Registries of Patients with Chronic Obstructive Pulmonary Diseases – Why Are They Important?

Registri bolesnika s hroničnim opstruktivnim bolestima pluća – zašto su važni?

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SUMMARY COPD is most probably not just a single disease, but a syndrome made up of numerous individual overlapping diseases. The concept of phenotyping COPD patients would not be feasible without major population-based studies and patient registries. The aim of setting up a COPD registry has been defined as the need to establish the disease prevalence, phenotype incidence, clinical features, co-morbidities, treatment specificities, together with monitoring of the disease's natural course and its outcome on a large sample of patients. In Serbia, an online registry of COPD patients has been operational since 2016, and the recent insight (before the manuscript's submission) shows over 4,200 entries.
Analysis of the population of patients entered shows that an average patient is male (63%), smoker or ex-smoker (90.48%), over 60 years of age (82.01%). Pulmonary function analysis shows that the majority of enrolled patients (82%) have moderate to severe obstruction, with an average FEV1 of 52.82% of the predicted value, while 45% of patients have FEV1 value below 50% of the predicted value. The Charlson Comorbidity Index shows that half of the patients (49.97%) have one comorbidity. Most common comorbidities are arterial hypertension, diabetes mellitus, liver disease, congestive heart failure, and coronary ischemic disease. Comorbidities such as osteoporosis, depression, and anxiety have been reported very rarely. The phenotype analysis showed equal shares of two predominant groups: non-exacerbators (51.12%), and exacerbators (48.88%) within which there are groups of patients with pulmonary emphysema (34.35%) and patients with chronic bronchitis (14.53%). The data indicate that strategy for COPD treatment in our environment is changing towards adoption of modern recommendations and guidelines for treatment of this disease. The data enable a comprehensive insight into the disease and drawing up of feasible treatment strategies that give us hope for success.

KEY WORDS: Chronic Obstructive Pulmonary Disease, registry, phenotype

SAŽETAK HOBP verovatno nije samo jedna bolest već sindrom sačinjen od brojnih, pojedinačnih bolesti koje se preklapaju. Koncept fenotipizacije pacijenata sa HOBP-om ne bi bio moguć bez velikih, populacionih studija i registara pacijenata. Cilj kreiranja registara pacijenata sa HOBP-om je definisan potrebom da se na velikom uzorku utvrdi prevalenca bolesti, učestalost fenotipova, kliničke karakteristike, komorbiditeti, specifičnosti terapije, uz praćenje prirodnog toka bolesti do njenog ishoda. U Srbiji od 2016. godine postoji elektronski (onlajn) registar pacijenata sa hroničnom opstruktivnom bolešću pluća, koji je u momentu pisanja ovog teksta brojao više od 4200 unosa. Analiza populacije pacijenta unetih u registar HOBP-a ukazuje na to da je prosečan pacijent muškarac (63% pacijenata), pušač ili bivši pušač (ukupno 90,48% pacijenata), stariji od 60 godina (82,01% pacijenata). Analiza plućne funkcije pokazuje da većina pacijenata (82%) ima umerenu i srednje tešku opstrukciju, sa prosečnom vrednošću FEV1 od 52,82% predviđene vrednosti, dok 45% pacijenata ima vrednost FEV1 nižu od 50% predviđene vrednosti. Čarlsonov indeks komorbiditeta je pokazao da polovina pacijenata (49,97%) ima jedan komorbiditet. Najučestaliji komorbiditeti su: arterijska hipertenzija, dijabetes melitus, bolesti jetre, kongestivna srčana slabost i koronarna ishemijska bolest. Komorbiditeti poput osteoporoze, depresije i anksioznosti su vrlo retko prijavljivani. U pogledu fenotipova zapaža se da je učestalost dve dominirajuće grupe bolesnika izjednačena: grupa neegzacerbatora (51,12%), zatim egzacerbatora (48,88%), u okviru kojih se nalaze grupe pacijenata sa emfizemom pluća sa 34,35% zastupljenosti i pacijenata sa hroničnim bronhitisom sa 14,53% zastupljenosti. Podaci ukazuju na to da se strategija lečenja HOBP-a u našoj sredini ipak menja, uz usvajanje savremenih preporuka i smernica za lečenje ove bolesti. Ovakvi podaci nam omogućavaju da sagledamo bolest iz svih uglova i kreiramo realno izvodljive strategije lečenja koje daju nadu za postizanje uspeha.

KLJUČNE REČI: hronična opstruktivna bolest pluća, registar, fenotip

Introduction

By definition, Chronic Obstructive Pulmonary Disease (COPD) is a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (1).

Most common respiratory symptoms associated with this disease include dyspnea, cough and/or sputum production. These symptoms are usually insufficiently recognized by patients and thus underreported.

Current knowledge and medical experience suggest that COPD is most likely not just a single disease, but a syndrome made up of numerous individual overlapping diseases. The current definition does not reflect the phenotype, distribution, varieties of clinical manifestations or response of the disease to treatment. Phenotyping of COPD patients has become a necessity in order to establish correlation of genetic factors with environmental factors that result in pathological processes, to identify clinical symptoms and physiological abnormalities that resulted in development of the disease, and to recognize response to treatment, as well as to understand the natural course of the disease. By definition, "phenotype is the set of observable structural and functional characteristics of an organism determined by its genotype and modulated by factors in its environment" (2, 3). An international group of experts defined the COPD phenotype as "those attributes of the disease alone or in combination that describe the differences between individuals with COPD in relation to parameters that have clinical significance (symptoms, exacerbations, response to treatment, rate of progression disease, and survival)" (2, 3).

The concept of phenotype in COPD has evolved significantly over time and to this date the classification of COPD patients into different phenotype groups is not absolutely final, although experts are clearly aware of the fact that severity of the disease and other features can no longer be perceived only through the level of obstruction and FEV1 numerical value. Instead, a more comprehensive understanding of individual patients and respective characteristics of the disease, analysis of symptoms present and exacerbation rate are also required, which are all reflected in the new GOLD guidelines (1). The fact that underlines the importance of the phenotype concept is that each phenotype is specific in terms of treatment, i.e. therapeutic modalities that yield better results, higher chances of success and improvement of quality of life of these patients.

Registries

The concept of COPD phenotyping would not be possible without large, population-based studies and registries of COPD patients.

Uvod

Hronična opstruktivna bolest pluća (HOBP) po definiciji je „česta bolest koja se može sprečiti i lečiti, a koja se karakteriše stalnim respiratornim simptomima i ograničenjem protoka vazduha koji nastaju usled abnormalnosti disajnih puteva i alveola, obično izazvanih velikim izlaganjem štetnim česticama i gasovima" (1).

Najčešći respiratorni simptomi povezani sa ovom bolešću su dispneja, kašalj i/ili produkcija sputuma. Njih pacijenti najčešće nedovoljno prepoznaju i nedovoljno prijavljuju svojim lekarima.

Dosadašnja saznanja i medicinsko iskustvo ukazuju na to da HOBP verovatno nije samo jedna bolest, već sindrom sačinjen od brojnih, pojedinačnih bolesti koje se međusobno preklapaju. Aktuelna definicija ne odražava fenotip bolesti, njenu rasprostranjenost, načine kliničkog ispoljavanja, kao ni odgovor na terapiju.

Fenotipizacija osoba obolelih od HOBP-a nameće se kao neminovnost, uz utvrđivanje povezanosti genetike sa faktorima okruženja koji dovode do razvoja patoloških procesa, prepoznavanje kliničkih simptoma i fizioloških promena koji su doveli do razvoja bolesti i utvrđivanje odgovora na terapiju i prepoznavanje prirodnog toka bolesti. Po definiciji, "fenotip predstavlja uočljive strukturne i funkcionalne karakteristike organizma determinisane genotipom i modulisane faktorima njegovog okruženja" (2, 3). Međunarodna grupa eksperata je definisala HOBP fenotip kao „jednu ili kombinaciju karakteristika bolesti bitnih u opisu razlika između pojedinaca sa HOBP-om, koje se odnose na klinički značajna obeležja bolesti (simptomi, egzacerbacije, odgovor na lečenje, brzina napredovanja bolesti i preživljavanje)" (2, 3).

Koncept fenotipova u HOBP-u se značajno menjao tokom vremena i do današnjih dana podela pacijenata sa HOBP-om u različite fenotipove još uvek nije apsolutno konačna, iako u stručnoj javnosti postoji potpuno izgrađena svest o tome da se težina bolesti i druge karakteristike više ne mogu sagledavati isključivo kroz stepen opstrukcije i numeričku vrednost FEV1, već kroz sveobuhvatniji uvid u karakteristike bolesti pojedinačnog pacijenta, kroz analizu prisutne simptomatologije i učestalosti egzacerbacija, što je prepoznao i novi GOLD u svojim smernicama (1). Činjenica koja posebno daje na značaju ideji fenotipizacije je ta da svaki fenotip ima svoje posebnosti i u terapijskom smislu, odnosno u terapijskim modalitetima koji daju bolje rezultate i imaju veću šansu za uspeh i poboljšanje kvaliteta života obolelih.

Registri

Koncept fenotipizacije pacijenata sa HOBP-om ne bi bio moguć bez velikih, populacionih studija i registara pacijenata sa ovom bolešću.

The POPE study (4), i.e. the registry of COPD phenotypes in Central and Eastern Europe that was conducted 2015 and 2016 has greatly contributed to the idea of COPD patient phenotyping. It was conducted as an international, multicenter, observational study of COPD patients in 11 Central and Eastern European countries: Austria, Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Poland, Russia, Slovakia, Slovenia and Serbia. The results were published in 2017. The study was motivated by the fact that in spite of the abundance of studies focusing on COPD clinical presentation, diagnosis and treatment, few of them focused on the region of Central and Eastern Europe (5). COPD patients in the region of Central and Eastern Europe might have different features of the diseases due to different risk factors they are exposed to, both in the environment and patient-related, i.e. age at onset, co-morbidities, access to healthcare services and medication.[5] The primary aim of this study was to assess the prevalence of COPD phenotypes according to predefined criteria in an unselected group of consecutively examined patients with stable COPD in the CEE region in a real-life setting. Secondary aims of the study included analysis of differences in symptom load, and diagnostic and therapeutic behavior in patients classified into different phenotypes (5).

The importance of understanding chronic obstructive pulmonary disease in a broader context – health, epidemiological, social and treatment aspects included – has been recognized and substantiated by predictions of the World Health Organization (WHO), according to which in the years and decades to come, the mortality rate of this disease globally will be on the rise in spite of efforts invested in its prevention and early detection (1). According to all of the above, a pulmonologist is faced with a new problem in management of the disease that requires his/her skills, knowledge, ability to recognize and understand the disease in a new way, and to seek new treatment approaches in partnership with patients themselves.

In light of the facts, the importance and magnitude of COPD-related problems in a country or region could be perceived realistically only if we know the prevalence and features of these patients, and if we take a new approach to treatment in real life. Countries in the region, including Serbia, do not have reliable epidemiological data; instead, all projections are based on assumptions resulting from major epidemiological studies conducted European-wide and globally, or in neighboring countries with similar epidemiological and population mentality features.

Therefore, the aim of setting up COPD patients registries has been primarily guided by the need to establish the actual prevalence of chronic obstructive pulmonary disease, the frequency of its phenotypes, their respective clinical features, co-morbidities and treatment specificities,

Poseban doprinos ideji fenotipizacije pacijenata sa HOBP-om dala je POPE studija[4,] odnosno registar fenotipova HOBP-a u centralnoj i istočnoj Evropi, koja je sprovedena 2015. i 2016. godine kao internacionalna, multicentrična, opservaciona studija pacijenata sa HOBP-om u 11 zemalja centralne i istočne Evrope: Austriji, Bugarskoj, Hrvatskoj, Češkoj, Mađarskoj, Letoniji, Poljskoj, Rusiji, Slovačkoj, Sloveniji i Srbiji, a čiji rezultati su publikovani 2017. godine. Motiv za sprovođenje ove studije bio je u činjenici da je, uprkos postojanju obilja studija koje su se bavile kliničkom prezentacijom, dijagnozom i lečenjem HOBP-a, malo onih koje su bile fokusirane na region centralne i istočne Evrope[5]. Pacijenti sa HOBP-om u regionu centralne i istočne Evrope mogu se predstaviti različitim karakteristikama bolesti, usled razlika u prisutnim faktorima rizika, kako onim iz okruženja, tako i onim od samog domaćina, starosti u vreme pojave bolesti, komorbiditeta, dostupnosti sistema zdravstvene zaštite i lekova (5). Primarni cilj studije je bio procena prevalence HOBP fenotipova prema predefinisanim kriterijumima u neselektovanoj grupi pacijenata u realnom okruženju. Sekundarni ciljevi su uključivali analizu razlika u opterećenju simptomima i dijagnostičkom i terapijskom ponašanju pacijenata klasifikovanih u različite fenotipove (5).

Značaj sagledavanja hronične opstruktivne bolesti pluća u širem kontekstu – zdravstvenom, epidemiološkom, socijalnom i terapijskom, nameće se kao neophodnost, što potvrđuju i predviđanja Svetske zdravstvene organizacije (SZO), prema kojima će u narednim godinama i decenijama smrtnost od ove bolesti u svetskim razmerama rasti i pored napora koji se ulažu u cilju njene prevencije i ranog otkrivanja (1). Zbog svega navedenog se pred lekara pulmologa postavlja novi problem u pristupu ovoj bolesti, koji od njega zahteva veštinu, znanje, sposobnost prepoznavanja i sagledavanja bolesti na novi način i traženje novih terapijskih pristupa u partnerstvu sa samim pacijentom.

U svetlu svih navedenih činjenica, značaj veličine problema HOBP-a u državi ili regionu se može sagledati realno samo ukoliko se zna prevalenca bolesti i karakteristike samih obolelih, ali i terapijski pristup u stvarnom životu. Zemlje regiona, pa samim tim i Srbija, ne raspolažu pouzdanim epidemiološkim podacima, već su sve projekcije zasnovane na pretpostavkama koje proizilaze iz rezultata velikih epidemioloških studija sprovedenih u zemljama Evrope, sveta i okruženja, sa sličnim epidemiološkim karakteristikama i osobenostima mentaliteta populacije.

Stoga je cilj kreiranja registara pacijenata sa HOBP-om prvenstveno definisan potrebom da se na velikom uzorku utvrdi prevalenca hronične opstruktivne bolesti pluća, učestalost njenih pojedinačnih fenotipova, njihove kliničke karakteristike, komorbiditeti, kao i specifičnosti terapije, uz

FIGURE 1. Sex distribution of patients

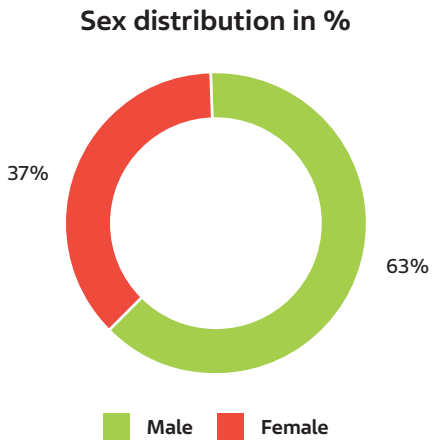
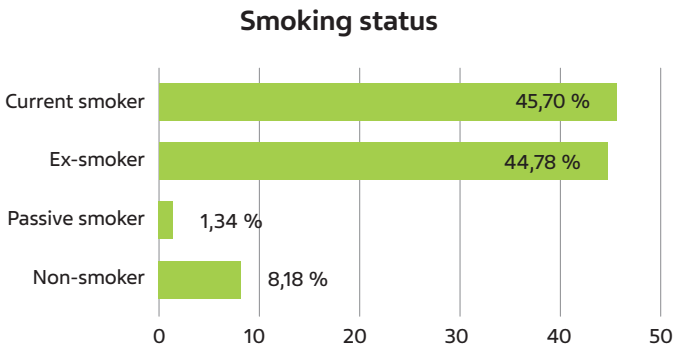


FIGURE 2. Distribution of patients by their smoking status



as well as to monitor the natural course of the disease to its outcome.

Since 2016 in Serbia there has been an online registry of patients with chronic obstructive pulmonary disease (COPD), with slightly over 4,200 patients registered before the manuscript's submission.

It was launched upon the initiative of the Hospital of Pulmonology, University Clinical Center of Kragujevac, and registered as a junior project at the Faculty of Medical Sciences, University of Kragujevac that provided technical support in the database design and data processing.

The registry itself was established as a national, multicenter, retrospective-prospective, observational, non-interventional, electronic (online) registry of patients with chronic obstructive pulmonary disease (COPD). A web application was developed to enable authorized users – physicians, to enter data on their patients and add information after subsequent visits at different time intervals, regardless of whether an out-patient is coming for a regular follow-up visit or has an exacerbation requiring hospitalization. The intention of this type of monitoring is to enable broader insight into dynamics and evolution of the disease together with changes in treatment combinations and approaches, as well as related outcome.

From the initial idea on setting up such a registry, to its realization, all legal requirements relating to the protection of personal and protected data of our patients have been met.

The current cross-section of patients in the database used for the presented analysis was made in December 2019 with 4,243 registered patients.

The patients were recruited in secondary and tertiary level healthcare institutions (general hospitals and university hospitals), as well as in specialized services of local healthcare centers – pulmonology/pneumophthysiology out-patient services. Over 25 healthcare services and 100 physicians all over Serbia participated in data collection. The study itself

praćenje prirodnog toka bolesti do njenog ishoda.

U Srbiji od 2016. godine postoji elektronski (onlajn) registar pacijenata sa hroničnom opstruktivnom bolešću pluća (HOBP), koji je u momentu pisanja ovog teksta brojao nešto više od 4.200 unosa.

On je pokrenut i stvoren na inicijativu koja je potekla sa Klinike za pulmologiju Kliničkog centra Kragujevac, a registrovan je kao junior projekat na Fakultetu medicinskih nauka Univerziteta u Kragujevcu, koji je pružio tehničku podršku u dizajnu baze i obradi podataka.

Sam registar je definisan kao nacionalni, multicentrični, retrospektivno-prospektivni, opservacioni, neintervencijski, elektronski (onlajn) registar pacijenata sa hroničnom opstruktivnom bolešću pluća (HOBP). Razvijen je kao veb-aplikacija koja omogućava autorizovanim korisnicima – lekarima da unose podatke o svojim pacijentima koji se mogu dopunjavati u različitim posetama u vremenskim razmacima, bez obzira na to da li je u pitanju ambulantni pacijent koji dolazi na redovni kontrolni pregled ili pacijent koji je zbog pogoršanja svoje bolesti morao da bude hospitalizovan. Namera ovakvog praćenja bolesnika je da se omogući sagledavanje dinamike i evolutivnosti same bolesti, ali i promene u terapijskim kombinacijama i pristupima, kao i njihovim ishodima.

U toku razvoja ideje o kreiranju ovakvog registra primenjeni su svi zakonskim standardima predviđeni načini zaštite ličnih i poverljivih podataka pacijenata.

Aktuelni presek stanja unetih pacijenata, koji je iskorišćen za analizu koja je predmet ovog teksta, napravljen je u decembru 2019. na 4.243 uneta pacijenta.

Pacijenti su regrutovani u ustanovama sekundarnog i tercijernog nivoa organizacije (opštim bolnicama i kliničkim centrima), kao i u specijalističkim službama domova zdravlja – pulmološkim/pneumoftiziološkim ambulantama. U prikupljanje podataka je uključeno preko 25 zdravstvenih ustanova širom Srbije i više od 100 lekara. Sama studija je neintervencijska i opservaciona, ali je pacijentima ponuđen

FIGURE 3. Age distribution of patients

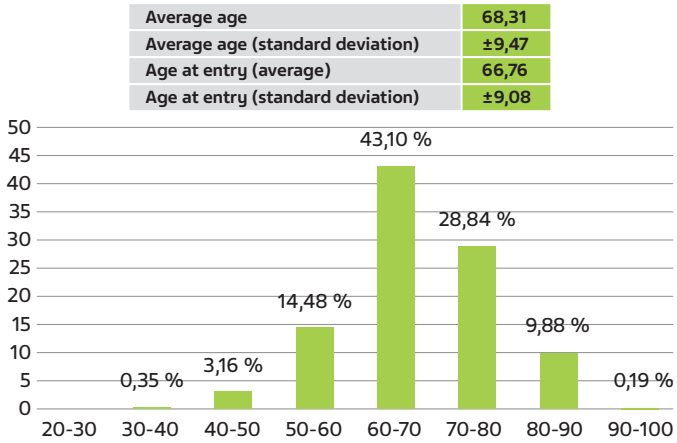
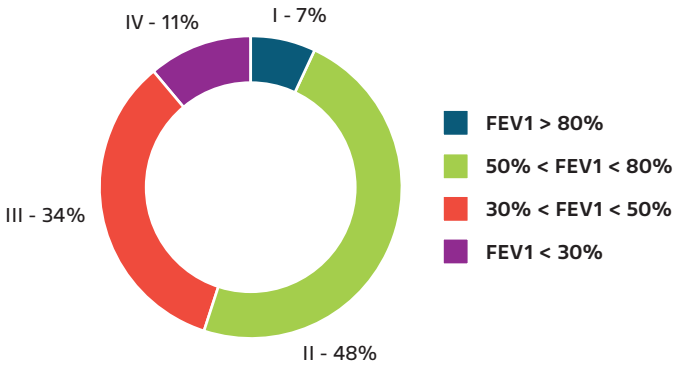


FIGURE 4. Patient distribution by FEV1 value



was observational, non-interventional, but the patients were nevertheless offered to sign an informed consent form for entry into the registry, with verbal explanation by the attending physician or study staff familiar with the idea and objectives of the study.

The patients were stratified by predefined phenotypes. The proposed phenotypes followed the recommendations of the Spanish and Czech guidelines (6, 7), that proposed classification into four clinically defined groups:

- NON-AE, non-exacerbators;
- Asthma-COPD overlap (ACO/ACOS);
- frequent exacerbators with chronic bronchitis (AE-CB), and
- frequent exacerbators without chronic bronchitis (AE NON-CB).

Results of the analysis

Population analysis of 4,243 patients entered into the COPD registry suggests that an average patient is male (63% of patients, Figure 1), smoker or ex-smoker (90.48% of patients, Figure 2), and over 60 years of age (82.01% of patients, Figure 3).

Pulmonary function analysis suggests that most of the patients in the registry (82%) have moderate or moderately severe obstruction with the average FEV1 52.82% of predicted value, while 45% of patients have FEV1 below 50% of predicted value (Figure 4).

The Charlson Comorbidity Index shows that a half of the patients (49.97%) had one comorbidity, while the second half had more than one. Most common comorbidities are arterial hypertension, diabetes mellitus, liver disease, congestive heart failure, and coronary ischemic disease, where the first three of these account for the total of 64% of all comorbidities (Figure 5).

There is abundance of data in medical literature on numerous COPD-associated comorbidities. Cardiovascular and metabolic co-morbidities are the most common, but

obrazac informisanog pristanka za uvršćenje u registar, uz usmeno objašnjenje dato od lekara ili medicinskog lica koje je upoznato sa idejom i ciljem istraživanja.

Pacijenti su stratifikovani prema predefinisanim fenotipovima. Predloženi fenotipovi su u skladu sa preporukama španskih i čeških HOBP smernica (6, 7), koje su predložile četiri klinički definisane grupe:

- neegzacerbatori (NON-AE),
- astma – HOBP preklapanje (ACO/ACOS),
- česti egzacerbatori sa hroničnim bronhitisom (AE-CB) i
- česti egzacerbatori bez hroničnog bronhitisa (AE NON-CB).

Rezultati analize

Analiza populacije od 4.243 pacijenta uneta u HOBP registar ukazuje na to da je prosečan pacijent muškarac (63% pacijenata, slika 1), pušač ili bivši pušač (ukupno 90,48% pacijenata, slika 2), stariji od 60 godina (82,01% pacijenata, slika 3).

Analiza plućne funkcije pokazuje da većina uvršćenih pacijenata (82%) ima umerenu i srednje tešku opstrukciju, sa prosečnom vrednošću FEV1 od 52,82% predviđene vrednosti, dok 45% pacijenata ima vrednost FEV1 nižu od 50% predviđene vrednosti (slika 4).

Čarlsonov indeks komorbiditeta pokazao je da polovina pacijenata (49,97%) ima jedan komorbiditet, druga polovina ima više od jednog. Najučestaliji komorbiditeti su: arterijska hipertenzija, dijabetes melitus, bolesti jetre, kongestivna srčana slabost i koronarna ishemijska bolest, pri čemu prva tri entiteta predstavljaju ukupno 64% svih komorbiditeta (slika 5).

U literaturi se sreću podaci o brojnim komorbiditetima povezanim sa HOBP-om. Najčešće pominjani su kardiovaskularni i metabolički komorbiditeti, ali i depresija, anksioznost, nesanica i anemija, i to sa većom učestalošću kod bolesnika koji su česti egzacerbatori, imaju naglašeniju simptomatologiju i iz svih navedenih razloga oblik bolesti

FIGURE 5. COPD co-morbidity rates

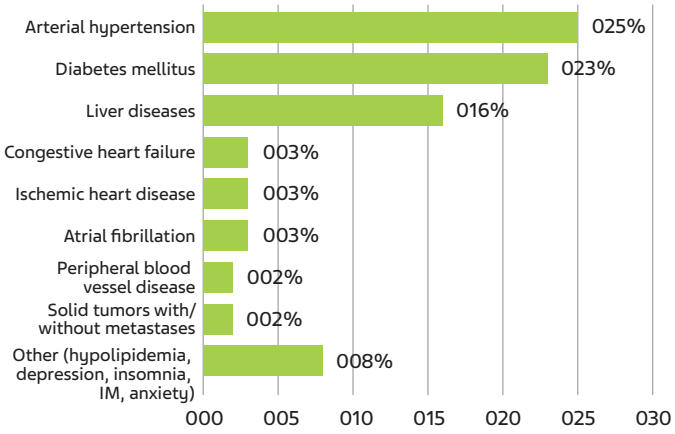
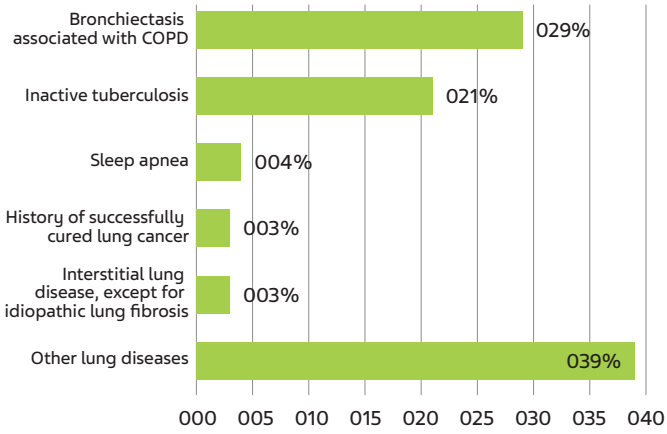


FIGURE 6. Rates of respiratory system co-morbidities



depression, anxiety, insomnia and anemia have also been reported and with higher frequency in patients defined as frequent exacerbators who have more prominent symptomatology. Accordingly, this is a form of the disease that requires higher cost of treatment and has a higher risk of fatal outcome in comparison with patients that are not frequent exacerbators (8, 9). Identification of these patients – with multiple co-morbidities, frequent exacerbations and more prominent symptoms – may be very important from the therapeutic point of view since it recognizes higher risk patients with a higher level of inflammation that should be diagnosed early and in whom the treatment of underlying disease and co-morbidities should be initiated early together with measures aimed at reducing the frequency and severity of exacerbations. These patients in the specific therapeutic sense may benefit from administration of specific anti-inflammatory treatment such as phosphodiesterase-4 inhibitors (10, 11).

Bronchiectasis is the most commonly reported co-morbidity of the respiratory system (29%). It is a frequent finding in COPD patients and a result of history of tuberculosis infection (21%). In this region, tuberculosis infections were quite common in previous decades, and since the population of patients in the registry is predominantly elderly, quite a number of these are expected to have had the infection with sequelae remaining in their lungs. Sleep apnea (4%) and history of treated lung cancer (3%) follow on the list of common co-morbidities of the respiratory system (Figure 6).

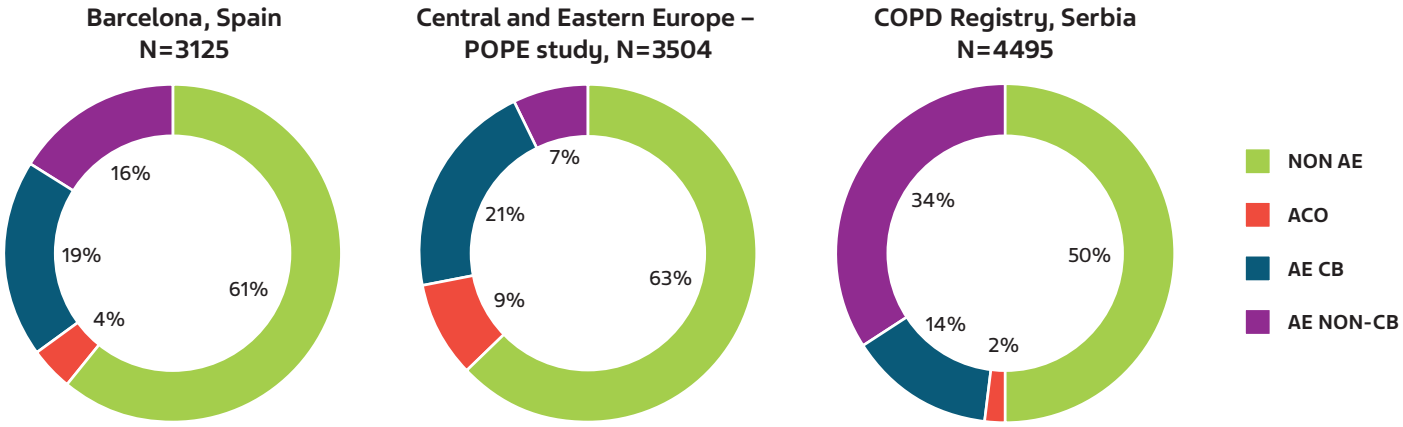
Analysis of the data reveals a significant issue since co-morbidities such as osteoporosis, depression and anxiety were very rarely reported (classified under "other co-morbidities", with cumulative 8% rate), suggesting that patients rarely report complaints that could help recognize these diseases and conditions, but physicians also rarely recognize them and definitely do not make efforts in search of them for early identification and timely treatment. The

koji iziskuje veće troškove lečenja i nosi sa sobom veći rizik od smrtnog ishoda u odnosu na bolesnike koji nisu česti egzacerbatori (8, 9). Identifikacija ovakvih pacijenata – sa više komorbiditeta, čestim egzacerbacijama i naglašenijim simptomima – može biti vrlo značajna i sa terapijskog aspekta, jer ukazuje na bolesnike povećanog rizika, sa većim stepenom inflamacije, koje treba što ranije prepoznati i započeti terapiju osnovne bolesti i komorbiditeta i sprovoditi mere sa ciljem smanjenja učestalosti i težine egzacerbacija, a koji u konkretnom terapijskom smislu mogu imati koristi od primene specifične antiinflamatorne terapije, kao što su inhibitori fosfodiesteraze-4 (10, 11).

Najučestaliji komorbiditeti respiratornog sistema su bronhiektazije (29%), koji su čest nalaz kod pacijenata sa HOBP-om, i posledice ranije preležane tuberukulozne infekcije (21%), koje su bile česte u ovom području u minulim decenijama, a budući da je populacija uvršćenih pacijenata pretežno starije životne dobi, onda je izvesno da među njima ima mnogo onih koji su ovu bolest preležali i koja je ostavila posledice na njihovim plućima. Sledeći po učestalosti komorbiditeti respiratornog sistema su slip apneja (4%) i istorija lečenog karcinoma pluća (3%) (slika 6).

Analizom ovih podataka uočava se značajan problem koji leži u činjenici da su komorbiditeti poput osteoporoze, depresije i anksioznosti vrlo retko prijavljivani (svrstani su u „druge komorbiditete", sa kumulativnom učestalošću od 8%), što govori u prilog činjenici da pacijenti retko prijavljuju tegobe koje bi omogućile prepoznavanje ovih bolesti i stanja, ali i lekari ih takođe retko prepoznaju i sigurno ne čine dovoljno u smislu „traganja" za njima, što bi omogućilo njihovo rano prepoznavanje i pravovremeno lečenje. Slično važi i za slip apneju, koja je prijavljena sa svega 4% učestalosti. Ovo su komorbiditeti čije postojanje značajno utiče na kvalitet života bolesnika sa HOBP-om, a čija je prevalenca u udruženosti sa HOBP-om izvesno u našoj sredini potcenjena, što se jasno uočava u poređenju

FIGURE 7. Comparison of COPD phenotype incidence



same applies to sleep apnea that is reported only in 4% of the cases. These are co-morbidities that significantly affect the quality of life of COPD patients; the prevalence of these diseases and/or conditions in association with COPD is definitely underrated in our population, as substantiated by comparison with data reported in reference literature (12 – 15), even in comparison with results of the POPE study analysis (4) and corresponding registry in Spain (16).

Focusing the phenotypes themselves reveals that the incidences of two predominant groups of patients in the registry are fairly equal; the group of non-exacerbators (51.12%), followed by exacerbators (48.88%) that include patients without bronchitis (i.e. those with pulmonary emphysema) with 34.35% and those with bronchitis (patients with chronic bronchitis) with a 14.53% rate. The rate of patients with overlapping asthma and COPD (ACO/ACOS) was the lowest, only 2%. When the results are divided among phenotypes of patients in our COPD registry and compared to the corresponding results in the POPE study (4) and Spanish registry (16), the shares of phenotypes are different. The share of non-exacerbators in our sample is the lowest, amounting to 50%, while it is higher in other comparative studies – 63% in the POPE sample (4) and 61% in the Spanish registry sample (16) (Figure 7).

Referring to the exacerbator population, in our sample their share is the highest amounting to 48% of the total population while in the POPE sample and Spanish registry their shares were 28% (4) and 35% (16), respectively.

Analysis of the population with overlapping asthma and COPD-a (ACO/ACOS), showed the lowest share in our sample (only 2% of the total population in the registry) in comparison with the POPE registry (9%) (4) and Spanish registry (4%) (16).

Analyses of the obtained data suggest multiple possible causes of the identified differences: one of the possible explanations for the lower share of non-exacerbator population (or the higher share of exacerbators) in our sa literaturnim podacima (12 – 15), pa čak i u poređenju sa rezultatima analize POPE studije (4) i sličnog registra u Španiji (16).

Kada se razmatraju sami fenotipovi, zapaža se da je učestalost dve dominirajuće grupe unetih bolesnika prilično izjednačena: grupa neegzacerbatora (51,12%), zatim egzacerbatora (48,88%) u okviru kojih se nalaze grupe nebronhitičara (odnosno, pacijenata sa emfizemom pluća) sa 34,35% zastupljenosti i bronhitičara (pacijenata sa hroničnim bronhitisom) sa 14,53% zastupljenosti. Pacijenti sa preklapanjem astme i HOBP-a (ACO/ACOS) najmanje su zastupljeni, sa svega 2% učestalosti. Ono što se zapaža kada se rezultati podele na fenotipove pacijenata iz našeg HOBP registra uporede sa sličnim rezultatima iz POPE studije (4) i španskog registra (16) jeste da se odnos učestalosti fenotipova razlikuje. Udeo neegzacerbatora u našem uzorku je najmanji i iznosi 50%, dok je u ostalim uporedivim studijama veći – 63% u POPE uzorku (4) i 61% u uzorku španskog registra (16) (slika 7).

Kada se analiziraju populacije egzacerbatora, u našem uzorku ona je najbrojnija i iznosi 48% ukupne populacije, dok je u POPE uzorku učešće ove populacije iznosilo 28% (4), a u španskom registru 35% (16).

Kada se analiziraju pacijenti sa preklapanjem astme i HOBP-a (ACO/ACOS), u našem registru njih je najmanje evidentiranih (svega 2% ukupne populacije) u poređenju sa POPE registrom (9%) (4) i španskim registrom (4%) (16).

Analize navedenih podataka ukazuju na više mogućih uzroka opisanih razlika: jedno od mogućih objašnjenja za manje učešće populacije neegzacerbatora (ili veće učešće egzacerbatora) u našem registru u odnosu na druga dva može biti usled neredovne primene i/ili neadekvatne terapije u našoj populaciji bolesnika sa HOBP-om, koja ne uspeva da spreči egzacerbacije u željenoj meri. Drugo moguće objašnjenje je u činjenici da je najveći deo pacijenata koji su uneti u naš registar „regrutovan“ iz bolničke sredine, u kojoj se i nalaze zbog pogoršanja osnovne bolesti, za razliku

FIGURE 8. Patient classification by GOLD criteria

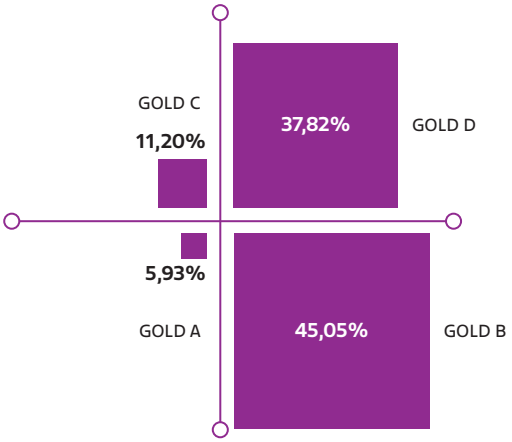
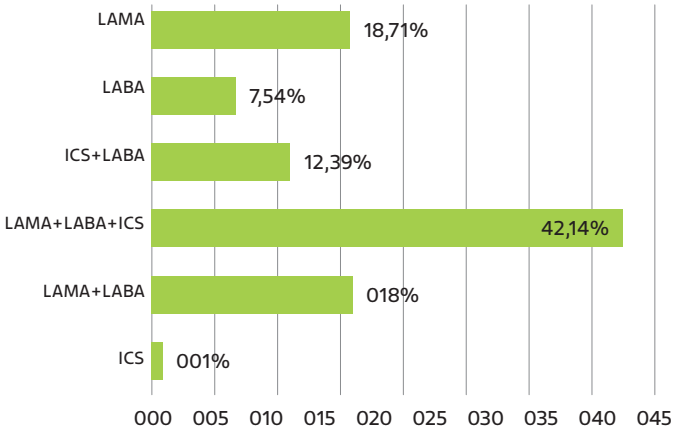


FIGURE 9. Treatment options use



registry in comparison with the other two registries could be a result of lack of compliance and/or inadequate treatment in our population of COPD patients, which does not manage to prevent exacerbations successfully to a desired level. Another possible explanation lies in the fact that most of the patients in our registry are recruited from the in-patient setting, contrary to the patients from other registries that mostly come from the pool of out-patient population, generally milder, less severe cases (4, 16). Also, one of the explanations for the described differences may lie in differences in identification, diagnosis and treatment of exacerbations among medical staff in the compared countries. Although the criteria for establishing the diagnosis of COPD exacerbation are uniform and exact, their application in practice is not all that consistent.

Another identified fact is the probably underestimated share of patients with overlapping asthma and COPD (ACO/ACOS) in our COPD population (only 2%), in comparison with the share of the same population in the comparative registries (POPE 9% (4), Spanish registry 4% (16)) and expected data published in medical literature (17 – 21). The explanation most probably lies in the insufficiently analytical approach to patients with this phenotype, according to the data from other registries, and especially according to our registry, suggesting that this phenotype is insufficiently considered, that evaluation and re-evaluation of patients are not conducted on a regular basis. Improved procedure would result in a larger pool of patients with this phenotype and thus, more adequate treatment to manage the exacerbations and complaints more successfully.

When we examine our COPD population sample by the GOLD ABCD quadrants (1), most of the patients are in quadrant B (45.05%), followed by those in quadrant D (37.82%), while there were substantially fewer patients in quadrants A and C (group A – 5.93%, group C – 11.20%). The analysis clearly indicates that more patients were clustered in the right half of the ABCD square, meaning those with more prominent and

od pacijenata iz drugih registara, koji su u najvećoj meri preuzeti iz populacije ambulantnih, dakle lakših, pacijenata (4, 16). Takođe, jedno od objašnjenja za opisanu razliku može ležati u razlikama u prepoznavanju, dijagnostikovanju i lečenju egzacerbacija između lekara u poređenim zemljama. Iako su kriterijumi za postavljanje dijagnoze HOBP egzacerbacije jedinstveni i egzaktni, u praksi njihova primena nije ujednačena.

Sledeća činjenica koja se zapaža je verovatno potcenjena učestalost populacije pacijenata sa preklapanjem astme i HOBP-a (ACO/ACOS) u našoj HOBP populaciji (svega 2%), u poređenju sa udelom iste populacije u drugim poređenim registrima (POPE 9% (4), španski registar 4% (16)) i sa očekivanim literaturnim podacima (17 – 21). Uzrok toga najverovatnije leži u nedovoljno analitičkom pristupu pacijentima sa ovim fenotipom, prema podacima iz drugih registara, a posebno prema našim podacima, što ukazuje na činjenicu da se o ovom fenotipu nedovoljno razmišlja i da se ne sprovodi evaluacija i reevaluacija pacijenata kojom bi se svakako došlo do većeg broja pacijenata koji imaju ovaj fenotip bolesti i kojima bi se na taj način obezbedila adekvatnija terapija i bolje „kupiranje“ tegoba i egzacerbacija.

Ukoliko se razmatra raspodela našeg uzorka HOBP populacije prema GOLD-ovim ABCD kvadrantima (1), uočava se da su najbrojniji pacijenti grupisani u kvadrant B (45,05%), a potom pacijenti grupisani u D kvadrant (37,82%), dok su pacijenti grupisani u kvadrante A i C mnogo manje zastupljeni (grupa A – 5,93%, grupa C – 11,20%). Navedena analiza jasno ukazuje na činjenicu da su brojniji pacijenti koji su grupisani u desnoj polovini ABCD kvadranta, a to su oni sa naglašenijom i stalno prisutnom simptomatologijom (rezultati mMRC skale ≥ 2 i rezultati CAT upitnika ≥ 10), odnosno moglo bi se reći da su ovakvi pacijenti, sa naglašenom i prepoznatljivom kliničkom slikom „vidljiviji“ svojim lekarima, što je samo po sebi jasno i razumljivo (slika 8).

Analiza primenjene terapije ukazuje na to da je najčešća

FIGURE 10. Comparison of treatments used in 2017 and 2019

COPD Registry – Serbia 2017 N=1756	
Medication	**%**
LAMA	18,91
LABA	10,82
ICS+LABA	14,01
LAMA+LABA+ICS	48,23
LAMA+LABA	7,23
ICS	0,80

COPD Registry – Serbia 2019 N=3714	
Medication	**%**
LAMA	18,71
LABA	7,54
ICS+LABA	12,39
LAMA+LABA+ICS	42,14
LAMA+LABA	18,26
ICS	0,97

persistently present symptoms (results on the mMRC scale ≥ 2 and results on the CAT questionnaire ≥ 10), i.e. it could be said that these patients with prominent and recognizable clinical presentation are "more visible" to their doctors, which is clear enough and self-explanatory (Figure 8).

Analysis of administered treatments suggests that the most common treatment option (in as many as 42.14% of the patients) was a triple combination ICS/LABA+LAMA (inhaled corticosteroid/long-acting beta 2-agonist + long-acting muscarinic antagonist), while the following two options were almost equally represented: LAMA (long-acting muscarinic antagonist) as monotherapy (18.71%) and a combination of two medicines LABA/LAMA (long-acting beta 2-agonist / long-acting muscarinic antagonist), used in 18%. Other treatment options were much less commonly used – the ICS/LABA combination (inhaled corticosteroid/long-acting beta-agonist) used in 12.39% and LABA (long-acting beta 2-agonist) as monotherapy used in 7.54% (Figure 9). The results of the analysis clearly show excessive prescribing of inhaled corticosteroids to COPD patients (as many as 54.53% of patients use them in their therapy), which is not in line with the current recommendations and GOLD guidelines for the treatment of this disease, which suggest this treatment option mostly for patients in GOLD quadrant D, particularly those with frequent exacerbations in spite of regular use of prescribed therapy, patients with elevated serum eosinophil count (≥ 300/mcL) or those with overlapping of asthma and COPD (ACO/ACOS). All of the above is suggestive of an inadequate prescribing routine with predominant use of maximum inhaled treatment without previous phenotyping and optimization of inhaled therapy. Nevertheless, the situation is improving over time as substantiated with the comparison of treatment options use between two cross sections: the first one made in 2017 with 1,756 patients in the registry and the second, made in 2019 with 3,714 patients in the registry. The comparison illustrates that the strategy of inhaled treatment prescriptions has

terapijska opcija (čak kod 42,14% pacijenata) bila trojna kombinacija ICS/LABA+LAMA (inhalacioni kortikosteroid/dugodelujući beta2-agonista+dugodelujući antiholinergik), dok su sledeće dve terapijske opcije, praktično izjednačene po zastupljenosti, bile LAMA (dugodelujući antiholinergik) kao monoterapija (18,71%) i dvojna kombinacija LABA/LAMA (dugodelujući beta2-agonista/dugodelujući antiholonergik), sa zastupljenošću od 18%. Ostale terapijske opcije su bile manje zastupljene – kombinacija ICS/LABA (inhalacioni kortikosteroid/dugodelujući beza-agonista) sa zastupljenošću od 12,39% i LABA (dugodelujući beta2-agonista) kao monoterapija sa 7,54% (Slika 9). Ono što se zapaža iz rezultata navedene analize je činjenica da se pacijentima sa HOBP prekomerno propisuju inhalatorni kortikosteroidi (čak 54,53% pacijenata ih koristi u terapiji), što ne odgovara savremenim preporukama i GOLD smernicama za lečenje ove bolesti, po kojima je ova terapijska opcija rezervisana za pacijente pretežno u GOLD kvadrantu D, i to one sa čestim pogoršanjima uprkos redovno primenjivanoj terapiji, pacijente sa povišenim brojem serumskih eozinofila (≥ 300/mcL) ili pak dijagnozom preklapanja astme i HOBP-a (ACO/ACOS). Sve navedeno najpre govori u prilog neadekvatnom prepisivanju terapije sa dominantnom maksimalizacijom inhalatorne terapije, bez fenotipizacije pacijenata i optimizacije inhalatorne terapije. No, stvari se ipak s vremenom menjaju u pozitivnom smeru. To najbolje dokazuje poređenje učestalosti terapijskih opcija između dva preseka stanja: prvog, koji je učinjen 2017. na 1.756 unetih pacijenata; i drugog, učinjenog 2019. godine na 3.714 unetih pacijenata. Ovo poređenje ukazuje na to da se s vremenom strategija prepisivanja inhalatorne terapije ipak menja, jer je učestalost prepisivanja trojne kombinacije ICS/LABA+LAMA u periodu između dva preseka stanja redukovana sa 48,23% na 42,14%, kombinacije ICS/LABA sa 14,01% na 12,39%, dok je učestalost prepisivanja dvojne kombinacije LABA/LAMA istovremeno porasla sa 7,23% na 18,26% (slika 10). To sve nedvosmisleno pokazuje da se, iako

been changing, since the frequency of prescribing the triple combination, ICS/LABA+LAMA, between the two cross sections was reduced from 48.23% to 42.14%, the ICS/LABA combination was reduced from 14.01% to 12.39%, while the frequency of prescribing the LABA/LAMA combination has risen from 7.23% to 18,26% (Figure 10). This is a positive sign that the COPD treatment strategy in our country is changing for the better, although slowly, and contemporary recommendations and guidelines for the treatment of the disease are adopted.

Conclusion

The presented data and results of their analysis provide an answer to the question on the importance of registries of patients with chronic obstructive pulmonary diseases – they are important because they provide reliable data on a large number of patients, characteristics of autochthonous population of patients suffering from COPD, not only in terms of their disease, but also relating to the risk factors causing the disease in the first place, share of individual phenotypes, specificities of treatment and applied therapy, patient compliance, rate of exacerbations and disease evolution. Only these data make it possible to understand the disease comprehensively and generate feasible treatment strategies that raise hope of success.

sporo, strategija lečenja HOBP-a u našoj sredini ipak menja, uz usvajanje savremenih preporuka i smernica za lečenje ove bolesti.

Zaključak

Navedeni podaci i rezultati njihove analize daju odgovor na pitanje zašto su važni registri pacijenata sa hroničnim opstruktivnim bolestima pluća – važni su jer daju pouzdane podatke, utvrđene na velikom broju pacijenata, o karakteristikama autohtone populacije pacijenata obolelih od HOBP-a ne samo u pogledu njihove bolesti već i u pogledu faktora rizika koji su do njenog nastanka doveli, zastupljenosti fenotipova, osobenosti lečenja i primenjene terapije, komplijanse pacijenata, učestalosti egzacerbacija i evolutivnosti bolesti. Samo ovakvi podaci nam omogućavaju da sagledamo bolest iz svih uglova i kreiramo realno izvodljive strategije lečenja koje daju nadu za postizanje uspeha.

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