance.

Education

Current opinions: Topics of education include smoking cessation, correct inhalation technique, early recognition of exacerbation, treatment adherence, nutrition, physical activity, correct decision-making and others[1,160]. Education can be a component of pulmonary rehabilitation. Patients instructed about the nature of COPD and the implications of therapy can better understand, recognize, and treat the symptoms of their disease. Longer-lasting self-management strategies are recommended for clinical practice rather than brief interventions[161].

Treatment recommendation of the expert group:
- All patients should receive adequate education to improve COPD self-management.

Psychological and social support

Current opinions: Severe COPD is a risk factor for the development of anxiety and depression. Patients with depression are more likely smokers and find smoking cessation more difficult. On the other hand, smokers are more likely to be depressed, that may be the result of nicotinic acetylcholine receptors' activation[162]. Furthemore, patients with severe COPD and dyspnea often reduce their physical activity, leading to progressive decondition. Depression and decondition may result in decreased participation in social activities, often including sexual activity. Pulmonary rehabilitation improves depression and should be used as first-line treatment of depression.

Treatment recommendations of the expert group:
- If necessary, psychological counselling and/or psychological therapies and/or pharmacotherapy should be used.
- Psychological counselling can also be beneficial as part of smoking cessation efforts.

10.4. PHENOTYPE-SPECIFIC TREATMENT

Patients with an expressed clinical phenotype should receive adequate phenotype-specific treatment. Patient with COPD can have none, one or multiple concurrent clinical phenotypes, that can overlap. Clinical phenotypes in this concept can be understood as treatable traits. Phenotype-specific treatment is assigned to each clinical phenotype. Patients with an overlap of ≥2 clinical phenotypes should receive combined treatment targeted on all present phenotypic labels.

10.4.1. FREQUENT EXACERBATOR PHENOTYPE

Patients with frequent exacerbations (≥2 during last year) despite optimal bronchodilator treatment should receive inhaled corticosteroids, phosphodiesterase-4 inhibitors, mucoactive drugs, selected antibiotics or combination of these drug regimens.

Inhaled corticosteroids (ICS)

Current opinions: ICS monotherapy does not reduce mortality and has no effect on lung function decline[132,163].

ICS in combination with bronchodilators reduced the exacerbation rate, particularly in patients with previous history of exacerbations[132]. The effect of ICS on reducing exacerbations is higher in patients with higher blood eosinophil count and seems to be lower in patients with lower blood eosinophil count[164,165].

Chronic use of ICS in COPD can be associated with adverse effects, particularly pneumonia, but also oral candidiasis, dysphonia, hematomas, skin bruising and reduction in bone mineral density. Greater risk of pneumonia has been found in patients treated by fluticasone furoate and in current smokers, patients with lower BMI and previous history of pneumonia. Withdrawal of ICS in low risk COPD patients was not associated with increase in exacerbation rate[166].

Withdrawal of inhaled corticosteroids in COPD patients using triple therapy (ICS+LABA+LAMA) did not result in higher risk of exacerbations and led only to a small decrease in lung function, regardless of exacerbation history[167,168]. However, patients without an exacerbation history and with a blood eosinophil count ≥300 cells/μL experienced increased risk of exacerbations after ICS withdrawal[168]. A recommendation regarding ICS withdrawal is described in a recent European Respiratory Society guideline[169].

Treatment recommendations of the expert group:

- ICS should be used in patients with frequent exacerbations and higher blood eosinophil count in the peripheral blood, either in stable phase or during COPD exacerbation.
- ICS should also be used in patients with frequent exacerbations and asthma-COPD overlap.
- ICS should be used in combination with long-acting bronchodilator therapy (i.e., added to basic treatment), usually as combination ICS+LABA or ICS+LABA+LAMA. ICS monotherapy is not recommended.
- ICS should be used with precaution and treatment should be reconsidered in patients with frequent exacerbations and lower blood eosinophil count, prior history of pneumonia and lower BMI, especially in patients with emphysematic and/or cachectic phenotype.
- In patients with low exacerbation rate (0-1 exacerbation/last year) with lower blood eosinophil count in peripheral blood, withdrawal of ICS may be considered.
- Cut-off value for high blood eosinophil count in peripheral blood is ≥300 cells/μL, cut-off value for low blood eosinophil count is <100 cells/μL. Blood eosinophil count between 100 and 300 cells/μL is considered grey zone; in these patients, blood eosinophil count assessement should be repeated and individual risks and benefits regarding ICS use should be considered.

Phosphodiesterase-4 inhibitors (PDE4 inhibitors)

Current opinions: Roflumilast is a once daily oral anti-inflammatory drug that reduces neutrophilic inflammation in the airways due to inhibition of intracellular cAMP degradation and subsequent effect on inflammatory cytokines and mediators[170]. Roflumilast reduces exacerbation rates in patients with severe and very severe COPD with chronic cough and sputum production, and with history of exacerbations[171]. Despite roflumilast has no direct bronchodilator activity, an add-on to LABA or LAMA improves lung function more than bronchodilators alone[171,172]. Roflumilast reduces exacerbations also in patients with chronic bronchitis[173]. Roflumilast can affect different types and isoforms of the PDE4 family of enzymes[170,174]. Therefore, roflumilast has more adverse events[170], the most common including diarrhoea, nausea, weight loss, sleep disturbance, headache, loss of appetite or impairment of preexisting depression. Adverse events ussually appear at roflumilast treatment initiation and may result in treatment discontinuation. On the other hand, adverse events can sometimes be prevented through intermittent administration of the drug at treatment initiation.

Treatment recommendations of the expert group:

- Roflumilast can be used in patients with frequent exacerbations and bronchitic phenotype. Particularly, roflumilast should be considered in patients with combination of these two phenotypes and severe airflow limitation and/or exacerbation history despite ICS+LABA treatment.
- Lower blood eosinophil count and/or higher neutrophilia can support the use of roflumilast in these patients, especially if a history of pneumonia is present.
- Roflumilast should not be used concurrently with theophylline and in patients with depression or pulmonary cachexia.
- In patients with adverse events, intermittent administration of the drug at treatment initiation can be considered.

Mucoactive drugs containing thiol group

Current opinions: Erdosteine and N-acetylcysteine are thiol-based mucoactive drugs. Both substances have mucomodulatory and antioxidant effect. Erdosteine reduces both the rate and duration of exacerbations in patients with COPD (ref.[175]). The most pronounced effect of erdosteine on exacerbation rate and duration was observed in patients with milder airflow obstruction. Erdosteine's effects on exacerbations are not substantially influenced by blood eosinophil count[176]. High doses of N-acetylcysteine reduced the number of COPD exacerbations per patient-year, but not the proportion of patients who remained exacerbation-free[6]. Mucolytics are well tolerated and safe drugs with rare adverse events.

Treatment recommendations of the expert group:

- Long-term treatment with thiol-based mucoactive drugs (erdosteine or N-acetylcysteine) should be used in patients with frequent exacerbations, BCO and bronchitic phenotype.
- Furthermore, they can be used as add-on therapy in patients with exacerbation phenotype without chronic

bronchitis, particularly in patients with early stages of COPD with less severe airway obstruction.
- Combination with other phenotype-specific drugs in frequent exacerbators (ICS, roflumilast) is possible and may be beneficial.

Long-term antibiotic treatment

Current opinions: Long-term azithromycin therapy significantly reduced the number of exacerbations[177], but was associated with increased bacterial resistance to macrolides and with adverse events, such as hearing loss and QT-interval prolongantion[178]. Similarly, intermittent treatment with fluoroquinolones (moxifloxacin 400 mg daily for 5 days every 2 months for 1 year) significantly reduced exacerbation rates in patients with purulent sputum production, but similarly was associated with bacterial resistance and with adverse events. The Spanish guidelines recommend long-term use of macrolides in patients with severe COPD and with at least 3 exacerbations in the previous year. The treatment should be administered in reference centers due to the need of strict monitoring of adverse effects and developments of antibiotic resistance[3].

Treatment recommendations of the expert group:
- Long-term antibiotic treatment (macrolides, fluoroquinolones) is reserved as special treatment for severe or very severe COPD patients with frequent bacterial exacerbations despite all usual therapy.
- Long-term antibiotic treatment may also be considered in COPD patients with frequent exacerbations and bronchiectases.
- The treatment should be administered in tertiary care centers and with precaution to all possible adverse effects and microbial resistances development.

10.4.2. BRONCHITIC PHENOTYPE

Mucoactive drugs containing thiol group

Current opinions: Basic characteristics of erdosteine and N-acetylcysteine are listed in the section describing treatment of frequent exacerbation phenotype. Above that, erdosteine and other thiol-based mucoactive drugs have antioxidant and antiinflammatory effect that improves symptoms of chronic bronchitis[179]. Chronic bronchitis phenotype is associated with higher risk of exacerbation and mortality[180]. Therefore, reduction of exacerbations with thiol-based mucoactive drugs treatment is beneficial[175,181].

Treatment recommendations of the expert group:
- Long-term treatment with thiol-based mucoactive drugs should be used in patients with bronchitic phenotype, with or without history of exacerbation.
- Mucoactive drug therapy may be beneficial for patients with mild or moderate COPD as an early intervention approach[182].
- The treatment can be adjusted to symptoms of chronic bronchitis (for example, erdostein twice daily during marked sputum production, or in contrast, interruption of mucoactive treatment when there is no cough and sputum).

Phosphodiesterase-4 inhibitors (PDE4 inhibitors)

Current opinions: General characteristics of roflumilast are presented in the section describing the treatment of frequent exacerbation phenotype. Anti-inflammatory effect of roflumilast on neutrophilic inflammation in the airways and beneficial effect on lung function can be a rationale for roflumilast use in patients with bronchitic phenotype, especially if frequent bacterial exacerbations are present[172].

Treatment recommendations of the expert group:
- Roflumilast can be used in patients with bronchitic phenotype of COPD, especially in patients with more severe stages of the disease, with a history of bacterial exacerbation or pneumonia.
- Higher neutrophils count (in airways and/or peripheral blood) supports the use of roflumilast.
- Roflumilast can be used in combination with thiol-based mucoactive drugs in patients with bronchitic phenotype.
- Roflumilast should be avoided in patients with pulmonary cachexia phenotype. Further limitations of roflumilast are presented in the section describing treatment of the frequent exacerbation phenotype.

Pulmonary rehabilitation

Current opinions: Airway clearance techniques improve mucus clearance and reduce airways inflammation.

Treatment recommendation of the expert group:
- Pulmonary rehabilitation and regular aerobic exercise should be routine part of treatment in patients with bronchitic phenotype as a tool to reduce symptoms and exacerbation rates.

10.4.3. EMPHYSEMATOUS PHENOTYPE

The main goals of therapy in patients with pulmonary emphysema are improvements of dyspnoea, respiratory mechanics, respiratory muscle strength, and reversal of macroscopic structural changes with the use of volume reduction procedures.

Methylxanthines

Current opinions: Theophylline is the only methylxanthine available for use in the Czech Republic. Theophylline improves dyspnea, especially when added to LABA (ref.[183,184]). Theophylline has a modest bronchodilator effect, enhanced in combination with LABA (ref.[184,185]). Theophylline is able to increase diaphragmatic muscle strength, reduce gas trapping and improve the mucociliary clearance[185]. Although the role of theophylline in the general COPD population is considered controversial[1], the mentioned features of theophylline allow to

expect its benefit in management of patients with emphysema. The role of theophylline in prevention of exacerbations has not been documented[186]. Theophylline has a narrow therapeutic range and frequent adverse effects. Theophylline is metabolized via cytochrome P450 1A2, therefore an interaction with other drugs may occur.

Treatment recommendations of the expert group:

- Theophylline should be used as phenotype-specific treatment in emphysematous phenotype of COPD.
- During long-term treatment, patient should be carefully monitored by a physician, including monitoring of adverse effects, plasma concentrations of theophylline and possible interactions with other drugs.

Pulmonary rehabilitation

Treatment recommendation of the expert group:

- Respiratory muscle training can improve the descreased respiratory muscle strength and should be used in patients with emphysematous phenotype.

Non-pharmacological treatment

Current opinions: Non-pharmacological therapeutic interventions in patients with advanced pulmonary emphysema include bronchoscopic lung volume reduction (BLVR) and lung volume reduction surgery (LVRS). BLVR procedures include endobronchial valves (EBV) and coils placement. Both valves and coils can be used in patients with severe hyperinflation, severe emphysema and absent airway disease (asthma, chronic bronchitis, bronchiectases) (Table 4) (ref.[187]).

Targeted implantation of endobronchial one-way valves into the airways of an isolated emphysematous lobe appears to be one of the most promising innovations[188-190]. After a valve placement, FEV_1 and walking distance (6MWT) should improve. The efficacy of valve placement depends on the presence of interlobar collateral ventilation. Major complications following a valve placement include COPD exacerbations, hemoptysis, valve migration, and pneumothorax[187,191].

Endobronchial coils can be used in patients with heterogeneous as well as homogeneous emphysema, independently on interlobar collateral ventilation[187]. The implantation of coils is usually permanent, only one or two coils can be removed. After a coil treatment, FEV_1 and walking distance (6MWT) should improve. Reported complications of the coil procedure include COPD exacerbations, hemoptysis, transient chest pain, pneumonia, pneumothorax, and noninfectious coil-associated opacities[187].

Further endoscopic lung volume reduction procedures include bronchoscopic thermal vapour ablation, biologi-

Table 4. Eligibility criteria for EBV, LVRS or bullectomy.

	EBV	LVRS	BULLECTOMY
Clinical characteristic	Dyspnoea (mMRC score ≥ 2)	Dyspnoea (mMRC score ≥ 2)	Dyspnoea (mMRC score ≥ 2)
		Low fitness	
	Stable prior to procedure	Stable prior to procedure	Stable prior to procedure
Chest HRCT	Heterogeneous emphysema (upper or lower lobe predominance)	Heterogeneous emphysema (upper lobe predominance)	Impairment of > 1/3 of affected hemithorax
	No collateral ventilation in the targeted lobe		Radiographic evidence of compressed lung
RV	> 175% of predicted value	> 175% of predicted value	
FEV_1	15–50% of predicted value	15–50% of predicted value	
TLco (DLco)	> 15–20% of predicted value	> 20% of predcited value	
$PaCO_2$	No hypercapnia	No hypercapnia	No hypercapnia
History	No severe pulmonary comorbidity	No severe pulmonary comorbidity	No severe pulmonary comorbidity
	Able to undergo sedation or general anesthesia	Able to undergo general anesthesia	Able to undergo general anesthesia
Smoking	Smoking cessation	Smoking cessation	Smoking cessation

(ref. [187-190, 194, 196-199]).
Abbreviations: EBV – endobronchial valve, FEV1 – forced expiratory volume in 1 second, HRCT – high resolution computer tomography, LVRS – lung volume reduction surgery, RV – residual volume, TLco – tranferfactor.

cal lung volume reduction (using the lung sealant system), or airway bypass stent[187,191-193].

Surgical methods (LVRS or bullectomy) are less frequently used compared to BLVR. LVRS should be considered in patients with upper-lobe predominant distribution of emphysema. LVRS in well-selected patients improved symptoms, dynamic hyperinflation, cardiopulmonary mechanics, exercise capacity, exacerbation rate and mortality[191,194-196].

Plasmatic levels of alpha-1 antitrypsin should be examined in each patient with COPD, especially with emphysematous phenotype in order to identify patients with severe forms of alpha-1 antitrypsin deficiency[47].

Treatment recommendations of the expert group:

- In patients with the large bullous type of emphysema, endoscopic or surgical volume reduction procedures should be considered in specialized tertiary care centers.
- Targeted implantation of endobronchial one-way valves (EBV) should be considered in patients with isolated emphysematous lobes.
- LVRS or bullectomy should be considered in patients with predominant upper-lobe distribution of emphysema, and low pre-procedure exercise capacity.
- Patients with alpha-1 antitrypsin deficiency should be referred to the specialized Center for treatment of alpha-1 antitrypsin deficiency (Thomayer Hospital, Prague) to consider alpha-1 antitrypsin augmentation therapy.

10.4.4. ASTHMA-COPD OVERLAP (ACO)

Patients with overlap of COPD and asthma (ACO) usually have a combination of symptoms of both diseases and some degree of eosinophilic inflammation in airways. Therefore, treatment of all patients with ACO phenotype should include inhaled corticosteroid, as phenotypical-specific treatment added to basic treatment with bronchodilators.

Inhaled corticosteroids(ICS) in combination with bronchodilators

Current opinions: The first option of phenotype-specific treatment of ACO is combination ICS+LABA. Similarly to asthma strategies, the dose of ICS should be set to the minimum dose necessary for disease control maintenance. Triple therapy ICS+LABA+LAMA should be used, if dual combination LABA+LAMA as basic treatment is necessary and ICS as phenotype-specific treatment is added-on or if ICS+LABA as phenotype-specific treatment is insufficient to achieve satisfactory disease control.

Treatment recommendations of the expert group:

- Combination of ICS+LABA should be used in patients with ACO.
- Triple therapy ICS+LABA+LAMA should be used if dual combination LABA+LAMA as basic treatment is necessary or if only ICS+LABA combination is insufficient to achieve satisfactory disease control.

Leukotriene receptor antagonists (antileukotrienes)

Current opinions: There is no evidence supporting the use of antileukotrienes in COPD. Antileukotrienes had no effect on lung funcion decline in a non-selected COPD population[200]. However, during long-term montelukast treatment in moderate-to-severe COPD patients, significant improvement of disease symptoms, reduction in ICS and inhaled bronchodilators' need as well as reduction in emergency department referrals and hospitalizations was observed, though no changes in FEV_1 were recorded[201]. These data can a be rationale for antileukotrienes' use in selected patients with ACO.

Treatment recommendation of the expert group:

- Leukotriene receptor antagonists can be considered in patients with ACO phenotype if allergic feature of asthmatic component is present and ICS+bronchodilator combination is not sufficient to achieve satisfactory control of the disease.

10.4.5. BRONCHIECTASES WITH COPD OVERLAP (BCO)

Mucoactive drugs containing thiol group

Current opinions: Basic characteristics of thiol-based mucoactive drugs are presented in the section describing the treatment of frequent exacerbation phenotype. Importantly, erdosteine has an antibacterial effect due to inhibition of bacterial adhesiveness. Erdosteine also increases antibiotic concentrations in the airway mucus[202]. Mucoactive drugs are recommended in patients with bronchiectasis and difficult expectoration[203].

Treatment recommendation of the expert group:

- Long-term erdosteine or other mucoactive drug (N-acetylcysteine) treatment should be used in patients with bronchiectases and COPD overlap phenotype.

Phosphodiesterase-4 inhibitors (PDE4 inhibitors)

Current opinions: General characteristics of roflumilast are presented in the section describing the treatment of frequent exacerbation phenotype. Data regarding effect of roflumilast in patients with bronchiectases or BCO are lacking. However, roflumilast inhibits neutrophilic airway inflammation in COPD and prevents exacerbations in COPD with chronic bronchitis. Neutrophils are the prominent cell type involved in pathogenesis of both bronchiectases and COPD (ref.[204]). This could be a rationale for roflumilast use in patients with COPD and bronchiectases.

Treatment recommendations of the expert group:
- Treatment with roflumilast can be considered as complemetary treatment in patients with BCO, especially if excessive sputum production and/or frequent exacerbations are present.
- The effect of roflumilast treatment should be evaluated and treatment with roflumilast should be continued only if it's beneficial.
- Limitations of roflumilast treatment are presented in the section describing the treatment of frequent exacerbation phenotype.

Antibiotics

Current opinions: Recent European guidelines recommend long-term treatment by inhaled antibiotics (colistin or gentamicin) as first-line treatment in patients with bronchiectases experiencing exacerbations and/or chronic *Pseudomonas aeruginosa* airway colonisation. The same guidelines support chronic macrolide therapy as a second-line treatment in selected patients with bronchiectases[203,204].

Treatment recommendation of the expert group:
- Chronic antibiotic treatment (or inhaled antibiotics) should follow the bronchiectases treatment guidelines, as mentioned above.

Pulmonary rehabilitation

Current opinions: Pulmonary rehabilitation improves exercise capacity and reduces exacerbation rates in patients with bronchiectases. Airway clearance techniques improve mucus clearance and airways inflammation. The ERS guidelines recommend pulmonary rehabilitation programme and regular aerobic exercise as tools to reduce exacerbation rates.

Treatment recommendation of the expert group:
- Pulmonary rehabilitation and airway clearance techniques should be routine part of treatment in patients with BCO.

Other treatments

Current opinions: There is interest in immunostimulating agents. These drugs consist of antigens of several bacterial strains and are designed to stimulate the immune response (for example Broncho-Vaxom). These agents reduced exacerbation rates in COPD patients. Novel treatments are under investigation, for example neutrophil elastase inhibitors or CXC chemokine receptor 2 antagonist CXCR2 (ref.[205]).

Treatment recommendation of the expert group:
- Immunostimulating agents can be considered as complemetary treatment in patients with BCO.

10.4.6. PHENOTYPE OF PULMONARY CACHEXIA

COPD patients with pulmonary cachexia should receive rigorous nutritional support, pulmonary rehabilitation and psychosocial support[206]. Since pulmonary cachexia more frequently occurs with advanced-stage COPD, treatment of respiratory insufficiency and supportive treatment may be necessary. If patients with pulmonary cachexia experience frequent bacterial exacerbations and/or bronchiectases, long-term antibiotic treatment should be considered. Roflumilast treatment should be avoided.

Treatment recommendations of the expert group:
- Nutritional support, complex pulmonary rehabilitation and supportive care should be used to revert poor prognosis of cachectic patients.
- Long-term antibiotic treatment is recommended if frequent bacterial exacerbations and/or bronchiectases are co-present with cachexia.

10.4.7. MULTIPLE PHENOTYPES' CO-PRESENCE

If more than one clinical phenotype is present, treatment strategy should follow the expression of each clinical phenotype separately. In such patients, multicomponental therapeutic regimens are required, often resulting in a fully individualized care.

10.5. TREATMENT OF RESPIRATORY FAILURE, LUNG TRANSPLANTATION AND PALLIATIVE CARE (END-OF LIFE CARE)

Long-term oxygen therapy

Current opinions: Long-term oxygen therapy (LTOT) for patients with COPD and chronic respiratory failure improves symptoms, exercise capacity, cognitive function, quality of life and hospitalisation rates. The effect of LTOT on mortality risk remains controversial[207,208]. Criteria for LTOT in the Czech Republic are: respiratory failure with resting p_aO_2 <7.3 kPa, or p_aO_2 between 7.3 and 8.0 kPa and at least one of four further criteria, i.e., pulmonary hypertension or secondary polyglobulia or arterial oxygen desaturation less than 90% during at least 30% time of sleep or exercise-induced arterial oxygen desaturation. Smoking abstinence is necessary. Possible sources of oxygen for LTOT include oxygen concentrator, portable oxygen concentrator or liquid oxygen. Oxygen should be administered for ≥16 h daily. Further indications for oxygen supplementation in COPD include nocturnal hypoxemia, oxygen administration during exercise or during airflight. If hypoxemia with hypercapnia is present, non-invasive ventilation should be considered[209].

Treatment recommendation of the expert group:
- LTOT should be considered in severe chronic hypoxemia (p_aO_2 <7.3 kPa) or in moderate hypoxemia coinciding with pulmonary hypertension, polyglobulia,

oxygen desaturation <90% during at least 30% time of sleep or exercise-induced arterial oxygen desaturation.

Domiciliary non-invasive ventilation

Current opinions: The use of long-term domiciliary non-invasive ventilation therapy (dNIV) is the method of choice in stable COPD patients with chronic hypercapnic respiratory failure (indication criteria are listed in Table 5), most frequently in patients with COPD stage/group 4/D. In many cases, there is need to combine dNIV and long-term oxygen therapy (LTOT).

Best clinical outcomes were observed with dNIV preset to achieve the physiological goal of maximal $PaCO_2$ reduction[210,211]. This dNIV concept, the so-called high-intensity NIV (HINIV), commonly uses high inspiratory pressures (20-40 mbar, according to patient's tolerance) at the respiratory rate that approaches the spontaneous rate of the patient. Expiratory pressure is usually preset low (3-6 mbar), unless there is need to compensate obstructive sleep apnea (OSA) (ref.[212,213]). OSA is a common condition and increases mortality in COPD patients[214]. We therefore recommend polygraphy prior to dNIV initiation[214].

In stable hypercapnic COPD patients HINIV treatment resulted in lower mortality risk, improvement in blood gases, lung function and quality of life (QoL) and enhanced effect of pulmonary rehabilitation[210,212,215-217]. While dNIV has no proven benefit in patients after acute hypercapnic COPD exacerbation when hypercapnia resolves[218], dNIV added to LTOT reduced risk of readmission or death when hypercapnia ($PaCO_2$ >7.0 kPa) persisted for at least 14 days after resolution of acute respiratory acidosis[219].

Treatment recommendation of the expert group:

- dNIV should be considered in hypercapnic COPD individuals; exact indications are summarized in Table 5.

Lung transplantation

Current opinions: COPD is one of the most frequent reasons for lung transplantation. Lung transplantation improves health status and functional capacity[1]. The majority of lung transplants in patients with COPD are bilateral lung transplantations. Of 19,135 lung transplantations for COPD performed worldwide between January 1992 and June 2017, the median survival was 7 years in patients receiving bilateral lung transplant and 5 years in patients receiving single lung transplant, respectively[220].

Lung transplantation should be considered in patients with very severe COPD with failing conservative treatment. In the Czech Republic, patients with COPD should be referred to the Czech Lung Transplantation Center once fulfilling these criteria: (1) progression of COPD despite maximal treatment including pharmacotherapy, pulmonary rehabilitation and LTOT, (2) BODE score ≥5, (3) $PaCO_2$ >6.6 kPa and/or PaO_2 <8 kPa, (4) FEV_1 <25% of predicted values.

Contraindications for lung transplantation include history of malignancy in the last 5 years, poorly controlled disease/dysfunction of another major organ system (e.g. heart, liver, kidney, brain), ischemic heart disease not amenable to revascularization, acute instability (including but not limited to acute sepsis, myocardial infarction or liver failure), uncorrectable bleeding disorder, poorly controlled chronic infection by virulent and/or resistant microbe, active tuberculosis, significant chest wall or spinal deformity, obesity with BMI >35 kg/m^2, psychiatric disorders, patient's non-adherence to treatment, patient's inadequate social support, functional limitation with inability to participate in a rehabilitation program, a history of drug abuse or dependence (e.g., alcohol, tobacco, marijuana, or other illicit substances) (ref.[221,222]).

Eligible patients are placed on the lung transplant waiting list once fulfilling at least one of the following criteria: (1) BODE score ≥7, (2) FEV_1 <15-20% of predicted values, (3) history of ≥3 severe exacerbations during last year, (4) history of at least one severe exacerbation with hypercapnic respiratory failure, (5) moderate to severe pulmonary hypertension. LVRS can be performed in selected patients prior to lung transplantation.

Treatment recommendation of the expert group:

- Patients with very severe COPD eligible for a lung transplant (criteria see above) should be referred to the Czech Lung Transplantation Center, University Hospital Motol, Prague.

Table 5. Indication for use of domiciliary non-invasive ventilation in COPD patients.

dNIV is indicated for stable COPD patients in presence of at least one of the following criteria:
Symptomatic daytime hypercapnia ($PaCO_2$ ≥ 6.5 kPa)
Nocturnal hypercapnia ($PaCO_2$ ≥ 7.3 kPa)*
Mild daytime hypercapnia ($PaCO_2$ 6.0–6.5 kPa) with nocturnal increase ≥ 1.3 kPa*
Persistent hypercapnia ($PaCO_2$ > 7.0 kPa) for at least 14 days after finishing acute ventilation therapy for acute respiratory acidosis
Hypercapnia increase ≥ 1.0 kPa after oxygen inhalation and concurrently exceeding $PaCO_2$ ≥ 6.0 kPa#

Legend:
$PaCO_2$ – partial pressure of carbon dioxide in arterial blood
kPa – kiloPascal
* measured by transcutaneous capnometry (or blood gases analysis at awakening)
# i.e., hypercapnia increase contraindicating LTOT indication

Palliative and end-of-life care

Current opinions: Patients with advanced-stage (end-stage) COPD should receive palliative care, that should prevent and relieve their suffering. Adequate communication or/and psychological care for patients and their families may be necessary. However, mortality risk prediction may be challenging in patients with severe COPD, since the gradual slow lung functions deterioration can be modified by acute exacerbations, often very frequent and with variable effect on both short-term and long-term outcome.

The main goal of best supportive care is achievement of sustainable quality of life for the patient and his/her family. End-of-life care should be provided to patients in final stage of the disease. Palliative and end-of-life care include various interventions, i.e., pharmacological therapy of COPD symptoms, pain, rehabilitation, oxygen therapy, non-invasive ventilation, administration of opioids, pharmacological sedation or treatment of depression and anxiety. The uncertainty regarding prognosis may play a significant role in discussions with patients and their families and can be a reason why patients with COPD are less likely to receive hospice care services[223,224].

Treatment recommendation of the expert group:

- Palliative and end-of-life care including pharmacological therapy of COPD symptoms, pain, rehabilitation, oxygen therapy, non-invasive ventilation, administration of opioids, pharmacological sedation or treatment of depression and anxiety should be offered to patients in final stage of the disease, with treatment choice depending on actual clinical problems.

10.6. TREATMENT OF COMORBIDITIES

All relevant comorbidities should be identified and adequately treated. In general, comorbidities should be treated in usual way, regardless of coincidence with COPD. There are several comorbidities, that deserve special attention since they may strongly influence the natural course of COPD. Some comorbidities are present in COPD patients very frequently and as such, can be perceived as treatable traits of COPD. Coincidence of COPD and multiple prevalent comorbidities can also be viewed as "comorbid phenotype".

Cardiovascular diseases

Current opinions: Cardiovascular diseases (CVD) coexist with COPD very frequently due to high prevalence of both disease categories in adult and senior populations. As stated above, increased levels of circulating inflammatory mediators and acute-phase proteins are drivers not only by COPD pathogenesis, but also contributors to the development of comorbidities, including CVD, skeletal muscle dysfunction, osteoporosis, depression, cachexia, diabetes mellitus or sleep apnoea syndrome[27-32].

The coexistence of COPD and CVD has a negative impact on prognosis[60]. CVD as a comorbidity of COPD includes chronic heart failure (CHF), ischemic heart disease, arrhythmias, atherosclerotic peripheral vascular disease and systemic hypertension. Acute worsening/decompensation of CVD, especially (but not limited to) CHF, ischemic heart disease or arrhythmias, may mimic or accomplish acute exacerbation of COPD and differential diagnosis can be very difficult. Furthermore, exacerbation of COPD may result in decompensation of CVD and *vice versa*. Treatment by oral selective $beta_1$-blockers and by inhaled selective $beta_2$-agonists can be used in patients with coexisting CVD and COPD (ref.[1]).

Treatment recommendation of the expert group:

- CVDs are main drivers of mortality in COPD patients; therefore, careful management of these comorbidities is warranted.

Gastroesophageal reflux disease (GERD)

Current opinions: Estimated prevalence of GERD among patients with COPD ranges from 17% to 54% (ref.[225]). Presence of GERD is associated with greater risk of acute COPD exacerbation[225]. It is speculated that GERD may be a driver of certain subtype of COPD exacerbations.

Treatment recommendation of the expert group:

- In patients with frequent exacerbations phenotype, GERD should be treated adequately once diagnosed.

Obstructive sleep apnea (OSA)

Current opinions: OSA is a relatively common comorbidity of COPD with similar physiological and molecular consequences, including hypoxia, systemic inflammation, CVD, pulmonary arterial hypertension and other comorbidities. OSA is rarely present in patients with emphysematous phenotype of COPD (usually associated with low BMI). In contrast, chronic bronchitic phenotype is characterized by peripheral airway mucosal edema, bronchial hypersecretion and increased BMI, and these conditions promote easier development of OSA. Patients with overlap of COPD and OSA have worse prognosis compared to both COPD or OSA alone[226].

Treatment recommendation of the expert group:

- Especially in COPD patients with bronchitic phenotype and overweight, OSA should be considered, eventually raising need for dNIV therapy.

Other comorbidities

Osteoporosis is frequently present with emphysematous phenotype and low BMI. Treatment of osteporosis should correspond to usual guidelines.

Depression and anxiety are important comorbidities associated with poorer prognosis. Therefore, psychological treatment (or even psychiatric care) and social support should be part of the basic treatment in COPD as mentioned above.

As already mentioned, lung cancer is often associated with COPD, and patients with larger degree of cigarette smoke exposure, with emphysematous phenotype or a

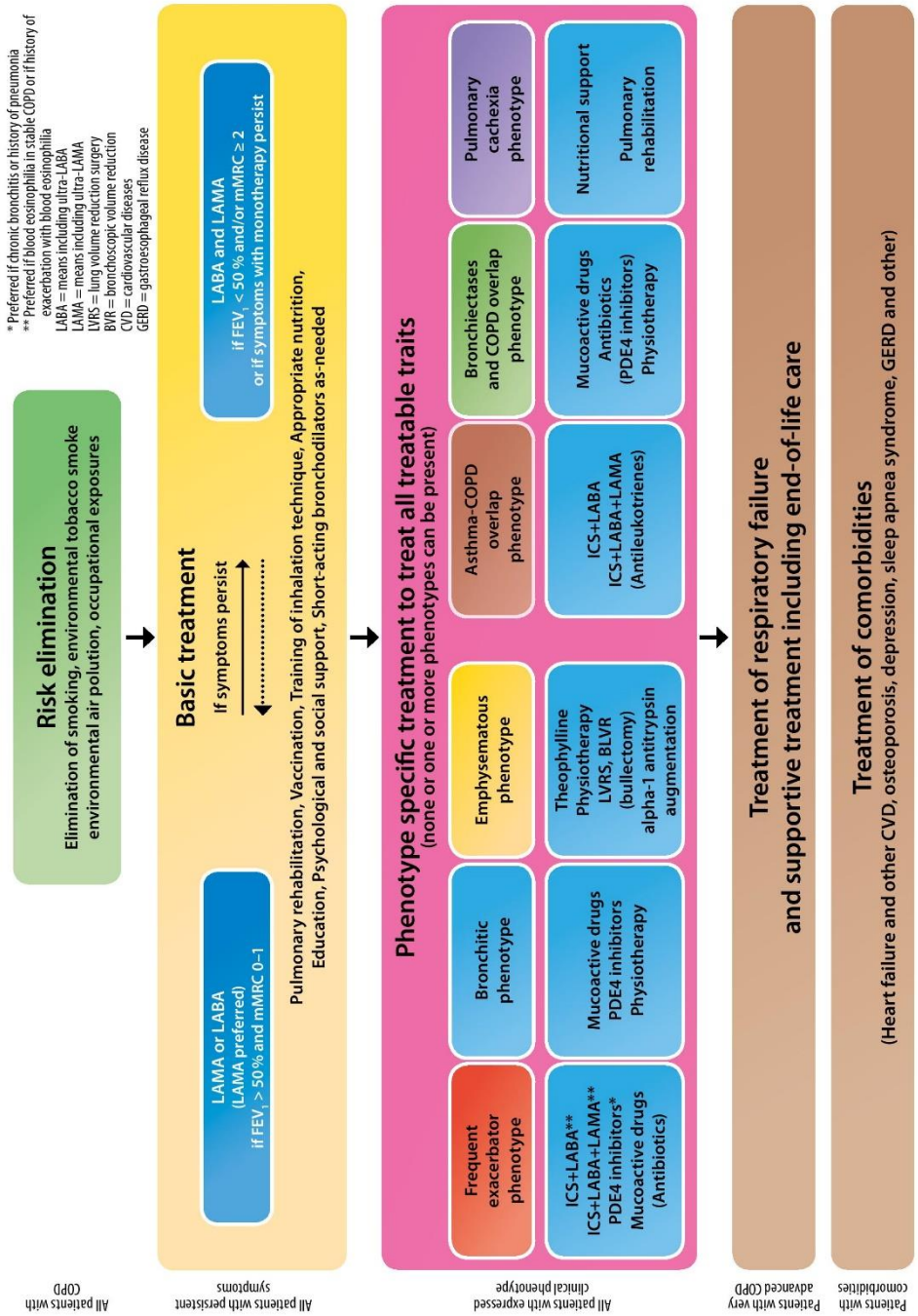


Fig. 11. Flow chart of stable COPD management (Details to each therapeutic modality see in text).

combination of emphysematous and bronchitic phenotypes express higher risk of lung cancer development[27,34].

11. FLOW CHART OF MANAGEMENT OF STABLE COPD

After COPD is diagnosed, maximal effort to eliminate risk factors should be made and basic treatment should be started. Clinical phenotype assessment should be done as soon as possible. If at least one phenotype/treatable trait is expressed, phenotype-specific treatment should be started in accordance with each patient's individual needs.

New phenotypes can develop in each individual patient and the present phenotypes may dynamically change over time. Therefore, treatment should be re-evaluated in about one-year periods and eventually adjusted to the actual clinical appearance and circumstances. Not only therapeutic adds-on, but also treatment reduction should be considered in case the current treatment is ineffective or obsolete or when long-term control of phenotype-specific symptoms has been achieved. For example, phenotype-specific treatment should be started with new detection of clinical phenotype or, it can be reduced if manifestation of a clinical phenotype has vanished.

Various types of non-pharmacological treatment are equally important to pharmacological therapies. Above that, all relevant comorbidities should be treated. Patients with advanced COPD and respiratory insufficiency should receive appropriate specialized treatment (e.g., dNIV, LTOT, rehabilitation, psychosocial support) and patients with terminal disease should receive the best supportive/palliative treatment. Complete elaboration is presented in Fig. 11.

12. FUTURE DIRECTIONS AND DEVELOPMENTS

Despite notable progress and changing paradigms during the last twenty years, the integrated effort of researchers and clinicians should be made in several areas in order to improve management and prognosis of COPD (ref.[227]).

Early diagnosis in symptomatic, previously undiagnosed populations with high inhalation exposure will probably lead to modifying disease progression. Especially, early smoking cessation is a key factor in effective COPD management. Therefore, screening or early detection programs should be advocated by national and local authorities[228-234]. In the Czech Republic, a pivotal early detection programme has been ongoing since 2019 and the results will show if implementation in daily clinical practice will be beneficial – see above Fig. 7 (ref.[235]).

The concept of predictive, preventive, personalized and participatory medicine (P4 medicine) for COPD patients has been discussed in recent years[26]. Personalized approach can better reflect the complexity and heterogeneity of COPD as it provides treatment tailored to the patient's individual needs[26]. Systems medicine explores disease networks at multiple levels, ranging from the molecular level, through cells, organs, to the population level[236]. A systems medicine approach, integrating genetic, (micro)biological, radiological, clinical, environmental and lifestyle factors in experimental and computational models may advance personalized treatment of COPD (ref.[236]).

Another important issue is to identify specific biomarkers or measures not only for early diagnosis and identification of patients responsive to specific treatments, but also for prediction of rapid lung function decline, comorbidities development, exacerbation and mortality risk[26,237]. Many of these points require a much deeper, integrative and more comprehensive understanding of COPD pathophysiology, natural course of the disease, its genetics and epigenetics and prenatal lung development, along with socioeconomic and environmental factors[26]. Currently, the most promising target for future therapy development is the pathway of cellular senescence that seems to play an important role in the pathogenesis of COPD and related comorbidities[35,238]. Other potential targets for new treatment developments include various cytokines or inflammatory molecules involved in the pathogenesis of COPD (ref.[239]).

In terms of treatment, a completely new class of inhaled drugs (PDE3/4 inhibitors – ensifentrine, and PDE4 inhibitors) are expected to enter clinical practice soon[240,241]. Bifunctional bronchodilator molecules with concurrent LABA and LAMA activity are already tested in clinical trials[242]. Similarly, biopharmaceuticals (particularly anti-IL-5) may be effective in specific subpopulations of patients[81,243,244]. For currently used treatments, real-life data from daily clinical practice are desired since only a minority of patients are eligible for participation in large RCTs (ref.[245]). This results in questionable effectiveness of approved treatments for the majority of patient populations. Of non-pharmacological treatment strategies, several new promising bronchoscopic treatment procedures have been developed in recent years, including endobronchial valves or coil placement or liquid nitrogen metered cryospray and targeted lung denervation procedures[187,246,247]. More emphasis should also be given to pulmonary rehabilitation programs and comorbidity management that are both evolving[1,248].

Last but not least, more effort (and at all levels) should be given into preventive programs, measures against smoking and into improvements in occupational and environmental health.

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2.5. Novel versus traditional inspiratory muscle training regimens as home-based, stand-alone therapies in COPD: protocol for a randomized controlled trial.

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Komentář:

Respirační fyzioterapie a její složky jsou významným prvkem v léčbě CHOPN. Cílem tohoto komplexu léčebných modalit a opatření je především zvýšení tolerance zátěže, redukce pocitu dušnosti, zlepšení celkové kondice, restituce nefunkčních fyziologických procesů a vzorců, zvýšení kvality života pacienta (142). Efekt respirační fyzioterapie na mortalitu je stále diskutován, dle některých systematických metaanalýz je sporný (143), dle jiných byl prokázán pozitivní efekt alespoň u hospitalizovaných pacientů s akutní exacerbací CHOPN (144). Obecně je ale úroveň důkazů efektu respirační fyzioterapie ve vztahu k redukci douhodobé mortality spíše nižší, úroveň doporučení je slabá (143, 144), což je dáno zejména heterogenitou charakteru a míry poskytované intervence. Problém proto vyžaduje další podrobné studium a provedení několika randomizovaných studií.

Racionálním základem pro tuto práci byl fakt, že i navzdory své jednoznačné efektivitě co se týče zlepšení kvality života a snížení úrovně symptomů, je adherence k respiračním fyzioterapeutickým programům obecně nízká (145). V České republice tento problém ještě prohlubuje poddimenzovaná síť zdravotnických zařízení poskytujících specializovanou respirační fyzioterapii a spíše menší povědomí pacientů, zdravotníků i plátců péče o užitečnosti této léčebné modality. Domácí léčba kontrolovaná telemonitoringem by

proto mohla být užitečnou alternativou k hospitalizačním nebo ambulantním typům programů respirační fyzioterapie, od níž by bylo možno očekávat lepší adherenci i možnost plošnějšího užití v péči o pacienty s CHOPN (146, 147). V rámci hledání nových přístupů a ověření jejich účinnosti jsme se rozhodli formulovat teze a sestavit reprodukovatelný protokol randomizované studie, jejímž cílem je srovnat efekt dvou typů domácího tréninku inspiračního svalstva pomocí speciálních tréninkových pomůcek proti „placebu“. Pro tuto studii navrhujeme randomizaci do 3 ramen v poměru 1:1:1, v každém z nich se jedná o domácí trénink inspiračního svalstva s telemonitoringem pod supervizí fyzioterapeuta (8 týdnů) následovanou 4 měsíci samostatného tréninku pacienta bez supervize. V prvním rameni budou pacienti používat přípravek Threshold IMT® (Philips Respironics, USA), který je aktuálně považován za zlatý standard léčby (148). Ve druhém rameni budou pacienti trénovat v programu TIRE, který zahrnuje tablet s instalovaným tréninkovým software-m, který měří přes zařízení PrO2 hodnoty MIP, SMIP a ID. Zároveň tato metoda může být použita jako plnohodnotný IMT trénink (149). Ve třetím rameni budou pacienti s přípravkem Threshold IMT®, který bude používán s jeho minimálním nastavitelným odporem (sham), prakticky jako placebo.

Hypotézou práce je, že domácí fyzioterapie pomocí TIRE je superiorní vůči tradičnímu IMT tréningu ve vztahu ke zlepšení funkce inspiračního svalstva i zmírnění projevů nemoci u pacientů s CHOPN.

Primárním sledovaným end-pointem bude SMIP, sekundárními endpointy budou FEV_1, FVC, TLC a RV, vzdálenost ušlá během 6-MWT, a SGRQ a CAT skóre.

Očekáváme, že IMT trénink metodou TIRE by měl být účinnější než trénink pomocí tradičnější metody s použitím Threshold IMT®, protože umožňuje real-time modulaci parametrů (biofeedback), které zajistí lepší efekt nejen na svalovou sílu, ale i na vytrvalost a pracovní kapacitu. Graficky je tento efekt zobrazen na Obrázku č. 1 v článku níže, kde ho

vyjadřuje plocha pod křivkou tlak-čas. Power analýza odhadla minimální velikost souboru k průkazu signifikantních rozdílů na 12 subjektů v každém rameni studie (=36 pacientů celkem). Studie byla registrována na ClinicalTrials.gov (identifikátor NCT04415788).

Závěrečné shrnutí jednou větou: Sestavili a publikovali jsme protokol malé randomizované studie zaměřené na vyhodnocení efektu 2 druhů IMT tréninku, jejíž hypotézou je, že IMT trénink pomocí metody TIRE je superiorní vůči tréninku pomocí Threshold IMT® ve vztahu k SMIP jako primárnímu endpointu (+ dalším sekundárním endpointům).

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STUDY PROTOCOL

Novel versus Traditional Inspiratory Muscle Training Regimens as Home-Based, Stand-Alone Therapies in COPD: Protocol for a Randomized Controlled Trial

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Background: Subjects with COPD frequently develop considerable weakness and deconditioning of the inspiratory musculature, which can be corrected with inspiratory muscle training (IMT). While rehabilitation centers may be able to provide IMT as part of the rather complex management of COPD, there is currently a lack of rehabilitation services in the Czech Republic. Remote IMT may then benefit subjects with COPD who are unable to attend or do not have access to rehabilitation programs. We aim at evaluating the utility of the test of incremental respiratory endurance (TIRE) as an at-home IMT method in subjects with COPD, while comparing the effectiveness of this novel training approach to the outcomes of traditional, threshold loading IMT protocols.

Methods/Design: This prospective, randomized controlled trial will comprise 8 weeks of at-home IMT sessions with remote supervision followed by 4 months of unsupervised, independent IMT. Eligible subjects will be randomly assigned to one of the following three distinct home-based IMT protocols: (1) TIRE, (2) Threshold loading, and (3) Sham training. Subjects allocated to the TIRE group will train once daily using an advanced IMT electronic system (PrO2), while the other two groups will receive threshold devices. Study outcomes will include measures of inspiratory muscle strength and endurance, pulmonary function, COPD-specific symptomatology, functional exercise capacity, surrogate markers of mortality risk, mental health status and health-related quality of life.

Discussion: While we acknowledge the value of threshold loading IMT protocols, we believe that the TIRE training method has the potential to provide additional clinical benefits in COPD given its sophisticated remote tracking system and ability to modulate all aspects of muscular performance, including not only strength but also endurance, power and work capacity, allowing users to achieve considerably higher inspiratory pressures throughout the full range of inspiration when compared to other more traditionally used IMT methods.

Keywords: chronic obstructive pulmonary disease, pulmonary rehabilitation, telemedicine, quality of life, inspiratory muscle training, test of incremental respiratory endurance

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Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent and complex disease characterized by a progressive decline in lung function, which is not fully reversible.[1] The prevalence of COPD is increasing worldwide, with high rates of mortality and morbidity impacting the quality of life of affected subjects.[2] Despite

optimal bronchodilator therapy, many patients suffer from intolerance of physical exercise and dyspnea of a multifactorial nature.[3] In the Czech Republic, approximately 800,000 people are estimated to have COPD (7–8% of the country's entire population).[4]

Pulmonary rehabilitation represents one of the most important and effective therapies in COPD. It is aimed at restoring function and has been shown to increase exercise tolerance, reduce dyspnea and improve quality of life in participants.[5] While pulmonary rehabilitation is a central component in the rather complex management of COPD, there is currently a lack of centers able to provide appropriate rehabilitation services in the Czech Republic. Therefore, a great discrepancy between the theoretical need and the actual availability of these programs exists.[2,6] The reasons for the absence of such outpatient programs in the Czech Republic include the lack of both experience and interest of health insurance companies in the context of secondary prevention programs, as well as unavailability of an adequate number of healthcare facilities specialized in the management of chronic respiratory conditions.[6] In the United States (US), adherence to pulmonary rehabilitation is extremely low among subjects with COPD, despite all its benefits.[7] This can be explained in part by the fact that pulmonary rehabilitation programs are typically hospital-based, which limits accessibility. Travel and transport issues have been cited as being the most common obstacles for program attendance.[7,8] Home-based therapies like inspiratory muscle training (IMT) are then a promising approach found to yield beneficial effects on exercise capacity and exertional dyspnea in subjects with COPD.[9]

The Test of Incremental Respiratory Endurance (TIRE) is a novel method to assess the inspiratory musculature of subjects diagnosed with COPD. The TIRE has recently been validated for use in this population, providing reliable measures of maximal inspiratory pressure (MIP), sustained maximal inspiratory pressure (SMIP) and inspiratory duration (ID).[10] The same method can be used as a more comprehensive IMT regimen which has not been fully examined in COPD.[11]

IMT has been shown to produce significant clinical benefits in obstructive lung disease.[12] The positive effects of IMT in COPD make it an attractive therapy due to its easy applicability. Optimizing IMT methods to elicit the most functional improvements in COPD is therefore of significant importance.[13] Traditional threshold loading IMT has important limitations, which are a limited workload (a maximal resistance of −41 cmH2O or less in such devices) and a limited inspiratory duration. By its nature, the TIRE promises to be a more efficient training tool because it allows patients to achieve considerably higher inspiratory pressures (up to −300 cmH2O) throughout the full range of inspiration, as shown in Figure 1, adapted from Cahalin et al.[14]

The main objective of this trial is to fully evaluate the utility of the TIRE as an IMT method in subjects with COPD, while comparing the effectiveness of this novel training approach to the outcomes of traditional, threshold loading IMT protocols. We hypothesize that, as a home-based stand-alone rehabilitative therapy, TIRE might be superior to traditional IMT in improving inspiratory muscle performance and COPD-related outcomes.

Methods/Design

Study Design

The intended study will include two treatment groups and one sham intervention group in a 1:1:1 ratio. All subjects will undergo a certain type of IMT regardless of group assignment, which will be performed via two different devices. The study will be conducted in cooperation with the Rehabilitation Department and the Department of Respiratory Diseases of University Hospital Brno. The trial will comprise an 8-week at-home training period with remote supervision followed by 4 months of unsupervised, independent respiratory training. The study will be prospective, controlled, and randomized. The patients will be

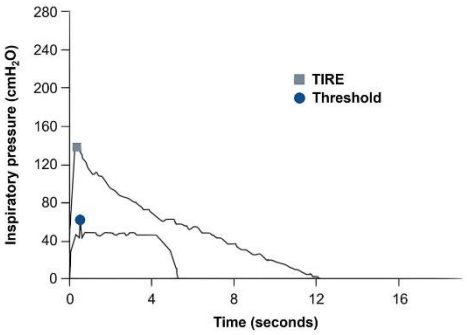

Figure 1 Comparison of the maximal inspiratory effort slopes obtained via the TIRE method and traditional inspiratory muscle assessment utilizing a threshold device.

Notes: The TIRE method elicits significantly higher inspiratory pressures that last throughout the entire inspiration, from residual volume (RV) to total lung capacity (TLC), while traditional IMT provides a square-shaped curve with limited pressures and inspiratory duration. SMIP derives as the area under the pressure-time curve in the TIRE assessment.

assigned 1:1:1 using a computerized random allocation sequence, which will be done through the use of opaque, sealed and numbered envelopes. This process will be administrated by a skilled, independent expert at the hospital center. They will also collect and store informed consents, questionnaires and other trial information. Electronic data will be stored in the hospital's private cloud and backed up to a flash drive. All data will be processed and backed up according to the currently valid General Data Protection Regulations. Although some healthcare providers will need to be informed about their patient's group assignment, subjects will be asked not to disclose their group assignment to the physician performing initial and final examinations, who will be blinded. The overall training regimen and data collection time points are shown in Figure 2.

All subjects will be recruited from the outpatient services of the Department of Respiratory Diseases at the University Hospital Brno. Subjects are expected to meet the following criteria: (a) subjects over the age of 40 with a clinical and functional diagnosis of COPD according to the Global Initiative of Chronic Obstructive Lung Disease (GOLD) guidelines – stages I to IV, (b) evidence of inspiratory muscle weakness, defined as a MIP $\leq$ 80 cmH2O and a SMIP $\leq$ 427 PTU (pressure time units),[15] (c) ability to operate a computer, tablet or smartphone independently and follow the training instructions, (d) clinical stability with no history of infections or exacerbation of respiratory symptoms for at least two months prior to study enrollment, and (e) non-participation in exercise programs in the past 12 months. The above criteria for inspiratory muscle weakness were chosen based upon a previous study by our research group, which found a SMIP value of 427 PTU to be equivalent to the MIP cut-off value of 80 cmH2O for stratification of clinically important inspiratory muscle impairment proposed by the ATS/ERS statement on respiratory muscle testing.[15,16]

We will exclude subjects with history of lung surgery, lung cancer, as well as individuals with any diagnosed cognitive (ie, Mini Mental State Examination score <24), orthopedic, neurological or neuromuscular disorders that might prevent them from appropriately performing the required physical tests and/or completing the study questionnaires. Subjects will not be excluded based upon their current bronchodilator regimen. If subjects experience acute exacerbations or respiratory infections during the training period, they will be examined by a pneumologist who will decide whether the participant should continue with the training or not. In the event that losses to follow-up or dropouts are observed, we will perform an intention-to-treat analysis.

Data will be collected in the following order: a) spirometry and body plethysmography, b) walking test, c) questionnaires, and d) inspiratory muscle performance via the TIRE. Subjects will be randomly divided into groups and familiarized with the proposed training regimens and their respective devices.

Training Description

Eligible subjects will be randomly assigned to one of the following three distinct home-based IMT protocols: (1) TIRE, (2) Traditional (Threshold loading IMT), and (3) Sham (ie, Low Resistance). All subjects will undergo 8 weeks of daily unsupervised IMT using either a PrO2 device (Design Net, Smithfield, USA) or Threshold device

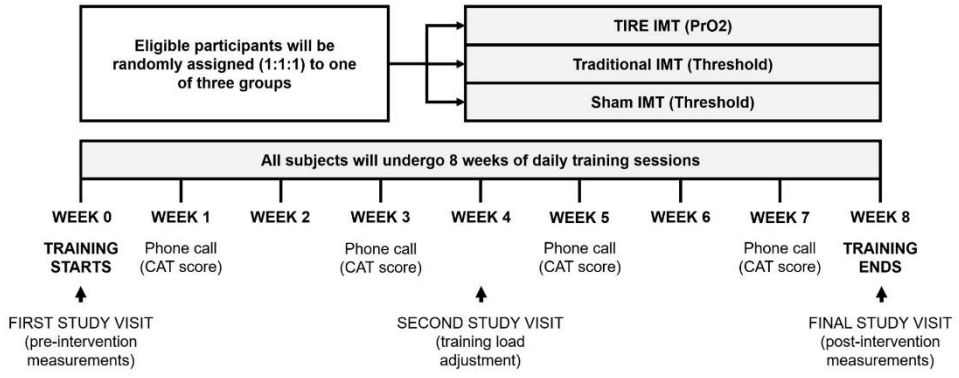

Figure 2 Outline of study design. Subjects are assigned to one of three home-based inspiratory muscle training groups and expected to train for 8 weeks.

at home. Table 1 presents a summary of the distinctive training characteristics per study group. All training modalities require the subjects to be seated and wearing a nose clip while performing the required breaths. Subjects will be instructed on their respective training procedures and complete their first training session in the presence of a research team member upon enrollment. Regardless of training method, subjects will be instructed to fill in diary cards at the end of each training session, in which they document how many breaths they were able to perform. This information will be later used for compliance assessment. They will be also provided with user guides developed by our research team with detailed instructions regarding equipment set-up, training protocol and contact information. In addition, subjects will receive weekly phone calls from week 0 to week 8 to encourage compliance and adherence to the study protocol, to address any subject questions or concerns, and to collect information regarding their current symptomatology (Figure 2).

Group 1 – TIRE IMT

The TIRE training regimen will involve the use of a tablet provided to assigned subjects with the training software installed and a PrO2 device through which they will train. The software allows subjects to track their inspiratory muscle performance via real-time graphic representations of their efforts as training progresses. Training will consist of six levels (A-F) with six inspirations at each level for up to 36 breaths per session. Pre-set recovery times between breaths decrease as subjects advance each level from 60 seconds at level A to 50, 40, 30, 20 and 10 seconds at levels B to F, respectively. TIRE data will be stored in the tablet and automatically synced to account on cloud-based online platform for subsequent interrogation and data retrieval. Each participant will get his or her own login and password to account. The research team will have access to the accounts of all subjects. This feature makes the TIRE system a powerful resource to ensure compliance and remotely track adherence to study protocol.

Before every training session, subjects will be required to complete one maximal and sustained inspiratory effort from which the training is based on for that day. This effort will be recorded on the software and visually redrawn on the tablet screen to a training template set at 50% of the entire effort. Subjects will be required to match or exceed the on-screen training template for their efforts to be considered successful, achieving pressures of at least 90% of the redrawn MIP and area under the curve (ie, SMIP). Although the achievement of the 50% pre-set training template is sufficient to allow for training continuation, subjects are instructed to perform maximal maneuvers from RV to TLC, not only matching but exceeding the effort requirement whenever possible. After each successful breath, a countdown clock will be trigged, and the subject will have to wait to perform the next breath following the pre-set recovery time for that level. If at least 90% of the redrawn MIP and SMIP are not achieved, the subject will receive a prompt that they had failed to generate the required pressures and will be automatically provided with two options: either terminate or continue the training. Subjects will be instructed to terminate the session in case of two consecutive failed inspiratory efforts. It is important to note that subjects will be instructed not to expire into the device. They will only use the device when prompted by the software to inspire at which time they will place the mouthpiece of the device in their mouth and perform the required sustained inspiratory effort.

Group 2 – Threshold IMT

Subjects assigned to the threshold loading training regimen will receive a traditionally used Threshold inspiratory muscle trainer (Threshold IMT; Philips Respironics, USA). This

Table 1 Proposed Training Characteristics per Study Group

Group	Device	Training Load	Training Volume	Training Frequency
TIRE IMT	PrO2	On-screen training template set at 50% of the subject's MIP and SMIP.	Six levels (A-F) with 6 inspirations per level for up to 36 efforts per session. Pre-set recovery times between breaths: 60 seconds at level A to 50, 40, 30, 20 and 10 seconds at levels B to F, respectively.	1/day, 8 weeks
Threshold IMT	Threshold	One-way spring-loaded valve set at 50% of the subject's MIP.	36 inspirations performed using the device within a 30-minute period.	1/day, 8 weeks
Sham IMT	Threshold	One-way spring-loaded valve set to its minimal resistance (~ 9 cmH2O).	36 inspirations performed using the device within a 30-minute period.	1/day, 8 weeks

Abbreviations: MIP, maximal inspiratory pressure; SMIP, sustained maximal inspiratory pressure; TIRE, test of incremental respiratory endurance.

device features a one-way spring-loaded valve at one end and a mouthpiece on the other through which subjects will be required to breathe in hard enough to overcome the resistance provided by the spring-loaded valve, allowing correct inspiration to happen. In other words, air flow is blocked until subjects generate sufficient inspiratory pressure to exceed the device pre-set pressure in cmH2O. The resistance will be set using the device's adjustable pressure setting which is fixed at 50% of the subject's MIP at the time of enrollment. The resistance will be readjusted as needed at week 4 to still reflect 50% of their inspiratory muscle strength at that time. Subjects will be coached to perform up to 36 breaths daily using the device. They will be also instructed to complete the training session within a 30-minute period.

Group 3 – Sham IMT (Low Resistance)

The Sham (Low Resistance) training regimen will use the same methods described above for the threshold loading IMT, except for the amount of resistance applied within the device. Subjects will receive a Threshold which has been set to its minimal resistance, which is 9 cmH2O. Again, subjects will be instructed to perform up to 36 breaths daily using the device within a 30-minute period.

Outcome Measures

Key outcome measures in the trial will be assessed at baseline and 8 weeks post training start date at the University Hospital Brno. TIRE and COPD Assessment Test data will also be collected during the second study visit. Data collection per study visit will take approximately 90 minutes.

The primary outcome measure will be SMIP, which will be obtained along with MIP and ID in every subject using the PrO2 device, an electronic pressure manometer which utilizes wireless technology to connect to a tablet containing the TIRE software.[15] The software provides the user with a real-time graphic representation as they perform the required inspiratory maneuver, as shown in Figure 3. The PrO2 has a 2 mm leak which provides a set resistance to inspiratory flow and avoids glottal closure during maximal inspiratory effort. Subjects will be instructed to exhale completely and then forcefully breathe in through the device generating as much pressure as possible within 1 to 2 seconds of inspiration and continue to inhale deeply for as long as possible. SMIP will be measured from residual volume (RV) to total lung capacity (TLC) and represents the area under the curve in PTU, while MIP will be recorded in cmH2O and represents the highest pressure generated during inspiration from RV. ID will document the total duration of full inspiration per trial in seconds. A single assessment session will consist of 3 to 5 sequential trials with rest intervals of 60 seconds between efforts. The greatest SMIP will be used to identify the best of the repeated trials within the session, providing the MIP and SMIP values to be documented and used for study purposes. All inspiratory maneuvers will be performed with the subjects seated in a chair and wearing nose clips according to American Thoracic Society (ATS) standards on respiratory muscle testing.[16]

Other key outcome measures will include pulmonary function tests which comprise post-bronchodilator spirometry using SpiroScout® and whole-body plethysmography using the PowerCube® Body+ (Ganshorn, Niederlauer,

Figure 3 Graphic presentation of a sustained maximal inspiratory effort performed using the PrO2 device and software. In this example, the user achieved a MIP of 90 cmH2O, a SMIP of 606 PTU reflecting the area under the pressure-time curve. The entire maneuver lasted 15 seconds.

Germany) following European Respiratory Society - ERS/ATS standards,[17] providing measures of forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), inspiratory capacity (IC), RV and TLC, obtained 15–20 min after 400μg salbutamol will administered via a metered dose inhaler through a spacer. Functional exercise capacity will be determined using the six-minute walk test (6MWT), which will be performed as recommended by ERS/ATS guidelines.[18] The severity of dyspnea, mental health status and health-related quality of life of the subjects will be assessed via the modified Medical Research Council (mMRC) dyspnea scale, the Hospital Anxiety and Depression scale (HADS) and the St. George's Respiratory Questionnaire, respectively.[19–21] The impact of disease-specific symptoms on the health status of the subjects will be quantified by the CAT,[22] while comorbidity burden will be assessed using the Charlson Comorbidity Index.[23] The BODE index will be also calculated and will serve as a surrogate marker of mortality risk in COPD.[24] The above scales, questionnaires and indices will use point-based grading systems with higher total scores indicating more severe conditions. Occurrence of adverse events and reasons for early termination of trial will be evaluated.

Data regarding medications and past medical history will be extracted from each individual's electronic medical record. A full tobacco history will be obtained at baseline, with subjects being asked to report the total number of years smoked, average number of cigarettes smoked per day, and current smoking status. Finally, subjects will be provided with a 5-item self-completed questionnaire developed by our research team that will measure their satisfaction with the intervention they received and the study in general. The items will be presented in the form of statements to which subjects will be asked to respond using a 1–5 Likert scale ("strongly agree", "agree", "not sure", "disagree", and "strongly disagree").

Sample Size

We performed a power analysis based on the report of previous studies on TIRE measures. Normative TIRE data yielded effect sizes ranging between 0.50–1.00 when comparing SMIP to different age groups.[25] A meta-analysis for inspiratory muscle strength demonstrated a significant summary effect size of 0.68 (95% CI 0.54–0.82; p = 0.001) for MIP.[26] Thus, we believe that an effect size of about 0.75 is a good estimate. We examined the number of subjects necessary to achieve such an effect size using Portney & Watkins test and concluded that the sample size needed for our statistical analyses is of at least 12 subjects in each of the three groups with 2 degrees of freedom and a power of 0.9 with an alpha level of 0.05. Subjects that are eventually excluded or decide to drop out will be replaced with new enrollees to ensure completion of at least 12 subjects per group.

Statistical Analysis

Baseline characteristics of the study sample will be analyzed and summarized using descriptive statistics. Differences in recorded variables between the three groups at baseline, and after four and eight weeks of training will be analyzed by a mixed-design analysis of variance and multiple linear regressions. Training compliance information will be expressed as a percentage. Statistical significance will be set at an alpha-level of 0.05. All analyses will be performed with IBM SPSS Statistics 24 (Armonk, New York, USA 10,504–1722) and Statistica 12 (TIBCO Software, INC Palo Alto, US).

Trial Status

This study will be performed in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethical Committee of the University Hospital Brno, Czech Republic. This trial follows the SPIRIT 2013 checklist standards of reporting trials and is registered at ClinicalTrials.gov with identifier: NCT04415788.

Discussion

Patients with COPD commonly develop significant deterioration in exercise capacity in association with weakness and deconditioning of the respiratory muscles. Particular impairment has been described in inspiratory muscle performance reflected by decreases in MIP.[27,28] Whereas inspiratory muscle function in COPD has mostly been described in terms of inspiratory muscle strength, the day-to-day relevance of measures like MIP is debatable. In fact, studies suggest greater clinical, perceptive, functional, psychological and prognostic values in the assessment of single-breath work capacity when compared to the evaluation of inspiratory muscle strength alone in COPD.[15,29,30] Besides the traditionally studied measure of MIP, the TIRE provides values of single-breath work capacity such as SMIP and ID, allowing for a more profound assessment of the musculature involved with inspiration. Moreover, the TIRE can serve as a novel

training method likely to result in better clinical outcomes in the COPD population.

While we acknowledge the value of traditional IMT protocols, which use Threshold devices, we believe that the TIRE training has the potential to provide added clinical benefits since it is able to modulate all aspects of muscular performance, including strength, endurance and work capacity. The real-time biofeedback and a training template that encourages the generation of higher pressures throughout the entire inspiration are also unique and superior features of the TIRE training, which facilitate a more controlled breathing pattern and possibly improved gas exchange during and post-training.

Additionally, we will be able to remotely and electronically track training compliance of the subjects assigned to the TIRE protocol, a distinct and important characteristic of this training approach that might allow us to reliably assess the subject's adherence to study protocol, unlike the other groups whose training compliance will be self-reported. We believe that more accurate conclusions as to changes observed in clinical outcomes from baseline can be drawn when actual compliance is accounted for; therefore, the TIRE device and software is a promising tool.

Whereas other inspiratory flow resistive loading (IRFL) techniques and devices exist, from simple dial-based equipment such as the Pflex (Philips Respironics, the Netherlands) to more sophisticated electronic instruments like the POWERbreathe (POWERbreathe International Ltd, United Kingdom), the TIRE method implemented via the PrO2 device is novel as it provides original features not available in other training approaches. The TIRE offers the possibility of assessing and training the unique SMIP, which can be defined as single-breath inspiratory work capacity, reflecting the ability of the inspiratory muscles to maintain force over time through a great resistive load imposed by a fixed 2 mm inspiratory orifice.[10,15] Other distinctive characteristic of the TIRE is its modern remote tracking system and cloud-based online platform, making the PrO2 an attractive alternative to devices such as the POWERbreathe which are currently unable to remotely interrogate and retrieve data as training happens. Finally, due to its fixed flow resistive load, the TIRE allows subjects to produce considerably higher pressures for longer periods of time (ie, total duration of inspiration can exceed 10 seconds), possibly resulting in greater improvements in inspiratory muscle endurance and work capacity.

Remote alternatives to traditional rehabilitation programs are important for subjects with COPD who are unable (or not willing) to attend such services. In 2015, the ERS/ATS published a political statement in which they commit to the promotion and expansion of home-based pulmonary rehabilitation.[31] Meta-analyses have shown that telerehabilitation technologies are of great importance in managing COPD as they can improve respiratory muscle pressures, functional lung capacity and the quality of life of those who are treated remotely.[32,33] Several telemedicine benefits have been reported following the rehabilitation of patients with other diseases.[34]

In conclusion, the main objective of this study will be to fully evaluate the utility of TIRE as an at-home inspiratory muscle training method in subjects with COPD, while comparing the effectiveness of this novel training approach to the outcomes of more traditional IMT protocols. We hypothesize that, as a home-based stand-alone rehabilitative therapy, TIRE will be superior to traditional, threshold loading IMT in improving measures of inspiratory muscle performance, pulmonary function, dyspnea, functional exercise capacity, overall and mental health, health-related quality of life and surrogate markers of mortality risk in COPD. We expect to publish the findings of this investigation in due course.

Abbreviations

ATS, American Thoracic Society; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative of Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; IC, inspiratory capacity; ID, inspiratory duration; IMT, inspiratory muscle training; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council; N, sample size; PTU, pressure time units; RV, residual volume; SMIP, sustained maximal inspiratory pressure; TIRE, test of incremental respiratory endurance; TLC, total lung capacity; US, United States; 6MWT, six-minute walk test.

Ethics Approval and Consent to Participate

This study is approved by The Ethical Committee University Hospital Brno, Czech Republic (Reference number: 01-020420/EK). Subjects will sign a written informed consent prior to enrolment.

Funding

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Disclosure

Marek Plutinsky reports personal fees from Boehringer Ingelheim, Berlin Chemie, and CSL Behring, outside the submitted work. The authors report no other potential conflicts of interest in this work.

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2.6. Breathing Out Completely Before Inhalation: The Most Problematic Step in Application Technique in Patients With Non-Mild Chronic Obstructive Pulmonary Disease.

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Komentář:

Správná inhalační technika je základní prerekvizitou nutnou k účinné inhalační medikamentózní léčbě CHOPN. Inhalační podání léčiv na rozdíl od celkového umožňuje minimalizaci dávek a tím i výskytu nežádoucích účinků. Termínem s širším významem je aplikační technika, která zahrnuje nejen inhalační podání samotné, ale i přípravu inhalátoru, nachystání inhalované dávky, inhalaci samotnou a ukončení celého procesu. Bez dokonalého zvládnutí aplikační techniky klesá účinnost léčby, zvyšuje se úroveň respiračních symptomů, riziko hospitalizací, morbidity a klesá kvalita života pacienta (150). Zvláštním problémem je i to, že existuje velký počet inhalačních systémů (inhalátorů) různé konstrukce a způsobu dodání inhalační dávky do dolních dýchacích cest, což může vést k vyšší chybovosti použití nejen ze strany pacientů, ale i zdravotníků. Nadto, péče o pacienty s CHOPN není koncentrována jen v rukou pneumologů, ale i praktických lékařů, u kterých může být erudice stran ideálního používání inhalačních systémů nižší. Až doposud nebyl stanoven žádný „zlatý standard“ upravující obecnou podobu aplikační techniky inhalačních léčiv.

Racionálním základem pro tuto práci byla snaha o standardizaci kroků aplikační techniky inhalačních léků s ohledem na jejich heterogenitu. Cílem práce bylo ověřit v praxi použití jednoduchého a přehledného systému kontroly aplikační techniky, tzv. „Five Steps Assessment“, který byl navržen v rámci založení Registru CHOPN a který by zdravotníkům umožnil ověření a optimalizaci aplikační techniky u všech pacientů a jejich inhalačních preparátů. „Five Steps Assessment“ se skládá z těchto pěti kroků: 1/ příprava aplikátoru k inhalaci, 2/ manipulace s aplikátorem před inhalací, 3/ pacient před inhalací (dechová příprava pacienta), 4/ vlastní inhalace, 5/ po inhalaci (kontrolní kroky, čištění a uzavření aplikátoru). Blíže také na webu CHOPN Registru: https://chopn.registry.cz/res/file/dokumenty/inhalacni-systemy-protokol.pdf.

Data pro tuto práci byla čerpána z Registru CHOPN. Demografické charakteristiky a plicní funkce kohorty byly prezentovány formou popisné statistiky. Četnost používání jednotlivých aplikátorů byla prezentována jako n (% z celé kohorty) a správnost/chybovost v jednotlivých krocích jejich používání byla vyjádřena v procentech z počtu pacientů užívajících daný aplikátor. Pacienti během ambulantní kontroly předváděli použití jednotlivých aplikátorů ve všech 5 výše uvedených krocích za vizuální kontroly proškoleného pneumologa. Za správnou aplikaci bylo připsáno 0 bodů, za nesprávnou 1 bod, a to pro každý jednotlivý krok „Five Steps Assessment“ zvlášť. Pokud pacient užíval více než jeden inhalační preparát, předváděl použití každého aplikátoru zvlášť.

Pro potřeby této studie mělo dostatečně vyplněná data celkem 546 pacientů z Registru CHOPN (z celkového počtu 784). Kohortu studie tvořilo 75% mužů, 90% bývalých či aktivních kuřáků, s průměrnou BMI 28 a s průměrnou hodnotou FEV_1 44,7% náležité hodnoty. Až 88% pacientů užívalo více než jeden inhalátor. Z nejčastějších samostatných typů inhalátorů byly zastoupeny dávkovače skupiny pMDI (83,3%), Aerolizer/Breezhaler® (53,7%), Handihaler® (43,9%), Diskus® (21,1%) a Respimat® (13,4%). Nejvyšší podíl

pacientů kompletně správně aplikujících daný preparát (= se skóre 0 bodů) jsme pozorovali u inhalátorů Genuair® (81%), Respimat® (53,4%) a Handihaler® (46,3%), nejnižší u tradičních pMDI (36,5%). Celkově za kohortu byl podíl pacientů správně užívajících všechny své inhalátory pouhých 30%. Nejvíc chybovým přitom byl krok č. 3 (správné vydechnutí před samotnou inhalací léku) s chybovostí v rozmezí 9,5-47,5% pro různé druhy inhalátorů.

V této práci jsme prokázali užitečnost a jednoduchou použitelnost nového nástroje tzv. „Five Steps Assessment“. Nástroj obsahuje všechny důležité kroky k posouzení správnosti aplikační techniky a je tak univerzálně použitelný pro všechny kategorie inhalátorů i jejich konkrétní typy. Dosavadní práce se zaměřovaly buď na jednotlivé typy inhalátorů ve smyslu 1 inhalátor = 1 samostatný postup pro ověření správnosti jeho používání (151) nebo používaly extenzivní a složité kontrolní seznamy (checklisty) kroků potřebných k ověření správnosti aplikace (152-154). V rutinní klinické praxi by to znamenalo práci s mnoha různými systémy kontroly správnosti aplikační techniky, navíc s výraznou časovou zátěží. Systém „Five Steps Assessment“ je intuitivní, jednoduchý, jednotný pro všechny inhalátory a jeho vypracování pro daný inhalátor u daného pacienta zabere nejvýš několik minut.

Co se týče samotných výsledků analýzy úspěšnosti / správnosti celé aplikační techniky i jednotlivých kroků, v kohortě Registru CHOPN jsme pozorovali bezchybnou aplikaci pouze u 30% subjektů. Tento výsledek je podobný výsledkům jiných prací; např. v práci Pothirata a kol. správnou aplikaci inhalačního léku bez kritické chyby provedla pouze čtvrtina (25%) pacientů (152). V jiné práci byla chybovost alespoň v jednom kroku aplikace dokonce na úrovni 82% pacientů kohorty (155). V naší práci byly chyby nejčastěji pozorovány v krocích č. 3, 4 a 5 (vydechnutí před samotnou inhalací účinné látky, inhalace účinné látky a ukončení manévru s vyčištěním inhalátoru). Tento nález koresponduje s výsledky předchozích prací, kde byly analogické kroky (v rámci dlouhých checklistů) rovněž provázeny největší chybovostí (152, 154, 155). Naše nálezy se také shodují s předchozími poznatky, že

chybovost v rámci aplikace je podobná pro aplikátory typů pMDI a DPI (153, 156). Důležitým momentem této práce je, že „Five Steps Assessment“ lze pro jeho jednoduchost a univerzálnost v čase re-evaluovat a při zjištění problémů s aplikací pacienta reedukovat. To stejné platí pro ošetřující zdravotníky, kteří si mohou ověřit správnost svých pracovních postupů rychle a elegantně během několika málo minut.

Závěrečné shrnutí jednou větou: V této práci jsme zkoumali použitelnost „Five Steps Assessment“ v rámci rutinního testování správnosti aplikační techniky u pacientů s CHOPN; metoda se ukazuje jako jednoduchá a reprodukovatelná pro pacienta i zdravotníka. Nejčastější chybou v aplikační technice v naší kohortě bylo nedostatečné vydechnutí před inhalací léčiva.

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Breathing Out Completely Before Inhalation: The Most Problematic Step in Application Technique in Patients With Non-Mild Chronic Obstructive Pulmonary Disease

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Background: Patient adherence to an inhaled medication application technique (A-ApplT) represents a major health-care issue in patients with chronic obstructive pulmonary disease (COPD). However, there is a lack of studies evaluating this issue thoroughly. The aim of our study was to introduce a universal easy-to-use method of assessing the A-ApplT to chronic medication in moderate to very severe COPD individuals.

Methods: The Czech Multicenter Research Database of COPD (COPD CMRD), a large observational prospective study, was used as a source of clinical data. A-ApplT was evaluated using our Five Steps Assessment. This measure is based on dichotomous evaluation of each of five predefined consecutive application technique steps and can be used in all settings for all currently available inhalation systems in COPD subjects.

Results: A total of 546 participants (75.0% men; mean age 66.7 years; mean forced expiratory volume in 1s 44.7%) were available for analysis. This represents 69.6% of all patients recruited in the COPD CMRD. Less than one third of patients presented their application technique without any erroneous steps. The most problematic steps were breathing out completely in one breath immediately before inhalation (step No. 3), and the actual inhalation maneuver (step No. 4). The total number of errors was similar for dry powder inhalers and pressurized metered-dose inhalers.

Conclusion: Our novel instrument, Five Steps Assessment, is comfortable for use in routine clinical practice to explore A-ApplT. The A-ApplT in real-life patients with non-mild COPD was inadequate and patients should be repeatedly trained by properly (re-)educated medical staff.

Keywords: chronic obstructive pulmonary disease, adherence to application technique, inhalation systems, inhalation adherence, five steps assessment, device mastery, inhaler mishandlings

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable progressive lung disease. Its prevalence is increasing worldwide, presenting a substantial medical, social and economic problem (GBD 2015 Chronic Respiratory Disease Collaborators, 2017; Global Strategy for the Diagnosis Management and Prevention of COPD, 2018). COPD is currently the fourth global leading cause of death (WHO Chronic Obstructive Pulmonary Disease, 2017). In the Czech Republic (10.6 million inhabitants), COPD has been reported to be responsible for 21,000 acute hospitalisations and 3,500 deaths annually (Maly et al., 2013).

Although the methods of "evidence-based medicine" have not yet conclusively proven the effect of any existing COPD medication on long-term decline in lung function, pharmacotherapy is fully indicated to reduce symptoms, frequency and severity of exacerbations and to improve exercise tolerance and health status. Currently, inhaled medication represents the cornerstone of COPD pharmacotherapy (Global Strategy for the Diagnosis Management and Prevention of COPD, 2018).

However, as with other chronic diseases, adherence to COPD treatment is often poor. The poor adherence results in increased COPD symptoms, hospitalisations, higher rates of morbidity, healthcare expenditures and reduced quality of life (Bourbeau and Bartlett, 2008; Restrepo et al., 2008; Vestbo et al., 2009; Rogliani et al., 2017). Even though adherence is frequently expressed quantitatively (e.g., percentage of doses used), it is worth noting that non-adherence has principally two forms: (1) a patient uses an incorrect dose of his/her medication and (2) a patient uses his/her medication in an incorrect manner (Boudes, 1998).

In respiratory medicine, however, the "qualitative" aspect is equally important. Incorrect application technique often reduces the effectiveness and can sometimes increase the risks of the used medication. In COPD patients, who are often of higher age and with multiple morbidities, failure to adhere to a specific application technique constitutes a major adherence problem. Inhaler mishandlings can be understood as a type of non-intentional non-adherence sometimes called inhalation non-adherence. We prefer and use the term adherence to application technique or application technique adherence (A-ApplT, also known as device mastery or inhalation adherence/compliance). "Application" is a broader term than "inhalation" and, in addition to the actual inhalation maneuver, includes actions closely associated with the application technique, such as pressing the piercing button, shaking the inhaler etc. For optimal use of an inhaler, it is necessary to manage the application in its entirety. When citing other studies, we use the wording used by their authors.

Studies have shown high rates of inhalation non-adherence and effective use of inhalers in only around 10% of patients (Fink and Rubin, 2005; Lavorini et al., 2008; Restrepo et al., 2008; Laube et al., 2011). Inhaler mishandling is associated with reduced lung drug delivery or deposition and with an increased risk of hospitalisations, emergency room visits, courses of oral corticosteroids and antimicrobials and poor disease control (Fink and Rubin, 2005; Melani et al., 2011). Pharmaceutical industry continues to develop new inhalers with the focus on ease-of-use. In addition, single-inhaler fixed drug combinations may provide greater comfort to patients, particularly those with severe COPD, and thus may secure greater efficacy (Montuschi et al., 2016). Despite the huge effort to make the inhalers more patient-friendly through emphasis on technological aspects and design, errors in an application technique are still frequent in both, pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) (Melani et al., 2004, 2011; Hammerlein et al., 2011; Rogliani et al., 2017). The use of various inhalation systems and frequent need for combination therapy further complicate the situation in this field (Laube et al., 2011; Global Strategy for the Diagnosis Management and Prevention of COPD, 2018).

At present, there is no methodological "gold standard" as to how to assess A-ApplT. Analyses of erroneous steps in application techniques of various inhalers often use different checklists or different scoring and, therefore, comparison of results is challenging. Furthermore, several studies have assessed A-ApplT in mixed cohorts of patients with various types of respiratory diseases, most frequently with bronchial asthma and COPD. However, there might be substantial differences in cohorts of patients affected by the various diseases in terms of socio-demographic and medical characteristics, leading to discrepancies in their skills and ability to adhere to a particular application technique (Kardas et al., 2013).

Chronic obstructive pulmonary disease management in the Czech Republic is primarily provided at the secondary care level. Unlike Western European countries, the majority of COPD patients in the Central and Eastern Europe are managed by respiratory specialists (Koblizek et al., 2014, 2017). General practitioners (GPs) are the first port of contact for all COPD-risk individuals in the Czech Republic but the COPD diagnosis is almost exclusively confirmed by respiratory specialists. Moreover, vast majority of COPD patients are subsequently managed at respiratory outpatients (in the Czech Republic,

Abbreviations: A-ApplT, adherence to application technique; CMDR, The Czech Multicenter Research Database; DPIs, dry powder inhalers; pMDIs, pressurized metered dose inhalers.

there are 330 respiratory specialist outpatients per 10.6 million inhabitants). In addition, it has been reported that A-ApplT in COPD patients varies depending on a clinician's speciality and their experience (Bourbeau and Bartlett, 2008; Restrepo et al., 2008). Speciality of a physician is also crucial in their own ability to cope with an application technique and the quality of education provided to patients (Melani et al., 2011; Arora et al., 2014). Consequently, our project involved respiratory physicians only and did not include any GPs.

The primary objectives of this study were:

(1) To introduce a universal easy-to-use method and
(2) To assess the rate of adherence to an application technique (A-ApplT) of chronic inhaled medications used in patients with non-mild COPD in routine clinical practice of respiratory physicians.

MATERIALS AND METHODS

Design and Participants

This study provided a baseline evaluation of adherence to an application technique (A-ApplT) within the Czech Multicenter Research Database of COPD (COPD CMRD) (Czech Multicenter Research Database of COPD, 2018). CMRD is an ongoing observational long-term prospective multicenter study with the primary objective of investigating all-cause mortality in patients with non-mild COPD in the Czech Republic, EU (ClinicalTrials.gov NCT01923051: registered 14th August, 2013). COPD patients were recruited to the CMRD from August 2013 to December 2016 by 14 outpatient secondary health care centers providing respiratory physician-based care to patients with COPD. Participation in the COPD CMRD was systematically offered to all consecutive patients who met the inclusion criteria and did not fulfill any exclusion criteria. The study was approved by the Ethics Committee of the University Hospital in Brno (16th January 2013) and then by the Institutional Review Boards and Ethics Committees of all participating centers. Written informed consent was required from all patients.

Inclusion criteria were: diagnosis of COPD, age $\geq$ 18 years, post-bronchodilator forced expiratory volume in 1s (FEV_1) $\leq$ 60 %, stable condition without exacerbations for at least 8 weeks prior to enrolment and a home address in close proximity to the research center. Patients were excluded on the grounds of: cystic fibrosis, terminal stages of a malignancy, end-stage COPD, uncooperative patient or bed-to-chair activity level. Further details on the inclusion and exclusion criteria have been published elsewhere (Novotna et al., 2014).

Within the CMRD study, A-ApplT evaluation was not mandatory but it was highly recommended that this assessment is conducted. Physical examinations, medical records, self-administered instruments and interviews with patients were used to assess socio-demographic and health characteristics (Novotna et al., 2014).

Outcome Measure

To assess the A-ApplT, five consecutive steps to be followed while using an inhalation system (inhaler) were observed as summarized in **Table 1**. All types of inhalers currently authorized and used in the treatment of COPD were evaluated (Laube et al., 2011; Czech Multicenter Research Database of COPD, 2018).

The group of pressurized metered dose inhalers (pMDI group) included three types of inhalers: traditional pMDI (aerosol), EASI–BREATHE and RESPIMAT (soft mist inhaler, SMI). The reasons to include SMI in the pMDI group were as follows: both inhalers are non-DPIs, both require slow and deep breathing in for at least 4 s. In addition, both types of inhalers are the method of choice for patients with low inspiratory flow (Laube et al., 2011). The group of dry powder inhalers (DPI group) comprised of six types of inhalers: HANDIHALER, AEROLIZER (Spinhaler)/BREEZHALER, DISKUS, TURBUHALER (Twisthaler), ELLIPTA, and GENUAIR.

Each patient was asked to carefully demonstrate the use of a placebo inhaler. Patients treated with a combination therapy with two or more different types of inhalers were asked to demonstrate the use of each type. A-ApplT was evaluated and recorded by a nurse under direct supervision (in the same room) of a respiratory physician. The duration of the

TABLE 1 | Adherence to application technique (A-ApplT) – a brief description of the five steps for the different groups of inhalation systems used in chronic COPD patients (Five Steps Assessment). (http://chopn.registry.cz/index-en.php).

Step No.	Group of inhalation systems	
	Aerosol inhalers (pMDI group)	**Dry powder inhalers (DPI group)**
1	**Getting the inhaler ready for use** (different for different types of inhalers)	
	Remove the mouthpiece cover from the inhaler, and hold the device upright.	Insert a capsule with dry fingers into the chamber (capsule inhalers) and hold the device in correct position
2	**Handling the inhaler before use** (different for different types of inhalers)	
	Shake well.	Press the piercing button(s), prepare a dose of drug (non-capsule inhalers).
3	**Immediately before inhaling**	
	Breathe out completely in one breath (full and slow exhalation).	
	Do not exhale into the device prior to actuating	
4	**Actual inhaling** (different for different types of inhalation devices)	
	While breathing in slowly (4–5 s) and deeply through your mouth, press down on the top of the inhaler with your thumb (press the button) to release a puff	Breathe in quickly and deeply.
5	**Immediately after inhaling**	
	Take your inhaler device out of your mouth, hold your breath for several seconds and then breathe out very slowly, away from the inhaler.	Take your inhaler device out of your mouth, hold your breath for several seconds and then breathe out very slowly, away from the inhaler. Inhale twice to empty the capsule completely, close the mouthpiece and clean as needed.

assessment was up to 5 min in a patient who is treated with 2–3 inhalation systems. Rate of non-adherence to an inhaler was expressed as errors (total score from 0 to 5) at each of the five clearly defined steps (Five Steps Assessment) for each type of an inhaler.

Each step was scored in a simple dichotomous manner: performed correctly (=0) or incorrectly (=1), i.e., used or not used in accordance with the respective manufacturer's instructions (Summary of Product Characteristics) and European Respiratory Society recommendation (Laube et al., 2011; Czech Multicenter Research Database of COPD, 2018).

Correct performance of the steps for all types of inhalers is elaborated upon in detail in a brief manual available to all participating medical staff (Czech Multicenter Research Database of COPD, 2018). Moreover, all investigators (nurses and respiratory physicians) were trained in the correct use of the Five Steps Assessment before the start of the study (February 2013) and re-trained every year (during annual COPD CMRD working meetings).

The Five Steps Assessment tool was validated by four investigators (authors of this study) who independently scored A-ApplT in a sample of 18 COPD outpatients not included in the present study. The level of agreement among the investigators was pre-set to 90%. The differences in scores between the investigators did not exceed 10% and divergence was always minor in all the tested inhalers.

Statistical Analysis

Continuous parameters were described with valid N, mean and median (5–95% quantile). Categorical parameters were described with frequencies. Relative frequencies were calculated from valid data. Statistical differences between groups in categorical variables were tested using the Mann-Whitney U test. Relationships between two categorical parameters were analyzed with Fisher's exact test. The data were analyzed using IBM SPSS Statistics 24.0.0.0. The level of significance was pre-set to $\alpha = 0.05$.

RESULTS

Thirteen centers measured adherence to an application technique (A-ApplT) and recruited 546 participants. This represents 69.6% of all patients (N = 784) included in the COPD CMRD. The ratio of participants to patients recruited in the COPD CMRD varied from 21.4 to 100.0% per center. Socio-demographic and main clinical characteristics of the participants are summarized in **Table 2**.

The most frequently used inhalation systems (inhalers) were traditional pMDIs and two types of DPIs: AEROLIZER and HANDIHALER (**Table 3**). Majority of participants (88%) used a combination of two or more inhalers. The most commonly used dual combinations were: AEROLIZER plus pMDI (N = 108; 20.2%) and RESPIMAT plus pMDI (N = 22; 4.1%). The most common triple combinations were: HANDIHALER plus AEROLIZER plus pMDI (N = 107; 20.0%) and HANDIHALER plus DISKUS plus pMDI (N = 59; 11.0%).

Only 164 (30.0%) participants adhered properly to each of the five steps. Full adherence to each type of inhaler, (i.e., all steps performed correctly) is shown in **Figure 1**.

For all types of inhalers, the highest rate of failure was observed at the step No. 3 (failure to breathe out completely in one breath immediately before inhalation of the drug). The second most problematic step was the step No. 4 (actual

TABLE 2 | Socio-demographic and main clinical characteristics of the participants (N = 546).

Basic demography	
Age at entrance into the study in years mean; median (5–95% quantile)	N = 546 67.0; 67.0 (51.0–80.0)
Duration of COPD from first diagnosis to study (years) mean; median (5–95% quantile)	N = 519 8.2; 6.6 (0.5–22.3)
Men (%)	408 (75.0)
Education level: years spent in pre-graduate school mean; median (5–95% quantile)	N = 515 12.0;12.0 (9.0–18.0)
Smoking status Ex-smokers (%) Non-smokers (%) Current smokers (%)	386 (71.0) 56 (10.0) 104 (19.0)
BMI (kg/m^2) mean; median (5–95% quantile)	N = 546 28.0; 27.0 (18.0–38.0)
Medical characteristics	
Moderate and severe exacerbations* during the last year mean; median (5–95% quantile)	N = 546 1.3; 1.0 (0.0; 4.0)
Total number (%) of patients who experienced at least one episode	296 (54.2)
FEV_1 (% pred) mean; median (5–95% quantile)	N = 546 44.7; 45.7 (25.1–60.0)
<30 (% pred)	73 (13.4)
30–50 (% pred)	266 (48.7)
>50 (% pred)	207 (37.9)
FVC (% pred)	N = 546 68.6; 67.9 (39.8–100.7)
FEV_1/FVC	N = 546 0.5; 0.5 (0.3–0.7)

*BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity. *deterioration of COPD symptoms which needs treatment with antibiotics and/or corticosteroids (oral or intravenous) during out-patient (moderate) or in-patient (severe) therapy.*

TABLE 3 | Inhalation systems used by study participants (N = 546).

Inhalation system	Participants, N (%)
Pressurized metered dose inhalers group (pMDI)	
Traditional pMDI (aerosol)	455 (83.3)
RESPIMAT (soft mist inhaler)	73 (13.4)
EASI - BREATHE	2 (0.4)
Dry powder inhalers group (DPI)	
AEROLIZER/BREEZHALER	293 (53.7)
HANDIHALER	240 (43.9)
DISKUS	116 (21.2)
TURBUHALER	40 (7.3)
GENUAIR	21 (3.8)
ELLIPTA	9 (1.6)

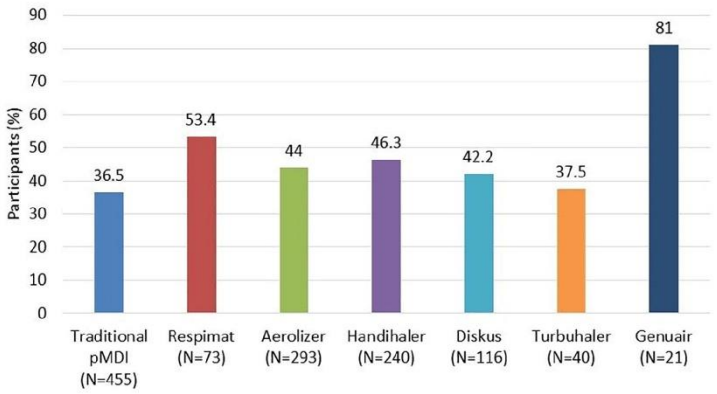

FIGURE 1 | Participants who performed all five steps of the application technique correctly (evaluated by the Five Steps Assessment; total *N* = 546 patients). *N* = number of participants who used the particular inhalation system. Since the majority of participants were treated with a combination of systems, categories are not mutually exclusive. pMDI, pressurized metered dose inhaler. Data for Ellipta and Easy-breathe are not shown, as these devices were used by a small number of participants only (9 Ellipta and 2 Easy-breathe).

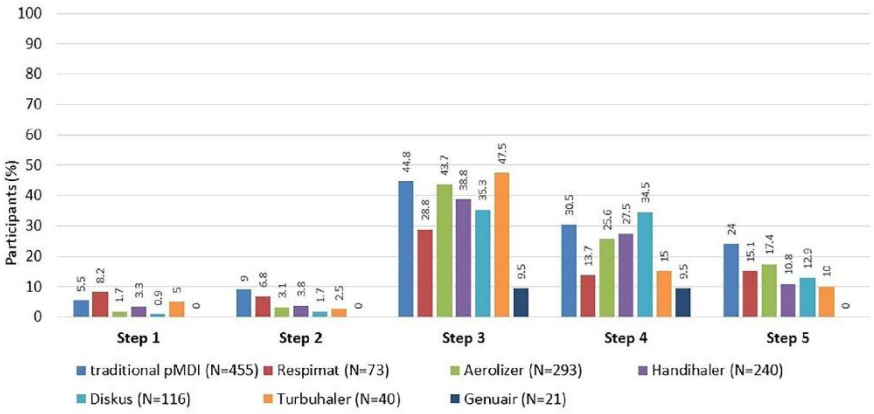

FIGURE 2 | Participants who made error(s) in the application technique (evaluated by the Five Steps Assessment; total *N* = 546 patients). *N* = number of participants who used the particular inhalation system. Since the majority of participants were treated with a combination of systems, categories are not mutually exclusive. pMDI, pressurized metered dose inhaler. Data for Ellipta and Easy-breathe are not shown, as these devices were used by a small number of participants only (9 Ellipta and 2 Easy-breathe).

inhalation). Erroneous steps for individual types of inhalers are shown in **Figure 2**.

In patients who used at least one type from each of the two groups of inhalers (DPI and pMDI, $N = 408$), the total number of errors was similar. There was no significant difference between the two groups when comparing the two most erroneous steps (No. 3 and No. 4). Significant differences were observed at the step No. 1 (5.9% in pMDI vs. 3.2% in DPI group, $p = 0.035$), and the step No. 2 (9.3% vs. 3.7%, $p < 0.001$) only.

DISCUSSION

We have introduced a unique tool for evaluation of adherence to an application technique (A-ApplT) applicable to all types of currently available inhalation systems used in the COPD population. Other studies assessing the A-ApplT (correctness of inhalation) used various types of extensive checklists consisting of a number of different steps relevant to a specific type of inhaler (Molimard et al., 2003; Khassawneh et al., 2008;

Rootmensen et al., 2010; Hammerlein et al., 2011; Melani et al., 2011; Pothirat et al., 2015; Price et al., 2017). Our tool is very simple and easy to use. Each step represents a generic type of action, detailed performance of which is specific to the type of inhaler (**Table 1**). The sequence of these steps is logical and intuitive, allowing facile use in clinical practice and reducing variability if assessed by different clinicians.

Optimal A-ApplT, i.e., application without any error as assessed by our Five Steps Assessment was observed in less than one third (30%) of participants. Pothirat et al. involved a population of COPD patients comparable to ours and identified 25% of patients performing without a critical error (Pothirat et al., 2015). Arora et al. assessed an inhalation technique in patients with asthma and COPD, who were notably younger than our cohort, and found that 82% of participants made at least one error (Arora et al., 2014). Evaluating inhalation techniques in patients affected with asthma and COPD by means of videotaped demonstrations, Rootmensen et al. (2010) concluded that 60% performed all essential steps correctly. However, the cohort of patients observed in the Rootmensen's study differed substantially from cohorts researched in other studies listed above, including ours. Almost half of their population were patients with asthma in whom bronchial obstruction is reversible and thus patients might feel the effects of their inhalation therapy immediately. Furthermore, their patients had considerably higher mean FEV_1 (71% predicted) and this can aid the application. On contrary, permanent lung hyperinflation associated with COPD may have fundamental impact on the inhalation technique (Laube et al., 2011).

Since there is no unanimous device to evaluate application techniques, comparison between studies is rather onerous. Nevertheless, available literature agrees on the most problematic steps of application. These are common to pMDIs and DPIs and include: breathing out completely before inhaling (corresponds to our step No. 3), inhaling correctly (step No. 4) and holding breath for several seconds and exhaling away from the inhaler (step No. 5) (Lavorini et al., 2008; Rootmensen et al., 2010; Hammerlein et al., 2011; Arora et al., 2014; Pothirat et al., 2015; Dudvarski Ilic et al., 2016; Bartolo et al., 2017; Price et al., 2017). These observations are in accordance with our findings.

It is clinically important that we observed similar frequency of errors in both groups of inhalers (pMDI and DPI groups) in patients using at least one type from each group. This finding is in accordance with two large studies by Melani et al. (2004, 2011) conducted in routine clinical practice of chest clinics with patients suffering mainly from asthma and COPD as well as with a German study carried out in pharmacies (Hammerlein et al., 2011). On the other hand, Pothirat et al. (2015) and Rootmensen et al. (2010) observed significantly more errors in patients using pMDIs. Molimard et al. (2003) and Khassawneh et al. (2008) made the same conclusions when studying outpatients with asthma and COPD in chest clinics. This may be associated with the different types of inhalers used in the studied cohorts; e.g., single-dose DPIs (Handihaler, Aerolizer), predominant in our study, might be a subject to more mishandlings than prefilled DPIs (Rootmensen et al., 2010). Furthermore, patients who switch to a new drug formulation (e.g., an inhaler recently approved and introduced to the market) can be more able (and willing) to adhere. Patients who are used to a certain type of an inhaler might be less responsive to treatment changes and a different application technique may be more difficult for them to adopt. This could also explain better A-ApplT of GENUAIR.

Incorrect performance of steps No. 1 and No. 2 was infrequent but significantly different between the pMDI and DPI groups. Even though manipulation of single-dose DPIs could be considered more difficult as it requires insertion of a capsule into the inhaler, the pMDI group was associated with more step No. 1 errors. This is probably due to frequently observed inappropriate grasp and positioning of the inhaler. The difference in error rate at the step No. 2 is most likely due to the need to shake the pMDI device. Patients might not consider this to be an important action as the actuation of the device follows. Other authors who focussed on pMDIs mishandling also showed that shaking of the device is one of the most problematic steps (Hammerlein et al., 2011; Pothirat et al., 2015; Bartolo et al., 2017).

No study participant used the spacer device as a tool to facilitate inhalation. In the Czech Republic, spacer devices are only used as an aid in end-stage patients and patients with moderate or severe exacerbations. However, these patients were excluded from the COPD CMRD (Novotna et al., 2014). Consequently, our cohort included patients with stabilized COPD only, in whom spacers are not used.

When we observed and reviewed the A-ApplT, we noticed that many patients breathe out insufficiently before breathing in through the inhaler (step No. 3). In addition, patients were frequently unable to correctly breathe in through the inhaler, e.g., their breathing in was too short or too weak (step No. 4). Therefore, it was necessary to provide patients with a training on the correct application technique. However, it cannot be assumed that all healthcare professionals are fully familiar with the application techniques for the various inhalers. To support health care professionals in their ability to train their patients, Murphy (2019) developed the 7-Steps to Success Inhaler Reminder Cards. We trained the participating respiratory physicians and nurses at workshops during COPD CMRD annual meetings.

If an incorrect breathing pattern is present during inhalation, respiratory physiotherapy techniques can be added to comprehensive treatment. It is possible to use breathing retraining, diaphragmatic breathing, respiratory muscle training, pursed lip breathing and thoracic expansion exercises focused on expansion of lower chest with the aim to improve chest mobility, increase inspiratory and expiratory muscle strength and improve patient's control of breathing. It is also very important to teach patients correct body positioning during an inhalation. The patient should be in a comfortable well-supported sitting position with his/her back straight and with relaxed upper chest and shoulders (Pryor and Prasad, 2008).

Strengths

Our study is strong in its use of a large homogenous cohort of patients with moderate to very severe COPD. All centers were secondary care pulmonary outpatient clinics, i.e., the evaluation of A-ApplT was conducted in a consistent manner by trained respiratory nurses under direct supervision of physicians.

Furthermore, our study included all types of inhalers currently used in COPD patients in the Czech Republic. In patients using

more than one type of an inhaler, all inhalers were assessed. This provided a comprehensive picture on the patient's A-ApplT.

Limitations

Assessments performed within the COPD CMRD within the COPD CMRD were categorized into mandatory and recommended (non-mandatory) ones. The evaluation of A-ApplT is recommended, not mandatory. Data on patients in whom mandatory data were not obtained are considered invalid and not included in analyses (Novotna et al., 2014). Patients who refused participation in the study might be less motivated with poorer health status compared to those who agreed to take part. Therefore, even lower A-ApplT can be expected in the entire real-life COPD population.

The assessment of A-ApplT was subjective, especially with respect to the steps involving exhalation and inhalation. In the absence of equipment to measure these objectively in routine clinical practice, we attempted to minimize the effect of subjectivity by providing unified training (and re-training) in the application technique and handling of each type of the inhaler to all participating nurses and physicians before the study.

It is worth noting that not all inhaler mishandlings reduce lung drug delivery or deposition. However, some of the errors (e.g., failing to coordinate actuation with the start of inspiration in pMDIs) could be critical (Fink and Rubin, 2005; Melani et al., 2011; Price et al., 2017). We did not study clinical impact of the different errors. Although some steps could be more important than others, the main aim still is to manage the application technique in its entirety.

Duration of inhaler use may also have an impact on A-ApplT (Arora et al., 2014). However, we did not measure this. We also did not know how many times a patient was trained in the application technique before entering the study. According to the national COPD guidelines (Koblizek et al., 2013), education should be a part of each patient visit but this is known not to be observed in clinical practice. Patients are properly educated only at the time of diagnosis, at the start of therapy or when it is modified, or when there is worsening of their health status. Finally, it has been suggested that the medication itself could affect A-ApplT (Restrepo et al., 2008; Darba et al., 2015; Koehorst-ter Huurne et al., 2016) but we did not focus on this in our analysis.

CONCLUSION

In summary, we developed and validated a unique, easy-to-use instrument, the Five Steps Assessment, which is applicable for evaluation of A-ApplT of all currently available inhalation systems. Our study has shown that the A-ApplT in patients with non-mild COPD is inadequate; only one third of our participants performed all five steps correctly. No significant differences were found between the pMDI and DPI groups. The most problematic steps were breathing out completely before inhalation (step No. 3) and actual inhalation (step No. 4). Therefore, application technique should be repeatedly trained with a focus on the most problematic steps. The training of correct application technique should be performed by properly (re-)educated medical staff.

DATA AVAILABILITY

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

MV presented the idea of the Five Steps Assessment, participated in data analysis and interpretation, and drafted the manuscript. TH participated in data analysis and interpretation, drafted the manuscript. TT participated in data visualization and interpretation. EZ participated in data interpretation, edited the manuscript. JV contributed to the conception of the manuscript. MS and KH performed data analysis and interpretation. LN, KB, MP, BN, PM, MC, and VK collected the data and supervised adherence evaluation. VK and KH organized the COPD CMRD. MS and VK contributed to writing of the manuscript. VK contributed significantly to data interpretation. All authors read and approved the final manuscript.

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3. ZÁVĚR

Tato habilitační práce pojednává o důležitosti stanovení prognózy pacienta s CHOPN a o metodách zlepšení výsledků léčby za pomoci respirační fyzioterapie a zdokonalení inhalační techniky. Součástí je také Poziční dokument ČPFS k léčbě stabilní fáze CHOPN, který je výsledkem mnohaleté práce expertní skupiny ČPFS, jejímž jsem členem.

V rámci stanovení prognózy pacienta s CHOPN jsme prokázali, že změna klasifikace CHOPN dle novějších systémů GOLD vedla ke ztrátě intuitivnosti klasifikace, která nyní vystihuje již pouze míru symptomů a výskyt exacerbací. Používáním systému GOLD skupin A-D největší část pacientů spadá do skupiny B, kde u části pacientů hrozí progrese nemoci, vznik začarovaného kruhu exacerbací a deteriorace stavu pacienta. Identifikace rizikových pacientů v tak velké skupině je klíčem k zamezení popsaných negativních jevů. V naší práci jsme zjistili, že pacienti skupiny B mají při současné přítomnosti závažné chronické hypoxémie s PaO_2 <7,3 kPa vysoké riziko dlohodobé mortality. Pacienti s SpO_2 <90% by tak měli mít podstoupit vyšetření arteriálních krevních plynů.

Zkonstruovali jsme nový prognostický index s názvem CADOT, který má oproti nejvíce používaným prognostickým indexům BODE a ADO vyšší prognostickou přesnost (vyšší hodnotu AUC) a lze ho použít i v situacích, kdy nelze provést 6-MWT (např. absence chodby s délkou 20-30m v ordinaci lékaře, pacient s pohybovým omezením, po amputaci dolní končetiny a podobně). CADOT byl vedle BODE indexu doporučen k používání v rutinní klinické praxi i v Pozičním dokumentu ČPFS k léčbě stabilní fáze CHOPN. Tento dokument ustanovuje aktuální rámec doporučené péče o pacienty s CHOPN v ordinacích pneumologů v České republice. Dokument vychází z moderního konceptu stratifikované klasifikace nemoci, která se následně odráží i v léčebném doporučení. Naší snahou bylo definovat co nejvyšší míru personalizace léčby na bázi fenotypů / léčitelných rysů nemoci,

které jsou u pacientů exprimovány s vysokou mírou variability a nesnesou tak simplexní paušalizaci.

Jak jsem zmínil v obecné části (v úvodu) této práce, existuje jen málo typů léčby CHOPN, a to použitelných jen ve přesně definovaných situacích, kdy má lékař šanci ovlivnit (snížit) riziko mortality pacienta s CHOPN. Primárním cílem farmakologické a nefarmakologické léčby tak i nadále zůstává zamezení nebo snížení výskytu exacerbací a snaha o zmírnění symptomů a zlepšení kvality života pacienta. V rámci snahy o optimalizaci efektu farmakologické léčby navrhujeme používat tzv. „Five Steps Assessment" – jednoduchý a univerzální nástroj k ověření míry kvality inhalační / aplikační techniky, který ale může sloužit i jako edukační nástroj pro pacienta i jeho ošetřující personál. V této práci jsme zároveň zjistili, že jen 30% pacientů s CHOPN v naší kohortě provedlo všech 5 kroků aplikační techniky správně.

V posledním článku navrhujeme protokol malé randomizované studie, která má najít odpověď na otázku, zda TIRE může být účinnější metodou nácviku respiračního svalstva než konvenční IMT tréning pomocí IMT Thresholdu. Respirační fyzioterapie má zásadní význam pro zlepšení: kondice a výkonnosti pacienta, mechaniky dýchání, ventilačních i respiračních funkcí. Na straně pacienta dochází ke zmírnění subjektivních symptomů a zlepšení kvality života.

Naše práce přispěli k hlubšímu poznání rizikových faktorů mortality u pacientů s CHOPN a dokládají význam správné aplikační techniky inhalační léčby i respirační fyzioterapie jako důležitých složek péče o pacienty s CHOPN.

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5. ABECEDNÍ SEZNAM POUŽITÝCH ZKRATEK

A1AT – alfa1-antitrypsin

ACO – Asthma / COPD Overlap

ADO – Age, Dyspnoea (mMRC score), Obstruction (FEV_1)

AUC – Area Under Curve

BODE – BMI, Obstruction (FEV_1), Dyspnoea (mMRC score), Exercise capacity (6-MWT)

BODEx – BMI, Obstruction (FEV_1), Dyspnoea (mMRC score), Exacerbation

BCO – Bronchiectases / COPD Overlap

BLVR – Bronchoscopic Lung Volume Reduction

BMI – Body Mass Index

CADOT – Chronic heart failure, Age, Dyspnoea (mMRC score), Obstruction (FEV_1), TL_{CO}

CAT – COPD Assessment Test

CO – Carbon Dioxide

CODEX – Comorbidity, Obstruction (FEV_1), Dyspnoea (mMRC score), Exacerbation

COTE – COPD specific comorbidity test

COVID-19 – nemoc způsobená virem SARS-CoV-2

CT – Computed Tomography

ČPFS – Česká Pneumologická a Ftizeologická Společnost

DDOT – douhodobá domácí oxygenoterapie

DPI – Dry Powder Inhaler

EKG – elektrokardiogram

FeNO – fraction of exhaled nitric oxide

FEV_1 – usilovně vydechnutý objem za první sekundu výdechu

FVC – usilovná vitální kapacita

GesEPOC – španělská guidelines pro léčbu CHOPN

GOLD – Global Initiative for Chronic Obstructive Lung Disease

HIV – virus lidské imunitní nedostatečnosti

HR – hazard ratio

CHOPN – chronická obstrukční plicní nemoc

CHSS – chronické srdeční selhání

IKS/LABA – fixní kombinace inhalačních kortikosteroidů a dlouhodobě působících $beta_2$-sympatomimetik

IKS/LAMA/LABA – fixní kombinace inhalačních kortikosteroidů, dlouhodobě působících parasympatolytik a dlouhodobě působících $beta_2$-sympatomimetik

ID – inspiratory duration

IMT – inspiratory muscle training

K_{CO} – transfer koeficient pro oxid uhelnatý

LVRS – lung volume reduction surgery

MIP – maximal inspiratory pressure

mMRC – modified Medical Research Council skóre

MZČR – Ministerstvo zdravotnictví České republiky

NIV – neinvazivní ventilace

NYHA – New York Heart Association

$PaCO_2$ – parciální tlak oxidu uhličitého v arteriální krvi

PaO_2 – parciální tlak kyslíku v arteriální krvi

pMDI – pressurized Metered-Dose Inhaler

ROC – Receiver Operating Characteristic

RV – Residual Volume

SD – Standard Deviation

SGRQ – St. George´s Respiratory Questionnaire

SMIP – sustained maximal inspiratory pressure

SpO_2 – periferní saturace hemoglobinu kyslíkem

TIRE – test of incremental respiratory endurance

TLC – celková kapacita plic

TL_{CO} – difuzní kapacita plic pro oxid uhelnatý

ÚZIS – Ústav zdravotnických informací a statistiky České republiky

6-MWT – šestiminutový test chůzí

95%CI – 95-procentní interval spolehlivosti

6. SEZNAM FULLTEXTOVÝCH PUBLIKACÍ AUTORA V ČASOPISECH S IMPAKT FAKTOREM

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