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ММР

Original article

SOME ASPECTS OF COVID-19 TREATMENT – CURRENT RECOMMENDATIONS AND OUR OBSERVATIONS

НЕКОИ АСПЕКТИ ВО ЛЕКУВАЊЕТО НА КОВИД-19 – АКТУЕЛНИ ПРЕПОРАКИ И НАШИ ПОЗНАВАЊА

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Abstract

Treatment of COVID-19 is currently a global challenge. Since the beginning of the infection, owing to a well-planned and organized research, knowledge in its treatment has been gained and recommendations have been made. These recommendations are flexible and subject to changes depending on the results obtained in the latest investigations. There is no officially accepted protocol for treatment of patients with COVID-19 in the Republic of North Macedonia. This has resulted in very diverse therapeutic regimens mainly based on individual experience and intuition and without sufficient consistency with the globally recommended therapeutic principles. By conducting a survey-questionnaire among doctors who are working in COVID-19 centers in our country, the aim of this paper was to verify this statement and to offer a solution for uniform approach to treatment of COVID-19 based on the recommenddations of renowned world health institutions. Each questionnaire distributed among those involved in treatment of COVID-19 contained 10 questions. A total of 194 questionnaires were filled-in anonymously on a voluntary basis, and of 1940 possible answers 851 (44%) were correct. To 6 of the 10 questions, the largest number of surveyed respondents has chosen the correct answer. The incorrect answers among the offered ones were in a range of 0 to 74%. The survey-questionnaire has shown distinct variations in the received answers, which in fact reflects the divergent attitudes to treatment of COVID-19. Therefore, it is indispensable to have a standardized approach to management of patients with COVID-19, supported by an organized and stimulated education of the involved health care workers.

Keywords: treatment, COVID-19, corticosteroid, oxygen

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Апстракт

Лекувањето на КОВИД-19 претставува глобален актуелен предизвик. Од неговата појава до денес, благодарение на осмислени и добро организирани иследувања се дојде до доста сознанија за третманот кои се преточени во соодветни препораки. Ваквите препораки се флексибилни и подложни на промени во зависност од резултатите кои се добиваат во најновите иследувања. Во Република Македонија не постои официјално прифатен протокол за лекување на пациентите со КОВИД-19. Резултат на тоа е постоење на најразлични тераписки шеми обично базирани на сопствени искуства и интуиција, честопати без соодветна научна поддржаност и без доволна усогласеност со глобално препорачаните тераписки принципи. Цел на трудот беше преку спроведена анкета - прашалник наменета за лекари кои работат во КОВИД-19 центри во нашата држава да се утврди веродостојноста на ваквото тврдење и да се понуди решение за унифициран пристап во лекување на пациентите, базирано на препораки на авторитетните светски здравствени институции. Меѓу 194 доброволно пополнети анонимни анкетни прашалници од кои секој содржеше по 10 прашања, од вкупно можни 1940 одговори точни беа 851 (44%). Кај 6 од десетте поставени прашања најголемиот број на анкетирани го имаа избрано точниот одговор. Застапеноста на избран неточен одговор меѓу понудените беше во интервал од 0 до 74%. Анкетата-прашалник утврди изразена дисперзија на добиените одговори, што всушност ги рефлектира дивергентните ставови околу лекувањето на пациентите со КОВИД-19. Заради тоа е неопходно да се изгради унифициран пристап во менаџирањето на пациентите со КОВИД-19, надополнет со организирана и стимулирана едукација на лекарите.

Клучни зборови: третман, КОВИД-19, кортикостероиди, кислород

Introduction

More than a year has passed since the beginning of COVID-19 pandemic and the medical science has already reached distinct achievements in fighting the new coronavirus. Rapid identification of virus genome [1], detection of the modes of its transmission [2], determination of the pathogenetic mechanisms [3-5] and consequently defining the stages of the disease [4,6] as well as development of effective vaccines [7] are a constituent part of the success in treatment of COVID-19. Many questions still remain unsolved and there are a lot of unknown issues related to this virus that have to be clarified in the future. The crucial question refers to treatment of patients having in mind that there are no confirmed and approved antiviral drugs [8,9], and on the other hand, the emphasis has been given to agents and procedures that have not yet proved clearly their effect in large randomized controlled studies (RCS), such as convalescent plasma (CP) and specific immunoglobulins [10-12], monoclonal antibodies, cytokine inhibitors, interferons, ivermectin, statins [2,10,11, 13], colchicine [14], numerous nutritional supplements [15], immunoadsoption [16], etc. Today, many universities in the world have prepared their own instructions and strategies (protocols) for treatment. However, they have presented divergent approaches since some institutions accept the attitudes based on the recommenddations of authoritative world organizations and institutions such as the National Institutes of Health of USA (NIH), Centers for Disease Control and Prevention of USA (CDC), United States Food and Drug Administration (FDA), Infectious Diseases Society of America (IDSA), World Health Organization (WHO), as well as the findings obtained in large RCS or large observational trials leading to systematic reviews and meta-analyses. Recommendations of other institutions, on the other hand, have been based on drugs and procedures that have not still been confirmed and have not passed adequate controls, but are usually inexpensive and promising [5,6].

The first attempt to create an adequate national strategy (protocol) for treatment of patients with COVID-19 in the Republic of North Macedonia was made in October 2020, 8 months after the onset of the first case in the country (conclusion of the Commission for Infectious Diseases at the Ministry of Health from 23.10.2020). Of reasons unknown to the author of this paper, this protocol [17], although prepared, has never been legitimately distributed to the doctors involved in treatment of COVID-19. Thus, in lack of a defined national strategy for treatment of COVID-19, from the very beginning each and every involved doctor has been compelled to manage patients by using different foreign protocols or, to a large extent, using individual experience. This resulted in evident discrepancies and individualism in the therapeutic approach not only among doctors, but among COVID-19 centers in the country; hence confusion and uncertainty have arisen among doctors regarding the treatment, and patients' confidence has also been reduced. Some of these discrepancies are the indications for use of empiric antimicrobial therapy, eventual antimicrobial choice, indications for application of corticosteroids, the choice of the agent and its dosage, indications for application of invasive mechanical ventilation, indications for application of thromboprophylaxis or thrombotherapy, indications for using antiviral and other immunomodulatory agents, etc.

This survey-questionnaire that contained items associated with treatment of COVID-19, based on voluntary will and anonymity, was conducted in order to:

1. recognize the level of essential knowledge among doctors who treat patients with moderate and severe forms of COVID-19 regarding the choice of certain therapeutic decisions;
2. offer well-argued instructions for efficient clarification of the existing dilemmas and to recommend uniform approach in management of this category of patients, predominantly based on the current recommendations given by renowned world health institutions, experts and experiences cited in journals with a high impact factor.

Methodology

This investigation was my personal initiative and the opinions expressed herein reflect my views and do not represent the official position of any institution or organization, nor there has been any financial interest. The author obtained the approval by the Ethics Committee of the Faculty of Medicine in Skopje.

A survey-questionnaire was prepared containing 10 questions with offered multiple answer options. The survey-questionnaire was designed to be anonymous and on a voluntary basis. It was prepared and distributed among doctors who were or were not specialists in some medical specialty. The only criterion for participation in the survey was at least several weeks of clinical experience in the work with patients with moderate and severe form of COVID-19 admitted in the COVID-19 centers in the Republic. The participants in the survey were asked to independently answer the questions and to present their knowledge based on their own experience and learnt by reading and retrieval of medical literature, attendance to webinar presentations or by contacts with medical experts.

Some doctors who are working in different COVID-19 centers in the Republic offered their help in distribution and collection of the filled-in questionnaires and their delivery as a hard copy or via viber to the author of this investigation. After receiving of all filled-in questionnaires, they were analyzed with the Excel program. The answer to the question was assessed as

correct or incorrect. If the question was not answered or if several answers were given, the answer was considered as incorrect. Furthermore, an additional analysis was made regarding the frequency of the selected answer from the offered options. The answers were presented as frequencies and percentages and displayed in figures.

Results

In a two-month period (December 2020-January 2021), a total of 194 filled-in questionnaires were received from 22 institutions from our country where patients with COVID-19 were treated. The survey-questionnaire was not distributed only among specialists from the University Clinic for Infectious Diseases and Febrile Conditions as well as among doctors who worked in the COVID-19 centers within the internal clinics in Skopje.
Of 1940 possible answers, 851 (44%) were correct, 1080 (55.5%) were incorrect, and no answer was given to 9 (0.5%) questions. Herein are the questions and the chosen answers presented in figures along with author's commentary.

Question 1. What is the difference between the severe and moderate form of COVID-19?

a) presence of clinical or chest x-ray verified pneumonia
b) comorbidities
c) age >70 years
d) saturation <94%
e) all of the above

Results 1. The choice whether the answer was correct or not (in frequencies and percentages) to question 1 is presented in Figure 1a. The selected answer from the offered options (in percentages) to question 1 is shown in Figure 1b.

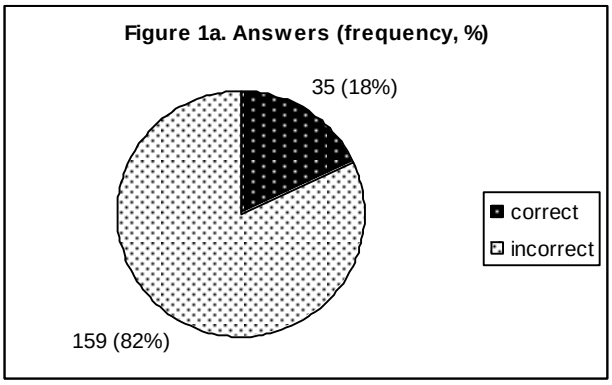

Fig. 1a. Correct/incorrect answer (frequency and %) to question 1

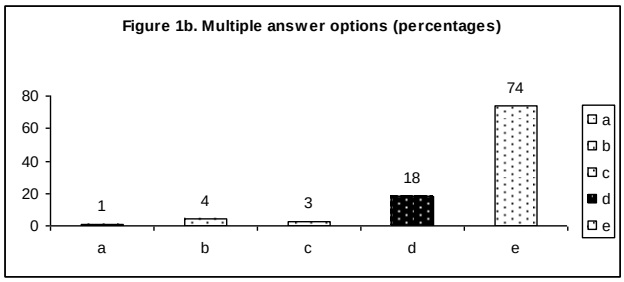

Fig. 1b. Choice between the offered answer options (in percentages) to question 1

Commentary 1. The correct answer is d). Moderate COVID-19 is present in patients with clinically or chest x-ray confirmed pneumonia in whom oxygen saturation (SpO2) is ≥94%. A severe form of the disease is seen in patients with pneumonia verified with clinical or x-ray examination plus one of the following parameters: (i) respiratory frequency >30/min., (ii) a severe respiratory distress (accessory muscle use, inability to complete full sentences, very severe chest wall indrawing, grunting, central cyanosis) and (iii) SpO2 <94% [10,18,19]. The value of SpO2 <94% in differentiation of a moderate from a severe illness has been presented in many clinical trials [20-23], whereas others have used different modifications of the SpO2 values such as ≤ 94% [11] or <90% [24]. However, it has to be pointed out that these values are arbitrary and should be interpreted cautiously depending on the clinical condition of patients, their previous diseases and eventual progression of the condition [25].
The advanced age and the presence of comorbidities are risk factors for the severity and progression of the disease and are an important indicator for careful monitoring of the patients, but these factors are not included in the definitions of moderate and severe clinical forms of COVID-19. On the other hand, pneumonia offered as one of the answers is characteristic for both forms.

Question 2. The easiest way to clinically verify a severe dyspnea is by observing the following:

a) persistent irritating cough
b) saturation <92%
c) intermittent speech
d) high levels of ferritin, CRP, DD and IL-6
e) no improvement in spite of administration of 10 L oxygen

Results 2. The choice whether the answer was correct or not (in frequencies and percentages) to question 2 is presented in Figure 2a. The selected answer from the offered options (in percentages) to question 2 is shown in Figure 2b.

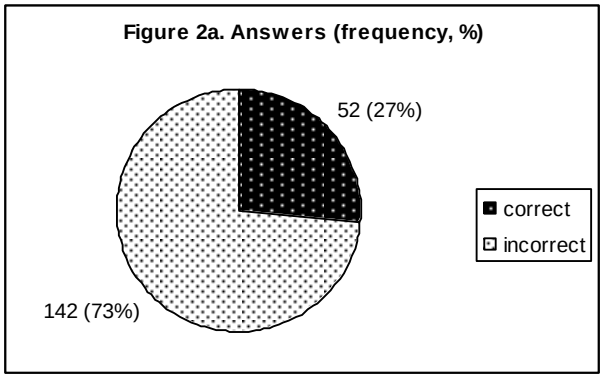

Fig. 2a. Correct/incorrect answer (frequency and %) to question 2

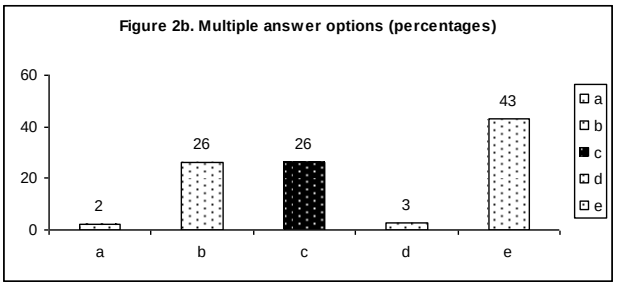

Fig. 2b. Choice between the offered answer options (in percentages) to question 2

Commentary 2. The correct answer is c). Dyspnea is a subjective feeling and is not always present during hypoxemia [6,26,27] and *vice versa*, there is normal oxygenation even if progressive or severe dyspnea is present [28]. Severe dyspnea is characterized with air hunger while resting, which is an indication for respiratory involvement. Patients cannot complete full sentences [28-30] neither can they perform basic functions for which they use accessory muscles [28]. The patient with COVID-19 has to be asked if his/her breath is so short that he/she cannot say more than a few words, and the assessment has to be made by a direct communication with the patient [31].

Answers listed under b) and e) are indicative of hypoxemia and not dyspnea; coughing is an independent clinical manifestation, and laboratory parameters along with dyspnea are associated with the severity and can serve in assessment of disease evolution, but are not in a direct correlation with dyspnea.

Question 3. In a severe form of COVID-19, the treatment must consist of:

a) convalescent plasma
b) antibiotic
c) oxygen
d) Janus kinase inhibitor (baricitinib)
e) non-specific immunoglobulin

Results 3. The choice whether the answer was correct or not (in frequencies and percentages) to question 3 is presented in Figure 3a. The selected answer from the offered options (in percentages) to question 3 is shown in Figure 3b.

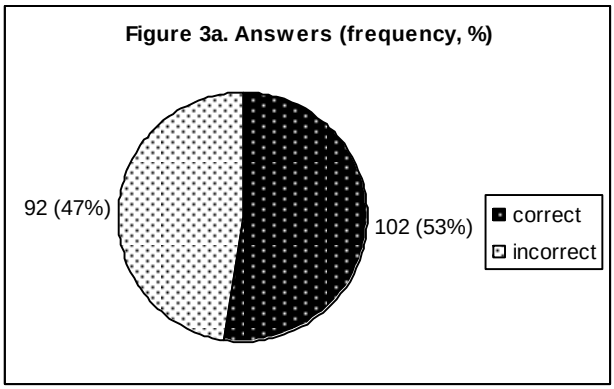

Fig. 3a. Correct/incorrect answer (frequency and %) to question 3

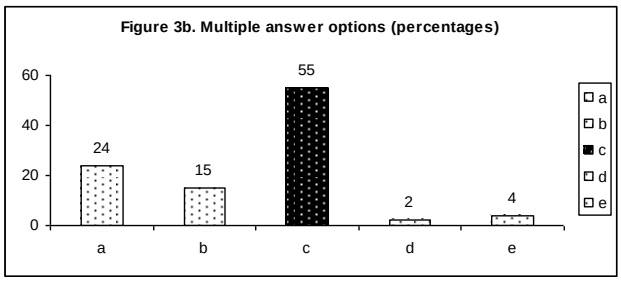

Fig. 3b. Choice between the offered answer options (in percentages) to question 3

Commentary 3. The correct answer is c) [10,21,25,30]. Having in mind that in the severe COVID-19 there is hyposaturation, an adequate oxygen substitution is a priority therapeutic procedure and it must be supplemented with a systemic corticosteroid [10,21,23,24]. Contrary to this, in the moderate COVID-19, neither oxygen supplementation nor corticosteroids are recommended [10,21,25,30,32].

The role of convalescent plasma (CP) in COVID-19 treatment including the severe form remains an unsolved puzzle. Certain benefits have been seen in those who received CP (better survival rate when the administration happened within the third day from the onset of symptoms) [12]. However, several randomized studies have found no clear clinical and prognostic benefit [12,19,28]. Currently, some of the institutions approve the use of CP alone in clinical trials [11,19,24], whereas others have no sufficient agruments either for or against the use of CP in the routine treatment [10].

In patients with COVID-19 routine application of empiric antimicrobial therapy is not needed if the suspicion of bacterial infection is small. Thus, the antimicrobial immediate and long-term adverse effects can be eliminated [11,24,33]. At this moment NIH has not enough arguments to recommend the use of a wide-spectrum empiric antimicrobial treatment in patients with severe and critical illness in absence of other indication [10]. Despite administration of antimicrobial thera-

py, clinical non-improvement in patients generally does not alert to bad choice of antibiotics but rather to bad decision for their use. The absence of clinical improvement during antibiotic administration most frequently indicates that there is no bacterial infection and that the cause should be in SARS-CoV-2 virus and the mechanisms it induces. Therefore, it is absolutely unjustified to replace the used antibiotics with others. But, however, antimicrobial therapy can be applied in patients with pneumonia in whom COVID-19 diagnosis has not been confirmed as well as in patients with confirmed COVID-19 when there is clinical suspicion of bacterial pneumonia [24,33,34]. The decision on the empiric antimicrobial treatment has to be made in conjugation with patients' characteristics and in line with the local epidemiological situation. This therapy should be evaluated on daily basis in order to be discontinued as soon as possible [10,24].
Insufficient data show that baricitinib, a Janus kinase inhibitor, gives certain hope in treatment of non-intubated patients with severe COVID-19 who cannot be given corticosteroids. In cases like these baricitinib must be given in combination with remdesivir [10,11]. Using a non-specific SARS-CoV-2 immunoglobulin in treatment of COVID-19 is not recommended, except in clinical trials or when there is another indication for its application [10,19].

Question 4. In which stage of the disease, if indicated, corticosteroids are recommended in COVID-19 patients?

a) as soon as possible from the onset of symptoms
b) up to the fifth day from the onset of symptoms at the latest
c) after the first week from the onset of symptoms
d) is not related to the onset of symptoms
e) only in patients with comorbidities independently of the onset of symptoms

Results 4. The choice whether the answer was correct or not (in frequencies and percentages) to question 4 is presented in Figure 4a. The selected answer from the offered options (in percentages) to question 4 is shown in Figure 4b.

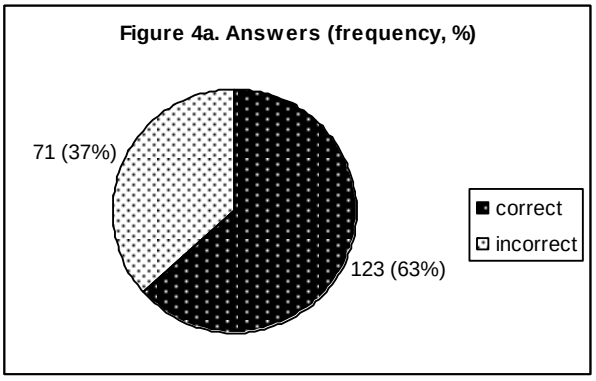

Fig. 4a. Correct/incorrect answer (frequency and %) to question 4

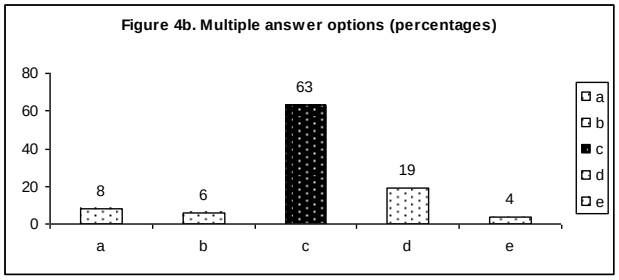

Fig. 4b. Choice between the offered answer options (in percentages) to question 4

Commentary 4. he correct answer is c) and this recomendation is found in several protocols [2,13,23,35]. The principal role of the corticosteroids in treatment of COVID-19 is to stop or alleviate the harmful systemic hyperinflammatory response. This response can be observed in some of the patients usually by the end of the first and the beginning of the second week. The onset of the systemic inflammatory response coincides with the period when there is an obvious regression of viral replication and of viral load [2,4,6,21]. Hyperinlammatory syndrome leads to respiratory failure and multiorgan dysfunction in some patients [10,11]. Timely administration of systemic corticosteroids can significantly influence on the course of the disease, with evident reduction in mortality [19]. Early administration of corticosteroids within the first week can result in unfavorable effect; it can inhibit the initiation and development of the host immune defense mechanisms and to enable prolonged intensive active viral replication by intensifying immunosuppression and aggravation of the course and outcome of the disease [2,4,32,36]. One study has demonstrated that corticosteroid administered within the second week after the onset of symptoms has improved the favorable outcome in comparison with their administration in the first or third week [37]. Definitely, an absolute precondition to apply corticosteroids in COVID-19 treatment is the existence of a severe or critical form of the disease, which almost always begins within the second week after the onset

Question 5. Corticosteroid therapy – recommended choice:

a) high doses of dexamethasone (≥20 mg/day)
b) low doses of dexamethasone (6-8 mg/day)
c) "pulse" doses of methylprednisolone (≥ 240 mg/day)
d) avoiding dexamethasone and insisting on methylprednisolone
e) start with "pulse" doses of methylprednisolone and continue with low doses of dexamethasone

of initial symptoms. Systemic corticosteroids are to be given during the first week if hypoxia appears, which is a very rare case [29]. The application of systemic corticosteroids in patients who are not oxygen-dependent can have an opposite effect and can result in higher mortality [10,11,30,32,38].

Results 5. The choice whether the answer was correct or not (in frequencies and percentages) to question 5 is presented in Figure 5a. The selected answer from the offered options (in percentages) to question 5 is shown in Figure 5b.

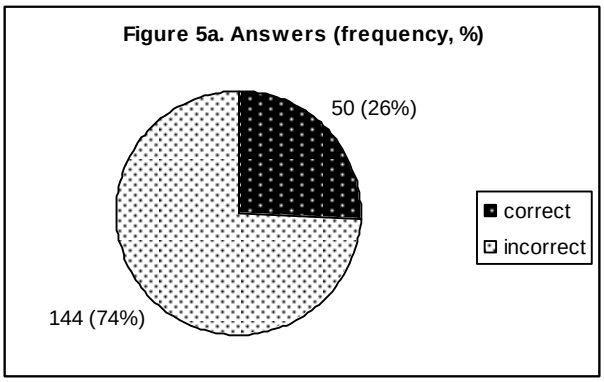

Fig. 5a. Correct/incorrect answer (frequency and %) to question 5

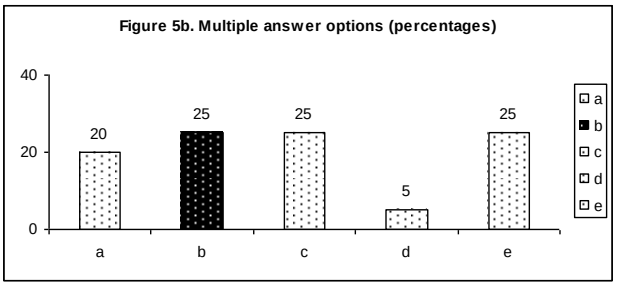

Fig. 5b. Choice between the offered answer options (in percentages) to question 5

Commentary 5. The correct answer is b). Currently, low doses of dexamethasone (6 mg/day) in duration of 10 days are recommended [10,11,21,38,39]. Low dose and short therapeutic courses with dexamethasone result in minimal adverse effects [19]. It is unknown whether the other corticosteroids show worse, simial or signifycant benefit than dexamethasone since there have been no studies that compared the efficacy of different corticosteroid formulations, but dexamethasone has been associated with the greatest therapeutic benefit compared to other corticosteroids in trials where comparison was between corticosteroid and non-corticosteroid regimens [19]. Still, if dexamethasone is unavailable, then alternative regimes are allowed with other corticosteroids with doses equivalent to 6 mg/day dexamethasone, 40 mg/day prednisone, 32 mg/day methylprednisolone and 160 mg/day hydrocortisone [2,10,11,32].

Contrary to dexamethasone, trials with other corticosteroid formulations have led to inconclusive results and have shown no benefit when compared to treatments with placebo [28,30,39]. There are a few RCS where high doses of dexamethasone have been used [29,30]. Also, there are just few recommendations that favor methylprednisolone as listed under c) and d) [5,6,40]. Higher doses (1-2 mg/kg) of methylprednisolone or other corticosteroids in equvalent doses are recommended in patients with onset of excessive inflammatory response and progressive deterioration of oxygenation, elevation or rising of laboratory markers (CRP>75 mg/L, ferritin>1,000 ng/mL, LDH>300 U/L, and D-dimer>1,000 ng/mL), rapid exacerbation of the x-ray finding and development of ARDS [6,23,32,36]. In situations like these, some suggest methylprednisolone at doses of 250-1000 mg/day as a salvage treatment [5,37,41-43]. The choice of a corticosteroid agent, optimal dose and treatment duration still remain unknown [29,37,44-46]. Also, so far there is no information on the association of high doses of corticosteroids with a greater benefit in comparison with low doses [45,47]. Also, when making decision about the corticosteroid dose and regimen, physicians should always have in mind the possibility of adverse effects, sometimes serious, associated with this category of drugs.

Question 6. Thromboprophylaxis in patients with COVID-19 is recommended in:

a) all subjects (from asymptomatic to critical)
b) all hospitalized patients
c) patients with confirmed pulmonary embolism/deep vein thrombosis
d) all oxygen-dependent patients
e) patients in whom corticosteroid administration was mandatory indicated

Results 6. The choice whether the answer was correct or not (in frequencies and percentages) to question 6 is presented in Figure 6a. The selected answer from the offered options (in percentages) to question 6 is shown in Figure 6b.

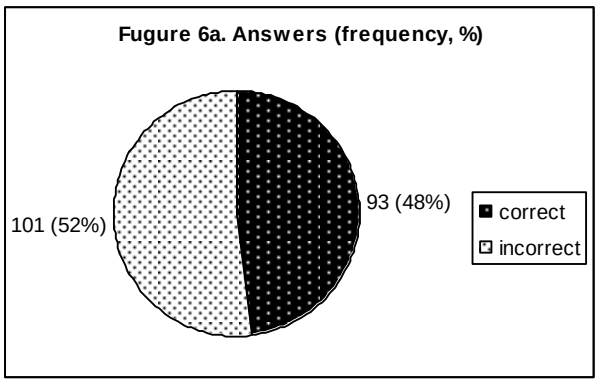

Fig. 6a. Correct/incorrect answer (frequency and %) to question 6

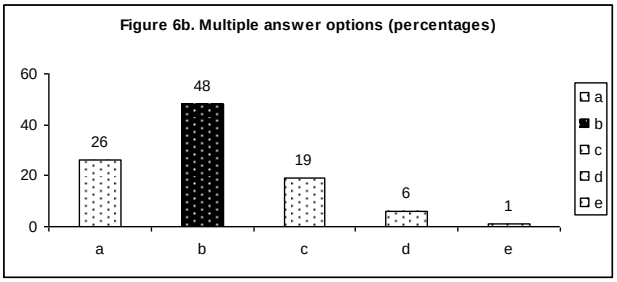

Fig. 6b. Choice between the offered answer options (in percentages) to question 6

Commentary 6. The correct answer is b). Hypercoagulability is an important pathogenetic characteristic of COVID-19. Therefore, all hospitalized adults with COVID-19 should receive anticoagulant prophylaxis if there are no contraindications [2,10,19,24,28]. Anticoagulant or antiaggregation prophylaxis in vein thromboembolism or arterial thrombosis is not recommended in non-hospitalized patients with COVID-19, unless there is another indication [2,10]. In patients with confirmed pulmonary embolism or deep vein thrombosis thrombotherapy is necessary and not prophylaxis.

Question 7. In a 74-year-old previously non-hospitalized patient with COVID-19, who was insulin-dependent, with no particular problems over the last year, who was sick for 7 days, with saturation of 86% and parameters indicating bacterial pneumonia, which empiric antimicrobial therapy would you recommend?

a) piperacillin/tazobactam monotherapy
b) meropenem monotherapy
c) ceftriaxone plus azithromycin
d) piperacillin/tazobactam plus vancomycin
e) azithromycin plus moxifloxacin
f) meropenem plus piperacillin/tazobactam plus vancomycin

Results 7. The choice whether the answer was correct or not (in frequencies and percentages) to question 7 is presented in Figure 7a. The selected answer from the offered options (in percentages) to question 7 is shown in Figure 7b.

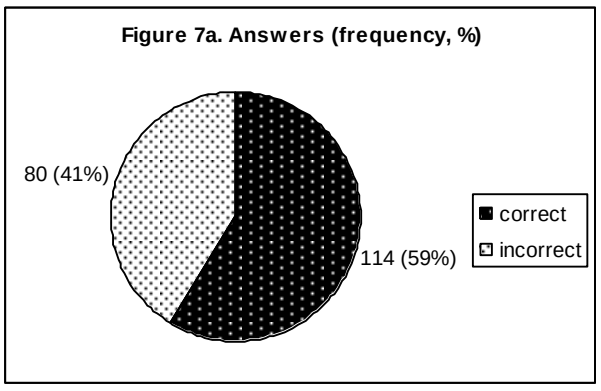

Fig. 7a. Correct/incorrect answer (frequency and %) to question 7

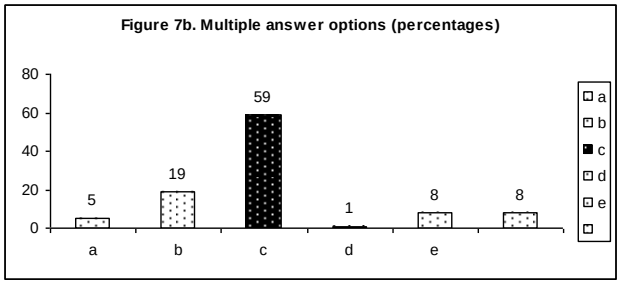

Fig. 7b. Choice between the offered answer options (in percentages) to question 7

Commentary 7. This is a case of a community-acquired pneumonia, which should be treated in line with the existing recommendations for treatment of this kind of pneumonia [13,32,35,48]. Consequnetly, the correct answer is c) having in mind that the listed combined therapy can have effect on all possible causes. The offered options a), b), d) should be considered in case of hospital-or ventilatory-acquired pneumonia and when there is a suspicion or proof of highly resistant strains of bacterial causes, whereas the antimicrobial combinations listed under e) and f) are absolutely illogical because of the overlap of the antimicrobial spectrum.

Question 8. If there is an indication of ceftriaxone administration for bacterial pneumonia, the dose should be:

a) 1 gram twice daily
b) 2 grams once daily
c) 2 grams twice daily
d) 4 grams once daily

Results 8. The choice whether the answer was correct or not (in frequencies and percentages) to question 8 is presented in Figure 8a. The selected answer from the offered options (in percentages) to question 8 is shown in Figure 8b.

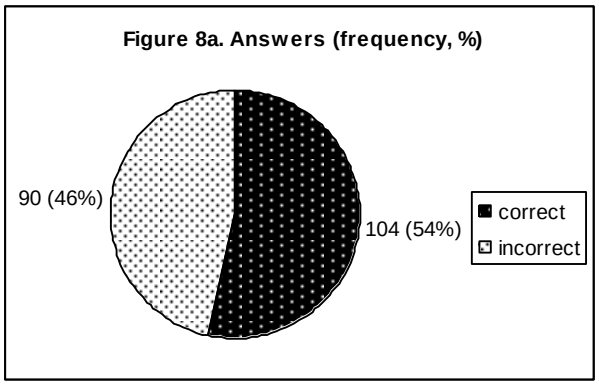

Fig. 8a. Correct/incorrect answer (frequency and %) to question 7

Commentary 8. The correct answer is b). Pharmacological and microbiological specifics of ceftriaxone enable its administration once daily at a dose of 1-2 grams for treatment of bacterial pneumonia [48, 49].

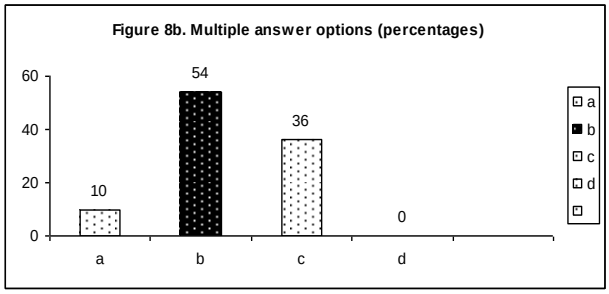

Fig. 8b. Choice between the offered answer options (in percentages) to question 7

Ceftriaxone is administered twice daily at a maximum dose of 4 grams if the main indication is bacterial neuroinfection [49].

Question 9. In a patient with COVID-19 and pneumonia, which laboratory parameter can in the best way exclude the bacterial etiology of pneumonia?

a) low ferritin level
b) low procalcitonin level
c) high ferritin level
d) low D-dimers level
e) high procalcitonin level

Results 9. The choice whether the answer was correct or not (in frequencies and percentages) to question 9 is presented in Figure 9a. The selected answer from the offered options (in percentages) to question 9 is shown in Figure 9b.

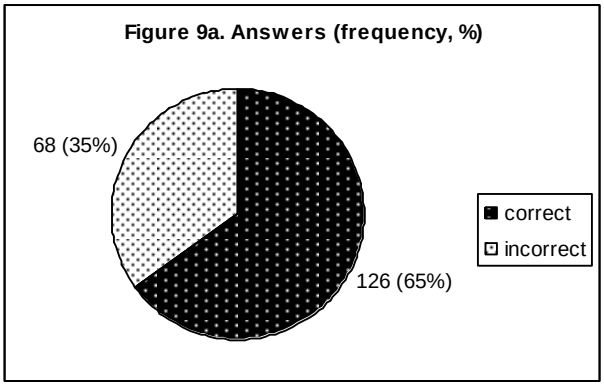

Fig. 9a. Correct/incorrect answer (frequency and %) to question 9

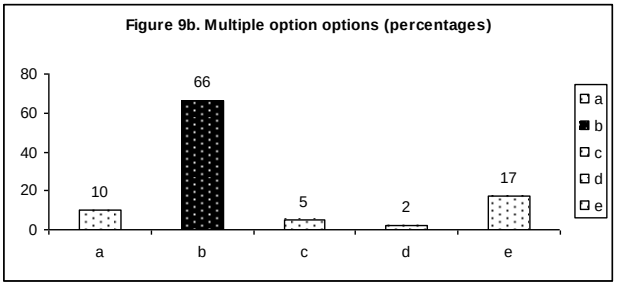

Fig. 9b. Choice between the offered answer options (in percentages) to question 9

Commentary 9. The correct answer is b). There are almost no bacterial coinfections or superinfections in patients with COVID-19 who have a low procalcitonin level and hence, these patients are not to be given antibiotics [35,50]. On the other hand, the increased level of serum procalcitonin in COVID-19 is not a sensitive marker for bacterial superinfection because sometimes it can be found in COVID-19 pneumonia, too [32,35]. D-dimers and ferritin are not sensitive markers for presence or absence of eventual bacterial infection.

Question 10. How long the empricial antimicrobial therapy has to be administered?

a) 5-7 days
b) no longer than two weeks
c) approximately three weeks
d) until normalization of D-dimers, LDH and CRP
e) until normal x-ray/CT finding of the lungs is obtained

Results 10. The choice whether the answer was correct or not (in frequencies and percentages) to question 10 is presented in Figure 10a. The selected answer from the offered options (in percentages) to question 10 is shown in Figure 10b.

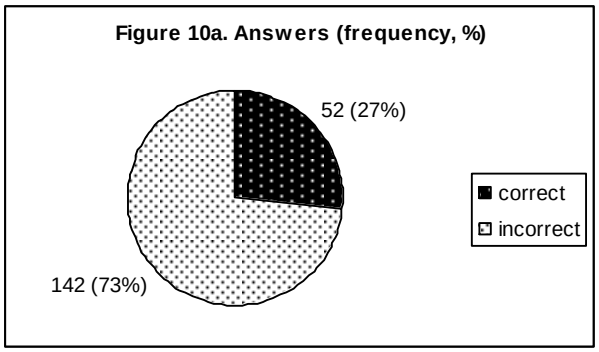

Fig. 10a. Correct/incorrect answer (frequency and %) to question 10

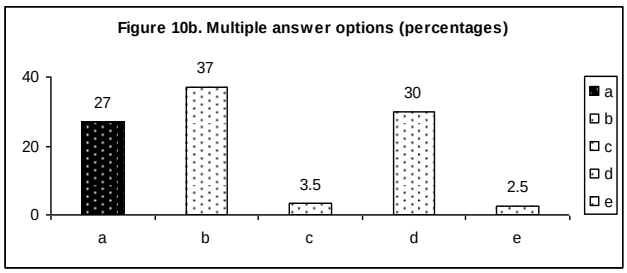

Fig. 10b. Choice between the offered answer options (in percentages) to question 10

Commentary 10. The correct answer is a). The duration of the empirical antimicrobial treatment should last as short as possible, in general 5-7 days [13,24, 35,51]. The duration of antimicrobial therapy should

be based on validated measures of achieved clinical stability-normalization of vital signs and conscience, and antibiotic therapy should be continued until the patient's condition is stabilized [48]. The given options under b) and c) refer to exceptional cases in population at high risk, in clinical instability or when microbiological testing suggest the need of a long-term therapy [51]. It might take longer for normalization of laboratory and radiological parameters after clinical improvement is achieved and they are not a sensitive marker for treatment discontinuation.

Discussion

The results obtained from the survey-questionnaire have shown that there are obvious distinctions in management of patients with a moderate and severe COVID-19 in our country from those of the current world recommendations (presented in Figures 1a-10a). At the same time, these results have demonstrated evident discrepancies among doctors in our country regarding the attitudes in treatment of COVID-19 (presented in Figures 1b-10b). The principal reason for this kind of inconsistency and variations is due to the lack of an uniform strategy for treatment of patients with COVID-19 that would comply with the current recommendations given by renowned world health institutions and consequently protocols given by distinguished universities. The acquired clinical experience, upon which almost without exception therapeutic procedures in the Republic of North Macedonia are based, is not usually grounded on the respected standards for clinical management, but on observation and without a review process. Also, the results obtained have shown insufficient level of information of the doctors included in this survey regarding the basic principles by which COVID-19 patients should be treated at the moment. Possible reasons for this situation might be absence of exchange of staff and experiences amongst health care workers from the neighboring countries and beyond, as well as amongst our doctors who work in COVID-19 centers worldwide, then lack of initiative by our doctors for personal broadening their knowledge by continual search of the available medical literature and participation to different online symposia and groups related to COVID-19 topic, as well as enforcement of non-flexible strategy by appointed coordinators, which differs from the current principles and is based on personal impressions and alleged experience of the coordinator. Overcoming of these discrepancies by education of the doctors and preparation of a uniform approach to management of patients with COVID-19 according to previously given principles might result in adequate benefit for patients' outcome, but at the same time, they can give doctors stimulus, security and motivation in treatment of these patients.

Recommendations (instead of conclusions):

1. Assessment of oxygen saturation is an important step in COVID-19. It enables differentiation of the moderate from severe form of the disease.
2. Treatment of the moderate form of the disease does not require administration of supplementary oxygen or systemic corticosteroid.
3. In patients with a severe form (SpO2 <94%) supplementary oxygen along with systemic low doses of dexamethasone must be administered. Severe form and need for this kind of therapy in general becomes obvious within the second week of the disease.
4. All hospitalized patients with COVID-19 (with moderate and with severe form) must receive tromboprophylaxis.
5. Antibiotics should be given only in rare situations when there is clinical or laboratory suspicion of bacterial coinfection or superinfection or when this infection has been confirmed.

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Conflict of interest statement. None declared.

References

1. Zhu N, Zhang D, Wang W, *et al*. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727-733. doi: 10.1056/NEJMoa2001017.
2. Travax. Coronavirus Disease 2019 Outbreak Report. 2021. https://www.travax.com/library/coronaviruses/events/coronavirus-disease-2019. Last updated January 20, 2021.
3. Dhama K, Patel SK, Pathak M, *et al*. An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies. *Travel Med Infect Dis* 2020; 37: 101755. doi: 10.1016/j.tmaid.2020.101755.
4. Siddiqu HK, Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. *J Heart Lung Transplant* 2020; 39: 405-407. doi: 10.1016/j.healun.2020.03.012.
5. Marik P. EVMS COVID-19 Management Protoco.l An overview of the MATH+ and I-MASK+ Protocols. Eastern Virginia Medical School. Updated December 27th, 2020. Available at: https://www.evms.edu/media/evms_public/departments/ internal_medicine/ EVMS_Critical_Care_COVID-19_Protocol.
6. Kory P, Meduri GU, Iglesias J, *et al*. Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19. *J Intensive Care Med* 2021; 36: 135-156. doi: 10.1177/0885066620973585.

7. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med* 2020: NEJMra2035343. doi: 10.1056/NEJMra2035343.
8. Beigel JH, Tomashek KM, Dodd LE, *et al*. ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; 383: 1813-1826. doi: 10.1056/NEJMoa2007764.
9. WHO Solidarity Trial Consortium; Pan H, Peto R, *et al*. Repurposed antiviral drugs for COVID-19-interim WHO Solidarity trial results. *N Engl J Med* 2020; DOI: 10.1056/ NEJMoa2023184.
10. NIH COVID-19 Treatment Guidelines. https://files.covid19 treatmentguidelines.nih.gov/guidelines/covid19treatmentg uidelines. Last updated 21.1.2021.
11. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. IDSA COVID-19 Treatment Guidelines, https://www. idsociety. org/practice-guideline/covid-19-guideline-treatment-and-management. Last updated, 1/8/2021.
12. Agarwal A, Mukherjee A, Kumar G, *et al*. PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020; 371: m3939. doi: 10.1136/bmj.m3939.
13. Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance. https// www.massgeneral.orgassetsMGH pdfnewscoronavirusmass-general-COVID-19-treatment-guidance. Version 7.1 12/11/2020.
14. Tardif JC, Bouabdallaoui N, L'Allier PL, *et al*. Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19. medRxiv. https:// doi.org/10.1101/2021.01.26.21250494.
15. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol* 2020; 92: 479-490. doi.org/10.1002/jmv.25707.
16. Yigenoglu TN, Ulas T, Dal MS, *et al*. Extracorporeal blood purification treatment options for COVID-19: The role of immunoadsorption. *Transfus Apher Sci* 2020; 59: 102855. doi: 10.1016/j.transci.2020.102855.
17. Milenkovik Z. Terapiski pristap kaj pacientite so KOVID-19. Preporaki na NIH COVID-19 treatment Guidelines. Izvadok so nasoki za koi ima dokazi. Protokol v.4/20. Objaven revidiran elektronski document na 22.10.2020.
18. Food and Drug Administration. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention. Guidance for Industry. May 2020. https://www.fda.gov/ regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention.
19. Alhazzani W, Evans L, Alshamsi F, *et al*. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU. First Update. *Critical Care Medicine* January 28, 2021. doi: 10.1097/CCM.0000000000004899.
20. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323: 1239-1242. doi: 10.1001/jama.2020.2648.
21. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. *N Engl J Med* 2020; 383: 1757-1766. doi: 10.1056/NEJMcp2009249.
22. Wang Y, Zhang D, Du G, *et al*. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395: 1569-1578. doi: 10.1016/S0140-6736(20)31022-9.
23. Ministarstvo zdravstva Republike Hrvatske. Smjernice za liječenje oboljelih od koronavirusne bolesti 2019 (COVID-19). verzija 2 od 19. studenoga 2020. https://bfm.hr/ koronavirus-aktualno/.
24. World Health Organization. COVID-19 Clinical management: living guidance, 25 January 2021 WHO/2019-nCoV/ clinical/2021.1.
25. World Health Organization. Therapeutics and COVID-19: living guideline, 17 December 2020. World Health Organization. https://apps.who.int/iris/handle/10665/337876.
26. Bass JB JR. Dyspnea. In: Walker HK, Hall WD, Hurst JW. editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd Edition. Boston: Butterworths; 1990. Chapter 36.
27. Xie J, Tong Z, Guan X, *et al*. Critical care crisis and some recommendations during the COVID-19 epidemic in China. *Intensive Care Med* 2020; 46: 837-840. doi: 10.1007/s00134-020-05979-7.
28. Cohen P, Blau J. Coronavirus disease 2019 (COVID-19): Outpatient evaluation and management in adults. Available from UpToDate, Waltham, MA. https://www. uptodate.com/contents/coronavirus-disease-2019-covid-19-outpatient-evaluation-and-management-in-adults. Last updated Jan 21, 2021.
29. Lamontagne F, Agoritsas T, Macdonald H, *et al*. A living WHO guideline on drugs for covid-19. *BMJ* 2020; 370: m3379. http://dx.doi.org/ 10.1136/bmj.m3379.
30. World Health Organization. Corticosteroids for COVID-19: living guidance, 2 September 2020. World Health Organization.https://www.who.int/publications /i/item/WHO-2019-nCoV-Corticosteroids-2020.1.
31. Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. *BMJ* 2020; 368: m1182. doi: 10.1136/bmj.m1182.
32. EMCrit Project. COVID 19 Complete Chapter by Josh Farkas. Updated January 17, 2021. https://emcrit.org/squirt/c19complete.
33. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020; 81: 266-275. doi: 10.1016/j. jinf. 2020.05.046.
34. Long B, Liang SY, Rosenberg H, *et al*. Just the facts: What drugs are safe and effective for COVID-19? *CJEM* 2020; 22: 591-594. doi: 10.1017/cem.2020.403.
35. Michigan medicine. University of Michigan. Guidance for treatment of COVID-19 in adults and children. http://www. med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf.
36. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect* 2020; 80: 607-613. doi: 10.1016/j.jinf.2020.03.037.
37. Ruiz-Irastorza G, Pijoan JI, Bereciartua E, *et al*. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. *PLoS One* 2020; 15: e0239401. doi: 10.1371/journal. pone.0239401.
38. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, *et al*. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med* 2020; NEJMoa2021436. Online ahead of print.
39. Siemieniuk R, Rochwerg B, Agoritsas T, *et al*. A living WHO guideline on drugs for covid-19. *BMJ* 2020; 370: m3379. doi: 10.1136/ bmj.m3379.
40. Draghici S, Nguyen TM, Sonna LA, *et al*. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. [published online May 19, 2020]. Medrxiv. doi:10.1101/ 2020.05.06.20076687.

41. Callejas-Rubio JL, del Castillo JDL, Fernandez JD, *et al*. Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection. *Med Clin-Barcelona* 2020; 155: 159-161.
42. So C, Ro S, Murakami M, *et al*. High-dose, short-term corticosteroids for ARDS caused by COVID-19: a case series. *Respirol Case Rep* 2020; 8: e00596. doi: 10.1002/rcr2.596.
43. Zhang Y, Li H, Zhang J, *et al*. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. *Diabetes Obes Metab* 2020; 22: 1443-1454.
44. Hasan SS, Capstick T, Ahmed R, *et al*. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. *Expert Rev Respir Med* 2020; 14: 1149-1163. doi: 10.1080/17476348.2020.1804365.
45. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, Diaz JV. Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. *JAMA* 2020; 324: 1330-1341. doi: 10.1001/jama.2020.17023.
46. van Paassen J, Vos JS, Hoekstra EM, *et al*. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care* 2020; 24: 696. doi: 10.1186/s13054-020-03400-9.
47. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, *et al*. A retrospective controlled cohort study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality. *Antimicrob Agents Chemother* 2020; 64: e01168-20. https://doi.org/10.1128/AAC.01168-20.
48. Metlay JP, Waterer GW, Long AC, *et al*. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; 200: e45-e67. doi: 10.1164/rccm.201908-1581ST.
49. Craig WA, Andes DR. Cephalosporins. In Bennett JE, Dolin R, Blaser MJ, editors. Mandell Douglas and Bennett's Principles and Practice of Infectious Diseases 8th Edition. *Philadelphia: Elsevier Co* 2015; 278-292.
50. Vaughn VM, Gandhi T, Petty LA, *et al*. Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study. *Clin Infect Dis* 2020: ciaa1239. doi: 10.1093/cid/ciaa1239.
51. Murphy S, Thomson L. NICE community-acquired pneumonia guideline review. *Arch Dis Child Educ Pract Ed* 2020: edpract-2020-319376. doi: 10.1136/archdischild-2020-31937.

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ММР

Original article

ARTERIALIZATION OF GREAT SAPHENOUS VEIN IN SITU FOR LIMB SALVATION: OUR CLINICAL EXPERIENCES

АРТЕРИЈАЛИЗАЦИЈА НА V. SAPHENA MAGNA ПРИ КРИТИЧНА ИСХЕМИЈА НА НОГАТА: НАШИ КЛИНИЧКИ ИСКУСТВА

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Abstract

Introduction. Critical lower limb ischemia in the absence of distal arterial circulation presents an urgent situation, which must be treated immediately if we want to save the foot or limb from amputation.
Approximately 14%-20% of patients with critical lower limb ischemia are unsuited for distal arterial reconstruction and face major distal amputation [1]. Arterialization of great saphenous vein is a unique procedure in which the venous bed is used as an alternative conduit for perfusion of peripheral tissues of lower limb.
Methods. We present our clinical experience in 6 patients who underwent *in situ* arterialization of great saphenous vein for treatment of critical below- and above-knee ischemia.
Maintaining the great saphenous vein *in situ* allows the arterialization with one anastomosis without removing the vein of its original bed. All patients were diagnosed with color Doppler ultrasound and with CT angiography.
Results. In all 6 patients we managed to safe the limb or foot from amputation in the first 6 months after the procedure. Postoperative color Doppler ultrasound was performed to assess arterial inflow and arterialized flow in the graft, the anastomosis and venous run-off.
In all patients with significant intraoperative reverse flow in upper and below the knee part of great saphenous vein the procedures were initially successful.
Conclusion. Distal revascularization of the limb with critical ischemia, by creating a reverse flow with *in situ* saphenous vein arterialization must be seriously considered as an attempt for salvage of the foot or below-knee without distal arterial run-off.

Keywords: arterialization of vein, great saphenous vein, critical limb ischemia, end-stage peripheral artery disease, gangrene

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Абстракт

Вовед. Критична исхемија на ногата настанува при отсуство на артериска циркулација на било кое ниво на ногата и претставува ургентна состојба кој мора веднаш да се лекува со цел да се спаси екстремитетот од ампутација. Приближно 14-20% од пациентите со критична исхемија на ногата не се погодни за дистална артериска реконструкција и се соочуваат со ампутација [1]. Артеријализацијата на v. saphena magna претставува единствена процедура во која се користи вената како пат за обезбедување на артериска крв во периферните ткива на ногата.
Методи. Во оваа студија ги презентираме нашите клинички искуства од изведувањето на артеријализацијата на v. saphena magna во третман на критична исхемија на ногата кај 6 пациенти. Кај оваа процедура се изведува само една анастомоза со задржување на v. saphena magna во нејзината анатомска положба. Пациентите вклучени во оваа студија беа дијагностицирани со Колор доплер ехотомографија и КТ ангиографија.
Резултати. Кај ниту еден пациент во првите 6 месеци после интервенцијата немаше потреба од ампутација. Процедурата за артеријализација на вената беше окарактеризирана како успешна кога со колор доплер ехотомографија се верифицира интраоперативен и постопретивен т.н. обратен крвен проток во стеблото на v. saphena magna. Постоперативно колор доплер ехотомографија се врши за да се прикаже иницијалниот артериски крвен проток во употребената v. saphena magna, процена на состојбата на местото на анастомозата и венскиот повраток низ длабокиот венски систем.
Заклучок. Реваскуларизација на ногата со критична исхемија преку создавање на обратен крвен проток во v. saphena magna преку нејзина артеријали-

зација треба да се земе како сериозен обид во клиничката пракса за зачувување на екстремитетот.

Клучни зборови: артеријализација на вена, голема сафенска вена, критична исхемија на екстремитет, краен стадиум на периферна артериска болест, гангрена

Introduction

Critical limb ischemia (CLI) is the clinical end-stage of peripheral artery disease (PAD) and is associated with high amputation and mortality rates, and poor quality of life [2].
It is estimated that 5-10% of patients with peripheral artery disease who are older than 50 years will develop severe or critical limb ischemia (CLI) within 5 years [3].
Critical lower limb ischemia in the absence of distal arterial circulation presents an urgent situation, which must be treated immediately if we want to save the foot or limb from amputation.
The reduced arterial flow in these situations is not adequate to provide metabolic requirements of lower limb even in rest.
According to Fountain these patients are classified in Class III or in Class IV.
Approximately 14%-20% of patients with critical lower limb ischemia are unsuited for distal arterial reconstruction and face major distal amputation [1].
In critical ischemia without arterial run-off, one of the treatment options to enable revascularization is to turn the course of the flow reversely through the venous system to treat rest pain, to promote healing of the ulcers or to salvage the limb from amputation [4].
Distal venous arterialization is a unique procedure in which the venous bed is used as an alternative conduit for perfusion of peripheral tissues of lower limb.
Patients with critical lower limb ischemia can be treated by arterialization of great saphenous vein.
Atherosclerosis obliterans (AO), especially associated with diabetes mellitus, thromboangiitis obliterans (TO) in most cases and popliteal artery aneurysms with distal bed thrombosis are conditions that justify the indication of this procedure [4].

Material and methods

Thise study was designed as a controlled, randomized, prospective, clinical study with predetermined protocol, which was conducted in the Private General Hospital "Remedika" in the period from January 2016 to July 2021.
All patients had stage IV Fontaine critical lower limb ischemia due to unreconstructable arterial disease and were considered unfit for endovascular or surgical reconstructive procedures. All patients had severe, persistent rest pain without gangrene.
Conventional treatment would have resulted in major amputation.
All 6 patients initially underwent color Doppler ultrasound for investigation of arterial and venous systems of both legs.
All patients also underwent CT angiography with 3D reconstruction.
The primary outcome measure was postoperative limb salvage at 6 months.
The secondary outcome measures were postoperative control with color Doppler ultrasound on the second postoperative day, 6 weeks after surgery, at 3-month intervals in the first year and at 6-month intervals in the second year, walking with or without orthopedic device one year after surgery, surgical site occurrence rate and need of amputations in the follow-up period after performing this surgical procedure.

Preoperative preparation

Preoperatively laboratory examination was made with the following analyses:

- Blood counts
- Protein status
- Urea and creatinine
- Liver function
- Electrolytes levels
- D-dimmers
- Blood group and Rh factor
- Screening for infectious disease transmissible through blood

Preoperative anesthesiology evaluation was performed in all patients.
Three patients were operated under general anesthesia and 3 patients underwent surgery in spinal anesthesia.
Once again preoperatively in the operating room, we performed color Doppler ultrasound of the venous system in order to recheck both venous systems for presence of thrombus and to perform mapping of collateral branches of great saphenous vein in the leg that would undergo a surgical procedure.
We intravenously administered 5000 IU heparin intraoperatively in all patients.

Surgical technique

We start all the procedures with separation of confluence of great saphenous vein into femoral vein on the leg that is to undergo surgery.
We create small separate incisions of the limb to identify previously mapped collateral branches and we perform ligation and resection of these branches.
We ligated and resected all collateral branches within three incisions in 3 patients of this group of treated patients and within 4 incisions in the remaining 3 patients.

The point of the beginning of great saphenous vein near medial malleolus was identified and at this point we opened the great saphenous vein.
In order to ensure arterial flow via vein, at this point we inserted a valvulotome in great saphenous vein and we destroyed all valves from the point of entrance to previous ligated entrance of great saphenous vein into femoral vein.
During destruction of great saphenous vein valves, we did not verify any large thrombotic masses to evacuate with valvulotome from the vein as we previously double checked the peripheral and deep venous system with color Doppler ultrasound.
In order to ensure the arterial flow on the dorsal part of the foot, we completed the destruction of valves at the level of the first interdigital space and ensured the exit point from dorsal venous arch via the system of small saphenous vein.
After preparing the vein, we continued the procedure with preparation of the place for anastomosis of the common femoral artery.
We created the anastomosis between great saphenous vein and the artery using continuous 6.0 polypropylene sutures.
Peroperatively we noticed presence of pulse and trill in the dorsal venous arch as well as weakened pulsation in proximal part of small saphenous vein.

Postoperative care

Patient (koj pacient) was admitted in Intensive care unit and we administered continuous heparin therapy with 25000 IU/24 hours in first four with targeted APTT over 60 seconds.
After four days patient was transferred to the surgical department and we switched the anticoagulant therapy on low molecular weight heparin at a dose of 1 mg/kg body weight.

Results

We succeed in our primary goal in all patients and postoperatively we saved all of the operated limbs from amputation in the first 6 months after surgery.
The follow-up period of 1.5 years showed an excellent quality of life in 4 patients. These patients could walk more than 1.5 kilometres without the help of orthopedic devices.
In 2 patients the follow-up period of 1 year a good quality of life was achieved and they could walk more than 1 km with one crutch.
Postoperatively color Doppler ultrasound was performed to assess arterial inflow and arterialized flow in the graft, the anastomosis, and venous run-off.
The waveforms appeared to behave analogously to those in hemodialysis grafts, with a mono- to biphasic arterial spectrum in the conduit to the anastomosis and low-resistance monophasic waveforms in the draining venous system.
The velocities in the postanastomotic venous system were typically high due to the small caliber of the venous arch or vena comitans. Follow-up color Doppler ultrasound was part of a regular surveillance program consisting of imaging performed after 6 weeks, at 3-month intervals in the first year, at 6-month intervals in the second year, and yearly thereafter at the discretion of the consultant vascular surgeon.
On the second postoperative day as per our postoperative protocol we performed a control color Doppler ultrasound with satisfactory arterial circulation in the great saphenous vein and in dorsal venous arch of the operated limb.
One patient required a postoperative intervention since residual venous valve in below the knee part of great saphenous vein was postoperatively noticed on color Doppler ultrasound. This patient underwent a local valvulectomy with Fogarty catheter.
In three patients we noticed subcutaneous hematoma at the place of anastomosis between the artery and the vein as well as few hematomas on the skin incision where we had cut the veins branches.
Two fingers of the foot were amputated in one patient one year after the surgical procedure.

Discussion

In 2006, Lu *et al.* performed a meta-analysis on the effectiveness of venous arterialization for limb salvage in critical limb ischemia [5].
They included seven studies comprising a total of 228 patients and found a pooled limb salvage rate of 71% at 12 months. The authors concluded that venous arterialization can be a viable option to save the limb when no arterial reconstruction is possible.
Not all patients are candidates for venous arterialization and even without intervention a proportion of patients with CLI will keep their limb. There is a lack of comparative studies, although Matzke *et al.* showed that wound care and pain relief led to 50% limb salvage after 12 months, which suggests that not all patients need revascularizsation [6].
In the studies by Djoric *et al.* 13% limb salvage was observed in those patients treated by conservative means, while 83% and 93% limb salvage was obtained in the venous arterialization group [7,8].
These findings and the differences in limb salvage rates in the studies included here suggest that patient selection might be important. Unfortunately, there are no data robust enough to support any recommendation on how to appropriately select patients for either venous arterialization or conservative treatment or amputation.

Conclusion

Decision for performing arterialization of great saphenous vein for limb salvation in patients with critical ischemia should be considered as necessary and adequate option for treatment in patients when other techniques will not provide good postoperative results.

A small number of performed procedures of venous arterialization in literature is not a limitation to draw conclusions and give strong recommendations.

Every performed procedure should obtain adequate follow-up of patients in order to measure the results from the surgical procedure and to collect necessary information so as to improve the technique and to share information on global level.

Arterialization of the venous system of the foot should be considered as first choice for salvage of the limbs where the absence of distal arterial bed leads to critical ischemia.

Conflict of interest statement. None declared.

References

1. Christoph Engelke, Robert A Morgan, John W Quarmby, *et al*. Distal venous arterialization for lower limb salvage: Angiographic appearances and interventional procedures, *RadioGraphics* 2001; 21(5): 1239-1248.
2. Sprengers RW, Teraa M, Moll FL, *et al*. Quality of life in patients with no-option critical limb ischemia underlines the need for new effective treatment. *J Vasc Surg* 2010; 52: 843e84.
3. Norgren L, Hiatt WR, Dormandy JA, *et al.* Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg* 2007; 33(1): S1e75.
4. Cesar Roberto Busato, Carlos Alberto Lima Utrabo, Ricardo Zanetti Gomes, *et al*. The great saphenous vein in situ for the arterialization of the venous arch of the foot. *J Vasc Bras* 2010, Vol. 9, Nº 3.
5. Lu XW, Idu MM, Ubbink DT, Legemate DA. Meta-analysis of the clinical effectiveness of venous arterialization for salvage of critically ischaemic limbs. *Eur J Vasc Endovasc Surg* 2006; 31(5): 493-499.
6. Mätzke S, Pitkänen J, Lepäntalo M. Does saphenous vein arterialisation prevent major amputation in critical leg ischaemia? A comparative study. *J Cardiovasc Surg* (Torino) 1999; 40(6): 845-847.
7. Djoric P. Early individual experience with distal venous arterialization as a lower limb salvage procedure. *Am Surg* 2011; 77(6): 726-730.
8. Djoric P, Zeleskov-Djoric J, Stanisavljevic DM, *et al*. Distal venous arterialization and reperfusion injury: focus on oxidative status. *Eur Surg Res* 2012; 48(4): 200-207.

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ММР

Original article

TWO SURGICAL APPROACHES IN IMPLANTATION OF TOTAL HIP ENDOPROSTHESIS - A SINGLE CENTER EXPERIENCE

ДВА ХИРУШКИ ПРИСТАПИ ПРИ ИМПЛАНТАЦИЈА НА ТОТАЛНА ЕНДОПРОТЕЗА НА КОЛК-ИСКУСТВА НА ЕДЕН ЦЕНТАР

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Abstract

Introduction. Degenerative hip diseases are one of the most common musculoskeletal disorders. The large number of patients and the large number of surgeries performed annually at the University Clinic for TOARILUC, due to degenerative hip diseases, as well as the existing controversy regarding the choice of optimal approach to implantation of total hip endoprosthesis, were the motivation for conducting this study.
Aim of the study. To perform a comparative analysis of the results obtained after the application of two approaches in the implantation of total hip endoprosthesis.
Methods. This retrospective-prospective study was performed at the University Clinic for TOARILUC in Skopje from January 2018 to May 2021. A total of 60 surgically treated patients with degenerative hip disease were included in the study. The patients were divided into 2 groups based on the approach chosen for implantation of a total hip endoprosthesis, a modified Watson Jones antero-lateral approach according to group A (AA), and group B with a posterior approach (PA).
Results. The mean age of patients was 62.6 years in AA group and 71 years in PA group. Most of the patients from the two groups were retired and had normal BMI. The difference between the level of preoperative and postoperative creatinine kinase in PA group was statistically significant ($p<0.0001$). We compared the postoperative creatinine kinase level between the two groups and found statistically significant difference ($p<0.00001$). In most of the patients (34%) treated with the posterior approach the surgery lasted for more than 2 hours, and in those with AP approach (100%) it lasted up to 2 hours. Only one complication occurred in the group with posterior approach to the hip, and it was dislocation of the prosthesis two weeks after the surgery.
Conclusion. Patients operated with a modified antero-lateral approach according to Watson Jones had shorter and more effective rehabilitation than patients operated with posterior approach. The duration of surgery was also shorter compared to the group treated with posterior approach. Only one complication occurred during the study in the group with posterior approach, and it was dislocation of the prosthesis two weeks after the surgery.

Keywords: modified antero-lateral approach, posterior approach, Harris Hip score

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Апстракт

Вовед. Дегенеративните заболувања на колкот се едни од најчестите нарушувања на мускулно-скелетниот систем. Големиот број на пациенти и големиот број на операции што се прават годишно на Универзитетската клиника за ТОАРИЛУЦ, поради дегенеративни заболувања на колкот, како и постојната полемика во врска со изборот на оптимален пристап за вградување на тотална ендопротеза на колкот, се мотив за тоа истражување.
Цел на студијата. Да се изврши компаративна анализа на резултатите добиени по примената на двата пристапа при имплантација на тотална ендопротеза на колкот.
Методи. Ова е ретроспективно-проспективно истражување извршено на Универзитетската клиника за ТОАРИЛУЦ во Скопје во период од јануари 2018 до мај 2021 година. Вкупно 60 хируршки третирани пациенти со дегенеративно заболување на колкот беа вклучени во студијата. Пациентите беа поделени во 2 групи врз основа на избраниот пристап за имплантација на тотална ендопротеза на колкот, модифицираниот антеро-латерален пристап според Watson Jones групата А и групата Б со заден пристап.
Резултати. Средната возраст беше 62,6 години во групата АП и 71 година во групата ПП. Повеќето пациенти од двете групи биле во пензија со нор-

мален БМИ. Разликата помеѓу вредноста на предоперативната и постоперативната креатин киназа кај групата ПП е статистички значајна со p<0,0001. Ние ја споредивме постоперативната вредност на креатин киназата помеѓу две групи и откривме дека разликата се смета за статистички значајна со p <0.00001. Повеќето пациенти, третирани со заден пристап имале оперативно време повеќе од 2 часа, 34% од ПП и 100% од пациентите од групата АП имале оперативно време до 2 часа. Само една компликација се појави во групата со заден пристап, дислокација на протезата две недели по операцијата.
Заклучок. Пациентите оперирани со модифициран антеро-латерален пристап според Watson Jones, имаат пократка и поефикасна рехабилитација отколку пациентите оперирани со заден пристап. Времетраењето на операцијата беше исто така пократко во споредба со групата третирана со заден пристап. Само една компликација се случи за време на студијата во групата со заден пристап, а тоа беше дислокација на протезата две недели по операцијата.

Клучни зборови: модифициран антеро-страничен пристап, заден пристап, Harris Hip резултат

Introduction

Osteoarthritis (OA), also known as age-related arthritis or degenerative joint disease, is among the most often joint disorders worldwide [1]. It can involve any joint, and primarily affect the articular cartilage and surrounding soft tissues [2]. The hip joint is body's largest weight-bearing joint, secondary to the knee, and is commonly affected by OA [3]. This process presents with progressive loss of the articular cartilage, osteophytes, subchondral cysts, muscle weakness, periartricular ligamentous laxity and synovial inflammation [2]. The involvement of the hip results in reduced mobility and physical impairment that often leads to loss of independence and to increased use of health services. It has serious impact on daily activities of patients and substantial disability or dependency in stair climbing, rising from a seated position, walking or using a public transportation.
OA of the hip may be primary, if it occurs in the absence of trauma or disease but is associated with the risk factors such as female gender, age of the patients, obesity, anatomical factors, etc. On the other hand, secondary OA occurs with pre-existing abnormality of the joint such as trauma or congenital disorder of the hip, avascular necrosis, inflammatory or infectious arthritis, osteoporosis, Marfan syndrome or hemoglobinopathy [4,5].
Its presentation and progression can vary from person to person, but it is mainly presented with joint pain, locomotor restriction and stiffness; it may also manifest as muscle weakness and balance issue. The diagnosis is based on the clinical examination with serious limitation on the range of motion and radiology findings.
OA of the hip is treated surgically by implantation of total hip endoprosthesis, for which different surgical approaches are used, and the choice of the optimal approach depends on the experience of the surgeon. Even today, there is still no general consensus among orthopedic surgeons around the world about the best approach for primary total hip arthroplasty, because both approaches (modified antero-lateral by Watson Jones and posterior) have their advantages and limitations. A review of studies by Jolles and Bogoch [6] to determine which approach is superior to the other showed that, despite numerous studies examining the effect of the surgical approach in total hip arthroplasty (THA), the quality and number of such examinations are insufficient to provide a firm conclusion as to whether one approach is superior to the other. Of the four prospective cohort studies included in this review, only one study by Barber *et al*. [7] included functional outcomes, using the Harris Hip Score and 2-year patient follow-up, involving 49 patients. The impact of the surgical approach on the rate of dislocation after primary total hip arthroplasty has also been the primary focus of a number of studies [8-12], but to date there is still no agreement as to which approach is associated with the higher dislocation rate.
The aim of our study was to perform a comparative analysis of the results obtained after the application of both approaches, modified antero-lateral Watson Jones and posterior approach, in the implantation of the total hip endoprosthesis as well as to determine the impact of the surgical approach on intraoperative complications, on the type and severity of postoperative complications. Also, it was our aim to determine the impact on the length and quality of rehabilitation.

Materials and methods

Patients and treatment

The study was conducted at the University Clinic for TOARILUC in Skopje, at the Clinic for Orthopaedic Diseases and the Clinic for Traumatology in a retrospective-prospective setting. A total of 60 surgically treated patients with degenerative hip disease were included in the study. The patients were assigned to 2 groups based on the approach chosen for implantation of a total hip endoprosthesis, a modified Watson Jones antero-lateral approach-group A, and a posterior approach-group B. Patients signed informed consent for the procedure itself, as well as for voluntary inclusion in the study, according to the principles of good clinical practice. We determined the following parameters:-clinical preoperative parameters [body mass index, laboratory (blood count, complete biochemical analysis, hemostasis with D-dimers)], -the level of creatini-

ne kinase, Harris Hip Score result and Visual Analogue Scale, (abduction, adduction, internal and external rotation of the hip), -intraoperative parameters (duration of operative intervention), -postoperative parameters (control laboratory -blood count, complete biochemical analysis, hemostasis with D-dimers), -functional results (active and passive movements in the hip) and complications (infection, endoprosthesis luxation, limb shortening, fracture). Follow-up of patients after discharge was scheduled on the 30th postoperative day, and subsequent check-ups 6 and 12 months after surgery.

Statistical analysis

All results were analyzed with the statistical program Statistics 8 for Windows, and the results obtained are presented in figures. Methods of descriptive statistics were used, such as non-parametric and parametric statistical analyses. Percentage and structure were determined for attributive series. The relationship between two samples with numerical features was determined with the Pearson correlation coefficient (p). Differences between two independent numerical samples were determined with t-test for independent samples and Mann-Whitney U test was used. Levels of probability for the realization of the null hypothesis, which were used in accordance with international standards for biomedical sciences, were 0.01 and 005.

Results

There were two groups of patients. The first group comprising 30 patients was treated with anterior approach (AA) and the second group of 30 patients was treated with posterior approach (PA). The mean age was 62.6 years in AA group and 71 years in PA group. Distribution of patients according to gender with female domination is presented in Figure 1.

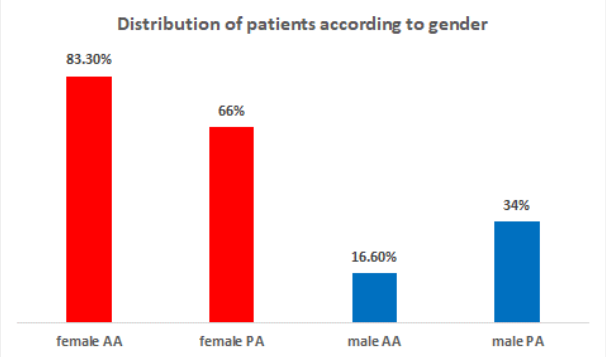

Fig. 1. Distribution of patients according to gender

Most of the patients from the two groups were retired (Figure 2).
Most of the patients who were treated with posterior and anterior approach had normal BMI (18.5-24.9) (Figure 3).

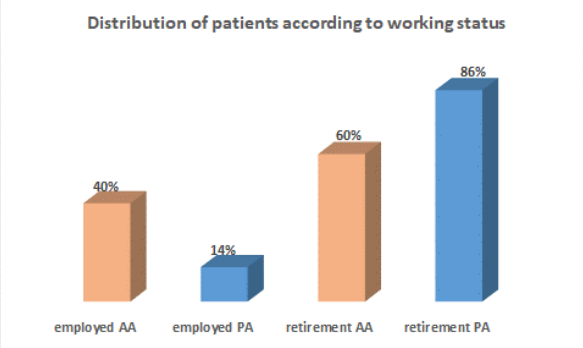

Fig. 2. Distribution of patients according to working status

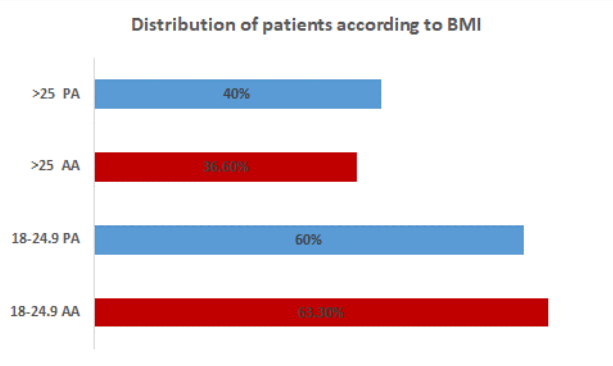

Fig. 3. Distribution of patients according to BMI

The average level of preoperative and postoperative creatine kinase is presented in Figure 4.
We used t-test to compare the value of preoperative and postoperative creatine kinase in PA group and we found an extremely statistically significant difference ($p<0.0001$); 95% confidence interval of this difference: from -3761.98 to -2933.28. Then, we used the Mann-Whitney U test and we compared postoperative level of creatine kinase between the two groups and we found a statistically significant difference ($p< 0.00001$). .

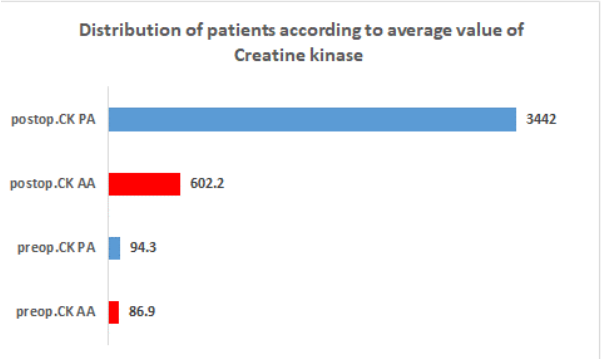

Fig. 4. Distribution of patients according to Creatine kinase

Distribution of patients according to diagnosis is presented in Figure 5.
In most of the patients (66%) treated with the posterior approach the surgery lasted for more than 2 hours,

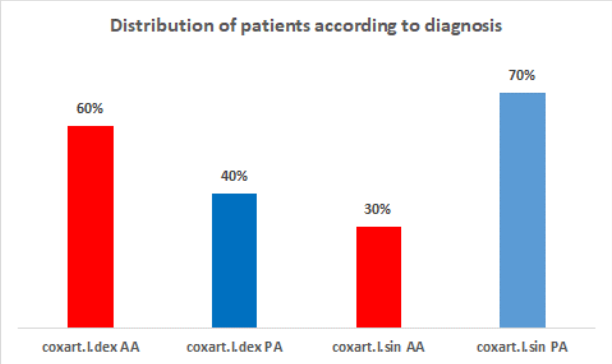

Fig. 5. Distribution of patients according to diagnosis

while 34% of patients in PA and 100% of patients in AP group had an operating time of 2 hours.
Distribution of patients according to time of hospitalization is presented in Figure 6.

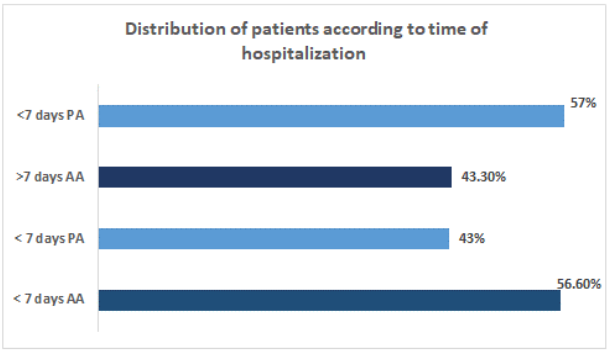

Fig. 6. Distribution of patients according to time of hospitalization

All patients (100%) from both groups had Harris hip score <70 on the first preoperative day.

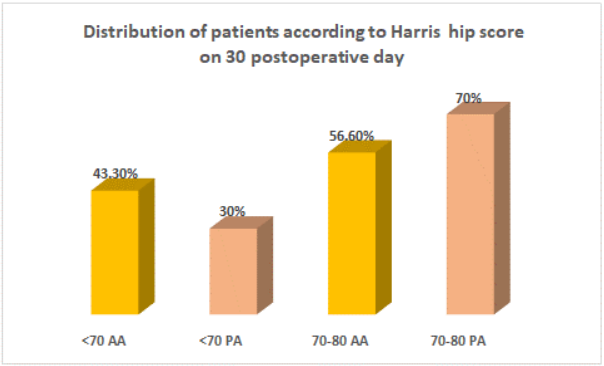

Fig. 7. Distribution of patients according to Harris hip score on 30th postoperative day

Figure 8 and Figure 9 show distributions of patients according to Harris hip score at 6 and 12 months postoperatively.
According to VAS scale preoperative patients had score 7 to 10 in AA and 8 to 10 in PA group (Figures 10 and 11).

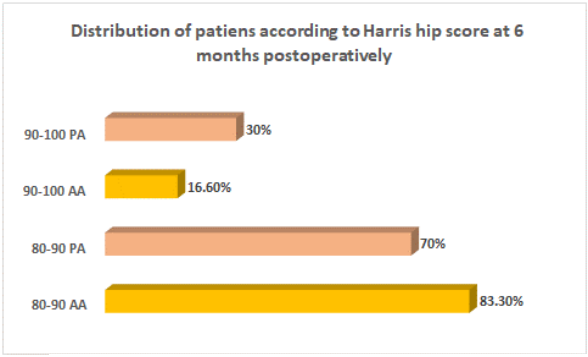

Fig. 8. Distribution of patients according to Harris hip score at 6 months postoperatively

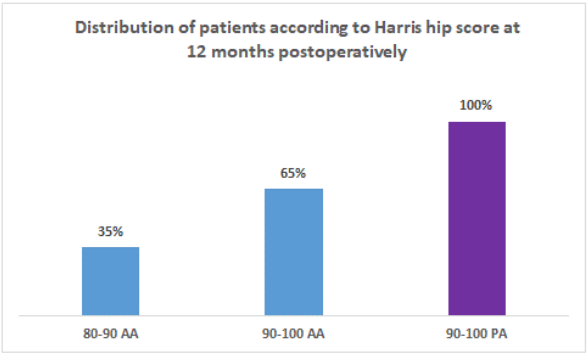

Fig. 9. Distribution of patients according to Harris hip score at 12 months postoperatively

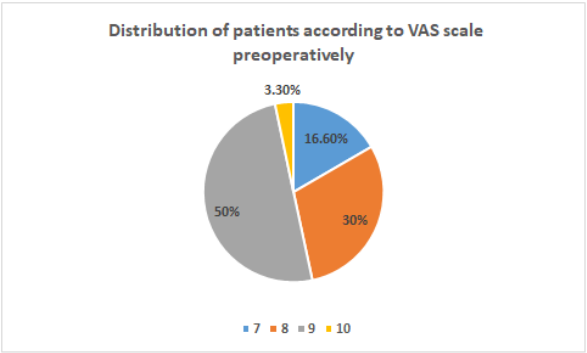

Fig. 10. Distribution of patients in AA group according to VAS scale preoperatively

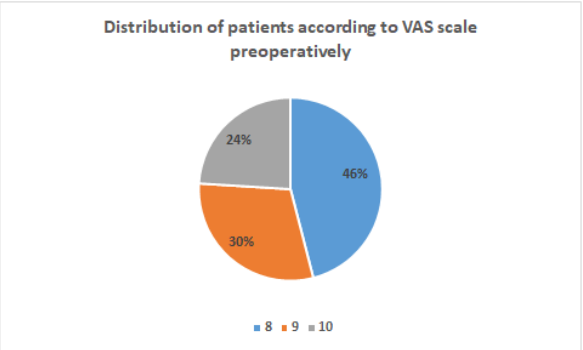

Fig. 11. Distribution of patients in PA group according to VAS scale preoperatively.

Distribution according to VAS scale on the 30th postoperative day is presented in Figures 12 and 13.

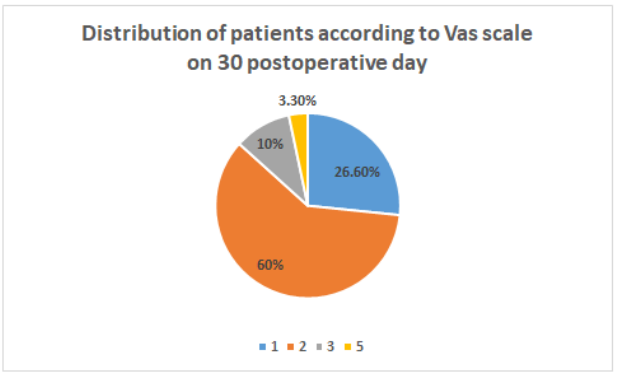

Fig. 12. Distribution of patients in AA group according to VAS scale on the 30th postoperative day

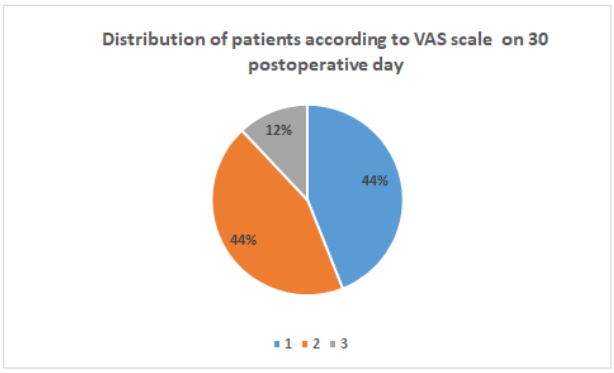

Fig. 13. Distribution of patients in PA group according to VAS scale on the 30th postoperative day

Assessment of pain according to VAS scale at 6 and 12 months postoperatively showed score 0 (no pain) in all patients from AA and PA groups.
The average operative and postoperative surgical drainage of blood was 461 ml in AA group and 680 ml in PA group. All patients (100%) received one unit of blood after surgery in PA group. In the anterior approach group 43.3% of patients received one unit of blood after surgery, and 56.6% received two units of blood after surgery (Figure14).

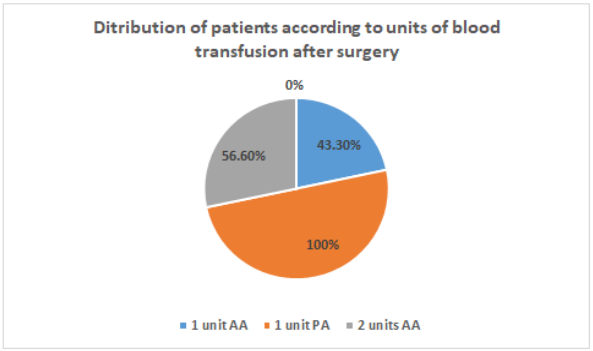

Fig. 14. Distribution of patients in AA and PA groups according to units of blood transfusion after surgery

Most of the patients underwent long rehabilitation lasting for more than 20 days (Figure 15).

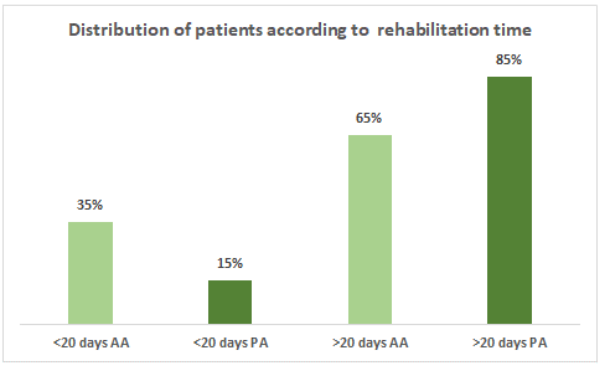

Fig. 15. Distribution of patients in AA and PA groups according to days of hospitalization

The mean value of preoperative and postoperative D-dimers in AA and PA groups is presented in Figure 16.

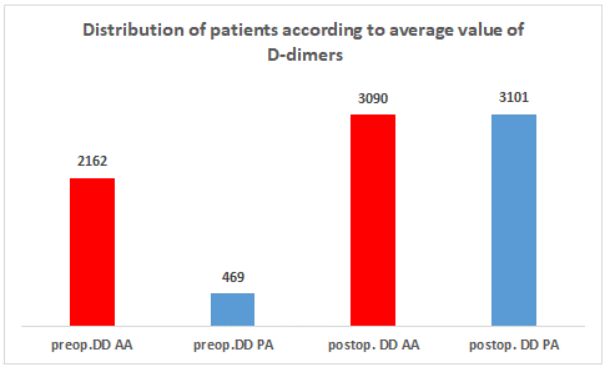

Fig. 16. Distribution of patients according to average value of D-dimers

We used t-test to determine preoperative and postoperative D-dimer levels and we found extremely statistically significant difference ($p<0.0011$); 95% confidence interval of this difference: from -4255.17 to -1129.49. We used the Mann-Whitney U test and we compared preoperative level of D-dimers between the two groups and we found a statistically significant difference ($p< 0.01$).

Discussion

According to gender most of the patients in our study were female. Most of the patients had normal BMI 18.5-24.9. The length of the skin incision was under 10 cm in both groups. Patients operated with modified antero-lateral approach according to Watson Jones had shorter operating time compared to patients operated with posterior approach. Patients operated with posterior approach had longer hospital stay than patients operated with modified antero-lateral approach according to Watson Jones. In this study we obtained similar results as those published in the study by Wang Gang *et al*. in 2010 [17].

The approach can be declared minimally invasive if the positioning of the prosthesis is associated with sparing as many anatomical structures as possible. Sparing the periarticular muscles is generally quite important, because the separation and reinsurance of the tendons, despite good healing, involves local "biological fatigue" and leads to a longer period of rehabilitation. There is a general consensus that the length of the skin incision is not what determines the success of the surgery, but the sparing of the soft tissue and neurovascular structures. Of particular importance is the adequate positioning of the patient, which will allow the surgeon to optimally position the femoral stem and the acetabular component, which is a supination position. This is generally the preferred position for surgeons, even when navigation systems are used. Anaesthesiologists also prefer the conventional supination position, due to the possible need for urgent intubation during regional anaesthesia. In our country and in our clinic, the most commonly used approach is the modified antero-lateral approach according to Watson Jones, mainly due to the rapid rehabilitation of patients and shorter hospital stay.

On the other hand, in implantation of a total hip replacement, a posterior approach can be used, for which there are several modifications. It was first described and applied in 1874 by Von Langenbeck. The modern posterior approach is closest and most reminiscent developed by Moore in 1957, and it is also known as the "Southern" or Moore approach [13-15].

Even today, there is still no general agreement among orthopaedic surgeons around the world, which is the best approach for primary total hip arthroplasty, because both approaches have their advantages and limitations. A review of studies by Jolles and Bogoch [16] regarding the most acceptable approach showed that, despite numerous studies examining the effect of the surgical approach in THA, the quality and number of such examinations are insufficient to provide a firm conclusion as to whether one approach is superior to the other.

Conclusion

In conclusion, in our patients operated on with a modified antero-lateral approach according to Watson Jones, postoperative rehabilitation was shorter and more effective than in patients operated on with a posterior approach. The duration of surgery in patients operated on with a modified antero-lateral approach was shorter than in patients operated on with a posterior approach. There was a lower rate of complications in the modified antero-lateral approach compared to the posterior; in our study only one complication was registered, and it was dislocation of the endoprosthesis, only two weeks after the surgical treatment.

Conflict of interest statement. None declared.

Reference

1. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2013-2015. *MMWR Morb Mortal Wkly Rep* 2017; 66(9): 246-253. DOI: https://doi.org/10.15585/mmwr.mm6609e1. [PMC free article] [PubMed] [Google Scholar]
2. Hutton CW. Osteoarthritis: The cause not result of joint failure? *Ann Rheum Dis* 1989; 48(11): 958-961. DOI: https://doi.org/10.1136/ard.48.11.958. [PMC free article] [PubMed] [Google Scholar]
3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med* 2010; 26(3): 355-369. DOI: https://doi.org/10.1016/j.cger.2010.03.001. Erratum in: Clin Geriatr Med 2013 May; 29(2):ix. DOI: https://doi.org/10.1016/j.cger.2013.01.013. [PMC free article] [PubMed] [Google Scholar]
4. Donahue SW. Krogh's principle for musculoskeletal physiology and pathology. *J Musculoskelet Neuronal Interact* 2018; 18(3): 284-291. [PMC free article] [PubMed]
5. Krishnan Y, Grodzinsky AJ. Cartilage diseases. *Matrix Biol* 2018; 71-72: 51-69. [PMC free article] [PubMed] [Reference list]
6. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum* 2006; 54: 226-229. [PubMed] [Google Scholar]
7. Barber TC, Roger DJ, Goodman SB, Schurman DJ. Early outcome of total hip arthroplasty using the direct lateral vs the posterior surgical approach. *Orthopedics* 1996; 19: 873-875. [PubMed]
8. Berry DJ, von Knoch M, Schleck CD, Harmsen WS. Effect of femoral head diameter and operative approach on risk of dislocation after primary total hip arthroplasty. *J Bone Joint Surg Am* 2005; 87: 2456-2463. [PubMed]
9. Hedlundh U, Hybbinette CH, Fredin H. Influence of surgical approach on dislocations after Charnley hip arthroplasty. *J Arthroplasty* 1995; 10: 609-614. [PubMed]
10. Kwon MS, Kuskowski M, Mulhall KJ, *et al*. Does surgical approach affect total hip arthroplasty dislocation rates? Clin Orthop Relat Res 2006; 447: 34-38. [PubMed]
11. Masonis JL, Bourne RB. Surgical approach, abductor function, and total hip arthroplasty dislocation. *Clin Orthop Relat Res* 2002; 405: 46-53. [PubMed]
12. Soong M, Rubash HE, Macaulay W. Dislocation after total hip arthroplasty. *J Am Acad Orthop Surg* 2004; 12: 314-321. [PubMed]
13. Von Langenbeck B. Uber die schussverletzungen des huftgelenks. *Arch Klin Chir* 1874; 16: 263.[Google Scholar]
14. Moore AT. The self-locking metal hip prosthesis. *J Bone Joint Surg Am* 1957; 39-A: 811-827. [PubMed] [Google Scholar]
15. Chechik O, Khashan M, Lador R, *et al*. Surgical approach and prosthesis fixation in hip arthroplasty world wide. *Arch Orthop Trauma Surg* 2013; 133: 1595-1600. [PubMed] [Google Scholar]
16. Jolles BM, Bogoch ER. Posterior versus lateral surgical approach for total hip arthroplasty in adults with osteoarthritis. *Cochrane Database Syst Rev* 2004; 1: CD003828. [PubMed]
17. Gang W, Gui-shan G, Dan L, *et al*. Comparative study of anterolateral approach versus posterior approach for total hip replacement in the treatment of femoral neck fractures in elderly patients. *Chinese Journal of Traumatology* 2010; 13(4): 234-239.

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Original article

CORRELATION BETWEEN DETECTED RESPIRATORY PATHOGENS AND LUNG FUNCTION IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

КОРЕЛАЦИЈА НА ДЕТЕКТИРАНИТЕ РЕСПИРАТОРНИ ПАТОГЕНИ И БЕЛОДРОБНАТА ФУНКЦИЈА КАЈ ПАЦИЕНТИ СО АКУТНА ЕГЗАЦЕРБАЦИЈА НА ХРОНИЧНА ОПСТРУКТИВНА БЕЛОДРОБНА БОЛЕСТ

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Abstract

Introduction. Acute exacerbations of COPD lead to disruption of stable phase of the disease and worsening of symptoms. The main etiological factor are infectious agents; their presence is associated with increased inflammation, decreased lung function and frequent exacerbations. The aim of our study was to detect respiratory pathogens in patients with acute exacerbation of COPD, using PCR method that simultaneously detects typical, atypical and viral microorganisms in a sputum sample and their correlation with respiratory function.
Methods. This prospective study included 49 patients with diagnosis of acute exacerbation of COPD, admitted to the hospital ward of the University Clinic for Pulmonology in Skopje in the period from October 2019 until February 2021. Sputum samples were analyzed with a new rapid PCR method. Patients were divided into two groups, with pathogen-positive and pathogen-negative exacerbations. The pathogen positive group was further subdivided to viral, bacterial and combined pathogen exacerbations. For statistical analyses we used the Mann-Whitney U test, one-way ANOVA test and Spearman's correlation analysis with p value ≤ 0.05 considering significant.
Results. In the study 25 patients had pathogen-positive exacerbation and 24 pathogen-negative. The most commonly detected respiratory pathogens were *Influenza A* virus (n=9), *Haemophilus influenzae* (n=7), *Pseudomonas aeruginosa* (n=6), *Streptococcus pneumoniae* (n=5) and *Human Rhinovirus/Enterovirus* (n=5). Correlation of detected respiratory pathogens with lung function (FEV1%) was not found. A significant difference existed only between the group with bacteria and the group with viruses as a causative agent (p=0.048), thus the lower the percentage of FEV1 (%), the greater is the likelihood of bacterial infection.
Conclusion. We found a positive correlation of bacterial presence with lower values of FEV1 % predicted, which indicates that bacterial infections as etiological trigger of exacerbation of COPD are more likely to be found in patients with severely compromised lung function.

Keywords: acute exacerbation, COPD, respiratory pathogens, PCR, FEV1

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Абстракт

Вовед. Акутните егзацербации на ХОББ доведуваат до нарушување во стабилната фаза на болеста и влошување на симптомите. Главен етиолошки фактор се инфективните агенси, нивното присуство е асоцирано со зголемена инфламација, опаѓање на белодробната функција и зачестени егзацербации. Целта на нашата студија беше да се детектираат респираторните патогени кај пациенти со акутна егзацербација на ХОББ со помош на PCR метода која симултано одредува типични, атипични бактерии и вируси од спутум и нивна корелација со белодробната функција.
Методи. Во оваа проспективна студија беа вклучени 49 пациенти со дијагноза на акутна егзацербација на ХОББ, примени на хоспиталниот оддел на Универзитетската клиника за пулмологија во Скопје во период од Октомври 2019 до Февруари 2021. Приемроци од спутум беа анализиран со нова брза PCR метода. Пациентите беа поделени во две групи на патоген-позитивна и патоген-негативна гру-

па. Патоген позитивната група понатаму беше поделена на вирусни, бактериски и комбиниран тип на егзацербации. За статистичка анализа на податоците ги користевме Mann-Whitney U тестот, ANOVA тестот и Spearman-овата корелациска анализа со значајност на вредноста на $p \leq 0.05$.

Резултати. Во студијата 25 пациенти беа со патоген-позитивна егзацербација а 24 со патоген-негативна. Најчести детектирани патогени беа Infuenza A (n=9), Haemophilus influenzae (n=7), Pseudomonas aeruginosa (n=6), Streptococcus pneumoniae (n=5) и Human Rhinovirus/Enterovirus (n=5). Корелација на детектирани патогени со белодробната функција (FEV1) не беше најдена. Значајна разлика беше добиена само меѓу групите со бактериски и вирусни причинители, така да ,колку е помала вредноста на FEV1% толку е поголема веројатноста за бактериска инфекција.

Закчучок. Во студијата добивме позитивна корелација на бактериското присуство со пониски вредности на предвидениот FEV1%, што укажува на тоа дека бактериските инфекции како причинител за егзацербации на ХОББ е поверојатно да се јават кај пациенти со нарушување на белодробната функција од потежок степен.

Клучни зборови: акутна егзацербација, ХОББ, респираторни патогени, PCR, ФЕВ1

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogenic inflammatory disease which is characterized with progressive, partly irreversible airflow limitation. It is associated with high mortality and morbidity and its prevalence coincides with the prevalence of cigarette smoking. In the evolutionary course of the disease, the stable phase is often disrupted by worsening of baselyne respiratory symptoms called acute exacerbations. They are considered to be one of the main reasons for the increased mortality as well as the deterioration of the overall health status of the patients with COPD and increased number of hospitalizations and treatment in general. Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines acute exacerbations as worsening of respiratory symptoms which needs additional therapy and divides them into mild, moderate and severe type [1]. In contrast, Antonizen gives definition and classified exacerbations of COPD based on the presence of three main symptoms (worsening of dyspnea, increased sputum production and purulent sputum) and several minor symptoms (cough, wheezing, fever, upper respiratory infection and increase in respiratory or heart rate by 20% of basal values) [2]. Numerous studies have shown that exacerbations play a role in disease progression, especially in milder forms of COPD and in "frequent exacerbators" [3]. The annual decline in FEV1 has been demonstrated in patients in COPD GENE studies who have been followed for 5 years, especially in moderate and severe COPD [4]. Similar results were obtained in the ECLIPSE study during the follow-up period where a decrease of FEV1 of 2 ml per year was proven [5,6].

The etiology of acute exacerbations of COPD is largely due to infectious agents and according to some studies, up to 78% of other causes are environmental factors such as polluted air and other harmful inhaled particles [7]. Application of the molecular methods like multiplex, polymerase chain reaction (PCR) enables simultaneous detection of a large number of respiratory pathogens in a short time. Their high sensitivity for virus detection in some studies showed quite high detection of viral pathogens, approximately in 40-60% of COPD exacerbations. The most common detected viral pathogens were human rhinovirus, influenza viruses, respiratory syncytial virus, and coronavirus, which are also found to be most common in healthy people [8,9]. Based on this, the importance of bacterial triggers in acute exacerbation of COPD (AECOPD) has gained an intermediate role, especially since in recent years the role of bacterial infections in exacerbations of COPD has been overestimated or misinterpreted. The advent of new molecular methods for sequencing and further detection of microbial genetic material has enabled the understanding of the lung microbiome as well as the new concept of immune and inflammatory profile in exacerbations of most chronic lung diseases including COPD [10-14]. The presence of bacterial pathogens in the lower respiratory tract in patients with COPD is associated with increased inflammation, decreased lung function, and frequent exacerbations [15-17]. Acquisition of a new type of respiratory pathogen is considered to be a risk factor for the development of AECOPD [7]. The most common causes detected in acute exacerbation of COPD are *Haemophilus influenzae* as the main bacterial causative agent followed by *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* [18]. At the onset of exacerbation, physiological changes such as a reduction in FEV1 or PEF are not so significant and do not play a major role in predicting exacerbations. Larger changes such as increased dyspnea and the onset of symptoms of cold, such as prodromal syndrome and cough are associated with viral triggers and therefore these should indicate earlier introduction of therapy especially that viral exacerbation are more severe [19].

The aim of our study was to detect respiratory pathogens in patients with acute exacerbation of COPD, using a new rapid molecular PCR method that simultaneously detects typical, atypical and viral microorganisms in a sputum sample and their correlation with respiratory function.

Materials and methods

In this prospective, observational study, we included 49 patients, over 40 years of age with diagnosis of acute exacerbation of COPD, admitted to the hospital ward of the University Clinic for Pulmonology and Allergology in Skopje in the period from October 2019 until February 2021. Sputum samples from all patients were analyzed with a new rapid PCR method. Patients were divided into two groups, with pathogen-positive and pathogen-negative exacerbations, depending on the detection of respiratory microorganisms. The pathogen positive group was subdivided to viral, bacterial and combined pathogen exacerbations.

Inclusion and exclusion criteria

Presence of COPD was diagnosed according to GOLD-2019 recommendations with postbronchodilatator FEV1 (Forced expiratory volume in 1 second)/FVC (Forced vital capacity) ratio <70%. The diagnosis of acute exacerbation was made also according to the criteria of the GOLD, which classifies them into-mild, which are treated only with short-term bronchodilators, - moderate, which are treated with short-term bronchodilators, antibiotics and/or oral corticosteroids, and - severe exacerbations that require hospital treatment [1]. All our patients were hospitalized, which meant all of them had severe exacerbation of COPD. Exclusion criteria were: presence of severe lung diseases such as tuberculosis, cystic fibrosis, pulmonary fibrosis and lung cancer, pneumonia and other severe infectious and neoplastic diseases. Patients who could not produce sputum even after the induced sputum procedure and patients who could not perform spirometry were not included in the study.

Methods

On admission we collected data about comorbidities, allergies, current therapy, smoking status, body temperature, body mass index (BMI), blood pressure, heart rate, chest radiography, blood gas analysis by measuring of pH, PaO2 (kPa), PaCO2 (kPa), SaO2 (%), HCO3- (moll/L) laboratory blood tests, including C-reactive protein (CRP), eosinophils and neutrophils, and a standard 12-channel electrocardiogram.
Sputum samples from all 49 patients were analyzed with a PCR method. We used a multiplex microarray PCR-based molecular method that enables rapid detection of a large number of deoxyribonucleic (DNA) sequences and thus a large number of targets at the same time in one sample. It uses a clinically approved BioFire Filmarray Pneumonia Plus panel that identifies 34 targets, which are 18 bacteria (11 gram-negative, 4 gram-positive and 3 atypical), 9 viruses and 7 markers of antibiotic resistance. It consists of a closed system containing all of the necessary reagents for sample preparation, reverse transcription, polymerase chain reaction (PCR) and detection in order to isolate, amplify and detect nucleic acids from multiple respiratory pathogens. All targets are qualitatively determined and marked as detected or not-detected except typical bacteria which are determined not only qualitatively but also quantitatively, thus expressing bacterial concentration as the number of genomic copies per milliliter. The result is considered positive if a value of 10^4 copies / mL and above is obtained.
The lung function was examined in all patients with spirometry several times during hospitalization. The Power Cube spirometer (Ganshorn, Niederlaner, Germany) was used for spirometry and performed according to current recommendations of the European Respiratory Society (ERS) and the American Thoracic Society. (ATS) [20]. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were determined. The lung function data were obtained from spirometry prior to discharging patients from the hospital.

Statistical analysis

Categorical parameters were summarized as percentages and continuous parameters as a mean ± standard deviation. The difference in parameters of lung function between the two groups was tested using the Mann-Whitney U test and difference among subdivided positive group was tested using the one-way ANOVA with Bonferroni correction for post-hoc analysis. Assessment of correlation was done using the Spearman's correlation analysis.
All data analyses were performed using the SPSS version 26.0 (IBM SPSS, Inc., Chicago, Illinois) and a p-value ≤ 0.05 was considered significant.

Results

The study included data analyzed for 49 patients with severe acute exacerbation of COPD. The demographic data and basal characteristics of the patients are shown in Table 1. A larger number of patients were men - 32 (65.3%), with mean standard deviation (SD) at the age of 63.51 ± 9.10. The largest percentage (51%) of patients were former smokers. The majority of patients belonged to GOLD II-GOLD IV stage of COPD with mean postbronchodilatatory FEV1 values of 1.08 ± 0.40 and 40.69 ± 13.13% of the predicted (Table1).
sputum samples, of which 28% were bacterial, 44% viral and 28% combined respiratory pathogens (Table 2). Of the 49 samples of sputum, the most commonly

Table 1. Basal characteristics of patients with acute exacerbation of COPD

Features	Values (n=49)
Age (years)	63.51 ± 9.10
Max-min	82-43
Gender (n/%)	
Male	32/65.3
Female	17/34.7
BMI (kg/m2)	31.52 ± 7.15
Max-min	53.33-19.00
Body temperature (C^0)	36.8 ± 0.6
Max-min	39.0- 36.2
SyBP (mmHg)	126.5 ± 15.2
Max-min	180-90
DiaBP (mmHg)	78.3 ± 7.6
Max-min	100-60
HR	90.3 ± 16.1
Max-min	129-59
Smoking status	
Pack/years of smoking	60.24 ± 31.12
Max-min	140-20
Current smoker (n/%)	18/36.7
Ex-smoker(n/%)	24/51.0
Non-smoker (n/%)	8/16.3
Lung function (postbronchodilatatory testing)	
FEV1 (L)	1.08 ± 0.40
FEV1 (%)	40.69 ± 13.13
FVC (L)	1.90 ± 0.63
FVC (%)	57.08 ± 14.20
FEV/FVC (%)	56.67 ± 9.65

Note: BMI: Body mass index; SyBP: Systolic blood pressure; DiaBP: Diastolic blood pressure; HR: heart rate; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity

detected respiratory pathogens were *Influenza A* virus (n=9, 18.4%), *Haemophilus influenzae* (n=7, 14.3%), *Pseudomonas aeruginosa* (n=6, 12.2%), Streptococcus pneumoniae (n=5, 10.2%) and *Human Rhinovirus / Enterovirus* (n=5, 10.2%). (Table 3).

In our study, using a multiplex PCR method, pathogens were detected in 51% of the examined

Patients with acute exacerbation of COPD were divided into a group with pathogen-positive exacerbations (n=25) and a pathogen-negative group (n=24). Although spirometry parameters were reduced in patients with detected pathogens, the comparison did not show significant differences between groups. Correlation of detected respiratory pathogens (by multiplex PCR method) with lung function (FEV1%) was not found.

Furthermore, pathogen-positive group of patients was subdivided according to the type of pathogens detected using the PCR method to bacterial (n=7), viral (n=11)

Table 2. Percentage of detected pathogens by PCR and type of pathogens

Features	Value (n=49)
Detected pathogens by PCR method (n /%)	
Present	25/51
Absent	24/49
Type of pathogen detected (n /%)	
Bacteria	7/28
Viruses	11/44
Combined (bacteria + viruses)	7/28

Table 3. Registered respiratory pathogens by PCR method

Features	Values (n=49)
Acinetobacter calcoaceticus-baumannii complex (n/%)	1/2.0
10^4 (n/%)	1/100%
Enterobacter cloacae complex (n/%)	2/4.1
10^4 (n/%)	2/100%
Escherichia coli (n/%)	1/2.0
10^4 (n/%)	1/100%
Haemophilis influenzae (n/%)	7/14.3
10^4 (n/%)	1/14.3
10^5 (n/%)	1/14.3
10^6 (n/%)	2/28.6
≥ 10^7 (n/%)	3/42.9
Moraxella catarrhalis (n/%)	3/6.1
10^4 (n/%)	1/33.3
≥ 10^7 (n/%)	2/66.7
Pseudomonas aeruginosa (n/%)	6/12.2
10^4 (n/%)	3/50%
10^6 (n/%)	1/16.7
≥ 10^7 (n/%)	2/33.3
Serratia marcescens (n/%)	1/2.0
10^4	1/100
Staphylococcus aureus (n/%)	3/6.1
10^4	2/66.7
10^6	1/33.3
Streptococcus pneumoniae (n/%)	5/10.2
10^4	1/20
10^6	1/20
≥ 10^7	3/60

Mycoplasma pneumoniae (n/%)	1/2.0
Coronavirus (n/%)	4/8.2
Human Rhinovirus/Enterovirus (n/%)	5/10.2
Influenza A (n/%)	9/18.4
Parainfluenza Virus (n/%)	1/2.0
Respiratory Syncytial Virus (n/%)	1/2.0

and combined (n=7) exacerbations. Using ANOVA-test to compare multiple groups we found a statistically significant difference between the groups in relation to FEV1 (%), which showed the lowest value in those with bacteria as a pathogen. The post-hoc analysis showed that the significant difference existed only between the group with bacteria and the group with viruses as a causative agent (p = 0.048) (Table 4).

Table 4. Comparison of lung function in patients divided by type of pathogen detected

Features	Bacteria (n=7)	Viruse (n=11)	Combined (n=7)	p
FEV1 (L)	0.81 ± 0.29	1.16 ± 0.55	0.97 ± 0.25	0.245
FEV1 (%)	29.00 ± 10.63	43.27 ± 12.25	38.71 ± 10.61	**0.051**
FVC (L)	1.62 ± 0.47	1.93 ± 0.87	1.84 ± 0.42	0.653
FVC (%)	46.71 ± 11.88	56.18 ± 15.34	57.57 ± 10.75	0.256
FEV/FVC (%)	47.85 ± 6.51	61.14 ± 8.53	53.35 ± 12.01	**0.020**

Note: FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity

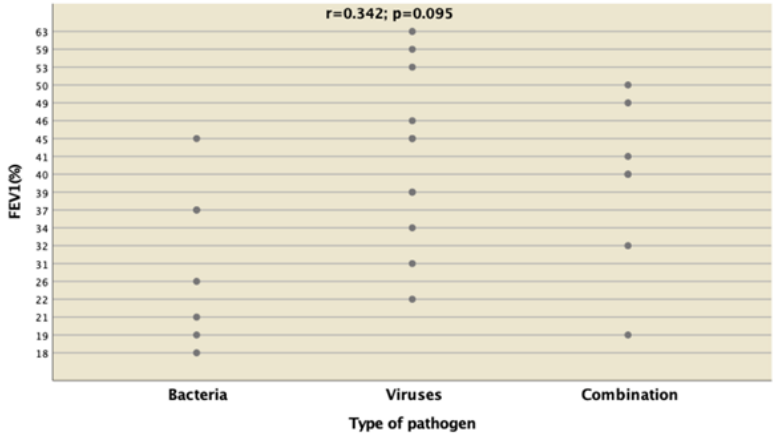

Fig 1. Correlation between type of pathogen found in the sputum using PCR Method and percentage of FEV1 assessed by spirometry

A positive borderline significant correlation was found between the existence of the type of detected pathogens only with the level of FEV1% (r=0.342; p=0.095). Thus, the lower the percentage of FEV1 (%), the greater was the likelihood of bacterial infection (Figure 1).

Discussion

Acute exacerbations are important events which lead to deterioration of health status and quality of life in patients with COPD. Respiratory infections are the most important etiological factor with a large percentage of bacterial infection isolated with classical microbiological culture. In the recent studies, using PCR molecular methods a higher percentage of viral pathogens was found (40-60%) with the results that correlated a direct viral presence with exacerbation of COPD. The combined presence of viral and bacterial infection has been proven to be associated with a more severe exacerbation [21-23].

In our study we found that 51% of exacerbation had respiratory infectious etiology with a prevalence of 28% of bacterial pathogens, 44% of viral pathogens and 28% of combined (viral+bacterial) pathogens. These data were easily obtained by using the new molecular PCR-based method, which simultaneously detected viral and bacterial pathogens in one sample. The most frequent isolated bacteria were *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae,* which was in agreement with most clinical studies using PCR methods [24,25]. Influenza A (n=9, 18.4%) was the most common viral pathogen, followed by Human Rhinovirus/Enterovirus (n=5, 10.2%). Prevalence of Influenza A coincided with the results presented by Tan *et al.* and Tping Y *et al*., but not with the results of West-European and American studies [26,27].

Our research found no significant difference between negative and positive pathogens group in regards to lung function (FEV1). There is a limited number of studies that have analyzed the correlation of lung

function and PCR detected respiratory pathogens; most of the studies only used microbiological culture and showed similar results [24,28].

The most relevant data found was by comparison of pathogen-positive subgroups: viral, bacteria and combined exacerbation. Most importantly in the bacterial subgroup there was a lower value of FEV1 in comparison to the other subgroups. There was a positive correlation with borderline significance about the type of detected pathogen and FEV1 parameter of lung function. The study of Groenewengen *et al*. found lower values of FEV1 in bacterial positive sputum culture with no differences in the type of bacteria. Fanny *et al*. in their study of sputum bacteriology in Hong Kong found that FEV1 >50% was associated with a positive growth of *Hemophilus influenzae* [29,30]. These results are consistent with ours regarding the correlation between lower FEV1 and presence of bacteria, but their big limitation was using only one method which did not include viral or atypical bacteria. Our study did not involve patients with mild and moderate exacerbations of COPD, so, we only have results from severe exacerbations of hospitalized patients.

Conclusion

The most common detected respiratory pathogens in our patients with severe acute exacerbation of COPD were *Influenza A*, followed by *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumonie* and *Human Rhinovirus/Enterovirus*. Although we detected pathogens in 25 subjects, we could not find a correlation between lung function and infectious etiology overall. We found a positive correlation of bacterial presence with lower values of FEV1 % predicted, which indicates that bacterial infections as an etiological trigger of exacerbation of COPD are more likely to be found in patients with severely compromised lung function. More studies are needed to evaluate this correlation in patients with stable COPD.

Conflict of interest statement. None declared.

References

1. Singh D, Agusti A, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *European Respiratory Journal* 2019; 53(5): 1900164.
2. Anthonisen NR, Manfreda J, Warren CP, *et al*. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Annals of internal medicine* 1987; 106(2): 196-204.
3. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57(10): 847-852.
4. Dransfield MT, Kunisaki KM, Strand MJ, *et al*. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2017; 195(3): 324-330.
5. Vestbo J, Edwards LD, Scanlon PD, *et al*. Changes in forced expiratory volume in 1 second over time in COPD. *New England Journal of Medicine* 2011; 365(13): 1184-1192.
6. Müllerova H, Maselli DJ, Locantore N, *et al*. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. *Chest* 2015; 147(4): 999-1007.
7. Papi A, Bellettato CM, Braccioni F, *et al*. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *American journal of respiratory and critical care medicine* 2006; 173(10): 1114-1121.
8. Rohde G, Wiethege A, Borg I, *et al*. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; 58(1): 37-42.
9. Mohan A, Chandra S, Agarwal D, *et al*. Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. *Respirology* 2010; 15(3): 536-542.
10. Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: a state-of-the-art review. *Clinical microbiology reviews* 2001; 14(2): 336-363.
11. Moghoofei M, Jamalkandi SA, Moein M, *et al*. Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Infection* 2020; 48(1): 19-35.
12. Wang Z, Bafadhel M, Haldar K, *et al*. Lung microbiome dynamics in COPD exacerbations. *European Respiratory Journal* 2016; 47(4): 1082-1092.
13. Mammen MJ, Sethi S. COPD and the microbiome. *Respirology* 2016; 21(4): 590-599.
14. Erb-Downward JR, Thompson DL, Han MK, *et al*. Analysis of the lung microbiome in the "healthy" smoker and in COPD. *PloS one* 2011; 6(2): e16384.
15. Wedzicha JA, Seemungal TA, MacCallum PK, *et al*. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thrombosis and haemostasis* 2000; 84(08): 210-215.
16. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. *The Lancet* 2011; 378(9795): 1015-1026.
17. Sethi S, Muscarella K, Evans N, *et al*. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 118(6): 1557-1565.
18. Provost KA, Frederick CA, Sethi S. Bacterial infection. *Acute Exacerbations of Pulmonary Diseases* 2017; 77: 97.
19. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respiratory care* 2003; 48(12): 1204-1215.
20. Pellegrino R, Viegi G, Brusasco V, *et al*. Interpretative strategies for lung function tests. *European respiratory journal* 2005; 26(5): 948-968.
21. Zwaans WA, Mallia P, van Winden ME, Rohde GG. The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease-a systematic review. *Journal of Clinical Virology* 2014; 61(2): 181-188.
22. Cameron RJ, de Wit D, Welsh TN, *et al*. Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive care medicine* 2006; 32(7): 1022-1029.
23. Seemungal T, Harper-Owen R, Bhowmik A, *et al*. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmo-

nary disease. *American journal of respiratory and critical care medicine* 2001; 164(9): 1618-1623.
24. Sethi S, Sethi R, Eschberger K, et al. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2007; 176(4): 356-361.
25. Garcha DS, Thurston SJ, Patel AR, *et al*. Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012; 67(12): 1075-1080.
26. Yin T, Zhu Z, Mei Z, *et al*. Analysis of viral infection and biomarkers in patients with acute exacerbation of chronic obstructive pulmonary disease. *The clinical respiratory journal* 2018; 12(3): 1228-1239.
27. Rohde G, Wiethege A, Borg I, *et al*. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; 58(1): 37-42.
28. Kuwal A, Joshi V, Dutt N, *et al*. A prospective study of bacteriological etiology in hospitalized acute exacerbation of COPD patients: relationship with lung function and respiratory failure. *Turkish thoracic journal* 2018; 19(1): 19.
29. Groenewegen KH, Wouters EF. Bacterial infections in patients requiring admission for an acute exacerbation of COPD; a 1-year prospective study. *Respiratory medicine* 2003; 97(7): 770-777.
30. Ko FW, Ng TK, Li TS, *et al*. Sputum bacteriology in patients with acute exacerbations of COPD in Hong Kong. *Respiratory medicine* 2005; 99(4): 454-460.

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Original article

SURGICAL TREATMENT OF PROXIMAL HUMERAL FRACTURES - OUR EXPERIENCE

ХИРУШКИ ТРЕТМАН НА СКРШЕНИЦИ НА ПРОКСИМАЛЕН ХУМЕРУС-НАШЕ ИСКУСТВО

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Abstract

Introduction. Fractures of the proximal end of the humerus are complex injuries and are seen most commonly in the elderly population, following a low-energy fall [5]. Proper treatment of these fractures requires a good knowledge of the shoulder joint anatomy, mechanics of movement, proximal humeral fracture classification and good knowledge of various surgical techniques. The purpose of our study was to evaluate the functional outcomes of surgically treated patients with fractures of the proximal end of the humerus (Neer III and IV), with open reduction with a locking Philos plate.
Methods. The study was performed at the University Clinic for Traumatology in the period from January 2014 to December 2016. In this study, fractures were classified according to the Neer classification for proximal humeral fractures [2] and 28 patients were included. Only patients with Neer III and IV fractures were included; 20 patients were classified as Neer III and 8 patients were classified as Neer IV with female to male ratio 1.33 (f: m=16:12). Standard X-rays and CT scans were used. All patients were surgically treated with PHILOS (Proximal humeral internal locking system).
Results. Follow-up was done on the 10th postoperative day, at 1 month, 3 months and 6 months. At 6 months, the functional outcome was tested using the Constant and Murley score for functional evaluation preoperatively and postoperatively. The Constant and Murley questionnaire was used as an indicator of the impact of impairment on the level and type of disability.
Discussion. What is the reason for the poor functional result despite the seemingly correct surgical treatment and good X-ray results? In a study by Südkamp, Bayer and Hepp for surgically treated fractures of the proximal humerus, the functional results of the operated limb were 70.6 plus or minus 13.7 [1]. The percentage of complications was 40%. In this study, the results were taken from a larger group of patients. The reason for such a large number of complications was in the incorrect surgical technique.
Conclusion. To ensure good functional recovery of patients with fractures of the proximal end of the humerus treated with deltoid approach and fixation with a locking Philos plate, it is necessary to have good knowledge of the anatomical features of the shoulder joint, thorough, precise surgical technique and adherence to appropriate principles and early physical therapy as a guide to proper functional recovery.

Keywords: proximal humeral fractures, humerus, PHILOS, adults, functional outcome

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Апстракт

Вовед. Скршениците на проксималниот крај на хумерусот се комплексни повреди и се забележуваат најчесто кај постара популација, после “low energy” повреда (повреда од дејство на слаба сила) [5]. За правилно лекување на овие фрактури потребно е добро познавање на анатомијата на раменият зглоб, механиката на движење, класификацијата на фрактурата на проксималниот хумерус и добро познавање на различните хируршки техники. Целта на нашата студија беше да се оценат функционалните исходи на хируршки третирани пациенти со фрактури на проксималниот крај на хумерусот (Neer III и IV), со отворена репозиција со заклучувачка (locking) PHILOS плочка.
Методи. Студијата беше извршена на Универзитетската клиника за трауматологија во периодот од јануари 2014 година до декември 2016 година. Во студијата, фрактурите беа класифицирани според Neer класификацијата за фрактури на проксималниот крај на хумерусот [2] и беа вклучени 28 пациенти. Вклучени се само пациенти со Neer III и IV фрактури, 20 пациенти се класифицирани како Neer III и 8 пациенти се класифицирани како Neer IV со сооднос жени и мажи 1,33 (f: m=16: 12). Користени се стандардни RTG и КТ-скенови. Сите пациенти

беа хируршки третирани со PHILOS (Proximal humeral internal locking system).
Резултати. Постоперативна контрола беше направена на 10-ти постоперативен ден, по 1 месец, по 3 месеци и после 6 месеци. На контролата на 6-тиот месец, беше тестиран функционалниот исход со употреба на Constant и Murley скор за функционална проценка предоперативно и постоперативно. Constant и Murley прашалникот се користеше како индикатор за влијанието на оштетувањето врз нивото и видот на попреченоста.
Дискусија. Која е причината за слабиот функционален резултат и покрај навидум правилниот хируршки третман и добрите резултати на РТГ снимките? Во студијата на Südkamp, Bayer и Hepp за хируршки третирани фрактури на проксималниот хумерус, функционалните резултати на оперираниот екстремитет беа 70,6 плус или минус 13,7 [1]. Процентот на компликации е 40%. Во оваа студија, резултатите се земени од поголема група на пациенти. Причината за толку голем број на компликации е во неправилна хируршка техника.
Заклучок. За да се обезбеди добро функционално закрепнување на пациентите со фрактури на проксималниот крај на хумерусот третирани со делтоиден пристап и фиксација со заклучувачка PHILOS плочка, потребно е добро да се познаваат анатомските карактеристики на рамениот зглоб, темелна, прецизна хируршка техника, придржување кон соодветни принципи и рана физикална терапија како водич за правилно функционално закрепнување.

Клучни зборови: фрактури на проксималниот хумерен тракт; хумерус. PHILOS; возрасни; функционален исход

Introduction

Fractures of the proximal end of the humerus are complex injuries. According to the Neer classification, there are four types of proximal humeral fractures [2]:
I part - includes surgical neck, anatomic neck, lesser tuberosity or greater tuberosity and fracture pattern with less than 1 cm displacement,
II part - includes surgical neck, anatomic neck, lesser tuberosity or greater tuberosity,
III part - includes surgical neck and greater tuberosity or surgical neck and lesser tuberosity,
IV part – includes surgical neck, lesser and greater tuberosities and in II, III and IV part the fragments must be displaced by 1 cm.
Most fractures are minimally displaced and can be managed non-operatively in adults. Displaced and unstable fractures are difficult to manage and should be treated [4]. There are different types of surgical techniques in order to achieve painless shoulder and full function. The aim of our study was to evaluate the functional outcomes of surgically treated patients with fractures of the proximal end of the humerus (Neer III and IV), with open reduction with a locking Philos plate.

Materials and methods

The study was performed at the University Clinic for Traumatology in the period from January 2014 to December 2016. In this study, fractures were classified according to the Neer classification for proximal humeral fractures and 28 patients were included. Only patients with Neer III and IV fractures were included. There were 16 female patients (9-right arm, 7-left arm) and according to the Neer classification-11 patients had a Neer III fracture and 5 patients had a Neer IV fracture. The average age among female patients was 61.7 years and 12 male patients (4-right hand, 8-left hand) and according to the Neer classification-9 male patients had a Neer III fracture and 3 male patients had a Neer IV fracture. The average age among male patients was 55.9 years. According to Neer classification 20 patients were classified as Neer III and 8 patients were classified as Neer IV with female to male ratio 1.33 (f: m=16:12). Standard X-rays and CT scans were obtained. All patients were surgically treated between the 2nd and 5th day of hospital admission and underwent open reduction with deltoid pectoral approach and internal fixation with locking Philos plate. Hospitalization period was 3-5 days, in average 3,5 days. Postoperatively all patients had immobilization, control X ray on the 2nd postoperative day (Figure 1) and were postoperatively treated with LMWH, antibiotic therapy and analgesic therapy. Follow-up was done on the 10th postoperative day (removed immobilization and referred to physical therapy), at 1 month (control X ray), at 3 months (control X-ray and depending on the functional status, tips for performing daily activities) and at 6 months (control X-ray). The sixth month is taken as the final recovery period, after which period complications are considered to occur that affect the functional recovery. At 6 months, the functional outcome was tested using the Constant and Murley score for functional evaluation preoperatively and postoperatively.

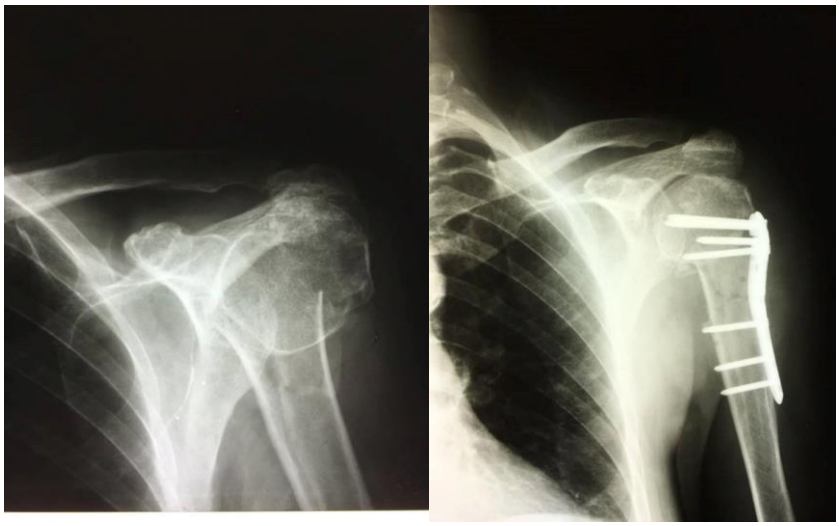

Fig. 1. A 70-year-old male fell from a standing height and sustained a displaced proximal humerus fracture. Open reduction and fixation with Philos plate. Control X ray on the 2nd postoperative day

Results

The Constant and Murley questionnaire was used as an indicator of the impact of impairment on the level and type of disability. The following four parameters were evaluated:

- Pain assessment
- Examination of shoulder joint function
- Shoulder movement range
- Strength measurement

According to the Constant and Murley shoulder score [3], the average value for female patients is 50.4, while for male patients it is 51.7 points. In the female population of a total of 16 patients -2 had excellent results, 1 very good result, 6 good results, 7 bad results. In the male population of a total of 12 patients -1 had excellent results, 2 very good results, 2 good results, 7 bad results. In our study, the male population on average was restored to the maximum possible function on average 5, 5 months after injury, while the female population was 4.6 months after injury.

Discussion

What is the reason for the poor functional result despite the seemingly correct surgical treatment and good X-ray results?

In a study by Südkamp, Bayer and Hepp on operatively treated fractures of the proximal humerus, the functional results of the operated limb were 70.6 plus or minus 13.7. The percentage of complications was 40% [1]. In this study, the results were taken from a larger group of patients. The reason for such a large number of complications was in the incorrect surgical technique which included the following:

- Unnecessary soft tissue trauma;
- Axillary nerve lesion;
- Inadequate treatment of the anterior capsule of the humerus-scapular joint;
- Late and inadequate rehabilitation;

Conclusion

To ensure good functional recovery of patients with fractures of the proximal end of the humerus treated with deltoid approach and fixation with a locking Philos plate, it is necessary:

- Good knowledge of the anatomical features of the shoulder joint;
- Thorough, precise surgical technique and adherence to appropriate principles;
- Early physical therapy as a guide to proper functional recovery.

Conflict of interest statement. None declared.

References

1. Südkamp N, Bayer J, Hepp P, *et al*. Open Reduction and Internal Fixation of Proximal Humeral Fractures with Use of the Locking Proximal Humerus Plate. Results of a Prospective, Multicenter, Observational Study. The Journal of Bone & Joint Surgery: 2009; 91(6): 1320-1328.
2. Neer CS. 2nd Displaced proximal humeral fractures: I. Classification and evaluation. *J Bone Joint Surg Am* 1970; 52: 1077-1089.
3. Constant CR, & Murley AH. A clinical method of functional assessment of the shoulder. *Clinical Orthopaedics & Related Research*, 1987; 214: 160-164.
4. Akram Muhammad Aliuddin, Zaki Idrees, Muhammad Kazim Rahim Najjad, Syed Amir Ali Shah. Functional Outcome of Proximal Humeral Fractures Treated With Philos Plate In Adults. *Journal of Ayub Med Coll Abbottabad* 2016; 8(2): 337-340.
5. Mark J. Corresponding author and Michael J. Gardner. Proximal humerus fractures. *Current Reviews Musculoskeletal Medicine* 2012; 5(3): 192-198.

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Original article

DIABETES AND ARTERIAL STIFFNESS, OUR EXPERIENCES

ДИЈАБЕТЕС И АРТЕРИСКА РИГИДНОСТ, НАШИ ИСКУСТВА

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Abstract

Introduction. The incidence and prevalence of diabetes mellitus (DM) has increased worldwide but also in the Republic of Macedonia, Diabetes is a high-ranking a cause of death, primarily as a cause of cardiovascular death. In the United States, 42% of diabetic patients have diabetic nephropathy, with a 20-fold increased risk of cardiovascular mortality. Arterial rigidity is another independent risk factor for CV death, which is a degenerative process of remodeling the large arteries wall. There is increased arterial rigidity in both: diabetic patients and in patients with arterial hypertension, but studies that address these issues do not have consistency in the results, which was our motive for this study.
Methods. This was a cross-sectional study that comaprised 62 patients with diabetes mellitus type 2, aged over 38 years, followed at the University Clinic for Nephrology for diagnosis of, or already diagnosed hypertension. The control group consisted of 22 healthy subjects who had not been diagnosed with either DM type 2 or arterial hypertension. We examined pulse wave velocity, and analyzed hypertension with data obtained from 24-hour ambulatory blood pressure monitoring. The obtained data were statistically processed.
Results. The results were displayed in tables.
Conclusion. Arterial stiffness (measured by PWV) was higher in patients with DM compared to the control group of healthy subjects. In our study HgA1c had impact on PWV which can serve as a tool for assessing CV risk and arterial rigidity.

Keywords: diabetes mellitus, arterial hypertension, arterial rigidity, pulse wave velocity

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Апстракт

Вовед. Инциденцата и преваленцата на дијабетес мелитус е зголемена во светски но и во рамки на Р. Македонија. Дијабетесот е на високо место како причина за смртност и тоа пред се како причина за кардиоваскуларна смрт. Во САД 42% од болните со дијабетес имаат дијабетична нефропатија, а кај нив за 20 пати е зголемен ризикот за кардиоваскуларна смртност. Но како независен ризик фактор за КВ смрт се јавува и артериската ригидност која е дегенеративен процес на ремоделирање на ѕидот на големите артерии. Зголемена артериска ригидност имаме кај болните со дијабетес и кај болните со артериска хипертензија, но немаме конзистентност во резулатите на досегашните студии што беше мотив за да се направи студијава.
Методи. Студијата е пресечна, анализирани се 62 пациенти со Дијабетес мелитус тип 2 на возраст од над 38 години следени на Клиника за нефрологија заради дијагностицирање или веќе дијагностицирана хипертензија. Во контролната група беа испитани 22 здрави испитаници (немаат дијагностициран ДМ тип 2 и артериска хипертензија). Испитувана е брзина на пулсен бран, анализирана е хипертензија со податоци земени од 24 часовно амбулаторно мониторирање на крвен притисок. Собраните податоци статистички се обработија.
Резултати. Резултатите се прикажаа во табели.
Заклучок. Артериската крутост измерена со PWV, очекувано е поголема кај болните кои имаат ДМ во однос на здравата популација во Р.Македонија. Во нашата студија односот помеѓу брзината на пулсниот бран и нивото на гликозилиран хемоглобин е статистички значаен во обете групи и може да послужи како алатка за проценка на КВ ризик.

Клучни зборови: дијабетес мелитус, артериска хипертензија, артериска ригидност, брзина на пулсен бран.

Introduction

The incidence and prevalence of diabetes mellitus (DM) has increased in the world as in the Republic of Macedonia. According to data from the World Health Organization there were 422 million individuals with DM in 2014 [1]. Prevalence increased from 4.7% in 1980 at 8.5% in 2014, and additionally it is growing. The International Diabetes Federation (IDF) provided information that there were 185,600 people with DM in the Republic of Macedonia in 2015, with a prevalence of 10.3% [2]. This silent killer was a cause of death for 1.6 million people in 2015. It is predicted that DM will be the seventh cause of death in 2030. Life expectancy is shortened by 10 years for diabetic patients, and 75% of them die from macrovascular complications. DM is a high-ranking cause of death, primarily as a cause of cardiovascular (CV) death worldwide.

Arterial stiffness, a degenerative process of remodeling large arteries wall, is another independent risk factor for CV death. There is an increased arterial stiffness in patients with DM. It is not known yet whether arterial rigidity primarily affects central or peripheral part of the arterial tree (trunk). The pathophysiology of increased arterial stiffness in diabetic subjects is also unclear and not clarifyed yet.

High values of arterial rigidity predict the development of CV diseases and death in general population and in subjects with DM type 2 [3].

It has been proven that the increase in the number of CV risk factors precedes the appearance of DM type 2, [4, 5] i.e. the macrovascular changes associated with DM type 2 are developing in the pre-diabetic phase. And *vice versa*, the very appearance and presence of micro and macrovascular complications in DM type 2 is associated with a further increase in arterial rigidity. DM is associated with arterial stiffness not only through arterial hypertension (HTA), but also with central obesity, higher fasting glucose and less with dyslipidemia.

HTA is a significant social problem because every third person has arterial hypertension. Fifty percent of diabetic patients have arterial hypertension [6,7]. Prevalence of HTA is doubled in diabetics compared to the general population [8, 9]. It is the dominant risk factor for increased arterial stiffness. Of particular importantce to prevent and delay DM complications are glycemic control, metabolic control and good hypertension regulation, because diabetic patients with hypertension have 4 times higher risk of CV diseases than the general population [7].

Hyperglycemia, hypertension, dyslipidemia and obesity are risk factors for CV disease.

We can treat DM, HTA and arterial stiffness with lifestyle changes, pharmacological drugs and other noninvasive and invasive procedures, and thus they can be brought under control which can contribute to a less as possible final organ damage. Therefore, their noninvasive assessment is important with methods such as: ambulatory monitoring of blood pressure (AMBP), pulse pressure, pulse wave velocity, frequent glycemic and occasional HgA1c monitoring.

These topics have been covered in studies but there is not consistency in the results, which gave us the motive for our study.

The primary aim of study was to assess arterial stiffness through PWV in DM type 2 patients without renal impairment and also to assess arterial hypertension using a 24-hour AMBP and finally to show expected difference of arterial stiffness between DM type 2 patients and healthy subjects. Our secondary aim was to assess the association between DM, hypertension, gender, age, fasting glucose, lipid status on one side with arterial stiffness in the subjects on the other side.

Material and methods

This cross sectional, observational study was conducted at the University Clinic for Nephrology from December 2017 to March 2020.

Examined population were 62 patients with DM type 2 over the age of 38 who were followed at the University Clinic for Nephrology for diagnosis of, or already diagnosed hypertension. The control group consisted of 22 healthy subjects. Exclusion criteria were: patients with DM type 1, patients with malignancies and CKD, patients at the stage of severe infection or other severe clinical condition and subjects with age under 38 years.

Methods

- *24-hour ambulatory monitoring of blood pressure (AMBP)* performed with 3 automatic readers (ASPEL S.A. produced in 2007) in use at our Clinic from January 22, 2008. We statistically processed only a part from the data obtained from 24-hour AMBP: average values of daily systolic blood pressure, average values of daily diastolic blood pressure, daily mean arterial pressure (MAP) and daily pulse pressure (PP). Furthermore, according to the previously obtained information from the 24-hour AMBP, for each patient it was assessed individually whether he/she was normotensive if he/she did not receive antihypertensive therapy or had arterial hypertension. In this way: stages of arterial hypertension were determined and the night fall of BP was estimated: dipper, non-dipper, reverse dipper [10].
- *Carotid-femoral pulse wave velocity (PWV)*=D (meters)/Dt (seconds). PWV was determined using ultrasound apparatus with a linear probe (Esaote MyLab) made in Italy. It has been in use at the University Clinic for Nephrology since 2016, and additionally as equipment of the ultrasound device electrocardiogram (ECG) for synchronization is

being used. This method was described by Calabia J in 2011, [11] and in the Republic of Macedonia this method was used and described for the first time by Avramoski P in 2013 [12].

- *Standard laboratory tests:* hematological blood tests and biochemical analysis of serum.
- *Questionnaire (Survey)* to record daily salt intake, physical activity and smoking status of subjects.

Statistical method

The data was statistically analyzed: summarily, with a description of the total sample as well as by groups of patients with diabetes mellitus and control subjects. The distribution of the continuous variables was checked using the Shapiro-Wilk test to test the normal distribution by groups. Variables that deviated from the normal distribution assumption were tested with the nonparametric test (Mann-Whiteny U), while variables that showed a normal distribution schedule were compared using the T-test between the two groups. Then, a correlation analysis was performed between different variables for the status of diabetes mellitus and the pulse wave velocity, using Pearson's r.

Results

Demographic and clinical characteristics are given in Table 1.

In our study participated 84 respondents, of which 62 were with DM type 2 (group 1), and 22 were a control group of healthy respondents (group 2).

The average age in Group 1 was 47.5+4.64 years, 32.3% of them were men, with average BMI of 30.63+5.8 kg/m2.

In group 2, the subjects had an average age of 45.32+ 4.38 years, with an average BMI of 26.49+4.17. There were 10 (45.45%) men.

In Group 1 active smokers were 46.8%, while in group 2 - 22.73%. Most of the respondents had a moderate salt intake, 43.54% in Group 1 and 54.54% in Group 2. Excessive salt intake of 5 grams and more during the day had 37.09% of patients with DM type 2 and only 18% of Group 2 with healthy subjects.

81.82% of the healthy subjects in the control group were physically active, while in Group 1 only 29% of the diabetics were physically active.

Table 1. Demographic and clinical characteristics

Sample, n = 84	**Patients with DM type 2 (n = 62)**		**Healthy subjects (n = 22)**		**Associated p-value**
Age (mean, SD)	47.53	4.64	45.32	4.38	0.043
Gender, male (%)	20	32.3%	10	45.45%	0.306
Duration of DM2 in months (mean, SD)	70.5	0.43	0	0.00	
Oral antidiabetic drugs (%)	39	62.9%	0	0.00%	
Insulin (%)	11	17.7%	0	0.00%	
Combined therapy (%)	12	19.4%	0	0.00%	
Glycosylated hemoglobin (%)	7.62	1.93	5.23	0.34	0.000
T. Cholesterol (mmol/l)	5.73	1.09	4.76	0.45	0.000
LDL-cholesterol (mmol/l)	3.55	1.01	2.73	0.36	0.000
Triglycerides (mmol/l)	2.42	1.01	1.07	0.55	0.000
Duration of HTA in months (mean. SD)	58.26	48.42	0	0.00	
Smoking status					0.076
Non-smoker (%)	31	50.0%	17	77.27%	
Abstained (Former smoker) (%)	2	3.2%	0	0.00%	
Smoker (%)	29	46.8%	5	22.73%	
Physical activity-active (%)	18	29.0%	18	81.82%	0.000
BMI m/kg^2 (mean. SD)	30.63	5.81	26.49	4.17	0.005
Hemoglobin. g/L. (mean. SD)	137.53	11.06	151.27	10.83	0.000
Creatinine clearance CKD EPI (mean. SD)	98.71	13.40	104.36	7.56	0.088

Part of the data obtained from the 24-hour AMBP for two groups are shown in Table 2. Table 2 presents mean values of carotid-femoral PWV for both groups.

The average daily systolic BP for Group 1 was 147.94 +18.55 mmHg, and the average daily diastolic BP was 91.55+10.81 mmHg. In Group 2, the average daily systolic BP was 117.46+9.37 mmHg, while the average daily diastolic BP was 72.65+8.61 mmHg.

Table 2. Part of the data obtained from the 24-hour AMBP

Sample, n = 84	Patients with DM2 (n = 62)		Healthy subjects (n = 22)		Associated p-value
Daily SBP (mmHg) (mean. SD)	147.94	18.55	117.4636	9.37	0.000
Daily DBP (mmHg) (mean. SD)	91.55	10.81	72.65	8.61	0.000
Average daily PP (mean. SD)	56.39	10.33	44.81364	2.04	0.000
Average daily MAP. (mmHg) (mean. SD)	110.31	12.99	87.6	7.96	0.000
Normotensive %	4	6.45%	22	100.00%	
Controlled arterial hypertension %	16	25.8%	0	0	
Dipper %	43	69.4%	16	72.73%	0.956
Non dipper %	16	25.8%	5	22.73%	
Reverse dipper %	3	4.8%	1	4.55%	
Augmentation pressure (mm Hg) (mean. SD)	8.44	4.35	5.86	1.61	
Augmentation index (mean. SD)	23.79	7.87	17.41	5.10	0.002
Pulse wave velocity (m/s) (mean.SD)	8.74	1.23	5.69818	0.50	0.000

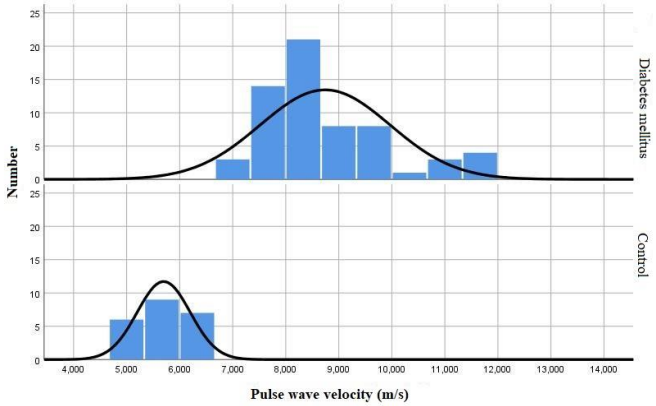

Fig. 1. Histogram of the distribution of pulse wave velocity values in groups

PWV was higher in Group 1 with an average value of 8.74±1.23 m/s compared to healthy respondents in Group 2 with an average value of 5.69±0.5 m/s (Figure 1). Finally, the relationship between pulse wave velocity and glycosylated hemoglobin level showed a graphically linear positive relationship in both groups of patients. The Pearson's correlation coefficient was 0.697, with an associated p-value below 0.0001 (Figure 2).

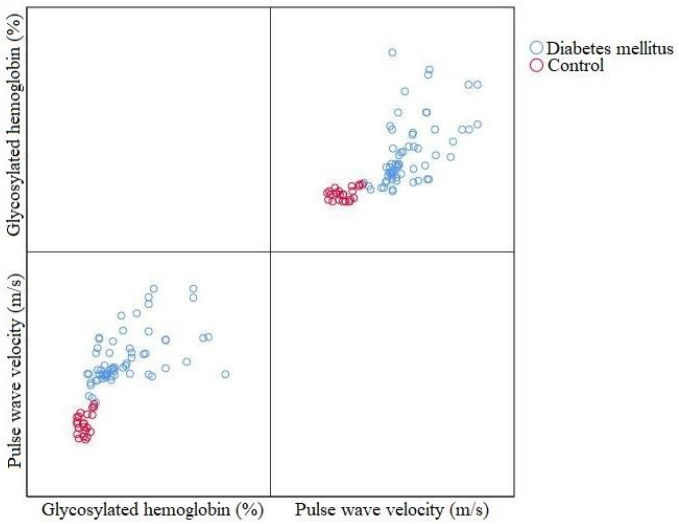

Fig. 2. Scatter-plot display between measured glycosylated hemoglobin values and pulse wave velocity. The red dots are obtained from the controls, while the blue dots show the values from the patients with diabetes mellitus.

Discussion

As expected, DM type 2 patients (Group 2) had higher values for PWV compared to the control group (Group 2) with healthy subjects. In our study these values were affected by the disease itself (DM), by arterial hypertension but also by obesity. According to SHIELD data, in a study by Green AJ *et al*. obese pa-

tients who had DM and HTA had a poorer quality of life, a higher incidence of depression, and an increased cost of health care compared to those who had only DM [13]. Obesity is a major pathogenic factor and is considered to contribute to the coexistence of DM and HTA in developed countries [14,15].

In this study women were represented with 67.7% in Group 1 (DM type 2). It was observed that women with DM had a higher risk of CV death than man [16]. According to a study by Chen G *et al*., prevalence of men and women with DM equals after age of 64 [17].

Arterial stiffness is a process in which the elasticity of the large arteries is lost mainly due to their remodeling, during which the elastic fibers are lost and replaced with solid collagen 4 fibers, therefore blood vessels become rigid. The remaining elastin, which is deformed, is the site of deposition of AGE (advanced glycation end) products leading to endothelial dysfunction. In turn, endothelial dysfunction increases smooth muscle tone and thus increases pulse pressure (PP) and mean arterial pressure (SAP). A result of this changes are isolated systolic hypertension, increased PP and PWV, rigid and deformed large arteries, reduced coronary circulation, peripheral circulatory damage and risk of cerebrovascular insult (CVI).

Possible mechanisms that contribute to increased arterial stiffness are inflammation, increased oxidative stress, [18] activation of the sympathetic nerve system [19], etc. Also, HTA has a major impact on arterial stiffness.

Arterial hypertension contributes to the progression of diabetic vascular complications, which are important factors for CV disease. Good control of BP in diabetic patients who have HTA contributes to later occurrence of micro and macrovascular complications [20,21], and thus reducing the risk of CV disease and death [22,23,24] It is being debated about the ideal systolic and diastolic BP values for "good BP control" because a number of studies has demonstrated that reaching target BP values below 130/80 mmHg makes no difference in reducing CV fatal and non-fatal outcomes compared to target systolic BP value under 140 mmHg except for CVI [25-30]. However, diabetic patients have the greatest benefit when achieving systolic BP values 130-135 mmHg and diastolic BP values from 80 to 85 mmHg, implying that an individual approach is required for each person [31]. Despite these debates, HTA has not yet been managed since 50% of hypertensive patients do not have a good BP control.

It is already known that different types of antihypertensive drugs have a different effect on arterial stiffness although they have the same effect on the BP reduction. Thus, different antihypertensive drugs have different effect on reducing CV disease and death in diabetic patients with hypertension.

It is established that hypertensive patients have higher values of PP. In our study these higher PP values indicated advanced changes in the artery wall of diabetic patients, i.e. increased arterial stiffness of the aorta and large arteries in Group 1 subjects. Namely, an increased arterial stiffness in large arteries leads to a decrease in their compliance and triggers a chain of mechanisms and reactions that eventually lead to increased load on the heart chambers and oxygen demand by the myocardium. At the same time, the higher PP values are a result of the reaction of the stroke volume and the elastic characteristics of the large arteries. Therefore, the values of systolic BP are significantly higher than the increased diastolic BP values in patients with DM type 2, and especially in patients with DM type 2 who have hypertension.

The analysis of PWV and glycosylated hemoglobin (HgA1c) level showed a linear positive relationship in both groups of patients, which would suggest that large arteries may be seized with atherosclerotic changes affecting the outcome. However, we did not analyze this issue in this paper. In patients with DM type 2, vascular complications are the cause of CV disease and mortality. In the literature, increased arterial stiffness has been presented and it appears in the early stages of DM type 2; therefore, stricter control of glucose and maintenance of the HgA_1c value around 7% is mandatory to prevent micro and macrovascular complications [32].

Further, coexistence of DM and hypertension increases the risk of CV disease and chronic kidney disease [22] compared to patients who have only DM or only hypertension.

Conclusion

In conclusion, our study has shown an increased arterial stiffness (measured with PWV) in diabetic patients compared to healthy subjects as expected, and HgA1c has an impact on PWV which can be used to assess CV risk and arterial stiffness in diabetic patients.

Conflict of interest statement. None declared.

References

1. Global Report on Diabetes World Health Organization 2016, ISBN 978 92 4 156525 7 (NLM classification: WK 810). Available www.who.Int.
2. IDF Diabetes Atlas Seventh Edition 2015, International Diabetes Federation. Available www.diabetesatlas.org.
3. Cruickshank K, Riste L, Anderson SG, *et al*. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function. Circulation 2002; 106: 2085-2090.
4. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol* 2006; 47: 1093-1100.
5. Haffner SM, Stern MP, Hazuda HP, *et al*. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes. *JAMA* 1990; 263: 2893-2898.

6. Sowers JR. Diabetes mellitus and vascular disease. *Hypertension* 2013; 61(5): 943947. [PubMed: 23595139].
7. Stamler J, Vaccaro O, Neaton JD, *et al*. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16: 434-444. [PubMed: 8432214].
8. Barrett-Connor E, Criqui MH, Klauber MR, Holdbrook M. Diabetes and hypertension in a community of older adults. *Am J Epidemiol* 1981; 113: 276-284.
9. Teuscher A, Egger M, Herman JB. Blood pressure in clinical diabetic patients and a control population. *Arch Intern Med* 1989; 149: 1942-1945.
10. Covic A, Gusbeth-Tatomir P, Mardare N, *et al*. Dynamics of the circadian blood pressure profiles after renal transplantation. *Transplantation* 2005; 80: 1168-1173.
11. Calabia J, Torguet P, Garcia M, *et al*. Doppler ultrasound in the measurement of pulse wave velocity: agreement with the Complior method. *Cardiovasc Ultrasound* 2011; 9: 13.
12. Avramoski P, Janakievska P, Koneska M, *et al.* Accelerated progression of arterial stiffness in dialysis patients compared with the general population. *Korean J Intern Med* 2013; 28: 464-474.
13. Green AJ, Bazata DD, Fox KM, *et al*. Quality of life, depression, and healthcare resource utilization among adults with type 2 diabetes mellitus and concomitant hypertension and obesity: a prospective survey. *Cardiol Res Pract* 2012; article ID 404107: doi:10.1155/2012/404107.
14. Sowers JR. Diabetes mellitus and vascular disease. *Hypertension* 2013; 61(5): 943-947. [PubMed: 23595139].
15. Ogden CL, Carroll MD, Kit BK, *et al*. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA* 2012; 307: 483-490. [PubMed: 22253364].
16. Hu G, DECODE Study Group. Gender difference in all-cause and cardiovascular mortality related to hyperglycaemia and newly-diagnosed diabetes. *Diabetologia* 2003; 46: 608-617. [PubMed: 12750769].
17. Chen G, McAlister FA, Walker RL, *et al*. Cardiovascular outcomes in Framingham participants with diabetes: the importance of blood pressure. *Hypertension* 2011; 57: 891-897. [PubMed: 21403089].
18. Plantinga Y, Ghiadoni L, Magagna A, *et al*. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. *Am J Hypertens* 2007; 20: 392-397.
19. Giannattasio C, Failla M, Lucchina S, *et al*. Arterial stiffening influence of sympathetic nerve activity: evidence from hand transplantation in humans. *Hypertension* 2005; 45: 608-611.
20. Cushman WC, Evans GW, Byington RP, *et al*. ACCORD Study Group. Effects of intensive bloodpressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1575-1585. [PubMed: 20228401].
21. American Diabetes Association. Standards of medical care in diabetes-2011. *Diabetes Care* 2011; 34: S11-S61. [PubMed: 21193625].
22. Garcia-Touza M, Sowers JR. Evidence-based hypertension treatment in patients with diabetes. *J Clin Hypertens* (Greenwich. 2012; 14: 97-102. [PubMed: 22277142].
23. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; 317: 703-713. [PubMed: 9732337].
24. Schrier RW, Estacio RO, Jeffers B. Appropriate blood pressure control in NIDDM (ABCD) trial. *Diabetologia* 1996; 39: 1646-1654. [PubMed: 8960857].
25. ACCORD Study Group. Cushman WC, Evans GW, *et al*. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1575-1585. [PubMed: 20228401].
26. Cooper-DeHoff RM, Gong Y, Handberg EM, *et al*. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010; 304: 61-68. [PubMed: 20606150].
27. American Diabetes Association. Standards of medical care in diabetes-2013. *Diabetes Care* 2013; 36: S11-S66. [PubMed: 23264422].
28. Redon J, Mancia G, Sleight P, *et al*. ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol* 2012; 59: 74-83. [PubMed: 22192672].
29. Bangalore S, Kumar S, Lobach I, *et al*. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011; 123: 2799-2810. [PubMed: 21632497].
30. Kim YS, Davis SC, Truijen J, *et al*. Intensive blood pressure control affects cerebral blood flow in type 2 diabetes mellitus patients. *Hypertension* 2011; 57: 738-745. [PubMed: 21357278].
31. Guido Lastra, Sofia Syed, L Romayne Kurukulasuriya, *et al*. Type 2 diabetes melitus and hypertension: An update. *Endocrinol Metab Clin North Am* 2014; 43(1): 103-122.
32. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012; 60(5): 850-886.

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ММР

Case report

SUCCESSFUL RECOVERY FROM RESPIRATORY FAILURE IN A CRITICALLY ILL PATIENT WITH COVID-19 USING EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT – A CASE REPORT

УСПЕШНО ОПОРАВУВАЊЕ ОД РЕСПИРАТОРНА СЛАБОСТ КАЈ КРИТИЧНО ТЕЖОК ПАЦИЕНТ СО COVID-19 КОРИСТЕЈЌИ ЕКСТРАКОРПОРАЛНА МЕМБРАНСКА ОКСИГЕНАЦИОНА ПОДДРШКА – ПРИКАЗ НА СЛУЧАЈ

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Abstract

SARS-CoV-2 is a novel virus of which transmission, incidence and mortality rates have made it a global emergency. In March 2020, the World Health Organization (WHO) published interim guidelines recommending the use of extracorporeal membrane oxygenation (ECMO) in Acute respiratory distress syndrom (ARDS) patients unresponsive to mainstream therapies, in order to maintain cardiorespiratory function [1], ECMO is currently a widely accepted support measure for selected patients with a life-threatening respiratory failure that does not respond to maximal support care with mechanical ventilation [2].
Here we report the first case using extracorporeal membrane oxygenation of a COVID-19 patient in Skopje, North Macedonia.

Keywords: extracorporeal membrane oxygenation, respiratory failure, ECMO, COVID-19, ARDS, COVID 19-pneumonia

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Апстракт

SARS-CoV-2 е нов вирус, чии стапка на пренос, инциденца и смртност претставуваат глобална итност. Во март 2020 година, Светската здравствена организација (СЗО) објави привремени упатства кои препорачуваат употреба на екстракорпоралната мембранска оксигенација (ЕКМО) кај пациенти со акутен респираторен дистрес синдром (ARDS) кои не реагираат на ординираната терапија, се со цел да се одржи кардиореспираторната функција. [1], ЕКМО во моментов е широко прифатена метода за поддршка на одредени пациенти кои имаат животозагрозувачка респираторна инсуфициенција која не реагира на максимална поддршка со механичка вентилација [2].
Тука го пријавуваме првиот случај на пациент со COVID-19 кој беше поставен на екстракорпорална мембранска оксигенација во Скопје, Северна Македонија.

Клучни зборови: Екстракорпорална мембранска оксигенација, респираторна инсуфициенција, ECMO, COVID-19, ARDS, COVID 19-пневмонија

Introduction

Coronaviruses are a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [3]. Coronaviruses were named from the way they looked under a microscope. The virus consists of a core of genetic material surrounded by an envelope with protein spikes. Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus, now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was similar to SARS and was being characterized primarily by fever and respiratory symptoms [7]. The virus was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China [1]. It rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. Currently, there is no effective cure for COVID-19, and supportive care remains the cornerstone of management [3].
COVID-19 is a multi-system disease with the respiratory system being the most commonly involved. In most patients, the illness produces mild to moderate symptoms but approximately 10% progress to severe pneumonia, about 1% of patients experience progression that can

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quickly progress to profound hypoxemia and/or ARDS [6] Given previous experience, extracorporeal membrane oxygenation (ECMO) has been proven to be an effective therapy in the treatment of respiratory failure or acute respiratory distress syndrome (ARDS) [3].

Case presentation

A 45-year-old male with no past medical history presented to the emergency department (ED) of our hospital with worsening shortness of breath for a few days on August 10, 2020. After admission, throat swab of the patient was harvested and tested positive for SARS-CoV-2 nucleic acid by the fluorescence quantitative RT-PCR. He denied any other symptoms including fever, dry cough and tiredness. On examination, he was tachycardic, anxious, and lung sounds were notable for crackles. The SpO2 (oxygen saturation) of the patient was 90-94%. Other vital signs were a blood pressure of 140/85 mmHg, heart rate of 100/min and temperature of 37.5°C. Initial laboratory tests were significant for C-reactive protein of 3.30 mg/dL, Urea 9.7 mmol/L, ALT 214 U/L, LDH 388 U/L, GGT 451 U/L, white blood cells of 19.01×109/L without lymphopenia, blood glucose of 8.45 mmol/L, procalcitonin of 0.02 ng/ml, fibrinogen 6,83 g/L and ferritin of 1599.8 ng/ml. His initial CT chest scan showed diffuse bilateral ground-glass pulmonary consolidations. Immediately after admission, the patient was given oxygen inhalation by a facial mask. The patient's condition became worse. The monitored oxygen saturation decreased to 90% (oxygen inhalation 4 L/min). Blood gas analysis: PO2 58 mmHg, PCO2 39 mmHg, FIO2 41%. Favipiravir, Flucosansole, Acetylcysteine, Vit D3 drugs were administered orally, while Meropenem, Azithromycin, Ascorbic acid, Diazepam, Furosemid, Gastrazol, HEPA MERZ (I ornithine, I aspartate) and methylprednisolone were given by an intravenous injection and infusion.

On August 14, 2020, the disease deteriorated; he had myalgia, body temperature was 37.6C, shortness of breath and chest pain. The monitored oxygen saturation decreased to 85% (oxygen inhalation 8 L/min). Laboratory tests were significant for C-reactive protein of 8.22 mg/dL, Urea 9.9 mmol/L, ALT 214 U/L, LDH 388 U/L, GGT 451 U/L, white blood cells of 17.69×10^9/L, LYM 0.75×10^9/L, LYM% 4.2%, ANC 16.44×10^9/L, NEU% 93%, RBC 3.61×10^12/L, HGB 105 g/L, blood glucose of 8.18 mmol/L, procalcitonin of 0.02 ng/ml, D-dimer 10.18 ug F.E.U./ml and Ferritin of 1312 ng/ml, IL-6 85 pg/ml.

On August 15, 2020, the patient's blood oxygen saturation declined again to 78% and mechanical ventilation was immediately performed by orotracheal intubation. The patient was provided the standard ARDS treatment with lung-protective ventilation, pronation, neuromuscular blockade with rocuronium, suxamethonium and inhaled epoprostenol. His initial ventilator settings were pressure-regulated volume control mode of ventilation with a tidal volume (V_t) of 360 mL (6 mL/kg of ideal body weight), respiratory rate (RR) of 24 breaths per minute, and positive end-expiratory pressure (PEEP) of 14 cm H_2O. He was sedated with morphine, fentanyl, and propofol continuous intravenous infusions. Dopamine was used to treat hypotension and low cardiac output. Tocilizumab, Linazolid, Azithromycin, Fluconasole, Human albumin, Octagam 10% (immunoglobulin), Kabiven peripheral, Heparin 25000/5ml, Ascorbic acid, Furosemid, Gastrazol, HEPA MERZ (I ornithine, I aspartate) and methylprednisolone were given by an intravenous injection and infusion.

On August 22, 2020 his chest computed tomography scan revealed extensive multifocal ground-glass opacities bilaterally. Examination of blood routine revealed WBC 26.29.1x10^9/L, LYM 3.09 x10^9/L; ANC 21.83 x10^9/L, NEU 81.8%, HGB 105 g/L, blood glucose of 11.52 mmol/L, procalcitonin of 0.02 ng/ml, D-dimer 0.75 ug F.E.U./ml. Due to the refractory hypoxemia despite maximal conventional medical management for ARDS, the patient was considered for ECMO by a multidisciplinary team consisting of experts from Anesthesiology and Intensive Care, Cardiac Surgery, Cardiology, and Infectious Diseases. Transthoracic echocardiogram revealed normal biventricular function with no valvular abnormalities.

On day 12 of hospitalization 22.08.2020 (approximately day 13-14 of the disease process), he was initiated on VV ECMO. Bifemoral cannulation was performed with ultrasound guidance at the bedside in the patient's room. During ECMO treatment, the patient also received deep sedation treatment. At the same time, anticoagulant heparin sodium during ECMO operation pumped continuously. Coagulation function was reviewed every 3 hours, and partial thromboplastin time (APTT) was maintained for 50-60 seconds. The patient had complications with unstable circulatory function in the early stage, while norepinephrine saline was pumped to maintain systolic pressure between 100-120 mmHg. Norepinephrine gradually decreased until stopped during ECMO treatment. Blood gas analysis was performed every 4 hours, ECMO rotation speed was regulated according to the patient's blood oxygen saturation and blood pressure level, blood flow was controlled to about 3.0-4.5 L/min, and PCO2 was maintained at about 40 mmHg and SPO2 at about 95%. ECMO oxygen concentration was given to 80% in the early stage and gradually decreased to 40% during the treatment. During ECMO treatment, the patient also continuously underwent pressure-controlled ventilation and his blood oxygen saturation was significantly improved. On day 20 of hospitalization he was successfully decannulated at the bedside, and VV ECMO was removed, and extubated on day 21 of hospitalization. His discharge chest computed tomography scan revealed still multifocal ground-glass opacities bilaterally.

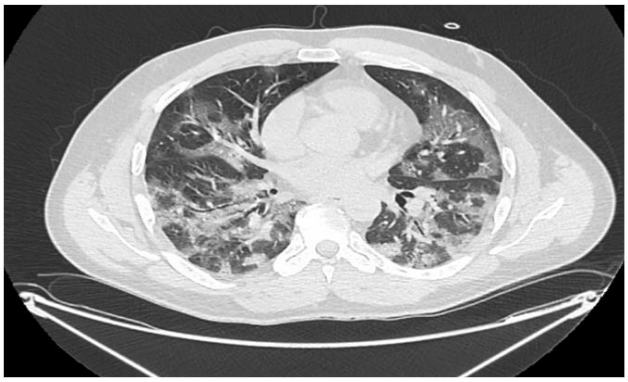

Fig. 1. 10.08.2020 CT scan of the chest showing bilateral ground glass opacities

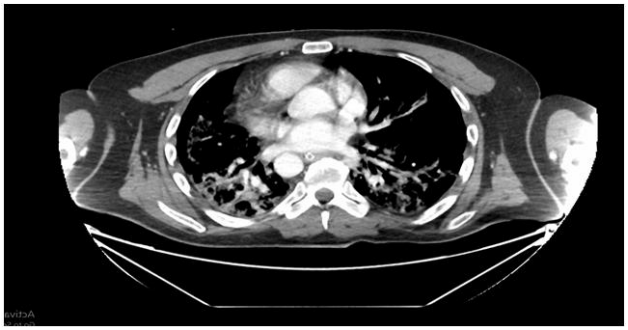

Fig. 2. 25.08.2020 CT scan of the chest, 3 days after ECMO

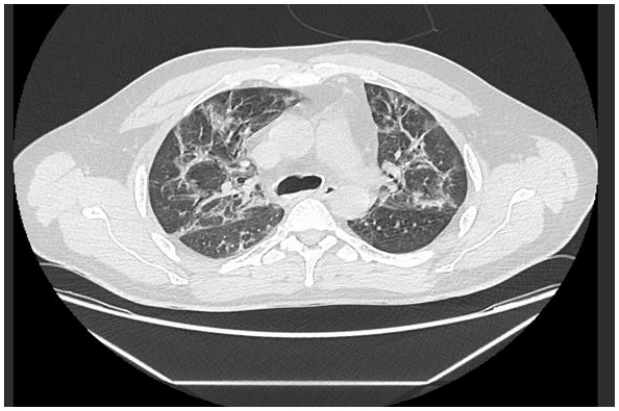

Fig. 3. 01.09.2020 Discharge CT scan of the chest, revealed still multifocal ground-glass opacities bilaterally

Discussion

The present report is the first case of COVID-19 successfully treated by ECMO in North Macedonia.

Most patients with COVID-19 have mild symptoms and can be cured. However, some can progress to severe illness, and patients can develop dyspnea and hypoxemia about one week after the onset of the disease. Severe patients can rapidly develop acute respiratory distress syndrome (ARDS), and subsequently multiple organ failures or even death [4]. The health status and virus susceptibility of a patient are important factors that need to be considered in order to establish a prognosis of the disease. Elderly individuals, patients with cardiovascular diseases and those with chronic underlying diseases have poor prognosis. Patients surviving critical illness often have disability that might require prolonged hospital stay or rehabilitation [2].

In this case, the authors chose to give ECMO support treatment at an early stage when oxygenation fell to about 78%.

Early ECMO support treatment for critically ill patients may help patients survive the most severe lung lesions and up-regulate the success rate of treatment [6]. For ECMO type, the authors chose VV-ECMO since the patient only had pulmonary failure but no basic cardiac diseases. The EF value of the heart measured by bedside B-ultrasound was about 67%. The authors monitored coagulation function, blood gas and made chest x-ray film regularly to prevent complications during ECMO treatment.

Finally, national and institutional protocols must be provided to guide physician decisions regarding resource allocation and patient selection for ECMO for critically ill patients with COVID-19.

Conclusion

Based on this successful experience, we recommend ECMO treatment for severe COVID-19 patients.

Conflict of interest statement. None declared.

References

1. World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak (https://www.who. int). 2020.
2. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011; 365: 1905-1914. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22087681. Cited 21 Apr 2020. [PubMed].
3. Infection prevention and control and preparedness for COVID-19 in healthcare settings-second update [Internet]. Available from: https://www.ecdc.europa.eu/en/ publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings. Cited 21 Apr 2020.
4. Extracorporeal Life Support Organization (ELSO) report in 2018. Available from: https://www.elso.org/
5. Schilcher G, Eisner F, Hackl G, *et al*. Candida infection of membrane oxygenator during ECMO therapy. *J Infect* 2019; 78(1): 75-86. [PubMed] [Google Scholar].
6. Ronco C, Navalesi P, Vincent JL. Coronavirus epidemic: Preparing for extracorporeal organ support in intensive care. *Lancet Respir Med* 2020; 8(3): 240-241. [PMC free article] [PubMed] [Google Scholar].
7. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): pooled analysis of early reports. *J Crit Care* 2020; 58: 27-28. doi:10.1016/j.jcrc.2020.03.011 [PMC free article] [PubMed] [CrossRef] [Google Scholar].

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ММР

Case report

FETAL ACHONDROPLASIA- ULTRASONOGRAPHIG FEATURES (CASE REPORT)

ФЕТАЛНА АХОНДРОПЛАЗИЈА-УЛТРАЗВУЧНИ КАРАКТЕРИСТИКИ (ПРИКАЗ НА СЛУЧАЈ)

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Abstract

Introduction. Achondroplasia is the most common non-lethal skeletal dysplasia and the main cause for dwarfism in humans.
Case presentation. A 27-year-old pregnant woman came into our hospital in the third trimester of pregnancy with a medical report of short fetal limbs (<5 percentile). Our US exam revealed rhizomelic shortening of the limbs, with frontal bossing, depressed nasal bridge and a trident hand. These findings were highly-suggestive for achondroplasia which was confirmed by DNA testing for FGFR3 mutation after a well-adapting male baby was born.
Conclusion. Achondroplasia displays US features that raise a suspicion for the disease prenatally.

Keywords: achondroplasia, shortening of the limbs, frontal bossing, trident hand, FGFR3 mutation

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Апстракт

Вовед. Ахондроплазија е најчестата форма на скелетна дисплазија и основна причина за џуџест раст кај луѓето.
Приказ на случај. 27 годишна бремена жена во трет триместар од бременоста дојде во нашата болница со медицински наод за кратки фетални екстремитети (<5 перцентила). Нашиот УЗ преглед утврди постоење на ризомеличен тип на скратување на екстремитетите, испакнатост на челниот предел, аплатирање на коренот на носната пирамида и „трозаба" дланка. Овие УЗ наоди побудија сериозно сомневање за постоење на фетална ахондроплазија, што (по раѓањето на витално машко бебе) беше и потврдено со ДНК анализа на FGFR 3 генот.

Заклучок. Ахондроплазијата пројавува УЗ карактеристики кои, уште во пренаталниот период, будат сомнеж за постоење на болеста.

Клучни зборови: ахондроплазија, скратување на екстремитетите, челно испакнување, трозаба дланка, FGFR 3 мутација.

Introduction

Achondroplasia is the most common and the best known non-lethal skeletal dysplasia [1]. The prevalence of the disease differs between the regions from 1 per 10 000 to 1 per 30,000 births [1,2]. The systematic review in 2020 found worldwide prevalence of 4.6 cases per 100,000 births [3] giving around 250,000 affected persons worldwide [4]. In our hospital, reviewed data from the past 10 years (2011-2020), revealed only 2 cases of suspected skeletal chondrodysplasias at birth (of which only one was DNA confirmed as a real achondroplasia) among 34,578 deliveries.
Achondroplasia is a genetic disorder caused by fibroblast growth factor receptor 3 gene (FGFR 3) mutation [5-7] which displays autosomal dominant inheritance pattern. The vast majority of the mutations are "de novo" paternal point mutations [8,9], and only 20% are mutations inherited from an already affected parent. This has implications in terms of genetic counseling the couple. It is important to emphasize to the couple that the recurrence rate in case of "de novo" mutation is very low-less than 1% [10]. On the other hand, with one affected parent, there is a 50% chance for transferring the disease to the offspring [11].
There are two types of achondroplasia. The homozygote type is clinically insignificant, because it is lethal in utero or during early infancy as a result of severe pulmonal hypoplasia [12]. The heterozygote type, contrariwise, despite obvious phenotypical appearance has near normal life expectancy. Some studies, however, dispute this claim, arguing that the life expectancy is

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up to 10 years shorter [13] primarily due to cardiovascular implications.

The main clinical feature in heterozygous achondroplasia (FGFR3 mutation prevents converting cartilage to bone) is dwarfism due to rhizomelic shortening of the limbs [11,14]. Intelligence is not affected. Deviation from the normal growth pattern of the fetal limbs starts after the 22th week of pregnancy and it aggravates over time [15,16]. In addition to the limb shortening, the fetal skeleton displays (in various proportion) some other signs, such as: frontal bossing, depressed nasal bridge, collar-hoop sign, trident hand, macrocephaly etc. [15,17,18]. These US findings can raise a suspicion for the disease and facilitate prenatal diagnosis by conducting invasive or non-invasive DNA testing. Having a diagnosis before the birth is of great importance: it gives the parents an opportunity to decide whether to continue or to terminate the pregnancy and allows the obstetrician to manage the perinatal period adequately.

Case presentation

A 27-year-old G2P1 woman was referred to our hospital after US finding of long bones shortening. Her first pregnancy went well and she delivered, 2 years ago, a healthy male baby weighing 3230 g and 51 cm tall. The patient denied a history of a short stature among hers, or her partner's family members. The patient's medical history, as well as paternal age were uneventful too. Regarding the obstetrical history, the US exam at 13th and 20th week showed normal fetal growth pattern. A deviation in terms of limbs shortening was first noticed at 34 gestational week, which was the woman's first US examination after the second trimester anomaly scan. The deviation was remarkable (<5 percentile).

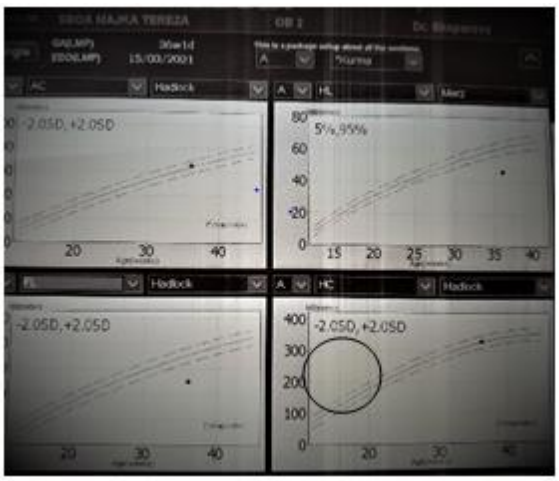

Fig 1. Long bones shortening

The patient came into our hospital in 36+ 1/7 week of gestation. Our US examination showed the following:

- All of the long bones measures were below 5 percentile. Proximal limb expressed more severe shortening on its upper portion, i.e., rhizomelic type of shortening (humerus adequate for 26+week while radius and ulna for 30+ week). The distal limb was equally affected (all three bones had measures adequate for 26+ week of gestation) (Figure 1).

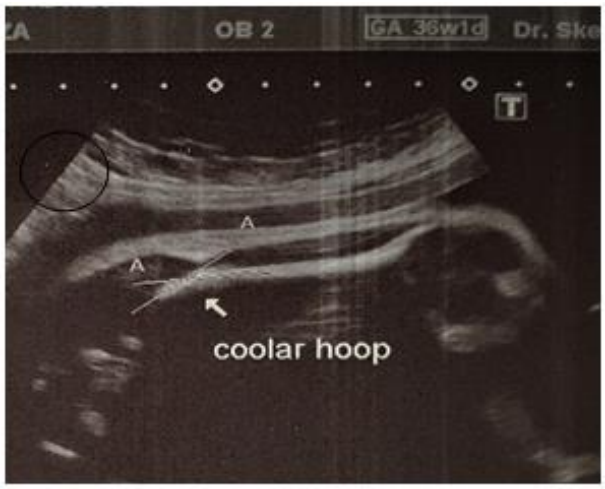

Fig 2. "Collar-hoop" sign

- Besides shortening, the femur also displayed "collar-hoop" sign. We measured the femoral proximal diaphysis-metaphysis angle of 149º (Figure 2).

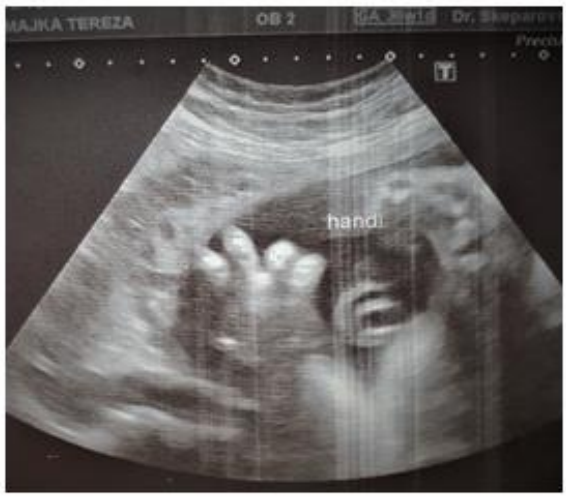

Fig 3. Tri-dent hand

- The hands and the fingers didn't appear significantly smaller. However, the presence of a trident hand was notified (Figure 3).
- The fetal head was bigger than average regarding the gestational age (BPD and HC above 90 percentile), but still the head did not reach criteria for macrocephaly (BDP and HC <95 percentile). The fetal profile displayed depressed nasal bridge and frontal bossing above (Figure 4).

Fig. 4. Depressed nasal bridge with frontal bossing

- Abdominal circumference was within the normal range, but the fetal chest compared to the abdomen on sagittal plane appeared narrow (Figure 5).

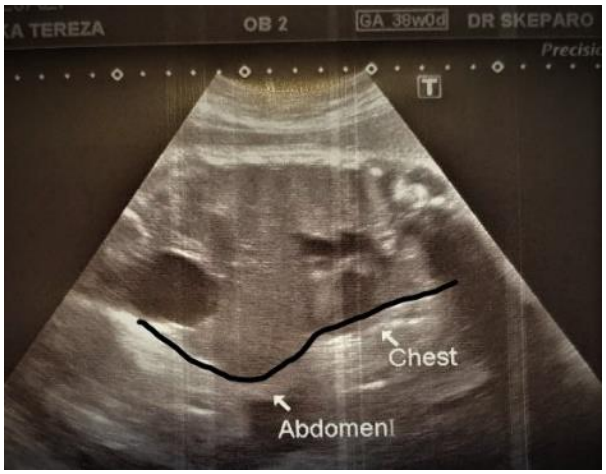

Fig 5. TC/AC discrepancy

- Polyhydramnios was also present. AFI equaled 170 mm, which was above 95 percentile regarding the gestational age.
- Uterine blood flow was uncompromised (mean PI 0.8).

Based on US findings, a suspicion for fetal achondroplasia was made. Proceeding to prenatal testing was offered to the patient. She declined the procedure. A regular antenatal care was carried out until spontaneous onset of labor occurred.

At 40+1/7 week of gestation, the woman gave spontaneous vaginal birth to a male baby weighing 2970 g and 47 cm tall. The initial inspection revealed correlation between our US findings and phenotypical appearance of the newborn. The baby had prominent forehead and flattened nasal bridge (Figure 6). His limbs were smaller than normal with obvious rhizomelic shortening of proximal one, thorax was a bit narrower than expected (circumference of 310 mm), which was emphasized by the baby's frog belly (Figure 7). The trident hand was present (Figure 8).

Fig 6. Flattened nasal bridge with prominent forehead

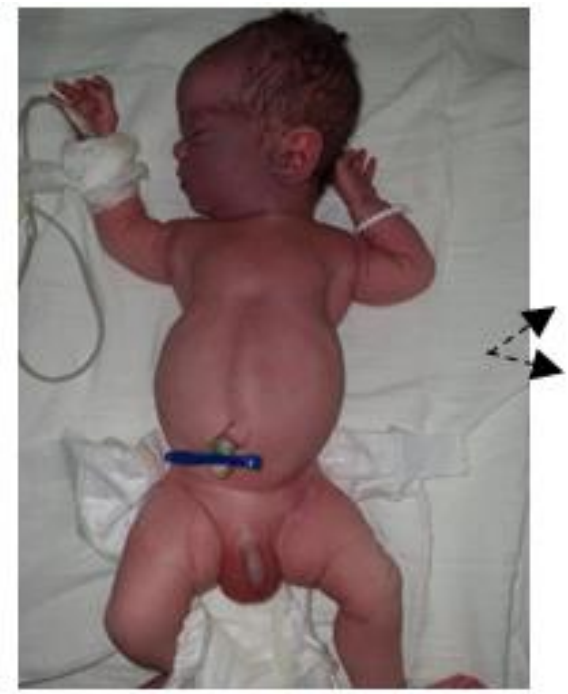

Fig.7. Rhizomelic limb shortening, narrowed thorax and frog bely

The blood samples were collected from the baby, the mother and the father and were sent to our National Research Center for Genetic Engineering and Biotechnology

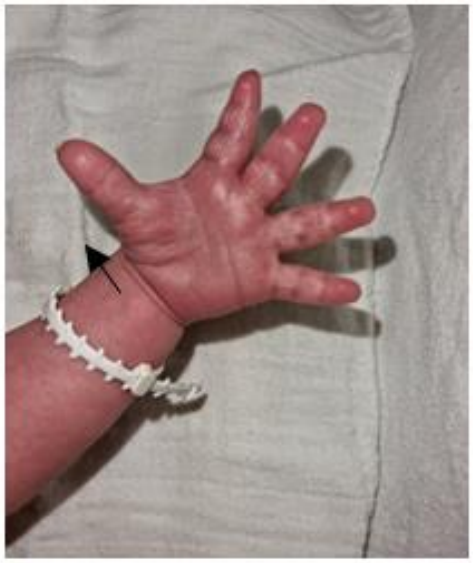

Fig 8. Tri-dent hand

(Macedonian Academy of Sciences and Arts) for molecular diagnosis. The analysis of newborn's DNA confirmed a mutation on FGFR3 gene in heterozygote manner with a pathological variant in exon 9 c.1138G>A, while the mother and the father had normal alleles for FGFR3 gene.

Discussion

Bone shortening in our case was notified in the third trimester of pregnancy which is typical for achondroplasia [18]. Unlike FGR, which also shows a deviation from the normal growth pattern in the third trimester, here the abdominal circumference and the uterine artery Doppler were within normal range, and oligohydramnios was not present. Moreover, we observed a moderate polyhydramnios which can be seen in 50% of achondroplasia cases [17]. Apart from the shortening, we revealed a "collar-hoop" sign on the femur which pretends to be one of the most prominent features of this entity [17].
The fetal head presented relative macrocephaly with depressed nasal bridge and prominent forehead, which are among the features of thanatophoric dysplasia, too [18]. However, unlike the later one, the fetal chest wasn't severely narrowed, and the long bones shortening wasn't brutal as it starts much latter in the pregnancy. Shortening of the ribs wasn't detected, too [18]. Trident hand, almost a pathognomonic sign for a skeletal dysplasia, was also observed.
DNA analysis of the newborn confirmed our suspicion, and showed the most frequent c1138G>A mutation on FGFR3 gene which is, along with c.1138G>C mutation, responsible for achondroplasia in 98% of the cases [9]. Lack of the parents' FGFR3-gene mutation, classified this case as "de novo" mutation in line with findings that 4/5 of achondroplasia cases are sporadic ones [9].

Conclusion

Achondroplasia expresses some features that can be detected by US examination in the late fetal period and accurately raises a physician's suspicion to the disease prenatally.

Conflict of interest statement. None declared.

References

1. Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet* 2007; 370: 162-172.
2. Baujat G, Legeai-Mallet L, Finidori G, *et al*. Achondroplasia. *Best Pract Res Clin Rheumatol* 2008; 22: 3-18.
3. Foreman P, Kessel v F, Hoorn v R, *et al*. Birth prevalence of achondroplasia: A systematic literature review and meta-analysis. *Am J Med Genet A* 2020; 182(10): 2297-2316.
4. Ireland PJ, Pacey V, Zankl A, *et al*. Optimal management of complications associated with achondroplasia. *Appl Clin Genet* 2014; 7: 117-125.
5. Shiang R, Thompson IM, Zhu YZ, *et al*. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell* 1994; 78: 335-342.
6. Rousseau F, Bonaventure J, Legeai-Mallet I, *et al*. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. *Nature* 1994; 371: 252-254.
7. Bellus GA, Hefferon TW, Ortiz de Luna RI, *et al*. Achondroplasia is defined by recurrent G380R mutations in FGFR3. *Am J Hum Genet* 1995; 56: 368-373.
8. Orioli IM, Castilla EE, Scarano G, *et al*. Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta. *Am J Med Genet* 1995; 59: 209-217.
9. Wilkin DJ, Szabo JK, Cameron R, *et al*. Mutations in fibroblast growth factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. *Am J Hum Genet* 1998; 63: 711-716.
10. Mettler G, Fraser FC. Recurrence risk for sibs of children with "sporadic" achondroplasia. *Am J Med Genet* 2000; 90: 250-251.
11. Mc Donald EJ, de Jesus O. Achondroplasia. Treasure Island. Stat Pearls. 2021.
12. Hall JG. The natural history of achondroplasia. *Basic Life Sci* 1988; 48: 3-9.
13. Hecht JT, Francomano CA, Horton WA, *et al*. Mortality in achondroplasia. *Am J Hum Genet* 1987; 41: 454-464.
14. Langer LO Jr, Baumann PA, Gorlin RJ. Achondroplasia: clinical radiologic features with comment on genetic implications. *Clin Pediatr (Philla)* 1968; 7: 474-485.
15. Kurtz AB, Filly RA, Wapner RJ, *et al*. In utero analysis of heterozygous achondroplasia: variable time of onset as detected by femur lenth measurements. *J ultrasound Med* 1986; 5: 137-140.
16. Witters I, Moerman PH, Fryns JP. Skeletal dysplasias: 38 prenatal cases. Genet Couns 2008; 19:267-75.
17. Khalil A, Morales-Rosello J, Morlando M, *et al.* Widening of the femoral proximal diaphysis-metaphysis angle in fetuses with achondroplasia. *Ultrasound Obstet Gynecol* 2014; 44(1): 69-75.
18. Chitty LS, Griffin DR, Meaney C, *et al*. New aids for the non-invasive prenatal diagnosis of achondroplasia: dysmorphic features, charts of fetal size and molecular confirmation using cell-free fetal DNA in maternal plasma. *Ultrasound Obstet Gynecol* 2011; 37(3): 283-289.

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ММР

Case report

COLLAPSING GLOMERULOPATHY-RARE VARIANT OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS-CASE REPORT

Kratok naslov: COLLAPSING GLOMERULOPATHY

КОЛАПСНА ГЛОМЕРУЛОПАТИЈА-РЕТКА ВАРИЈАНТА НА ФОКАЛНОСЕГМЕНТНА ГЛОМЕРУЛОСКЛЕРОЗА- ПРИКАЗ НА СЛУЧАЈ

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Abstract

Focal segmental glomerulosclerosis (FSGS) is classified into five variants, with the collapsing variant being the most rare one. However, the number of idiopathic cases is increasing and the presentation becoming more routine.

We report the case of a 77-year-old female patient, with nephrotic syndrome and histopathologic features of glomerular capillary collapse. She presented with chronic renal failure with serum creatinine-126…154…174 μmol/L. Nephrotic syndrome with feet and ankles edema, progressively extended, at first failed to respond to diuretic therapy. The level of total serum protein fraction was 54g/l, albumin-29…24…28g/L. Urinalysis demonstrated proteinuria 7.8 g/l… 6.15g/L and 12.3 g/24 h. Presence of 25-30 erythrocytes and 2-3 leukocytes in urine sediment was also noticed. Renal biopsy was performed to determinate the presence of glomerular disease. The histopathological analysis showed fibrously thickened Bowman's membrane, with discretely thickened glomerular basal membrane and collapsed vascular lumen on TEM analysis. The treatment of the patient included corticosteroids, angiotensin-converting enzyme inhibitor and lipid lowering agents, which resulted in lowering of the proteinuria, followed by withdrawal of the edema.

Keywords: focal segmental glomerulosclerosis (FSGS), genetic, renal biopsy, capillary collaps

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Апстракт

Фокално сегментната гломерулосклероза е класифицирана во 5 варијанти, од кои колапсната варијанта е најретка. Како и да е, бројот на идиопатски случаи расте и презентацијата станува се почеста.

Прикажуваме пациентка на 77 годишна возраст со нефротски синдром и хистопатолошки наод за колапсна гломерулопатија. Таа пројави хронична бубрежна инсуфициенција со креатинин во серум 126...154...174 микромол/л. Нефротскиот синдром со едеми на стопалата и глуждовите, кои прогресивно се зголемуваат, во почетокот беа без ефект од терапијата со диуретици. Нивото на вкупни протеини беше 54 г/л, албумини 29...24...28 г/л. Анализата на урина покажа протеинурија 7,8 г/л...6,15 г/л и 12,3 г/24 часа. Забележано беше присуство на 25-30 еритроцити и 2-3 леукоцити во уринарниот седимент исто така. Ренална биопсија беше направена за да се детерминира гломеруларното заболување. Хистопатолошката анализа покажа фиброзно задебелена Бовманова мембрана, со дискретно задебелена гломеруларна базална мембрана и колабиран васкуларен лумен на ТЕМ анализа. Третманот на пациентката вклучуваше кортикостероиди, инхибитори на ангиотензин конвертирачки ензим, хиполипемици. Успешно лекувањето беше пратено со намалување на протеинуријата и повлекување на едемите.

Клучни зборови: фокалносегментна гломерулосклероза, генетика, ренална биопсија, капиларен колапс

Introduction

Focal segmental glomerulosclerosis (FSGS) is defined as an increase in the mesangial matrix in some glomeruli with obliteration of capillary lumens, sclerosis, hyalinosis, foam cells, and adhesions to the Bowman's capsule.

Collapsing glomerulopathy is a morphologic variant of focal segmental glomerulosclerosis (FSGS) characterized by segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes, and severe tubulointerstitial disease. The cause of this disorder is unknown [1-3].

Depending on the cause, it could be classified as:

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- Primary, when no underlying cause is found; usually presents as nephrotic syndrome
- Secondary, when an underlying cause is identified; usually presents with kidney failure and proteinuria. This is actually a heterogeneous group including numerous causes: toxins and drugs such as heroin and pamidronate, familial forms, secondary to nephron loss and hyperfiltration, such as chronic pyelonephritis and reflux, morbid obesity, diabetes mellitus.

There are also many other classification schemes.

Pathological variants

Five variants of focal segmental glomerulosclerosis may be distinguished by the pathological findings seen on renal biopsy:

1. Collapsing variant
2. Glomerular tip lesion variant
3. Cellular variant
4. Perihilar variant
5. Not otherwise specified (NOS) variant.

Recognition of these variants may have prognostic value in individuals with primary focal segmental glomerulosclerosis (i.e., where no underlying cause is identified) [4,5].
It is proposed that collapsing glomerulopathy is a distinct entity characterized by massive proteinuria, relatively rapidly progressive renal insufficiency, and distinctive pathological findings. The data suggest that collapsing glomerulopathy is clinically, pathologically, and epidemiologically different from noncollapsing FSGS [6,7]. Although collapsing glomerulopathy resembles HIV-nephropathy both pathologically and clinically, it differs clinically by having no evidence for associated HIV infection and other viruses, and differs pathologically by lacking endothelial tubuloreticular inclusions. Collapsing glomerulopathy may occur in an idiopathic (primary) form and in association with a wide spectrum of infectious and inflammatory conditions and medications [8-10].

Case report

We report the case of a 77-year-old female patient, with nephrotic syndrome and histopathologic features of glomerular capillary collapse. She was admitted to our Department with present edema and incipient chronic renal failure. The medical history showed arterial hypertension, 2 years ago, without clinical symptomatology. The follow-up presented chronic renal failure with serum creatinine -126…154…174 μmol/L. Nephrotic syndrome with feet and ankles edema, progressively extended, at first failed to respond to diuretic therapy. The level of total serum protein fraction was 54 g/l, albumin -29…24…28g/L. Urinalysis demonstrated proteinuria 7.8 g/l… 6.15g/L and 12.3 g/24 h. Presence of 25-30 erythrocytes and 2-3 leukocytes in urine sediment was also noticed. Renal biopsy was performed to determinate the presence of glomerular disease.

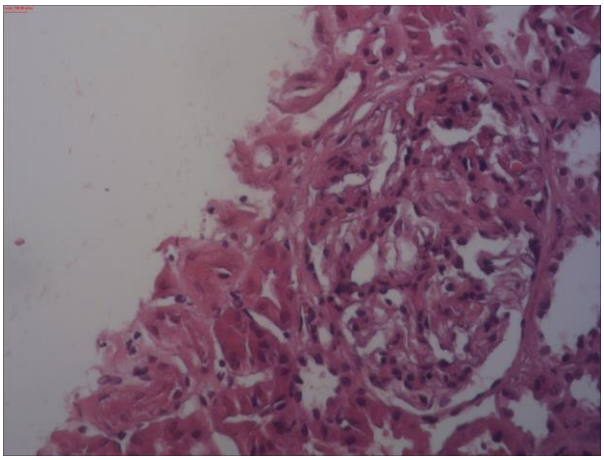

Fig. 1. HE 400 x Nikon 80: Glomerulus with collapsed glomerular basement membrane and synechial between Bowman's parietal and visceral epithelium

Collapsing glomerulopathy and FSGS biopsy specimens were evaluated by light microscopy using standard paraffin section techniques. The pathological characteristic for a diagnosis of collapsing glomerulopathy was the presence of focal, segmental or global glomerular capillary collapse (Figure 1). Glomeruli were with enlarged volume, discrete fibrously thickened glomerular basal membrane, because of the mesangial cell proliferation. Protein resorption in tubular epithelium with acute dilatation were seen. The vessels were with lightly hypertensive changes. This lesion was characterized by collapse and wrinkling of glomerular basement membranes, obliteration of capillary lumens, disappearan-

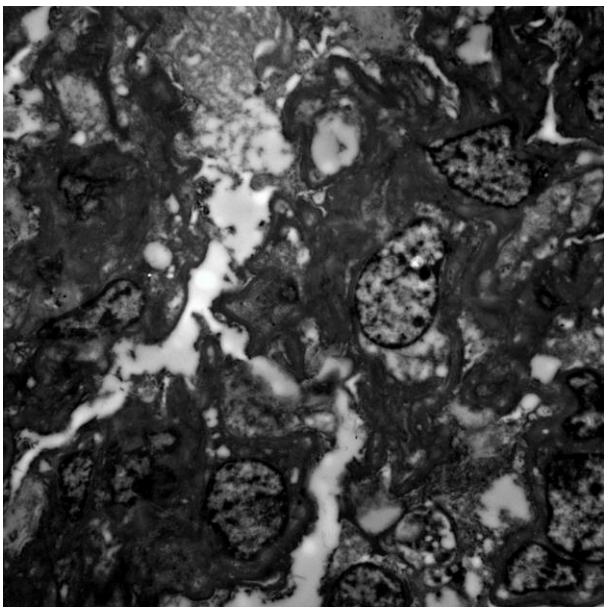

Fig. 2. TEM analysis: collapsed glomerular basement membrane with cloudy subendothelial deposits-there is segmental fussion of the podocytes

ce of endothelial and mesangial cells, and hypertrophy and hyperplasia of adjacent visceral epithelial cells.
Under electron microscopy Bowman's membrane was fibrously thickened and ischemic, with proliferative parietal epithelium. GBM was thickened with deposition of basal membrane material (Figure 2). Mesangial matrix was with an enlarged number of mesangial cells. Renal biopsy finding suggested collapsing glomerulopathy, with probably idiopathic or genetic disorders.
The treatment of the patient included corticosteroids, angiotensin-converting enzyme inhibitor and lipid lowering agents, which resulted in lowering the proteinuria, followed by withdrawal of the edema.

Discussion

Collapsing glomerulopathy is a distinct entity characterized by massive proteinuria, relatively rapidly progressive renal insufficiency, and distinctive pathological findings. The data suggest that collapsing glomerulopathy is clinically, pathologically, and epidemiologically different from noncollapsing FSGS. In fact, secondary collapsing glomerulopathy is a heterogeneous group including numerous causes: toxins and drugs such as heroin and pamidronate, familial forms, vasculitis [9-11], Lupus erithematosus, secondary to nephron loss and hyperfiltration, such as chronic pyelonephritis and reflux, morbid obesity, diabetes mellitus.
Focal segmental glomerulosclerosis may also develop acquired loss of nephrons from reflux nephropathy. Proteinuria is nonselective in most cases and may be in subnephrotic range (nephritic range <3.0g/24hr) or in nephritic range.

Genetic causes

The first gene involved with this disorder is ACTN4, which encodes alpha-actinin 4. This protein crosslinks bundles of actin filaments and is present in the podocytes. Mutations in this protein associated with FSGS result in increased affinity for actin binding, formation of intracellular aggregates, and decreased protein half-life.
A second gene associated with FSGS is TRPC6, which encodes member of the canonical family of TRP channels. This family of ion channels conduct cations in a largely non-selective manner. As with ACTN4, TRPC6 is expressed in podocytes [11].
Another gene that may be involved in hereditary forms of FSGSis the gene known as CD2A (CD2 associated protein) or CMS (Cas binding protein with multiple SH3 domains). The protein expressed by this gene is expressed in podocytes [11].
Another gene associated with FSGS is INF2, which encodes a member of the formin family of actin-regulating proteins [12,13].
Mutations in the NPHS2 gene, which encodes for the protein called podocin, can cause focal segmental glomerulosclerosis [14-16]. This is a recessive form of FSGS. NPHS-mediated FSGS is resistant to treatment with steroids.

Treatment of FSGS

In our presented case,treatment of FSGS included symptomatic and immunosuppressive therapy.
The objective of the symptomatic treatment is to treat the imbalances brought about by the illness: edema, hypoalbuminemia, hyperlipemia, hypercoagulability and infectious complications. There are a number of recommendations such as: rest, medical nutrition therapy, medication (especially loop diuretics, such as furosemide). Hypoalbuminemia is treated using the medical nutrition therapy described as a treatment for edema. It includes a moderate intake of foods rich in animal proteins. For hyperlipidemia lipid lowering agents are used. Thrombophilia also must be controlled with anticoagulant therapy.
For infectious complications an appropriate course of antibacterial drugs can be taken according to the infectious agent. Blood pressure control includes ACE inhibitors as a drug of choice. Independent of their blood pressure lowering effect, they have been shown to decrease protein loss.
The treatment of kidney damage may reverse or delay the progression of the disease. Kidney damage is treated by prescribing drugs; in our practice, we use corticosteroids and immunosuppressors [17-19]. Prednisone is usually prescribed at a dose of 60 mg/m^2 of body surface area/day during the first treatment for 4-8 weeks. After this period, the dose is reduced to 40 mg/m^2 for the next 4 weeks. People suffering a relapse or children are treated with prednisolone 2 mg/kg/day till urine becomes negative for protein.
We used methylprednisolone as a pulse therapy 500 mg/day, for 3 days and then continuing with therapy *per os,* 0.5 mg/kg/day for 4 weeks. Frequent relapses are treated with cyclophosphamide or ciclosporin. Patients can respond to prednisone in a number of different ways:

- Patients with corticosteroid sensitive or early steroid-responder: the subject responds to the corticosteroids in the first 8 weeks of treatment. This is demonstrated by a strong diuresis and the disappearance of edemas, and also by a negative test for proteinuria in three urine samples taken during the night.
- Patients with corticosteroid resistant or late steroid-responder: the proteinuria persists after the 8-week treatment. The lack of response is indicative of the seriousness of the glomerular damage, which could develop into chronic kidney failure.

- Patients with corticosteroid intolerance: complications such as hypertension appear, and they gain a lot of weight and can develop aseptic or avascular necrosis of the hip or knee, cataracts and thrombotic phenomena and/or embolisms.
- Patients with corticosteroid dependent: proteinuria appears when the dose of corticosteroid is decreased or there is a relapse in the first two weeks after completed treatment.

Immunosuppressors (cyclophosphamide, ciclisporin) by protocol: only indicated in recurring nephrotic syndrome in corticosteroid-dependent or intolerant people [19-21]. In the first two cases, the proteinuria has to be negated before treatment with the immunosuppressor can begin, which involves a prolonged treatment with prednisone. The negation of the proteinuria indicates the exact moment when treatment with cyclophosphamide can begin.

The treatment is continued for 8 weeks at a dose of 3 mg/kg/day, the immunosuppression is halted after this period. In order to be able to start this treatment, the person should not be suffering from neutropenia nor anemia, which would cause further complications. Cyclophosphamide can cause side effect such as alopecia. Blood count tests are carried out during the treatment in order to give advance warning of a possible infection.

In our case, the effect was achieved with the treatment with corticosteroids, angiotensin-converting enzyme inhibitor and lipid lowering agents, which resulted in lowering the proteinuria, followed by withdrawal of the edema. Renal function remains the same without deline of the creatinin values.

In conclusion, the treatment of the collapsing glomerulopathy needs complex therapy depending on the manifested symptoms and course of the disease. The therapy is individually modified, according to the guidelines for treatment of the disease.

Conflict of interest statement. None declared.

References

1. Albaqumi M, Soos TJ, Barisoni L, Nelson PJ. Collapsing glomerulopathy. *J Am Soc Nephrol* 2006; 17(10): 2854-2863.
2. Schwimmer JA, Markowitz GS, Valeri A, Appel GB. Collapsing glomerulopathy. *Semin Nephrol* 2003; 23(2): 209-218.
3. Detwiler RK, Falk RJ, Hogan SL, Jennette JC. Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis. Kidney Int 1994; 45: 1416-1424.
4. Weiss MA, Daquioag E, Margolin EG, *et al*. Nephrotic syndrome, progressive irreversible renal failure, and glomerular 'collapse': a new clinicopathologic entity? *Am J Kidney Dis* 1986; 7: 20-28.
5. Valeri A, Barisoni L, Appel GB, *et al*. Idiopathic collapsing focal segmental glomerulosclerosis: A clinicopathologicstudy. *Kidney Int* 1996; 50: 1734-1746.
6. Stokes MB, Davis CL, Alpers CE. Collapsing glomerulopathy in renal allografts: a morphological pattern with diverse clinicopathologic associations. *Am J Kidney Dis* 1999; 33: 658-666.
7. Nicholas Cossey L, Christopher P Larsen, and Helen Liapis. Collapsing glomerulopathy: a 30-year perspective and single, large center experience. *Clin Kidney J* 2017; 10(4): 443-449.
8. Grcevska L, Polenakovik M. Collapsing glomerulopathy: clinical characteristics and follow-up. *Am J Kidney Dis* 1999; 33(4): 652-657.
9. Jun Yamazaki, Eriko Kanehisa, Wakaba Yamaguchi, *et al*. Idiopathic collapsing focal segmental glomerulosclerosis in an 81-year-old Japanese woman: a case report and review of the literature. *CEN Case Rep* 2016; 5(2): 197-202.
10. Thomas DB, Franceschini N, Hogan SL, *et al*. "Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants". *Kidney Int* 2006; 69(5): 920-926.
11. Mukerji N, Damodaran TV, Winn MP. "TRPC6 and FSGS: The latest TRP channelopathy". *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 2007; 1772(8): 859-868.
12. Genovese G, Friedman DJ, Ross MD, *et al*. "Association of Trypanolytic ApoL1 Variants with Kidney Disease in African-Americans". *Science* 2010; 329(5993): 841-845.
13. Brown EJ, Schlöndorff JS, Becker DJ, *et al*. "Mutations in the formin protein INF2 cause focal segmental glomerulosclerosis". *Nature Genetics* 2010; 42(1): 72-76.
14. Franceschini N, North KE, Kopp JB, *et al*. "NPHS2 gene, nephrotic syndrome and focal segmental glomerulosclerosis: a HuGE review". *Genet Med* 2006; 8(2): 63-75.
15. Tsukaguchi H, Sudhakar A, Le TC, *et al*. "NPHS2 mutations in late-onset focal segmental glomerulosclerosis: R229Q is a common disease-associated allele". *J Clin Invest* 2002; 110(11): 1659-1666.
16. Boute N, Gribouval O, Roselli S, *et al*. "NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome". *Nature Genetics* 2000; 24(4): 349-354.
17. Jianni Huang, Li Lin, Jingyuan Xie, *et al*. Glucocorticoids in the treatment of patients with primary focal segmental glomerulosclerosis and moderate proteinuria. *Clinical and Experimental Nephrology* 2018; 22: 1315-1323.
18. Campbell KN, Tumlin JA. Protecting Podocytes: A Key Target for Therapy of Focal Segmental Glomerulosclerosis. *Am J Nephrol* 2018; 47(1): 14-29.
19. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-Glomerular-Diseases-Guideline-2021-English.pdf.
20. Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. *Am J Kidney Dis* 1994; 23(6): 773-783.
21. Soumita Bagchi, Sanjay Agarwal, Mani Kalaivani, *et al*. Primary FSGS in Nephrotic Adults: Clinical Profile, Response to Immunosuppression and Outcome. *Nephron* 2016; 132(2): 81-85.

Case report

ANALYSIS OF THE DIFFUSION CAPACITY OF THE LUNGS FOR CARBON MONOXIDE - CLINICAL BIOMARKER IN SETTINGS OF POST-ACUTE CARE OF PATIENTS WITH COVID-19

АНАЛИЗА НА ДИФУЗИОНИТ КАПАЦИТЕТ НА БЕЛИТЕ ДРОБОВИ ЗА ЈАГЛЕНОРОДЕН МОНОКСИД - КЛИНИЧКИ БИОМАРКЕР ВО ПОСТАВКИ ЗА ПОСТАКУТНА НЕГА НА ПАЦИЕНТИ СО COVID-19

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Abstract

COVID-19 is an infectious disease resulting in respiratory, neurological, cardiovascular, and digestive disorders that are likely to stem from a systemic endothelial dysfunction. Even though the lungs are the major organ affected by COVID-19, the clinical manifestations of this disease are widely unpredictable, ranging from asymptomatic to severe respiratory dysfunction (in about 5% of the cases), which leads to an intensive care.

In all patients affected with pulmonary problems, the lung function is disturbed in varying degrees of intensity, while the findings deviate in both the functional and radiological examinations. The diffusing capacity of the lungs for carbon monoxide (DLCO) is one of the parameters that reflect the damage to the alveolocapillary membrane. DLCO/VA considers the differences in lung size. For this reason, it is sometimes considered as a more accurate expression of its own function of gas exchange in the lungs. The observation that the DLCO may be impaired while the DLCO/VA may not be impaired in patients after COVID-19, may be an indication that the diffuse membrane change plays a significant role in causing lung dysfunction in comparison to the reduced VA.

The systemic functional assessment should be taken in consideration for all moderately severe patients infected with COVID-19 at the time of their discharge from hospital, and such a multidisciplinary approach can be provided by individualized rehabilitation programs. Lung function tests can be considered as necessary tools for monitoring of the functional impairment, planning of the rehabilitation, managing of the possible complications, as well as for prevention of the long-term side effects.

Keywords: diffusion capacity of the lungs, KOVID-19, rehabilitation

Абстракт

COVID-19 е инфективна болест со респираторно, невролошко, кардиоваскуларно и дигестивно засегање веројатно како резултат на системска ендотелијална дисфункција Иако, белите дробови се главниот орган погоден од COVID-19, клиничките манифестации на болеста се широко непредвидливи, почнувајќи од оние кои се без симптоми до сериозни нарушувања на дишењето (во околу 5% од случаите), што доведува, до прием на интензивна нега.

Кај сите пациенти кои имаат белодробно засегање настанува пореметување на белодробната функција од различен интензитет и отстапување на наодите во функционалните и рентгенолошки испитувања. Капацитетот на дифузија на белите дробови за јаглерод моноксид (diffusing capacity of the lungs for carbon monoxide-DLCO) е параметар кој ги рефлектира оштетувањата на алвеолокапиларната мембрана. DLCO/VA ги зема предвид разликите во големината на белите дробови, па затоа понекогаш се смета како поточен израз на сопствената функција за размена на гасови во белите дробови. Набљудувањето дека кај пациентите после COVID-19, DLCO може да биде нарушено, додека DLCO/VA може да не биде нарушено, може да е индикација на тоа дека промената на дифузната мембрана има значајна улога во предизвикувањето на дисфункција на белите дробови во споредба со намалената VA.

Треба да се разгледа системската функционална проценка за сите умерено тешки пациенти со COVID-19 во моментот на испуштање од болница, а таков мултидисциплинарен пристап може да се обезбеди со индивидуализирани програми за рехабилитација. Тестовите на функцијата на белите дробови може да се сметаат како неопходни

алатки за следење на функционалното оштетување, за планирање на рехабилитација, за управување со евентуалните компликации, како и за спречување на долгорочни несакани последици.

Клучни зборови: дифузионен капацитет на бели дробови, КОВИД-19, рехабилитација

Introduction

In December 2019, the new SARS-CoV-2 was responsible for the onset of the COVID-19 pandemic, from Wuhan, China. Shortly after the infection spread around the world, on March 11, 2020, the World Health Organization (WHO) declared a global COVID-19 pandemic. COVID-19 is an infectious disease with respiratory, neurological, cardiovascular, and digestive disorders that most likely occur because of a systemic endothelial dysfunction [2]. Although the lungs are the major organ affected by COVID-19, the clinical manifestations of the disease are widely unpredictable, ranging from asymptomatic to severe respiratory distress (in about 5% of cases) which leads to an intensive care due to the acute respiratory failure and acute respiratory distress syndrome [3].

In some patients, even after denigration of the swab test (which excludes the risk of further transmission of the infection), the negative result does not indicate the end of the disease itself. Persistent symptoms have been reported in patients recovering from the disease, suggesting the presence of 'post-COVID-19 syndrome', even in patients with mild to acute illness [4]. In this regard, several studies postulate that patients with COVID-19 may not return to baseline functional status and baseline levels of post-infection health requirements. Hence, given the complexity and variability of clinical manifestations, as well as the possible long-term consequences, the implementation of post-acute care strategies for patients with COVID-19 could be a step forward regarding the management of health in these patients after a negative swab test [5, 6].

Persistent and long-lasting symptoms because of an impaired lung function and decreased respiratory capacity have been previously reported in both SARS and MERS. In patients recovering from SARS, significant diffusing capacity of the lungs for carbon monoxide (DLCO) has been documented in 27.3% of cases [7], with this percentage being even higher (37%) for patients with MERS after only a one-year follow-up [8].

Similarly, upon completion of hospital treatment for acute attack, patients with COVID-19 may still have residual computed tomography (CT) changes and functional impairments. The most common radiographic finding is represented by changes like blurred glass, while reduced DLCO with restrictive ventilatory defects are considered as common functional and more acute consequences. The severity and duration of both DLCO damage and restrictive ventilatory defects appear to be related to the severity of the acute illness. In general, pulmonary function abnormalities may persist for up to 6 months or more, with the possibility of vascular and alveolar remodeling evolving into pulmonary fibrosis in many patients [9].

In a study of 110 COVID-19 discharged patients with mild to severe clinical picture, Mo *et al.* reported changes in the percentage of DLCO in 47.2% of cases, total vital capacity (TLC) in 25%, forced expiratory volume, or expiratory volume in the first second (FEV1) in 13.6%, changes in forced vital capacity (FVC) in 9.1%, FEV1/FVC in 4.5% and changes in small airway function in 7.3% of cases. The changes in DLCO correlated with the severity of pneumonia, and were observed in 30.4% of mild, 42.4% of moderate, and up to 84.2% of severely affected patients [10].

In a prospective study that was conducted 12 weeks after the onset of symptoms in previously hospitalized patients with COVID-19, an abnormal DLCO was observed in 52% of the cases, while 45% of them had concomitant restrictive ventilatory defect. Interestingly, all patients who exerted oxyhemoglobin with physical exertion had an abnormal DLCO. A strong correlation was documented between the number of days spent with the addition of oxygen during the acute phase and changes in the DLCO and CT findings. In a similar manner, a strong association of dyspnea severity with DLCO changes (deviations) was observed [11]. Also, both DLCO and TLC displayed a moderately strong negative correlation with the ventilation duration ($r=-0.43$; $p=0.008$ and $r=-0.42$; $p=0.01$).

In a meta-analysis comprising 380 patients after COVID-19, altered DLCO was observed in 39% of the general population, while 66% were observed in patients with severe disease [12]. Similar results were reported in a retrospective study of 57 patients with COVID-19 conducted by Huang *et al.* [13]. During the 30-day follow-up, various forms of CT scan changes were documented in 94.1% of severe and 37.5% of mild cases. Furthermore, deviations in DLCO were reported in more than 50% of the surveyed population. In addition, there was a higher incidence of DLCO damage (76.5 *vs*. 42.5%) and TLC, as well as a 6-minute gait test compared to the mild cases.

In another study conducted on 55 non-critical COVID-19 patient survivors, who were evaluated three months after their hospitalization, radiological and pulmonary abnormalities were observed in 25%. Decreased DLCO was the most common pulmonary abnormality reported in 16% of the observed patients. In addition, the authors of the study found that elevated D-dimer values on admission suggested changes in DLCO three months after hospitalization [14].

One large national study in Switzerland has recently investigated the pulmonary effects of COVID-19 within

four months after the onset of symptoms. Impairment of pulmonary function and physical performance was reported as more pronounced in patients with severe and critical COVID-19 than in those affected with mild to moderate form of the disease. In this regard, DLCO was particularly reduced in the severe/critical patients with COVID-19, which was associated with the reduced walking distance and oxygen desaturation exercise in the post-acute phase. At the same time, a negative correlation between the duration of ventilation and the abnormality of DLCO and TLC was observed in patients who underwent mechanical ventilation during their hospitalization [15].

A direct correlation between the disease severity and functional consequences of COVID-19 was not confirmed when patients were evaluated in the early stages of this disease (30 days after the onset of symptoms). More specifically, a recent study documented that DLCO, FVC, and TLC (% predicted values) did not differ significantly between the groups of clinical and radiological severity, although they were still significantly impaired in the overall population affected by the disease [16].

Based on the results of the above studies, DLCO can be generally identified as a useful functional biomarker for patients with COVID-19 on discharge from hospitals, i.e., on discharge from acute care and admission to post-acute care facilities (nursing homes, care centers, rehabilitation facilities, public health facilities, etc.). DLCO reflects the gas exchange function of the alveolar-capillary barrier of the lung, which is the product of the carbon monoxide (CO) multiplied by the alveolar volume (VA) [17]. CO reflects the gas exchange per unit volume of the lungs and depends mainly on the thickness and area of the alveolar capillary membrane, the volume of blood in the capillaries that supply ventilated alveoli, as well as on the concentration of hemoglobin in the alveolar capillary blood.

The decrease in DLCO may occur due to a decrease in CO, VA, or both. Thus, it may be difficult to interpret which is the dominant mechanism of impaired DLCO [17]. The pathological changes seen in the lungs of deceased patients with COVID-19 to some extent may explain the impairment of DLCO, since the main characteristic of SARS-CoV-2 lung infection is an extensive injury to the alveolar epithelium and endothelial cells, followed by secondary fibroproliferation [18].

Interestingly, in approximately 50% of patients with COVID-19 with altered DLCO, the DLCO/VA value remained within the normal range, as reported by Mo *et al.* [10]. DLCO/VA considers differences in lung size, so it is sometimes considered a more accurate expression of its own function of gas exchange in the lungs. The observation that DLCO may be impaired while DLCO/VA may not be impaired in patients after COVID-19, may present an indication that diffuse membrane change plays a significant role in causing lung dysfunction compared to reduced VA [10].

Conclusion

In conclusion, provided we also consider the tropism of SARS-CoV-2 for alveolar epithelial cells [19], the evidence for abnormal lung function tests in patients after COVID-19 raises doubts and fears associated with the possible fibrotic evolution of disease. This requires an urgent need for specially designed more acute care strategies to timely predict and manage the consequences of COVID-19 in patients.

In this respect, DLCO has the potential to become a useful functional biomarker for patients after COVID-19, especially in patients admitted to post-acute care facilities. Systemic functional assessment should be considered for all moderately severe patients with COVID-19 at the time of their discharge from hospital, and such a multidisciplinary approach can be provided by individualized rehabilitation programs. Lung function tests can be considered as necessary tools for monitorring of the functional impairment, planning of the rehabilitation, management of the possible complications, as well as for prevention of long-term side effects.

Conflict of interest statement. None declared.

Reference

1. Zhu N, Zhang D, Wang W, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382(8): 727-733.
2. Roberts KA, Colley L, Agbaedeng TA, *et al*. Vascular manifestations of COVID-19-thromboembolism and microvascular dysfunction. *Front Cardiovasc Med* 2020; 7: 598400.
3. George PM, Barratt SL, Condliffe R, *et al.* Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax* 2020; 75(11): 1009-1016.
4. Ambrosino P, Papa A, Maniscalco M, Di Minno MND. COVID-19 and functional disability: current insights and rehabilitation strategies. *Postgrad Med J* 2020; doi:10.1136 /postgradmedj-2020-138227. (Epub ahead of print).
5. Polastri M, Nava S, Clini E, *et al*. COVID-19 and pulmonary rehabilitation: preparing for phase three. *Eur Respir J* 2020; 55(6): 2001822.
6. Ambrosino P, Fuschillo S, Papa A, *et al*. Exergaming as a supportive tool for home-based rehabilitation in the COVID-19 pandemic era. *Games Health J* 2020; 9(5): 311-313.
7. Xie L, Liu Y, Fan B, *et al.* Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. *Respir Res* 2005; 6(1): 5.
8. Park WB, Jun KI, Kim G *et al.* Correlation between pneumonia severity and pulmonary complications in MERS. *J Korean Med Sci* 2018; 33(24): e169.
9. Nusair S. Abnormal carbon monoxide diffusion capacity in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020; 56(1): 2001832.
10. Mo X, Jian W, Su Z, *et al.* Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020; 55(6): 2001217.
11. Shah AS, Wong AW, Hague CJ, *et al.* A prospective study of 12-week respiratory outcomes in COVID-19-related

hospitalizations. *Thorax* 2020; doi:10.1136/thoraxjnl-2020-216308 (Epub ahead of print).
12. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, *et al.* Respiratory function in patient's post-infection by COVID-19: a systematic review and meta-analysis. *Pulmonology* 2020; doi: 10.1016/j.pulmoe.2020.10.013 (Epub ahead of print).
13. Huang Y, Tan C, Wu J, *et al.* Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res* 2020; 21(1): 163.
14. Zhao YM, Shang YM, Song WB, *et al.* Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; 15: 100463.
15. Guler SA, Ebner L, Beigelman C, *et al.* Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J* 2021; doi:10.1183/13993003.03690-2020 (Epub ahead of print).
16. Frija-Masson J, Debray MP, Gilbert M, *et al.* Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection. *Eur Respir J* 2020; 56(2): 2001754.
17. Hughes JM, Pride NB. Examination of the carbon monoxide diffusing capacity (DL(CO)) in relation to its KCO and VA components. *Am J Respir Crit Care Med* 2012; 186(2): 132-139.
18. Copin MC, Parmentier E, Duburcq T, *et al.* Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. *Intensive Care Med* 2020; 46(6): 1124-1126.
19. Ziegler CGK, Allon SJ, Nyquist SK, *et al.* SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 2020; 181(5): 1016-1035.e19.

УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Тимес Нењ Роман големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и

заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeCX (Medical Sibject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).

Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):

а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

б) заеднички автор

GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) ***без автор*** **-** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; и :1217-8).

г) ***поглавје во книга или монографија***

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

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Известување за членовите на МЛД

Сите што сакаат и натаму да го добиваат списанието треба да ја имаат уплатено членаринатa за 2022 година во висина од 1500 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или преку телефон.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД - 3162 557.