

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 June 6; 9(16): 3796-4115



### REVIEW

- 3796** COVID-19 and the digestive system: A comprehensive review  
*Wang MK, Yue HY, Cai J, Zhai YJ, Peng JH, Hui JF, Hou DY, Li WP, Yang JS*

### MINIREVIEWS

- 3814** COVID-19 impact on the liver  
*Baroiu L, Dumitru C, Iancu A, Leşe AC, Drăgănescu M, Baroiu N, Anghel L*
- 3826** Xenogeneic stem cell transplantation: Research progress and clinical prospects  
*Jiang LL, Li H, Liu L*

### ORIGINAL ARTICLE

#### Case Control Study

- 3838** Histopathological classification and follow-up analysis of chronic atrophic gastritis  
*Wang YK, Shen L, Yun T, Yang BF, Zhu CY, Wang SN*

#### Retrospective Study

- 3848** Effectiveness of sharp recanalization of superior vena cava-right atrium junction occlusion  
*Wu XW, Zhao XY, Li X, Li JX, Liu ZY, Huang Z, Zhang L, Sima CY, Huang Y, Chen L, Zhou S*
- 3858** Management and outcomes of surgical patients with intestinal Behçet's disease and Crohn's disease in southwest China  
*Zeng L, Meng WJ, Wen ZH, Chen YL, Wang YF, Tang CW*
- 3869** Clinical and radiological outcomes of dynamic cervical implant arthroplasty: A 5-year follow-up  
*Zou L, Rong X, Liu XJ, Liu H*

#### Observational Study

- 3880** Differential analysis revealing APOC1 to be a diagnostic and prognostic marker for liver metastases of colorectal cancer  
*Shen HY, Wei FZ, Liu Q*

#### Randomized Clinical Trial

- 3895** Comparison of white-light endoscopy, optical-enhanced and acetic-acid magnifying endoscopy for detecting gastric intestinal metaplasia: A randomized trial  
*Song YH, Xu LD, Xing MX, Li KK, Xiao XG, Zhang Y, Li L, Xiao YJ, Qu YL, Wu HL*

## CASE REPORT

- 3908** Snapping wrist due to bony prominence and tenosynovitis of the first extensor compartment: A case report  
*Hu CJ, Chow PC, Tzeng IS*
- 3914** Massive retroperitoneal hematoma as an acute complication of retrograde intrarenal surgery: A case report  
*Choi T, Choi J, Min GE, Lee DG*
- 3919** Internal fixation and unicompartmental knee arthroplasty for an elderly patient with patellar fracture and anteromedial osteoarthritis: A case report  
*Nan SK, Li HF, Zhang D, Lin JN, Hou LS*
- 3927** Haemangiomas in the urinary bladder: Two case reports  
*Zhao GC, Ke CX*
- 3936** Endoscopic diagnosis and treatment of an appendiceal mucocele: A case report  
*Wang TT, He JJ, Zhou PH, Chen WW, Chen CW, Liu J*
- 3943** Diagnosis and spontaneous healing of asymptomatic renal allograft extra-renal pseudo-aneurysm: A case report  
*Xu RF, He EH, Yi ZX, Li L, Lin J, Qian LX*
- 3951** Rehabilitation and pharmacotherapy of neuromyelitis optica spectrum disorder: A case report  
*Wang XJ, Xia P, Yang T, Cheng K, Chen AL, Li XP*
- 3960** Undifferentiated intimal sarcoma of the pulmonary artery: A case report  
*Li X, Hong L, Huo XY*
- 3966** Chest pain in a heart transplant recipient: A case report  
*Chen YJ, Tsai CS, Huang TW*
- 3971** Successful management of therapy-refractory pseudoachalasia after Ivor Lewis esophagectomy by bypassing colonic pull-up: A case report  
*Flemming S, Lock JF, Hankir M, Reimer S, Petritsch B, Germer CT, Seyfried F*
- 3979** Old unreduced obturator dislocation of the hip: A case report  
*Li WZ, Wang JJ, Ni JD, Song DY, Ding ML, Huang J, He GX*
- 3988** Laterally spreading tumor-like primary rectal mucosa-associated lymphoid tissue lymphoma: A case report  
*Wei YL, Min CC, Ren LL, Xu S, Chen YQ, Zhang Q, Zhao WJ, Zhang CP, Yin XY*
- 3996** Coronary artery aneurysm combined with myocardial bridge: A case report  
*Ye Z, Dong XF, Yan YM, Luo YK*
- 4001** Thoracoscopic diagnosis of traumatic pericardial rupture with cardiac hernia: A case report  
*Wu YY, He ZL, Lu ZY*

- 4007** Delayed diagnosis and comprehensive treatment of cutaneous tuberculosis: A case report  
*Gao LJ, Huang ZH, Jin QY, Zhang GY, Gao MX, Qian JY, Zhu SX, Yu Y*
- 4016** Rapidly progressing primary pulmonary lymphoma masquerading as lung infectious disease: A case report and review of the literature  
*Jiang JH, Zhang CL, Wu QL, Liu YH, Wang XQ, Wang XL, Fang BM*
- 4024** Asymptomatic carbon dioxide embolism during transoral vestibular thyroidectomy: A case report  
*Tang JX, Wang L, Nian WQ, Tang WY, Xiao JY, Tang XX, Liu HL*
- 4032** Transient immune hepatitis as post-coronavirus disease complication: A case report  
*Drăgănescu AC, Săndulescu O, Bilașco A, Kouris C, Streinu-Cercel A, Luminos M, Streinu-Cercel A*
- 4040** Acute inferior myocardial infarction in a young man with testicular seminoma: A case report  
*Scafa-Udriste A, Popa-Fotea NM, Bataila V, Calmac L, Dorobantu M*
- 4046** Asymptomatic traumatic rupture of an intracranial dermoid cyst: A case report  
*Zhang MH, Feng Q, Zhu HL, Lu H, Ding ZX, Feng B*
- 4052** Parotid mammary analogue secretory carcinoma: A case report and review of literature  
*Min FH, Li J, Tao BQ, Liu HM, Yang ZJ, Chang L, Li YY, Liu YK, Qin YW, Liu WW*
- 4062** Liver injury associated with the use of selective androgen receptor modulators and post-cycle therapy: Two case reports and literature review  
*Koller T, Vrbova P, Meciarova I, Molcan P, Smitka M, Adamcova Selcanova S, Skladany L*
- 4072** Spinal epidural abscess due to coinfection of bacteria and tuberculosis: A case report  
*Kim C, Lee S, Kim J*
- 4081** Rare complication of inflammatory bowel disease-like colitis from glycogen storage disease type 1b and its surgical management: A case report  
*Lui FCW, Lo OSH*
- 4090** Thymosin as a possible therapeutic drug for COVID-19: A case report  
*Zheng QN, Xu MY, Gan FM, Ye SS, Zhao H*
- 4095** Arrhythmogenic right ventricular cardiomyopathy characterized by recurrent syncope during exercise: A case report  
*Wu HY, Cao YW, Gao TJ, Fu JL, Liang L*
- 4104** Delayed pseudoaneurysm formation of the carotid artery following the oral cavity injury in a child: A case report  
*Chung BH, Lee MR, Yang JD, Yu HC, Hong YT, Hwang HP*
- 4110** Atezolizumab-induced anaphylactic shock in a patient with hepatocellular carcinoma undergoing immunotherapy: A case report  
*Bian LF, Zheng C, Shi XL*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Gwo-Ping Jong, FCCP, MD, MHSc, PhD, Associate Professor, Department of Public Health, Chung Shan Medical University, Taichung 40201, Taiwan. cgp8009@yahoo.com.tw

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJCC as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yan-Xia Xing, Production Department Director: Yun-Xiaoqian Wu, Editorial Office Director: Jin-Lai Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

June 6, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## COVID-19 impact on the liver

Liliana Baroiu, Caterina Dumitru, Alina Iancu, Ana-Cristina Leșe, Miruna Drăgănescu, Nicușor Baroiu, Lucreția Anghel

**ORCID number:** Liliana Baroiu 0000-0002-7602-8435; Caterina Dumitru 0000-0002-2955-8580; Alina Iancu 0000-0001-5901-0818; Ana-Cristina Leșe 0000-0002-1569-8187; Miruna Drăgănescu 0000-0003-2198-7847; Nicușor Baroiu 0000-0002-1334-7025; Lucreția Anghel 0000-0002-9477-6760.

**Author contributions:** Baroiu L and Dumitru C designed the research; Baroiu N and Anghel L analyzed the data; Baroiu L, Iancu A and Leșe AC wrote the paper; Drăgănescu M made critical revisions related to important content of the revised manuscript; Baroiu L, Dumitru C, Iancu A, Leșe AC, Drăgănescu M, Baroiu N and Anghel L provided the final approval of the version to be published.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

**Liliana Baroiu, Miruna Drăgănescu, Lucreția Anghel**, Clinical Medical Department, Faculty of Medicine and Pharmacy, “Dunarea de Jos” University of Galati, Galati 800008, Romania

**Caterina Dumitru**, Pharmaceutical Sciences Department, Faculty of Medicine and Pharmacy, “Dunarea de Jos” University of Galati, Galati 800008, Romania

**Alina Iancu**, Department of Morphological and Functional Sciences, Faculty of Medicine and Pharmacy, “Dunarea de Jos” University of Galati, Galati 800008, Romania

**Ana-Cristina Leșe**, Design Department, Faculty of Visual Arts and Design, “George Enescu” National University of Arts, Iasi 700451, Romania

**Nicușor Baroiu**, Department of Manufacturing Engineering, Faculty of Engineering, “Dunarea de Jos” University of Galati, Galati 800008, Romania

**Corresponding author:** Nicușor Baroiu, PhD, Associate Professor, Department of Manufacturing Engineering, Faculty of Engineering, “Dunarea de Jos” University of Galati, 47 Domneasca St., Galati 800008, Romania. [nicusor.baroiu@ugal.ro](mailto:nicusor.baroiu@ugal.ro)

### Abstract

The coronavirus disease 2019 (COVID-19) pandemic imposed restructuring of global health systems by rethinking spaces used for the care of these patients and the additions of intensive care, infectious diseases and pneumology departments. This paper provides evidence on the presence of severe acute respiratory syndrome coronavirus 2 in hepatocytes and its direct cytopathic activity, as well as the degree of liver damage due to drug toxicity, inflammation and hypoxia in COVID-19. A review of clinical trials has quantified liver damage through both pathology and biochemistry studies. Additionally, we briefly present the results of a study conducted in our clinic on 849 patients admitted for COVID-19 treatment, of which 31 patients had pre-existing chronic liver disease and 388 patients had values above the normal limit for alanine aminotransferase, aspartate aminotransferase, and total bilirubin. It was observed that patients with abnormal liver tests were significantly statistically older, had more comorbidities and had a higher percentage of unfavourable evolution (death or transfer to intensive care). The conclusion of this paper is that the main causes of liver damage are direct viral aggression, coagulation dysfunction and endothelial damage, and patients with impaired liver function develop more severe forms of COVID-19 which requires special care by a multidisciplinary team that includes a hepatologist.



the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Romania

**Peer-review report's scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**Received:** February 4, 2021

**Peer-review started:** February 4, 2021

**First decision:** March 14, 2021

**Revised:** March 28, 2021

**Accepted:** April 29, 2021

**Article in press:** April 29, 2021

**Published online:** June 6, 2021

**P-Reviewer:** Liu HQ

**S-Editor:** Gao CC

**L-Editor:** A

**P-Editor:** Li X



**Key Words:** COVID-19; Liver injury; Cytopathic effect; Hyper-inflammatory reaction; Drug toxicity; Biochemical changes

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** The lung damage of these patients is primordial in the cascade of care that they receive, but also the liver damage induced by the direct action of the virus and the toxicity of the medication administered, has determined the active involvement of hepatologists in the care of these patients. The present paper aims to summarize the data published so far and personal experience, which may clarify the extent of liver damage in coronavirus disease 2019 and effective ways of therapeutic approach.

**Citation:** Baroiu L, Dumitru C, Iancu A, Leşe AC, Drăgănescu M, Baroiu N, Anghel L. COVID-19 impact on the liver. *World J Clin Cases* 2021; 9(16): 3814-3825

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i16/3814.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i16.3814>

## INTRODUCTION

On March 28, 2021, 127331692 cases and 2790624 deaths from coronavirus disease 2019 (COVID-19) were noted worldwide[1]. After a year of this pandemic, individuals think and work in a different way than they did a year ago. Adaptations to the new challenges of pathology were made rapidly by all medical specialties, including hepatologists who were included in multidisciplinary teams for the treatment of patients with COVID-19 and liver damage. Coronaviruses are large viruses, with sizes between 27 and 34 kilobases, and are enveloped single-stranded RNA viruses, from the family Coronaviridae and the subfamily Orthocoronavirinae. The epidemics of 2003 and 2012 were caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). The new coronavirus (SARS-CoV-2), the etiological agent of the COVID-19 pandemic, seems to be a chimeric variant of a coronavirus identified in bats in 2015 by Benvenuto *et al*[2] and has 82% genomic similarities to SARS-CoV and 50% genome sequence homology to MERS-CoV[3]. In 2003, in the SARS-CoV epidemic, approximately 60% of patients developed liver damage, and phylogenetic similarities suggested the possibility of the SARS-CoV-2 aggression on the liver[4].

## THE PATHOPHYSIOLOGICAL MECHANISMS OF HEPATIC AGGRESSION OF SARS-COV-2

The idea of hepatic impairment in COVID-19 arose after the first evaluations of these patients, when alterations in liver function were observed and certified when the presence of SARS-CoV-2 in liver tissue was confirmed[5].

Liver damage in COVID-19 has been attributed to the direct attack by SARS-CoV-2, drug toxicity in COVID-19 therapy, acute inflammatory damage and hypoxia caused by pneumonia.

Direct attack by SARS-CoV-2 on the liver includes the direct cytopathic effect on hepatocytes and cholangiocytes, and the effects of coagulopathy and endothelial aggression in small intrahepatic vessels.

The mechanisms of direct hepatic destruction, in COVID-19, include its presence on the surface of endothelial cells in small blood vessels (endothelial layer of small blood vessels), and hepatocytes (2.6%), but especially on the surface of bile duct cells (cholangiocytes) (59.7%) of angiotensin 2 converting enzyme (ACE2) receptors, which are considered the cellular receptor for SARS-CoV-2. The expression level of these cholangiocyte receptors is also similar to that of lung type 2 alveolar cells, suggesting that the liver may be a potential target for SARS-CoV-2[6].

Another receptor, transmembrane protease serine 2 (TMPRSS2), which interacts with SARS-CoV-2, what is present on cholangiocytes and hepatocytes, is important for

proteolytic activation and also for spread of virus particles[7].

Ultrastructural analysis of post-mortem liver biopsies from patients who died of COVID-19 observed coronavirus particles in the cytoplasm of hepatocytes[8]. Hepatocyte lesions included cell membrane dysfunction, mitochondrial swelling, and dilated endoplasmic reticulum. These observations documented the ability of the virus to replicate in hepatocytes and demonstrated the link between cytopathic damage to hepatocytes and impaired liver function[8].

Another mechanism involved in liver injury is the extensive vascular damage to the hepatic portal system in the acute form (thrombosis and luminal ectasia) or chronic changes (fibrous thickening of the vascular wall), identified post-mortem in patients with COVID-19. These observations suggest that endothelial damage and coagulation dysfunction may be the major trigger in the pathogenesis of COVID-19 liver lesions[9].

The hyper-inflammatory reaction of COVID-19 may cause liver damage. In the evolution of COVID-19, a massive release of pro-inflammatory cytokines was observed, with increasing interleukin (IL)-6, lactate dehydrogenase, C-reactive protein, and ferritin concentrations.

This cytokine storm syndrome is accompanied by organ dysfunction, including progressive liver damage and liver failure[10-13]. IL-6 is a potent cytokine involved in inflammation and liver regeneration[14]. IL-6 production occurs in immune cells[14], fibroblasts, endothelial cells[15] and hepatocytes[13,16]. In correlation with the pathophysiology of the implication of systemic inflammation and specifically IL-6 on liver damage, clinical studies have observed that the growth of IL-6, in patients with COVID-19 with increased aspartate aminotransferase (AST), serves as a fuel for liver injury, which is more pronounced in patients with COVID-19, with a more severe inflammatory response (sometimes requiring intensive care measures)[17]. The concomitant increases in IL-6, ferritin, and alanine aminotransferase (ALT) levels, and also the decreases in platelet count and albumin concentration, show significant hepatic lesions during COVID-19[18]. Another study suggested collateral liver damage caused by SARS-CoV-2, induced by cytotoxic T cells 2[19].

Hypoxia caused by respiratory failure in COVID-19 affects hepatocyte metabolism and may cause liver damage. A study reported the association of liver enzyme abnormalities with higher radiological scores, disease severity, higher alveolar-arterial oxygen partial pressure difference, higher ferritin, higher gamma-glutamyl transferase, lower albumin, and decreased lymphocytes B and CD4+ T cells[8]. Other clinical studies have observed the predictive nature of aggressive lung damage, observed on computer pulmonary tomography, for liver damage and the need for careful monitoring of liver function in these patients.

Post-drug hepatotoxicity in COVID-19 was argued by the occurrence of hepatic cytolysis during hospitalization and its association with allergic eruptions in convalescence. Pathological studies have detected moderate microvesicular steatosis with mild liver inflammation that can be attributed to drug hepatotoxicity[20].

The drugs used in the treatment of COVID-19 with hepatotoxic potential are as follows: (1) Remdesivir is a nucleotide analogue, which was developed for the treatment of chronic hepatitis C, and later tested for Ebola virus but without clinical efficacy, now in the COVID-19 treatment guidelines. The manufacturer indicates very common side effects in the leaflet (these may affect more than 1 in 10 patients), such as elevated liver enzymes without recommending dose adjustments for liver or kidney failure. Remdesivir therapy was not performed in patients with AST and ALT greater than 5 times the normal amount. A study of 53 patients observed increased liver enzymes, in 23% of patients, and remdesivir was discontinued in 2 patients[21]. Another multicentre study observed that aminotransferases increased by 5% and serum bilirubin increased by 10% in the remdesivir-treated group[22]; (2) Favipiravir is a guanine analogue approved in Japan for the treatment of influenza, in which the manufacturer notes only teratogenic side effects and has been shown to be well tolerated by the liver in the treatment of patients with COVID-19. Clinical studies on favipiravir therapy noted elevated liver enzymes between 2.6% and 7.6% of patients with COVID-19[23,24]; (3) Lopinavir-ritonavir, a protease inhibitor-used for treatment of HIV has reported hepatotoxicity of 2%-10% in the Cao study in patients with severe forms of COVID-19 and increased the rate of liver damage 4 times in the Cai study[25,26]. The ELACOI trial, observed 4.8% of patients with a 2.5 fold elevation in liver enzymes[27]; (4) Antipyretics, especially paracetamol, have hepatotoxic potential, and the dose should not exceed 2-3 g/d, which is considered a safe dose in patients with chronic liver disease[28]; (5) Dexamethasone, with its anti-fibrotic and anti-inflammatory properties, is one of the most studied immunomodulators in SARS-CoV-2 therapy[29], with possible benefits in patients with COVID-19 and acute liver failure; (6) Tocilizumab is a anti IL-6 receptors, humanized monoclonal antibody that is being



used in severe forms of COVID-19 for cytokine release syndrome[10]. Liver enzyme elevation occurs frequently after tocilizumab treatment, with rare descriptions of severe liver injury[30]. Tocilizumab increases the risk of reactivation of hepatitis B virus[31]; (7) Hydroxychloroquine is a possible treatment, with a low incidence of drug-induced liver failure but it may concentrate in the liver and should be used with caution in patients with chronic liver disease[32]; and (8) Azithromycin may cause idiosyncratic drug-induced liver failure, which is manifested by cholestatic hepatitis 1-3 wk after initiation of treatment. Hepatocellular necrosis is rare and begins a few days after starting treatment. A hepatocellular pattern is predominant, and most patients recover completely[33].

The recommendations regarding the diagnosis of drug-induced liver failure, included clinical and paraclinical criteria. Paraclinical criteria are an increase in ALT greater than 5 times the normal value or an increase in alkaline phosphatase greater than 2 times the normal value, in the absence of a known bone pathology or an ALT increase greater than 3 times the normal value with a simultaneous increase in total bilirubin (TBIL) greater than 2 times the normal value. Clinical criteria are the presence of classic symptoms of hepatic injury: jaundice, encephalopathy, haemorrhage (secondary to coagulopathy), ascites or non-specific symptoms, such as fatigue, anorexia, nausea, vomiting, fever, abdominal pain, itching, and rash[34].

The principles of drug-induced liver failure treatment are based on discontinuation of hepatotoxicity. This principle is difficult to follow in patients with severe COVID-19, and the decision to change treatment must be made by a multidisciplinary team of infectious diseases, intensive care and gastroenterology physicians respecting the risk-benefit principle[35,36].

## COVID-19 LIVER PATHOLOGICAL ANATOMY

The first post-mortem liver biopsies were performed by Xu *et al*[20]. They observed a moderate rank of microvesicular steatosis and mild lobular and portal activity. Liver damage may appear as an effect of the direct cytopathic action of SARS-CoV-2 or drug toxicity. Another study found thrombosis, luminal ectasia and fibrous thickening of the vascular wall, suggesting that endothelial damage and coagulation dysfunction are involved in pathogenesis of hepatic impairment in COVID-19[9].

Wang *et al*[8]'s study observed mainly moderate microvesicular and mild macrovesicular steatosis, and focal lobular inflammation with lymphocytes infiltration. Portal tracts inflammation with lymphocytic infiltrate was rare. Lesions suggestive of hepatic ischemia (centrilobular necrosis), septic aggression (centrilobular necrosis, canalicular/ductular cholestasis, or non-bacterial cholangitis), or post-drug toxicity (eosinophiles infiltration, fibrin deposition, cholestasis, granuloma, interface hepatitis, massive central necrosis) have not been observed, suggesting that these mechanisms are not significantly involved in liver injury.

The Cai *et al*[24]'s study highlighted the presence of SARS-CoV-2 viral particles in the cytoplasm of hepatocytes, demonstrating the possibility of the virus entering the hepatocyte, as well as its replication in the hepatocyte. The changes described in hepatocytes were: swelling of the mitochondria and, dilation of both the endoplasmic reticulum and affected cell membrane, demonstrating the cytopathic effect of SARS-CoV-2 in hepatocytes. Ki67 immunohistochemistry has shown that the main histological changes in the liver of patients with COVID-19 are the presence of massive apoptosis and syncytial and multinucleated hepatocytes. CD4 and CD8 cells are rare in liver tissue which emphasizes that the direct viral cytopathic effect is the main factor of aggression and not immune conflict.

## BIOCHEMICAL CHANGES IN COVID-19 HEPATIC INJURY

Liver damage in COVID-19 is common in clinical practice (Table 1). The change in AST/ALT levels can be attributed to hepatocyte, myocardial and muscular lesions. Most patients (60%) with abnormal AST/ALT values show a slight increase between 1-2 normal values; approximately 30% of patients had moderate liver injury (between 2 and 5 times higher than the normal value); and less than 10% of patients had severe liver injury (ALT more than 5 times higher than the normal value)[37,38]. But, much higher values, such as ALT = 7590 U/L and AST = 1445 U/L, were also reported in a patient with a severe form of COVID-19[39].

**Table 1 Biochemical changes in patients with coronavirus disease 2019 and pre-existing chronic liver diseases in clinical trials**

Ref.	Patients with COVID-19	Patients with abnormal liver function (%)	Patients with pre-existing liver diseases (%)
Guan <i>et al</i> [67]	1099	21.3 abnormal ALT; 22.2 abnormal AST	2.3
Huang <i>et al</i> [68]	41	31	2
Chen <i>et al</i> [39]	99	43	NA
Wang <i>et al</i> [69]	138	NA	2.9
Shi <i>et al</i> [70]	81	53.1	8.6
Xu <i>et al</i> [71]	62	16.1	11
Yang <i>et al</i> [72]	52	29	NA
Zhang <i>et al</i> [3]	56	28.6	3.6
Cai <i>et al</i> [25]	298	14.8 abnormal ALT; 8.7 abnormal AST	2.7
Cao <i>et al</i> [26]	128	43.8 abnormal ALT; 44.1 abnormal AST	NA
Zhang <i>et al</i> [73]	82	30.6 abnormal ALT; 61.1 abnormal AST; 30.6 abnormal TBIL	2.4
Fan <i>et al</i> [74]	148	21.6 abnormal AST; 18.2 abnormal ALT; 17.6 abnormal GGT; 6.1 abnormal TBIL	NA
Huang <i>et al</i> [75]	36	13.3 abnormal ALT; 58.1 abnormal AST; 12.9 abnormal TBIL	NA
Li <i>et al</i> [76]	85	24.7 abnormal ALT	7.05
Xie <i>et al</i> [77]	79	31.6 abnormal ALT; 35.4 abnormal AST; 5.1 abnormal TBIL	0
Zhang <i>et al</i> [78]	115	9.57 abnormal ALT; 4.78 abnormal AST	0
Zhao <i>et al</i> [79]	19	27.78 abnormal ALT; 44.4 abnormal AST; GGT	5.26
Sultan <i>et al</i> [32]	Meta-analysis of 47 studies 10890 patients	15.0 abnormal AST; 15.0 abnormal ALT; 16.7 abnormal TBIL	NA
Effenber <i>et al</i> [17]	96	42 abnormal AST	NA
Mantovani <i>et al</i> [80]	Meta-analysis of 11 studies 2034 patients	NA	3
Hundt <i>et al</i> [81]	1827	Abnormal at admission (AST 66.9, ALT 41.6, ALP 13.5, and TBIL 4.3) and peak hospitalization (AST 83.4, ALT 61.6, ALP 22.7, and TBIL 16.1)	NA
Cai <i>et al</i> [24]	417	76.3 abnormal ALT, AST, TBIL and GGT	NA
Wang <i>et al</i> [8]	156	41.0 abnormal ALT and, AST	NA
Velarde-Ruiz Velasco <i>et al</i> [82]	99	35 abnormal AST; 28 abnormal ALT; 98 abnormal albumin	NA
Our unpublished data	849	38.39 abnormal ALT 39.33 abnormal AST 3.18 abnormal TBIL	3.65

COVID-19: Coronavirus disease 2019; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TBIL: Total bilirubin; NA: Not available.

The increase in ALT, AST in children is usually below twice the normal value, severe liver damage being very rare in children[40,41].

The TBIL is, in most cases of COVID-19, normal or modestly elevated[37,42-44]. Elevated gamma glutamyl transferase was observed in 6% of COVID-19 patients and elevated alkaline phosphatase was observed in 21% of COVID-19 patients[45]. Elevated alkaline phosphatase was associated with an increased risk of death of COVID-19[46].

Low serum albumin was considered a marker of severe evolution of COVID-19[37,47-50].

Studies also found correlations between the degree of liver damage and severity of COVID-19, as well as the negative prognosis of patients with COVID-19 and liver injury[45,51].

In our clinic, the Second Infectious Diseases Clinic of the Infectious Diseases Clinical Hospital "Sf. Cuv. Parascheva", Galati, Romania, we conducted a retrospective study of 849 patients hospitalized with COVID-19 between January 3, 2020 and November 30, 2020. Of these, 31 patients (3.65%) had a history of chronic liver disease, and 388 patients (45.70%) presented at biochemical evaluation with either ALT or AST or TBIL above normal values. The characteristics of the group with pre-existing chronic liver injury and of the group with acute liver injury were compared with the characteristics of the total group of patients with COVID-19 and are presented in Table 2. Statistical analysis was performed with MedCalc version 19.6.4.[52].

The group of 31 patients with pre-existing chronic liver disease included one patient with toxic liver cirrhosis, 11 patients with chronic hepatitis B, 2 patients with chronic hepatitis B and D, 6 patients with chronic hepatitis C, 6 patients with chronic toxic hepatitis and 5 patients with hepatic steatosis.

An increase in ALT between 1 and 3 times the normal value was observed in 261 patients (30.74%) and, between 3 and 5 times the normal value in 65 patients (7.65%). An increase in AST between 1 and 3 times the normal value was observed in 299 patients (35.21%) and, between 3 and 5 times the normal value in 35 patients (4.12%). Lastly, an increase in TBIL above the normal value was observed in 27 patients (3.18%).

The study conducted in our clinic observed the appearance of COVID-19 with the need for hospitalization in patients with an average age of 50.21 years, and patients with liver damage were significantly older (average age 53.04 years).

Cumulation of comorbidities, quantified by the Charlson score, was significantly higher in the group with pre-existing liver diseases and in the group with COVID-19-induced liver injury. Patients with abnormal liver function had a, statistically significant, higher percentage of unfavourable evolutions (death or transfer of intensive care) compared to patients in the total group with COVID-19.

## THE IMPACT OF COVID-19 ON LIVER WITH PRE-EXISTING CHRONIC INJURY

Nonalcoholic fatty liver disease (NAFLD) is affecting a quarter of the world's population[53] and is reported in 2-11% of patients with chronic liver disease who have had COVID-19[3].

Patients with obesity, diabetes mellitus and hypertension are frequently associated with NAFLD and are the recognized category of patients at risk of severe evolution of COVID-19[54].

NAFLD is noted in clinical trials as an independent risk factor for increased TGP in patients with COVID-19[19,55,56] and it is accompanied by a longer period of viral clearance compared to patients without NAFLD ( $17.5 \pm 5.2$  d *vs*  $12.1 \pm 4.4$  d,  $P < 0.0001$ )[19].

The association of NAFLD in the comorbidity palette of the patient with COVID-19 is considered by some clinical studies as an unfavorable prognostic factor[19,38,57] and by other clinical studies without influence on the prognosis of COVID-19[55,56] which argues the need to conduct studies on larger batches of COVID-19 patients for clear conclusions.

Chronic viral hepatitis was shown to be a negative prognostic factor in patients with COVID-19. A meta-analysis of 257 patients with COVID-19 of which 235 with chronic hepatitis B and 22 patients with chronic hepatitis C scoring a 6% death rate in those with HBV and 13% in those with HCV, the transfer rate in the ICU 14.1% in HBV and 21.4% in HCV, significantly increased compared to patients without chronic viral hepatitis[58,59].

Few clinical trials have examined the risk of reactivation of hepatitis B in patients with severe forms of COVID-19 requiring immunosuppressive therapy[60,61]. The conclusion of these studies and the AASLD guideline is to consider prophylactic antiviral therapy in these patients[38,61].

Patients with autoimmune hepatitis were not associated with an increased risk of severe progression or death from COVID-19[62].

Alcohol-associated liver diseases, cirrhosis and hepatocellular carcinoma are associated with high mortality rates through COVID-19[50,63-66].

Chronic liver disease as a whole is associated with an increased risk of mortality from COVID-19 (risk ratio 2.8 in a cohort of 2780 patients) but cirrhosis appears to have the highest risk of mortality (risk ratio 4.6)[63].

Table 2 Demographic and clinical characteristics

	Total COVID-19 patients	Patients with abnormal liver function	Patients with pre-existing liver disease
Age (yr)			
Minimum-maximum	0.083-97	0.33-97	32-88
Average	50.21	53.04 ( $P = 0.0215$ )	55.70 ( $P = 0.1351$ )
95%CI	48.85-51.58	51.09-54.99	51.08-60.33
Female (%)	54.18	52.31 ( $P = 0.5820$ )	48.38 ( $P = 0.6506$ )
Charlson score (%patients)			
0	41.08	34.02 ( $P = 0.0190$ )	16.12 ( $P = 0.0094$ )
1-2	32.58	34.79 ( $P = 0.4664$ )	41.93 ( $P = 0.3592$ )
3-4	16.29	18.55 ( $P = 0.3585$ )	29.03 ( $P = 0.1049$ )
5-11	10.03	12.62 ( $P = 0.2034$ )	12.90 ( $P = 0.8281$ )
Number of days of hospitalization			
Minimum-maximum	1-80	1-52	1-35
Average	11.06	11.53 ( $P = 0.3034$ )	11.35 ( $P = 0.8097$ )
95%CI	10.55-11.58	10.83-12.24	9.12-13.58
Curb 65 score (%)			
0	12.43	10.34 ( $P = 0.3355$ )	10.00 ( $P = 0.8997$ )
1	62.18	59.41 ( $P = 0.3869$ )	63.33 ( $P = 0.9531$ )
2	23.11	26.52 ( $P = 0.2194$ )	23.33 ( $P = 0.8506$ )
3	3.51	3.71 ( $P = 0.9914$ )	3.33 ( $P = 0.6573$ )
Unfavourable evolution (death or transfer to intensive care) (%)	4.71	7.73 ( $P = 0.0454$ )	12.90 ( $P = 0.1126$ )

COVID-19: Coronavirus disease 2019; CI: Confidence interval.

The recommendations of the AASLD guide are for the continuation of liver transplants, respecting all the rules for minimizing the transmission of SARS-CoV-2 and the local protocols of each transplant clinic that optimizes the existence of the resources necessary for performing the liver transplant[38].

## CONCLUSION

Phylogenetic similarities with SARS-CoV and MERS-CoV suggest that SARS-CoV-2 may cause liver damage. The identification of ACE2 receptors on the surface of hepatocytes and cholangiocytes has opened research on the direct aggression of SARS-CoV-2 on the liver. The detection of viral particles in hepatocytes certified the direct aggression of the virus on the liver. The study of post-mortem liver biopsies suggested that endothelial damage and coagulation dysfunction are the leading cause of liver injury in COVID-19. Elevated levels of acute phase proteins, especially IL-6, correlate with elevated transaminases and severe forms of COVID-19 in clinical trials. Hypoxia caused by respiratory failure in COVID-19 affects hepatocyte metabolism, and clinical trials have noted correlations between massive pulmonary destruction, quantified by computer pulmonary tomography, and acute liver failure. Antivirals, antibiotics, antipyretics, and immunomodulators used in COVID-19 therapy may cause hepatotoxicity, but to a small extent, and should be discontinued and replaced if drug-induced acute liver failure is suspected. Moderate ALT and AST changes in COVID-19 are common in clinical practice. Significant changes in AST and ALT are predictive of unfavourable evolution of COVID-19. Our study observed that patients with elevated ALT, AST, and TBIL were significantly older, had more comorbidities and more unfavourable evolution than the total group of patients with COVID-19. Chronic liver

diseases are associated with an increased risk of mortality from COVID-19, especially cirrhosis and hepatic adenocarcinoma.

## REFERENCES

- 1 **Worldometer.** Report coronavirus cases. [cited 28 March 2021]. In: Worldometer [Internet]. Available from: [https://www.worldometers.info/coronavirus/?utm\\_campaign=homeAdvegas1](https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1)
- 2 **Benvenuto D,** Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. *J Med Virol* 2020; **92**: 455-459 [PMID: 31994738 DOI: 10.1002/jmv.25688]
- 3 **Zhang C,** Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]
- 4 **Jothimani D,** Venugopal R, Abedin MF, Kaliathoorthy I, Rela M. COVID-19 and the liver. *J Hepatol* 2020; **73**: 1231-1240 [PMID: 32553666 DOI: 10.1016/j.jhep.2020.06.006]
- 5 **Ridruejo E,** Soza A. The liver in times of COVID-19: What hepatologists should know. *Ann Hepatol* 2020; **19**: 353-358 [PMID: 32425991 DOI: 10.1016/j.aohp.2020.05.001]
- 6 **Chai X,** Hu L, Zhang Y, Han W, Lu Z, Ke A. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. 2020 Preprint. Available from: bioRxiv: 2020.02.03.931766 [DOI: 10.1101/2020.02.03.931766]
- 7 **Bestle D,** Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moulton H, Stein DA, Hardes K, Eickmann M, Dolnik O, Rohde C, Klenk HD, Garten W, Steinmetzer T, Böttcher-Friebertshäuser E. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. *Life Sci Alliance* 2020; **3** [PMID: 32703818 DOI: 10.26508/Lsa.202000786]
- 8 **Wang Y,** Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; **73**: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]
- 9 **Sonzogni A,** Previtali G, Seghezzi M, Alessio MG, Gianatti A, Licini L, Zerbi P, Carsana L, Rossi R, Lauri E, Pellegrinelli A. Nebuloni M. Liver and COVID 19 infection: a very preliminary lesson learnt from histological post-mortem findings in 48 patients. 2020 Preprint. Available from: Preprints 2020, 2020040438 [DOI: 10.20944/preprints202004.0438.v1]
- 10 **Mehta P,** McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]
- 11 **Moore JB,** June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020; **368**: 473-474 [PMID: 32303591 DOI: 10.1126/science.abb8925]
- 12 **Giamarellos-Bourboulis EJ,** Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntanganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020; **27**: 992-1000. e3 [PMID: 32320677 DOI: 10.1016/j.chom.2020.04.009]
- 13 **Schmidt-Arras D,** Rose-John S. IL-6 pathway in the liver: From physiopathology to therapy. *J Hepatol* 2016; **64**: 1403-1415 [PMID: 26867490 DOI: 10.1016/j.jhep.2016.02.004]
- 14 **Gauldie J,** Richards C, Harnish D, Lansdorp P, Baumann H. Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. *Proc Natl Acad Sci USA* 1987; **84**: 7251-7255 [PMID: 2444978 DOI: 10.1073/pnas.84.20.7251]
- 15 **Bode JG,** Albrecht U, Häussinger D, Heinrich PC, Schaper F. Hepatic acute phase proteins--regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF-κB-dependent signaling. *Eur J Cell Biol* 2012; **91**: 496-505 [PMID: 22093287 DOI: 10.1016/j.ejcb.2011.09.008]
- 16 **Fielding CA,** Jones GW, McLoughlin RM, McLeod L, Hammond VJ, Uceda J, Williams AS, Lambie M, Foster TL, Liao CT, Rice CM, Greenhill CJ, Colmont CS, Hams E, Coles B, Kift-Morgan A, Newton S, Craig KJ, Williams JD, Williams GT, Davies SJ, Humphreys IR, O'Donnell VB, Taylor PR, Jenkins BJ, Topley N, Jones SA. Interleukin-6 signaling drives fibrosis in unresolved inflammation. *Immunity* 2014; **40**: 40-50 [PMID: 24412616 DOI: 10.1016/j.immuni.2013.10.022]
- 17 **Effenberger M,** Grandner C, Grabherr F, Griesmacher A, Ploner T, Hartig F, Bellmann-Weiler R, Joannidis M, Zoller H, Weiss G, Adolph TE, Tilg H. Systemic inflammation as fuel for acute liver injury in COVID-19. *Dig Liver Dis* 2021; **53**: 158-165 [PMID: 32873520 DOI: 10.1016/j.dld.2020.08.004]
- 18 **Metawea MI,** Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. *Dig Liver Dis* 2021; **53**: 146-152 [PMID: 32988758 DOI: 10.1016/j.dld.2020.09.010]
- 19 **Ji D,** Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]



- 20 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: [32085846](#) DOI: [10.1016/S2213-2600\(20\)30076-X](#)]
- 21 **Grein J**, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastrì E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernett J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanagan T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med* 2020; **382**: 2327-2336 [PMID: [32275812](#) DOI: [10.1056/NEJMoa2007016](#)]
- 22 **Wang Y**, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569-1578 [PMID: [32423584](#) DOI: [10.1016/S0140-6736\(20\)31022-9](#)]
- 23 **Chen X**, Zheng F, Qing Y, Ding S, Yang D, Lei C, Yin Z, Zhou X, Jiang D, Zuo Q, He J, Lv J, Chen P, Chen Y, Peng H, Li H, Xie Y, Liu J, Zhou Z, Luo H. Epidemiological and clinical features of 291 cases with coronavirus disease 2019 in areas adjacent to Hubei, China: a double-center observational study. 2020 Preprint. Available from: medRxiv 2020.03.03.20030353 [DOI: [10.1101/2020.03.03.20030353](#)]
- 24 **Cai Q**, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: [32298767](#) DOI: [10.1016/j.jhep.2020.04.006](#)]
- 25 **Cai Q**, Huang D, Ou P, Yu H, Zhu Z, Xia Z, Su Y, Ma Z, Zhang Y, Li Z, He Q, Liu L, Fu Y, Chen J. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy* 2020; **75**: 1742-1752 [PMID: [32239761](#) DOI: [10.1111/all.14309](#)]
- 26 **Cao W**, Shi L, Chen L, Xu X, Wu Z. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. 2020 Preprint. Available from: medRxiv 2020.02.23.20026963 [DOI: [10.1101/2020.02.23.20026963](#)]
- 27 **Li Y**, Xie Z, Lin W, Cai W, Wen C, Guan Y, Mo X, Wang J, Wang Y, Peng P, Chen X, Hong W, Xiao G, Liu J, Zhang L, Hu F, Li F, Zhang F, Deng X, Li L. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). 2020 Preprint. Available from: medRxiv 2020.03.19.20038984 [DOI: [10.1101/2020.03.19.20038984](#)]
- 28 **Chandok N**, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 2010; **85**: 451-458 [PMID: [20357277](#) DOI: [10.4065/mcp.2009.0534](#)]
- 29 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: [32678530](#) DOI: [10.1056/NEJMoa2021436](#)]
- 30 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [PMID: [31643176](#)]
- 31 **Chen LF**, Mo YQ, Jing J, Ma JD, Zheng DH, Dai L. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. *Int J Rheum Dis* 2017; **20**: 859-869 [PMID: [28160426](#) DOI: [10.1111/1756-185X.13010](#)]
- 32 **Sultan S**, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, Falck-Ytter Y, El-Serag HB; AGA Institute. Electronic address: ewilson@gastro.org. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. *Gastroenterology* 2020; **159**: 320-334. e27 [PMID: [32407808](#) DOI: [10.1053/j.gastro.2020.05.001](#)]
- 33 **Martinez MA**, Vuppalanchi R, Fontana RJ, Stolz A, Kleiner DE, Hayashi PH, Gu J, Hoofnagle JH, Chalasani N. Clinical and histologic features of azithromycin-induced liver injury. *Clin Gastroenterol Hepatol* 2015; **13**: 369-376. e3 [PMID: [25111234](#) DOI: [10.1016/j.cgh.2014.07.054](#)]
- 34 **Olry A**, Meunier L, Délibre B, Larrey D, Horsmans Y, Le Louët H. Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. *Drug Saf* 2020; **43**: 615-617 [PMID: [32514859](#) DOI: [10.1007/s40264-020-00954-z](#)]
- 35 **Luca L**, Baroiu L, Ciubara AB, Anghel R, Bulgaru-Iliescu AI, Anghel L, Ciubara A. Covid-19 and the Spanish Flu. From Suffering to Re-silience. *BRAIN* 2020; **11**: 01-07 [DOI: [10.18662/brain/11.3Sup1/116](#)]
- 36 **Voicu DF**, Anghel L, Baroiu L, Stan D. About Minimal Hepatic Encephalopathy. *BRAIN* 2020; **11**: 70-77 [DOI: [10.18662/brain/11.1Sup1/30](#)]
- 37 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: [32473607](#) DOI: [10.1002/hep.31404](#)]

- 38 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: [32298473](#) DOI: [10.1002/hep.31281](#)]
- 39 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: [32007143](#) DOI: [10.1016/S0140-6736\(20\)30211-7](#)]
- 40 **Lu X**, Zhang L, Du H, Zhang J, Li YY, Qu J, Zhang W, Wang Y, Bao S, Li Y, Wu C, Liu H, Liu D, Shao J, Peng X, Yang Y, Liu Z, Xiang Y, Zhang F, Silva RM, Pinkerton KE, Shen K, Xiao H, Xu S, Wong GWK; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020; **382**: 1663-1665 [PMID: [32187458](#) DOI: [10.1056/NEJMc2005073](#)]
- 41 **D'Antiga L**. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; **26**: 832-834 [PMID: [32196933](#) DOI: [10.1002/lt.25756](#)]
- 42 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: [32320003](#) DOI: [10.1001/jama.2020.6775](#)]
- 43 **Ferm S**, Fisher C, Pakala T, Tong M, Shah D, Schwarzbach D, Cooley V, Hussain S, Kim SH. Analysis of Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY. *Clin Gastroenterol Hepatol* 2020; **18**: 2378-2379. e1 [PMID: [32497637](#) DOI: [10.1016/j.cgh.2020.05.049](#)]
- 44 **Redd WD**, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, Shen L, Chan WW. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. *Gastroenterology* 2020; **159**: 765-767. e2 [PMID: [32333911](#) DOI: [10.1053/j.gastro.2020.04.045](#)]
- 45 **Kulkarni AV**, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, Talukdar R, Sharma M, Qi X, Rao PN, Reddy DN. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020; **52**: 584-599 [PMID: [32638436](#) DOI: [10.1111/apt.15916](#)]
- 46 **Ponziani FR**, Del Zompo F, Nesci A, Santopaolo F, Ianiro G, Pompili M, Gasbarrini A; "Gemelli against COVID-19" group. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2-positive patients. *Aliment Pharmacol Ther* 2020; **52**: 1060-1068 [PMID: [32628793](#) DOI: [10.1111/apt.15996](#)]
- 47 **Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: [32170806](#) DOI: [10.1111/liv.14435](#)]
- 48 **Liu W**, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, Wei S, Deng Y, Liu J, Liu HG, Yang M, Hu Y. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)* 2020; **133**: 1032-1038 [PMID: [32118640](#) DOI: [10.1097/CM9.0000000000000775](#)]
- 49 **Pereira MR**, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, Arcasoy S, Aversa MM, Benvenuto LJ, Dadhania DM, Kapur S, Dove LM, Brown RS Jr, Rosenblatt RE, Samstein B, Uriel N, Farr MA, Satlin M, Small CB, Walsh TJ, Kodiyankal RP, Miko BA, Aaron JG, Tsapepas DS, Emond JC, Verna EC. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant* 2020; **20**: 1800-1808 [PMID: [32330343](#) DOI: [10.1111/ajt.15941](#)]
- 50 **Iavarone M**, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, Perricone G, Massironi S, Spinetti A, Buscarini E, Viganò M, Carriero C, Fagioli A, Aghemo A, Belli LS, Lucà M, Pedaci M, Rimondi A, Rumi MG, Invernizzi P, Bonfanti P, Lampertico P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**: 1063-1071 [PMID: [32526252](#) DOI: [10.1016/j.jhep.2020.06.001](#)]
- 51 **Marin IM**, Petropolou M, Baroiu L, Chiroasca AC, Anghel L, Luca L. Schizophrenia and the Family Burden during the Pandemic. *BRAIN* 2020; **11**: 89-97 [DOI: [10.18662/brain/11.3Sup1/125](#)]
- 52 **MedCalc**. MedCalc version 19.6.4. [cited 15 January 2021]. In: MedCalc [Internet]. Available from: <https://www.medcalc.org/order.php>
- 53 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: [26707365](#) DOI: [10.1002/hep.28431](#)]
- 54 **Centers for Disease Control and Prevention**. Coronavirus Disease 2019 (COVID-19): Groups at higher risk for severe illness. [cited 27 March 2021]. In: Centers for Disease Control and Prevention [Internet]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html>
- 55 **Huang R**, Zhu L, Wang J, Xue L, Liu L, Yan X, Huang S, Li Y, Zhang B, Xu T, Li C, Ji F, Ming F, Zhao Y, Cheng J, Wang Y, Zhao H, Hong S, Chen K, Zhao XA, Zou L, Sang D, Shao H, Guan X, Chen X, Chen Y, Wei J, Zhu C, Wu C. Clinical features of COVID-19 patients with non-alcoholic fatty liver disease. *Hepatol Commun* 2020 [PMID: [32838108](#) DOI: [10.1002/hep4.1592](#)]
- 56 **Mushtaq K**, Khan MU, Iqbal F, Alsoub DH, Chaudhry HS, Ata F, Iqbal P, Elfert K, Balaraju G,

- Almaslamani M, Al-Ejji K, AlKaabi S, Kamel YM. NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression - The debate continues. *J Hepatol* 2021; **74**: 482-484 [PMID: 33223215 DOI: 10.1016/j.jhep.2020.09.006]
- 57 **Mahamid M**, Nseir W, Khoury T, Mahamid B, Nubania A, Sub-Laban K, Schifter J, Mari A, Sbeit W, Goldin E. Nonalcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study. *Eur J Gastroenterol Hepatol* 2020 [PMID: 32868652 DOI: 10.1097/MEG.0000000000001902]
- 58 **Mirzaie H**, Vahidi M, Shokoohi M, Darvishian M, Sharifi H, Sharafi H, Karamouzian M. COVID-19 among patients with hepatitis B or hepatitis C: A systematic review. 2020 Preprint. Available from: medRxiv 2020.10.22.20216317 [DOI: 10.1101/2020.10.22.20216317]
- 59 **Trifan A**, Stanciu C, Iliescu L, Sporea I, Baroiu L, Diculescu M, Luca MC, Miftode E, Cijevski C, Mihai C, Sparchez ZA, Pojoga C, Streinu-Cercel A, Gheorghe L. Effectiveness of 8- and 12-Week Treatment with Ombitasvir/ Paritaprevir/Ritonavir and Dasabuvir in Treatment-Naïve HCV Patients in a Real-Life Setting in Romania: the AMETHYST Study. *J Gastrointest Liver Dis* 2021; **30**: 88-93 [PMID: 33723561 DOI: 10.15403/jglid-3373]
- 60 **Liu J**, Wang T, Cai Q, Sun L, Huang D, Zhou G, He Q, Wang FS, Liu L, Chen J. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res* 2020; **50**: 1211-1221 [PMID: 32761993 DOI: 10.1111/hepr.13553]
- 61 **Rodriguez-Tajes S**, Miralpeix A, Costa J, López-Suñé E, Laguno M, Pocurull A, Lens S, Mariño Z, Forns X. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. *J Viral Hepat* 2021; **28**: 89-94 [PMID: 32969557 DOI: 10.1111/jvh.13410]
- 62 **Marjot T**, Buescher G, Sebode M, Barnes E, Barritt AS 4th, Armstrong MJ, Baldelli L, Kennedy J, Mercer C, Ozga AK, Casar C, Schramm C; contributing Members and Collaborators of ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis, Moon AM, Webb GJ, Lohse AW. SARS-CoV-2 infection in patients with autoimmune hepatitis. *J Hepatol* 2021 [PMID: 33508378 DOI: 10.1016/j.jhep.2021.01.021]
- 63 **Singh S**, Khan A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. *Gastroenterology* 2020; **159**: 768-771. e3 [PMID: 32376408 DOI: 10.1053/j.gastro.2020.04.064]
- 64 **Bajaj JS**, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, Shaw J, Pearson M, Chew M, Fagan A, de la Rosa Rodriguez R, Worthington J, Olofson A, Weir V, Trisolini C, Dwyer S, Reddy KR. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut* 2021; **70**: 531-536 [PMID: 32660964 DOI: 10.1136/gutjnl-2020-322118]
- 65 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]
- 66 **Kim D**, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, Perumalswami P, Roytman M, Li M, Vogel AS, Catana AM, Wegermann K, Carr RM, Aloman C, Chen V, Rabiee A, Sadowski B, Nguyen V, Dunn W, Chavin K, Zhou K, Lizaola-Mayo B, Moghe A, Debes J, Lee TH, Branch A, Viveiros K, Chan W, Chascsa D, Kwo P, Dhanasekaran R. Predictors of Outcomes of COVID-19 in Patients with Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2020 [PMID: 32950749 DOI: 10.1016/j.cgh.2020.09.027]
- 67 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
- 68 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
- 69 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
- 70 **Shi H**, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]
- 71 **Xu XW**, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, Wang HY, Zhang S, Gao HN, Sheng JF, Cai HL, Qiu YQ, Li LJ. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020; **368**: m606 [PMID: 32075786 DOI: 10.1136/bmj.m606]

- 72 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: [32105632](#) DOI: [10.1016/S2213-2600\(20\)30079-5](#)]
- 73 **Zhang B**, Zhou X, Qiu Y, Song Y, Feng F, Feng J, Song Q, Jia Q, Wang J. Clinical characteristics of 82 cases of death from COVID-19. *PLoS One* 2020; **15**: e0235458 [PMID: [32645044](#) DOI: [10.1371/journal.pone.0235458](#)]
- 74 **Fan Z**, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: [32283325](#) DOI: [10.1016/j.cgh.2020.04.002](#)]
- 75 **Huang Y**, Yang R, Xu Y, Gong P. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. 2020 Preprint. Available from: medRxiv 2020.02.27.20029009 [DOI: [10.1101/2020.02.27.20029009](#)]
- 76 **Li L**, Li S, Xu M, Yu P, Zheng S, Duan Z, Liu J, Chen Y, Li J. Risk factors related to hepatic injury in patients with corona virus disease 2019. 2020 Preprint. Available from: medRxiv 2020.02.28.20028514 [DOI: [10.1101/2020.02.28.20028514](#)]
- 77 **Xie H**, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. *Liver Int* 2020; **40**: 1321-1326 [PMID: [32239591](#) DOI: [10.1111/liv.14449](#)]
- 78 **Zhang Y**, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int* 2020; **40**: 2095-2103 [PMID: [32239796](#) DOI: [10.1111/liv.14455](#)]
- 79 **Zhao D**, Yao F, Wang L, Zheng L, Gao Y, Ye J, Guo F, Zhao H, Gao R. A Comparative Study on the Clinical Features of Coronavirus 2019 (COVID-19) Pneumonia With Other Pneumonias. *Clin Infect Dis* 2020; **71**: 756-761 [PMID: [32161968](#) DOI: [10.1093/cid/ciaa247](#)]
- 80 **Mantovani A**, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int* 2020; **40**: 1316-1320 [PMID: [32329563](#) DOI: [10.1111/liv.14465](#)]
- 81 **Hundt MA**, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology* 2020; **72**: 1169-1176 [PMID: [32725890](#) DOI: [10.1002/hep.31487](#)]
- 82 **Velarde-Ruiz Velasco JA**, García-Jiménez ES, Remes-Troche JM. Hepatic manifestations and impact of COVID-19 on the cirrhotic patient. *Rev Gastroenterol Mex* 2020; **85**: 303-311 [PMID: [32553772](#) DOI: [10.1016/j.rgmex.2020.05.002](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

