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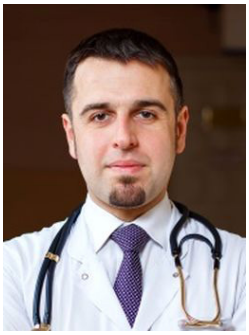

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Liver Injuries Associated with Coronavirus Disease 2019: View on the Problem

Introduction. It has been discovered that the presence of comorbidity is one of the unfavorable circumstances of the Coronavirus Disease 2019 (COVID-19) severe natural course. By now it has been postulated that concomitant cardiovascular, pulmonary diseases, diabetes mellitus, and certain cancers are among those pathologies which are associated with a higher risk of severe COVID-19 clinical course [3, 29, 33]. In the meta-analysis made by Bajgain K. T. et al. [3] which includes a total of 27 studies from seven countries, namely China, South Korea, Italy, USA, Mexico, UK, and Iran, it had been shown that among more than 22 thousand COVID-19 patients 42.3 % were not diagnosed with any chronic comorbid pathology, while 57.7 % had one or more comorbidities. The most frequent of those were arterial hypertension, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), cancer, chronic kidney diseases. Further examination of country-specific major comorbidities also revealed arterial hypertension as one of the most common conditions which prevailed in China, Italy, USA, UK, whereas other cardiovascular diseases were the most frequent in South Korea and diabetes - in Iran. In effect, the authors of the study point out that diabetes was the second most common comorbidity in five of seven countries reviewed [3].

In another retrospective case study, data was collected from 575 hospitals in China and 1590 patients were involved. Of all the cases investigated, at least one comorbidity accounted for 25.1 % was reported. It was specified that the most frequent comorbidities included hypertension, other cardiovascular diseases, cerebrovascular diseases, diabetes, hepatitis B infection, COPD, chronic kidney diseases, malignancy and immunodeficiency. The primary end-point of the above-cited study was a composite measure that involved the admission to intensive care unit, invasive ventilation or death. This composite end-point was more than four times higher in patients with comorbidity in comparison with non-comorbid patients, resulting in increased admission to the intensive care unit and lethal outcomes. Further investigations done by the authors revealed that patients with two or more comorbidities had worse primary end-points as compared to those with one comorbid disease [29]. One of the substantive concomitant pathologies in COVID-19 positive patients are liver diseases as well as liver injuries, this combination being far too less discussed in the literature

The aim of the study was to analyse the available data regarding impact of liver pathologies on the course and outcome of COVID-19, as well as reciprocal influences of COVID-19 on hepatic function indeces.

Materials and methods. Content analysis, systematic and comparative analysis, bibliosemantic method of current reports on coronavirus disease-2019 associated with liver damage were used. Literature sources were searched in PubMed and Medline databases using keywords as follows: coronavirus disease 2019, liver, cytokine storm, drug induced liver injury, liver transplantation. In total 64 articles were analyzed.

Results and discussion. COVID-19 and the liver. Guan W. et al. [30] detected abnormal liver function in as much as 37.0 % of COVID-19 patients. This frequency is higher compared to the patients with diagnosed severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and seasonal influenza. Alqahtani S. and Schattenberg J. [1] reported alterations of liver function tests in 50.0 % of the patients with COVID-19.

Liver injury in SARS-CoV-2 infected patients could occur due to the influence of angiotensin-2 converting enzyme (ACE2) receptor protein [31, 38], since it was found by Tortorici M. A. et al. [56] that virion S-glycoprotein of the virus can attach to the ACE2 receptor of human cells. Chai X. et al. [13] discovered that ACE2 expression in cholangiocytes is significantly higher than that in the hepatocytes (59.7 vs. 2.6 %); ACE expression in cholangiocytes is comparable to that of alveolar type 2 cells, which are the major SARS-CoV-2 targeting cell type in the lungs.

Zhang C. et al. [64] detected increased gamma-glutamyl transferase (GGT) activity due to the disruption of

cholangiocytes in 54.0 % of the patients hospitalized in their clinic. This mechanism could be one of the probable pathophysiological pathways of SARS-CoV-2, further causing the direct injury of the liver

On the other hand, Ji D. et al. [35] noted that pattern of liver injury in COVID-19 patients with nonalcoholic fatty liver disease (NAFLD) was predominantly hepatocellular rather than cholestatic, in other words, these patients exposed increased activity of alanine aminotransferase (ALT) more frequently in comparizon to alkaline phosphatase (ALP) and GGT. Thus, there could also be other possible pathways of liver injury in COVID-19 patients.

The second mechanism of liver injury is the cytokine storm, which leads to an elevated output of pro-inflammatory cytokines affecting the liver. SARS CoV 2 induced the acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome leading to hypoxia and shock, which can cause liver ischemia and hypoxia reperfusion injury [63].

Another potential mechanism of COVID-19 and liver interaction is shifting of polarization status of hepatic macrophages from inflammation-promoting M1 macrophages to inflammation-suppressing M2 macrophages, leading in case of NAFLD to progression of COVID-19 [35]. In addition to this option, patients with COVID-19, especially with moderate to severe course, could suffer from drug induced liver injury (DILI) as a result of adverse events of certain medication used for the treatment of this condition [37].

Currently over 20 investigations have documented abnormal levels of aminotransferases in patients with COVID-19. In particular, Chen N. et al. [15] reported about 28.0 % of their patients having increased ALT activity, 35.0 % - aspartataminotranspherase (AST) level, and 18.0 % - bilirubin.

Another investigation from China that included 1099 patients showed increased AST and ALT levels in 22.2 and 21.3 % respectively. Interestingly, elevated AST levels were twice as likely to be detected in patients with severe course of COVID-19 compared to patients with non-severe course of the disease. Similarly, ALT levels were more than 8.0 % higher in severe vs. non-severe patients. Total bilirubin content was elevated in 10.0 % of all patients enrolled, with less difference detected between patients of severe and non-severe course [30]. Besides the increased transaminases and GGT activities, the patients with COVID-19 infection showed abnormal levels of albumin and lactate dehydrogenase (LDH) in 98.0 and 76.0 % of cases respectively [15].

Lastly, as it was shown in the meta-analysis done by Kulkarni A.V. et al. [37] the incidence of elevated liver enzymes in non-severe COVID-19 patients was 19.9 %, while in severely infected patients - 41.1 %. Moreover, non-survivors were at a higher risk of having elevated liver enzymes at initial admission than survivors [37]. Fan Z. et al. [21] had found that baseline abnormal liver function was associated with prolonged hospital stay, whereas abnormal liver function during admission had little effect on the length of hospitalisation.

Drug induced liver injury in patients with COVID-19. Another probable threat for liver impairment in COVID-19 patients is DILI which can potentially appear in patients treated with certain antiviral agents and supportive therapy. A randomized controlled trial from China involving 199 patients among whom 99 were treated with lopinavir/ritonavir (LPN/r) gives promising results demonstrating elevated levels of AST, ALT, and total bilirubin as adverse events only in few patients [11]. Meanwhile, Cai Q. et al. [10] had found that the use of LPV/r appeared to lead to increased odds of liver injury (OR from 4.44 to 5.03, $p < 0.01$); patients who were given LPV/r had higher levels of total bilirubin and GGT during hospitalization.

A detailed systematic review article regarding DILI in COVID-19 patients was written by Kulkarni A.V. et al. [37]. The authors of the above-mentioned meta-analysis had analyzed 12 academic reports about DILI. The overall incidence of DILI accounted for 25.4 %. In particular, DILI was diagnosed in 15.2 % patients treated with remdesivir [37], a prodrug of an adenosine nucleoside analogue which restricts viral ribonucleic acid (RNA) synthesis by inhibition of RNA-dependent RNA polymerase [22], while this rate accounted for 37.2 % with LPV/r treatment. Hyperbilirubinaemia was the most frequent adverse event of LPV/r, followed by elevated aminotransferases contents, whereas remdesivir more frequently induced elevated aminotransferases activity. As a result of SARSTer multicentre real-world study, it was also found that patients treated with LPV/r experienced significantly more adverse events (39.0 %) compared to those treated with remdesivir (20.0 %). The most frequent among those receiving LPV/r were diarrhea (25.0 %), nausea (8.5 %), vomiting (6.2 %) and prolongation of the QT interval (5.2 %) [22]. The above-quoted study from Poland is consistent with the systemic meta-analysis data [37], because the former shows that patients treated with remdesivir most frequently experienced elevation of aminotransferases (9.8 %), while other adverse events appeared sporadically [22].

Chloroquine – a synthetic 4-aminoquinoline related to quinine – has recently been tried in patients infected with SARS-CoV-2. Early clinical trials reported apparent efficacy of chloroquine phosphate in treating COVID-19 [25, 27]. Meanwhile, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial reported no significant difference in mortality rate between patients treated with hydroxychloroquine and those receiving standard treatment [51]. Nonetheless, hepatotoxicity related to chloroquine or hydroxychloroquine has rarely been reported [37].

Tocilizumab, a humanized monoclonal antibody to the interleukin-6 (IL-6) receptor, is used in the therapy of severe cases of COVID-19 [28, 58]. It was demonstrated that IL-6 levels have been significantly elevated in some COVID-19 patients and are involved in the excessive inflammatory response or cytokine storm triggered by SARS-CoV-2 infection [18]. As per Liver Tox data, serum aminotransferase elevations occurred in 10.0 to 50.0 % of patients receiving tocilizumab. ALT elevations often rose in 3 times above the upper limit of norm 2 weeks after

each infusion, however, they turned back to baseline by the time of the next 4-weekly administration and were usually normal within 8 weeks of stopping the infusions [41]. Serviddio G. et al. [55] reported that even in patients with strongly elevated liver enzymes (up to five times above the upper limit of norm) at baseline who received tocilizumab for life-threatening COVID-19 in dosage 8.0 mg/kg/day for two consecutive days, liver function test normalized within 3 weeks of treatment. The authors of the abovementioned study suppose that tocilizumab may be effective for the treatment of severe COVID-19 course, even in patients with elevated liver function tests [55].

Gatti M. et al. [26] had analyzed the United States Food and Drug Administration Adverse Effect Reporting System database and found that DILI associated with tocilizumab administration occurred in 91 cases out of total of 2433 designed medical events after a median of 15 days after injection. The authors suggest that liver test monitoring (i.e. serum transaminases, total bilirubin, alkaline phosphatase levels) should be performed in the first 7-10 days after tocilizumab administration and, when convenient, liver ultrasound examination should be conducted with further monitoring of liver function over 8-week span after tocilizumab administration.

Corticosteroids are among the classes of medications actively discussed in the treatment of COVID-19 patients. The World Health Organization (WHO) initially has not recommended the routine use of systemic corticosteroids for the treatment of viral pneumonia, unless they were indicated for another reason [28]. However, in later guidance, WHO recommends systemic corticosteroids administration for the treatment of patients with severe and critical COVID-19 omitting their application in patients with non-severe COVID-19 course [62]. Likewise, the RECOVERY trial demonstrated that dexamethasone treatment of patients with COVID-19 who received invasive mechanical ventilation or oxygen alone, resulted in decreased 28-day mortality rate [34]. Anyway results regarding the administration of corticosteroids in patients with severe and critical COVID-19 course are still controversial. In recent nationwide prospective study from Spain, it has been postulated that early use of corticosteroids in critically COVID-19 affected patients was associated with lower mortality as compared to delayed use of corticosteroids or their complete omitting [46]. On the opposite, in a retrospective study from China, it was figured out that early initiation of corticosteroid use ($\leq$3 days after intensive care unit admission) was associated with an increased 90-day mortality [40]. Finally, as concluded in WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group meta-analysis, administration of systemic corticosteroids to critically ill patients with COVID-19, compared with usual care or placebo, was associated with lower 28-day all-cause mortality [60].

It is noteworthy that prescribing corticosteroids for several groups of patients with severe forms of COVID-19 might require special caution. On the first hand, these are patients with chronic hepatitis B and C viruses. In the case of chronic hepatitis B, corticosteroids can induce elevation in viral replication and serum hepatitis B virus DNA levels [59] via two potential pathways: hepatitis B virus (HBV) genome includes a glucocorticoid-responsive transcription regulatory element that is up-regulated by steroid derivates which can lead to increased viral replication and direct inhibitory effect on T-cells which are engaged in HBV control [57]. Corticosteroid therapy can lead to the increase of hepatitis C virus RNA level as well [23, 41]. In case of need for corticosteroids prescription, the risk of other infections and viral shedding may increase in patients with decompensated liver cirrhosis. Under such circumstances, antimicrobial prophylaxis and HBV reactivation should be taken into consideration [9].

Another group of liver disease patients who should be carefully treated with corticosteroids are NAFLD patients. Corticosteroids can cause steatosis by decreasing mitochondrial β-oxidation and lipid β-peroxidation enzymes, causing accumulation of lipids within hepatocytes [36]. Corticosteroids can augment insulin resistance and cause the increased level of insulin in blood and influence fatty acid metabolism forming inconvenient metabolic conditions for NAFLD progression [36, 54]. It was found that NAFLD is associated with COVID-19 progression as well as underlying comorbidity, male gender, age >60 years, higher body mass index (BMI). Moreover, NAFLD was associated with longer viral shedding time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days) compared to the patients without NAFLD [11]. Taking into account the NAFLD global prevalence increase, a large proportion of the population might be at risk of severe COVID-19 [12, 50].

Venous thromboembolism and arterial thrombosis are the common complications in COVID-19 patients with high probability of lethal outcome [7]. Reacting to this issue, various professional organizations have recommended the use of anticoagulation prophylactic for these patients [4, 47]. Rentsch C. T. et al. [52] in a nationwide cohort study concluded that early initiation of prophylactic anticoagulation therapy in patients hospitalized with COVID-19 is associated with a decreased risk of mortality. Furthermore, Martinelli I. et al. [42] postulated that patients with COVID-19 receiving a high dosage of enoxaparin (1.0 mg/kg twice daily in patients admitted to intensive care units, 0.7 mg/kg twice daily in high-intensity care wards and 1.0 mg/kg daily in low-intensity care wards) demonstrated a 60.0 % reduction of mortality and clinical deterioration and a 50.0 % reduction of venous thromboembolism compared to standard dosage prophylaxis (enoxaparin 40.0 mg daily increased to 60.0 mg daily in obese persons) with relatively rare non-fatal major bleeding complications. The potential risk of hemorrhage while anticoagulants treatment could be challenging, especially in patients with advanced chronic liver disease who are prone to decreased thrombocytes count and hypocoagulation [8].

The number of liver injury cases related to low molecular heparin level is relatively sparce. These are mainly case reports regarding complication of antithrombotic therapy [2, 39, 43]. The Food and Drug Administration's Adverse Event Reporting System informs that up to

4.0 % of all enoxaparin-related adverse events relay to hepatic injury [32]. Christiansen H. M. et al. [16] found an increased ALT activity in 17.0 % of patients who were subjected to enoxaparin treatment for thromboprophylaxis after total hip replacement surgery which returned to preoperative levels within the 14 days [16].

Regarding the supportive and symptomatic treatment of COVID-19 in patients with liver diseases, it should be noted that patients with liver cirrhosis should be carefully managed with regard to acetaminophen. This drug overdosing should be prevented; however the administration of 2.0-3.0 g daily is considered safe in patients with active alcohol consumption [9]. Acetaminophen-induced liver injury can be favored by increased hepatic cytochrome P450 family 2 subfamily E member 1 (CYP2E1) activity. This should be especially taken into consideration in patients with NAFLD who are prone to increased activity of CYP2E1 and in this condition, additional potentiation of CYP2E1 activity by acetaminophen could cause the generation of greater hepatic amounts of the highly toxic metabolite N-acetyl-p-benzoquinone imine [44]. Moreover, non-steriodal anti-inflammatory drugs should be avoided in patients with liver cirrhosis and portal hypertension [9, 14].

Treatment of post liver transplant patients with COVID-19. Another challenge in hepatology under COVID-19 pandemic conditions includes special management of liver transplant patients due to the necessaty of immunosuppressive therapy continuation in this group. In a European multicentre prospective study of liver transplant recipients, Becchetti C. et al. [5] reported that COVID-19 was associated with an overall and intra-hospital mortality rate in 12.0 % (95.0% CI 5.0% to 24.0%) and 17.0 % (95.0% CI 7.0% to 32.0%) respectively.

Patients subjected to liver transplantation are usually polymedicated; therefore, drug-to-drug interactions are very likely to appear. In certain cases amendment of immunosuppressive therapy is needed. In the abovementioned study, the immunosuppressive drugs administration was reduced in 39.0 % of patients and discontinued in 7.0 % [5]. It is recommended to substitute mammalian target of rapamycin (mTOR) inhibitors with calceneurin inhibitors considering pulmonary adverse events of the first one [48]. Possible drug-to-drug interactions between SARS-CoV-2 antiviral drugs and commonly used immunosuppressants for liver transplant recipients were widely investigated. There is a potential interaction of LPN/r with cyclosporin, mycophenolate, tacrolimus, certain steroids [19]. In case of the need for simultaneous use of LPN/r and tacrolimus, its plasma concentration should be maintained between 6.0 and 8.0 ng/mL [49]. Cyclosporine has less severe interactions with LPN/r than tacrolimus, but an increase in its plasma level, especially when used simultaneously with hydroxychloroquine, could develop [45]. Cyclosporine target plasma concentration is evaluated on the level 100.0-200.0 ng/mL and daily plasma concentration monitoring is recommended [20]. LPN/r is not recommended to be co-administered with sirolimus [19].

So far there no observations on remdesivir interactions with other drugs used in the management of liver transplant patients. Favipiravir increases the concentration of pioglitazone, rosiglitazone, paracetamol, oseltamivir, and hormonal replacement therapy; however, no significant interactions with either immunosuppressive medications or steroids were reported. Chloroquine demonstrated strong interaction with cyclosporine since it increases levels of cyclosporin by decreasing its metabolic rates [19]. Consequently, the cyclosporine level should be monitored and the dose should be decreased if necessary [53]. Apart from this, chloroquine increases levels of tacrolimus by the same mechanism, but to a lesser extent [19]. A prominent example of the aforementioned drug-to-drug interaction was reported by Dajti E. et al. [17], who detected the elevation of tacrolimus plasma concentration in young liver-transplant patients receiving darunavir/ritonavir and hydroxychloroquine to treat COVID-19 infection. It is noteworthy that in this case the level of tacrolimus remains elevated for several days even after its expulsion [17]. Tocilizumab has relatively minor interaction with cyclosporin, tacrolimus, and sirolimus and is not recommended to simultaneous prescription with basiliximab [19]. Special caution is required in case of simultaneous prescription of LPN/r or chloroquine and hydroxychloroquine with tacrolimus, regarding potential QT interval prolongation.

From all observations collected so far, it should be emphasized that the immunosuppressants' intake does not obviously put a patient at a higher risk for COVID-19 natural course. Spectacular results were received by Belli L. S. et al. [6], according to which tacrolimus was associated with better survival in liver transplant patients, these observations opening a perspective for further examination of the calcineurin inhibitor usage in COVID-19 patients. Another promising results for immunosuppressants application in moderate and severe COVID-19 affected patients were obtained by Galvez-Romero J. L. et al. [24] showing supreme effect on patients' survival rate of cyclosporine/corticosteroids combination in comparison with corticosteroids alone.

Conclusions. This literature survey revealed the fact that liver diseases are among substantive comorbidities in coronavirus disease-2019 patients and, reciprocally, liver injuries are frequent complications of COVID-19. Potential drug induced liver injury in patients treated with combination of antiviral agents and supportive therapy drugs could develop. Special precautions should be taken to consideration in order to prevent the potential drug-to-drug interactions in case of COVID-19 treatment in liver transplant patients.

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Conflict of interest
The authors of this article argue that there is no conflict of interest.

Liver Injuries Associated with Coronavirus Disease 2019: View on the Problem

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Introduction. Major cardiovascular and pulmonary comorbidities, as well as diabetes mellitus and certain cancers, are associated with worse clinical outcomes of coronavirus disease-2019 (COVID-19). Meanwhile, the impact of concomitant liver diseases on the COVID-19 natural course together with the influence of the COVID-19 on the hepatic tissues have been rarely investigated.

The aim of the study was to analyse the available data regarding impact of liver pathologies on COVID-19 natural course and outcome, and, reciprocally, hepatic injuries development induced by COVID-19.

Materials and methods. Content analysis, systematic and comparative analysis, bibliosemantic method of investigation of current scientific research results on liver damage associated with COVID-19 were used.

Results. The potential mechanism of liver injury in COVID-19 is complex and includes direct cytopathic viral injury, proinflammatory cytokine outbreak, hypoxia/reperfusion damage and potential drug induced liver injury. Among the medications used for the treatment of COVID-19 patients, there are certain that could potentially cause drug-induced liver injury. Treatment of liver transplant patients can be challenging taking into consideration the possible necessity of immunosuppressive therapy correction combined with the needs to find a balance between the risk of graft rejection and effective elimination of the virus.

Conclusions. Current review of the available database revealed that liver diseases are among substantive comorbidities in COVID-19 patients alongside with liver injuries which are rather frequent complications of COVID-19 treatment. Potential drug-induced liver injuries in patients subjected tocertain antiviral agents in combination with supportive therapy drugs should be taken into consideration. Special precautions are required to prevent potential drug-to-drug interactions in case of COVID-19 treatment in liver transplant patients.

Keywords: COVID-19, liver, cytokine storm, drug induced liver injury, liver transplantation.

Ураження печінки, асоційовані з коронавірусною хворобою-2019: погляд на проблему

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Вступ. Серцево-судинні та легеневі супутні хвороби, а також цукровий діабет і деякі онкологічні недуги асоціюються тяжчим клінічним перебігом із коронавірусною хворобою-2019 (COVID-19). Водночас вплив супутніх хвороб печінки на перебіг COVID-19 разом із впливом COVID-19 на печінку досліджений менш детально.

Мета. Проаналізувати результати наукових досліджень про ураження печінки, асоційовані з коронавірусною хворобою.

Матеріали й методи. Використано контент-аналіз, метод системного та порівняльного аналізу, бібліосемантичний метод вивчення актуальних наукових досліджень щодо уражень печінки, асоційованих із COVID-19. Пошук джерел здійснено в наукометричних базах інформації PubMed і Medline за ключовими словами: COVID-19, печінка, цитокіновий шторм, медикаментозне ураження печінки, трансплантація печінки. Проаналізовано 64 наукові статті за обраною тематикою.

Результати. Потенційний механізм ураження печінки за наявности COVID-19 включає безпосереднє цитопатичне вірусне ураження, гіперпродукцію прозапальних цитокінів, гіпоксійне/реперфузійне ураження та потенційне медикаментозне ураження печінки. Серед лікарських засобів, які застосовуються для лікування хворих на COVID-19, є й такі, що потенційно можуть призвести до медикаментозного ураження печінки. Іншою складною проблемою у сучасній гепатології є лікування пацієнтів із трансплантованою печінкою, із огляду на можливу потребу корекції імуносупресивної терапії та потребу знайти баланс між ризиком відторгнення трансплантата й ефективною елімінацією вірусу.

Висновки. Аналіз результатів досліджень за темою підтвердив, що хвороби печінки належать до клінічно значимих супутніх хвороб у хворих на COVID-19. Водночас ураження печінки є досить частими ускладненнями коронавірусної хвороби. У пацієнтів, які отримують певні противірусні лікарські засоби й допоміжне лікування, потенційно можуть виникати медикаментозно асоційовані ураження печінки. Особливої уваги щодо запобігання можливій міжмедикаментозній взаємодії потребує наявність COVID-19 у людей із трансплантованою печінкою.

Ключові слова: COVID-19, печінка, цитокіновий шторм, медикаментозне ураження печінки, трансплантація печінки.

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