

World Journal of *Hepatology*

World J Hepatol 2020 August 27; 12(8): 413-532



OPINION REVIEW

- 413 Mechanisms and consequences of COVID-19 associated liver injury: What can we affirm?
Brito CA, Barros FM, Lopes EP

REVIEW

- 423 Review: Pathogenesis of cholestatic liver diseases
Yokoda RT, Rodriguez EA
- 436 Lipidomics in non-alcoholic fatty liver disease
Kartsoli S, Kostara CE, Tsimihodimos V, Bairaktari ET, Christodoulou DK
- 451 Update on diagnosis and management of sepsis in cirrhosis: Current advances
Philips CA, Ahamed R, Rajesh S, George T, Mohanan M, Augustine P

MINIREVIEWS

- 475 Cell competition in liver carcinogenesis
Marongiu F, Laconi E
- 485 Management of hepatitis C in children and adolescents during COVID-19 pandemic
Pokorska-Śpiewak M, Śpiewak M
- 493 Glucagon-like peptide-1 receptor agonists in non-alcoholic fatty liver disease: An update
Sofogianni A, Filippidis A, Chrysavgis L, Tziomalos K, Cholongitas E

META-ANALYSIS

- 506 Racial disparities in nonalcoholic fatty liver disease clinical trial enrollment: A systematic review and meta-analysis
Patel P, Muller C, Paul S

CASE REPORT

- 519 Non-islet cell tumor hypoglycemia as an initial presentation of hepatocellular carcinoma coupled with end-stage liver cirrhosis: A case report and review of literature
Yu B, Douli R, Suarez JA, Gutierrez VP, Aldiabat M, Khan M

LETTERS TO THE EDITOR

- 525 "Six-and-twelve" score for outcome prediction of hepatocellular carcinoma following transarterial chemoembolization. In-depth analysis from a multicenter French cohort
Adhoute X, Pénaranda G, Raoul JL, Bronowicki JP, Anty R, Bourlière M

ABOUT COVER

Editorial board member of *World Journal of Hepatology*, Dr. Alberto Ferrarese is a Gastroenterologist devoted to the field of hepatology. He obtained his MD degree at Padua University Hospital, Italy, where his ongoing career research has focused mainly on decompensated cirrhosis and liver transplantation. His main research interests are complications of cirrhosis, bacterial infection in cirrhosis, organ allocation in liver transplantation, and adherence and quality of life after liver transplantation. He has authored 40 articles published in international peer-reviewed journals and he serves as a reviewer for several international journals in the field of hepatology. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; Production Department Director: *Yun-Xiaojuan Wu*; Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pylsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

August 27, 2020

COPYRIGHT

© 2020 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>

Mechanisms and consequences of COVID-19 associated liver injury: What can we affirm?

Carlos Antunes Brito, Fabio Marinho Barros, Edmundo Pessoa Lopes

ORCID number: Carlos Antunes Brito 0000-0002-5963-8178; Fabio Marinho Barros 0000-0003-1446-7739; Edmundo Pessoa Lopes 0000-0002-3470-1564.

Author contributions: All contributing authors participated in the study to the conception or design of the work or the acquisition, analysis or interpretation of the papers and subsequent revisions of the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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

Manuscript source: Unsolicited manuscript

Carlos Antunes Brito, Edmundo Pessoa Lopes, Department of Internal Medicine, Center of Medical Sciences of Federal University of Pernambuco, Recife, Pernambuco 50740600, Brazil

Carlos Antunes Brito, Edmundo Pessoa Lopes, Clinical Hospital of Federal University of Pernambuco, Recife, Pernambuco 50740900, Brazil

Carlos Antunes Brito, Edmundo Pessoa Lopes, Post-graduation Program of Tropical Medicine of Federal University of Pernambuco, Recife, Pernambuco 50670901, Brazil

Carlos Antunes Brito, Autoimmune Research Institute, Recife, Pernambuco 52011010, Brazil

Fabio Marinho Barros, Português Hospital of Pernambuco, Recife, Pernambuco 52010075, Brazil

Corresponding author: Carlos Alexandre Brito, MD, MSc, PhD, Adjunct Professor, Internal Medicine Department, Center of Medical Sciences, Federal University of Pernambuco, Av. Prof. Moraes Rego, 1235-Cidade Universitária, Recife, Pernambuco 50740600, Brazil. carlos.brito@ufpe.br

Abstract

Since the first reports of coronavirus disease 2019 (COVID-19) cases in December 2019 in China, numerous papers have been published describing a high frequency of liver injury associated with severe acute respiratory syndrome coronavirus 2 infection, many of them proposing a link between these findings and patient outcomes. Increases in serum aminotransferase levels (ranging from 16% to 62%) and bilirubin levels (ranging from 5% to 21%) have been reported and seem to be more often observed in patients with severe forms of COVID-19. Although absolute changes in these parameters are frequently seen, other variables, such as the ratio above the upper limit of normal, the onset of liver injury as a complication in severe cases and histopathological findings, reinforce that liver changes are of dubious clinical relevance in the course of this disease. Other factors must also be considered in these analyses, such as the repercussions of hemodynamic changes, the presence of thrombotic events, and, mainly, the possible drug-induced liver injury with the current, yet off-label, treatment. This paper aimed to analyze the currently available data on liver injury in patients with COVID-19.

Key words: COVID-19; SARS-CoV-2; Liver injury; Liver enzymes; Drug induced liver

Received: May 14, 2020

Peer-review started: May 14, 2020

First decision: June 2, 2020

Revised: June 5, 2020

Accepted: August 1, 2020

Article in press: August 1, 2020

Published online: August 27, 2020

P-Reviewer: Khoury T, Scalinci SZ

S-Editor: Zhang L

L-Editor: A

P-Editor: Li JH



injury; Pandemic

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The coronavirus disease 2019 (COVID-19) pandemic has affected millions worldwide, with high lethality. Papers have been describing liver injury but with divergent results; some have suggested a positive relationship between liver involvement and severity of infection. To evaluate this matter, some aspects, such as the frequency and severity of liver enzyme abnormalities, should be analyzed according to clinical and histopathological findings; other associated factors, such as interactions with the drugs used in COVID-19 treatment, should be analyzed as well. An overview of the aspects related to liver injury during COVID-19 infection was analyzed in this study according to evidence known to date.

Citation: Brito CA, Barros FM, Lopes EP. Mechanisms and consequences of COVID-19 associated liver injury: What can we affirm? *World J Hepatol* 2020; 12(8): 413-422

URL: <https://www.wjgnet.com/1948-5182/full/v12/i8/413.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v12.i8.413>

INTRODUCTION

The first reports of what is now known as coronavirus disease 2019 (COVID-19) came out in December 2019 in China, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the COVID-19 etiologic agent, subsequently spread worldwide. Currently, more than 200 countries have been affected, with approximately 3 million confirmed cases and more than 200000 deaths to date (as of May 5, 2020). Severe disease is observed in up to 20% of affected patients with a lethality rate that may eventually exceed 10%^[1-4].

Recently, many papers have been published reporting gastrointestinal manifestations, including acute liver injury, with increased levels of aminotransferases, in COVID-19 patients; these manifestations have been reported more frequently in patients with severe forms of this disease. However, there is a wide variation of these findings in different studies^[5-18].

Despite frequent reports of liver injury in patients with COVID-19, some questions remain: What is the liver enzymes' curve and how often do they rise above the upper limit of normal (ULN) serum level? Are these abnormalities correlated with COVID-19 disease severity? Can increased serum aminotransferase levels reflect the degree of injury? What is the liver injury frequency in cases with a severe course of disease with complications and death? What do histopathological findings suggest? Are the liver parenchymal changes due to the systemic disease consequences or a direct effect of SARS-CoV-2? May drug use for COVID-19 be the cause of liver injury?

FREQUENCY OF INCREASE IN LIVER FUNCTION ENZYMES IN COVID-19 PATIENTS

Liver injury related to SARS-CoV-2 disease has been defined by increased liver enzyme serum levels, mainly aminotransferases and bilirubin, during the infection course in patients with or without previous liver disease^[5-18]. Wide variability in deviations of liver enzyme serum levels from normal values is observed in infected patients, with an elevation frequency ranging from 16% to 62% for aminotransferases and from 5% to 21% for bilirubin. These abnormalities are seen mostly in severe forms of COVID-19 (Tables 1 and 2)^[6,10,12,14,16].

In fact, the study by Guan *et al.* found high aminotransferase serum levels in 22% of 757 hospitalized patients, with elevated aspartate transaminase (AST) in 18.2% (112/615) of non-severe patients, in 39% (56/142) of severe patients and in 50% (26/52) in those with complicated outcomes such as intensive care unit (ICU) hospitalization, mechanical ventilation or death. In addition, bilirubin values above the ULN were present in 13.3% of non-severe patients and 20.8% of severe patients^[6].

Table 1 Different studies that evaluates liver enzymes according to disease severity and treatment protocol

	<i>n</i>	Disease severity, <i>n</i> (%)	Death, <i>n</i> (%)	Complications, <i>n</i> (%)	Treatment (%), Antiviral therapy; Antibiotic therapy; Antimalarial	Treatment (Drugs)
Xie <i>et al</i> ^[12]	79	Moderate: 51 (64.5%), Severe: 28 (2.5%)	0	NR	NR	NR
Huang <i>et al</i> ^[5]	41	Non-severe: 28 (68.3%), Severe: 13 (31.7%)	6 (15%)	Acute respiratory distress: 12 (29%); Acute cardiac injury: 5 (12%); Acute kidney injury: 3 (7%); Secondary infection: 4 (10%); Shock: 3 (7%)	All patients: AV (93%); AB (100%) Non-ICU care: AV (93%); AB (100%) ICU care: AV (92%); AB (100%)	Antiviral: Oseltamivir Antibiotic: NR
Guan <i>et al</i> ^[6]	1099	Non severe: 926 (84.3%), Severe: 173 (15.7%)	15 (1.4%)	Acute respiratory distress: 37 (3.4%); Acute kidney injury: 6 (0.5%); Septic Shock: 12 (1.1%); Disseminated intravascular coagulation: 1 (0.1); Rhabdomyolysis: 2 (0.2)	All patients: AV (35.8%); AB (58%) Non-severe: AV (33.8%); AB (53.8%) Severe: AV (46.2%); AB (80.3%)	Antiviral: Oseltamivir Antibiotic: NR
Zhang <i>et al</i> ^[13]	115	Non severe: 84 (73%), Severe: 31 (27%)	1 (0.9%)	NR	NR	NR
Cao <i>et al</i> ^[31]	128	Non severe: 107 (83.6%), Severe: 21 (16.4%)	0%	NR	NR	NR
Chen <i>et al</i> ^[9]	99	Non severe: 76 (77%), Severe (ICU): 23 (23%)	11 (11%)	Acute respiratory injury: 8 (8%); Acute kidney injury: 3 (3%); Septic Shock: 4 (4%); Ventilator-associated pneumonia: 1 (1%)	All patients: AV (76%), AB (71%)	Antiviral: Oseltamivir, ganciclovir, lopinavir/ritonavir Antibiotic: Cephalosporins, quinolones, carbapenems, tigecycline, linezolid
Richardson <i>et al</i> ^[18]	5700	Non severe: 4414 (77.4%), Severe (ICU): 1286 (22.6%)	553/2634 (21%)	Acute kidney injury: 1370 (24%); Acute Hepatic injury 89 (1.6%)	NR	NR
Zhang <i>et al</i> ^[10]	221	Non severe: 166 (75%), Severe: 55 (25%)	12 (5.4%)	Acute respiratory injury: 48 (21.7%); Acute kidney injury: 10 (4.5%); Acute cardiac injury: 17 (7.6%); Arrhythmia: 24 (11%); Shock: 15 (6.8)	All patients: AV (88.7%) Non-severe: AV (88%), Severe: AV (90.9%)	Antiviral: NR Antibiotic: NR
Bhatraju <i>et al</i> ^[11]	24	Severe: 24 (100%)	12 (50%)	Shock: 17 (71%)	All patients: AV (29.2%)	Antiviral: Remdesivir
Zhou <i>et al</i> ^[8]	191	General: 72 (38%), Severe: 66 (35%); Critical: 53 (28%)	54 (28%)	Sepsis: 112 (59%); Respiratory failure: 103 (54%); Heart failure: 44 (23%); Septic shock: 38 (20%); acute cardiac injury: 33 (17%); Acute kidney injury: 28 (15%); Secondary infection: 28 (15%)	All patients: AV (21%), AB (95%) Survivors: AV (21%), AB (93%) Non-survivors: AV (22%), AB (98%)	Antiviral: Lopinavir/ritonavir Antibiotic: NR
Pan <i>et al</i> ^[15]	204	NR (total)	36 (17.6%)	NR	All patients: AV (90.2%), AB (64.7%)	Antiviral: Lopinavir/ritonavir Antibiotic: NR
Wang <i>et al</i> ^[7]	138	Non severe: 102 (74%), Severe (ICU): 36 (26%)	6 (4.3%)	Respiratory failure: 27 (19.6%); Arrhythmia: 23 (16.7%); Shock: 12 (8.7%); Acute cardiac injury: 10 (7.2%); Acute Kidney injury: 5 (3.6%)	All patients: AV (89.9%); AB (100%) Non-ICU care: AV (88.2%); ICU care: AV (94.4%)	Antiviral: Oseltamivir Antibiotic: Moxifloxacin, ceftriaxone, azithromycin
Fu <i>et al</i> ^[16]	350	Common: 211 (60.3%), Severe: 88 (25.2%); Critical ill: 51 (14.5%)	34 (9.8%)	NR	NR	NR
Chen <i>et al</i> ^[17]	113	NR	113 (41%)	Type I respiratory failure: 18/67 (27%), Sepsis: 179 (65%), Acute cardiac injury: 89/203 (44%), Heart failure: 43/176 (24%), Acute kidney injury: 29 (11%)	All patients: AV (86%); AB (91%); Recovered: AV (91%); AB (89%) Deaths: AV (79%); AB (93%)	Antiviral: Oseltamivir, arbidol, lopinavir/ritonavir Antibiotic: Moxifloxacin, cefoperazone, or azithromycin

NR: Not report; ICU: Intensive care unit; AV: Antiviral therapy; AB: Antibiotic therapy; AM: Antimalarial.

Moreover, among 24 hospitalized ICU patients, Bhatraju *et al*^[11] found increases of 41% and 32% in AST and alanine transaminase (ALT) levels, respectively. Huang *et al*^[5,7], when assessing the frequency of abnormalities among 41 patients, found AST alterations in 62% of ICU patients compared to 25% of non-ICU hospitalized patients, similar to the findings in other studies.

According to these findings, the frequency of aminotransferase elevation during COVID-19 is directly related to the disease severity; that is, the higher the COVID-19 severity, the greater the chance of liver enzyme elevation. Then, increases of aminotransferases serum levels would be a predictor factor of severity of SARS-CoV-2 infection.

SERUM LEVELS OF LIVER ENZYMES AND LIVER INJURY

It must be acknowledged, however, that in acute liver injury, hepatocyte necrosis extension is reflected by aminotransferase serum levels. Although these changes are often described in COVID-19 cases, the aminotransferase serum level abnormalities are discrete^[6-8,10-16].

In a study by Cao *et al*^[14] 107 non-severe COVID-19 patients had a mean AST of 30.63 U/L (30.63 ± 18.85), and even among the 21 severe cases, serum levels were lower than 100 U/L (44.13 ± 36.26)^[14]. In another study involving 115 patients, 27% were categorized as severe, and among them, 85% had serum AST levels below 50 U/L, with no cases presenting an AST above 150 U/L and just one case with an ALT level above this value. For bilirubin, only seven cases presented with serum levels higher than ULN (> 21 µmol/L), and they did not exceed 31.5 µmol/L^[13].

Using a stratification score for the variability in serum levels among 341 patients, Cai *et al*^[19] found 25% of AST abnormalities at admission, with most of these cases (91%) having serum levels between one and two times above ULN; 8% had an elevation range of two and three times above ULN, and only 1% had an elevation above three times the ULN^[19].

In the evaluation of cases that progressed to a fatal outcome, the same pattern persisted. In the study by Chen *et al*^[17], 52% (59/113) of deceased patients presented an AST increase, with median serum levels of 45 U/L (IQR: 31.0-67.0). On the other hand, only 25 out of 161 (16%) patients who recovered presented AST levels higher than the ULN, with median serum levels of 25.0 (IQR: 20.0-33.3)^[17].

In an analysis of 82 deaths, Zhang *et al*^[10] compared the aminotransferases and bilirubin values at admission and 24 h before the fatal outcome. The alterations were higher close to the timing of death, with AST, ALT and bilirubin values above the ULN occurring in 70%, 40% and 30.6%, respectively. However, the absolute values

Table 2 Frequency and serum levels of hepatic enzymes abnormalities in different studies

	AST abnormalities % ¹	Serum levelsAST U/L ¹	ALT abnormalities %	Serum levelsALT U/L ¹	Total bilirubinabnormalities %	Serum levels, Total bilirubin mol/L ¹
Xie <i>et al</i> ^[12]	35.4%	² All patients: 30 (20-50); Moderate: 28 (22-48); Severe: 35 (22-55)	31.6%	² All patients: 34 (18-67); Moderate: 28 (21-43.5); Severe: 36.5 (17.5-71.5)	5.1%	² All patients: 13.6 (8.8-17.6); Moderate: 13.9 (8.9-18.7); Severe: 12.7 (8.1-15.4)
Huang <i>et al</i> ^[5]	² All patients: 37%, Non-ICU: 25%; ICU: 6%	² All patients: 34 (26-48); Non-ICU: 34 (24-40.5); ICU: 44 (30-70)	NR	² All patients: 32 (21-50); Non-ICU care: 27 (19.5-40); ICU care: 49 (29-115)	NR	² All patients: 11.7 (9.5-13.9); Non-ICU care: 10.8 (9.4-12.3); ICU care: 49 (11.9-32.9)
Guan <i>et al</i> ^[6]	All patients: 22.2%; Non-severe: 18.2%; Severe: 39.4%; ICU/IMV/Death: 50%	NR	All patients: 21.3%; Non-severe: 19.8%; Severe: 28.1%; ICU/IMV/Death: 40.8%	NR	All patients: 10.5%; Non-severe: 9.9%; Severe: 13.3%; ICU/IMV/Death: 20.8%	NR
Zhang <i>et al</i> ^[13]	17%	² All patients: 28.3 ± 15.6; ULN ≤ 50 U/L: 85%; 50-150 U/L: 15%; > 150: none	11%	² All patients: 25.71 ± 21.8; ULN: ≤ 50 U/L: 90.4%; 50-150 U/L: 8.7%; > 150: 0.9%	6.96%	² All patients: 11.31 ± 5.8; ULN: ≤ 21 μmol/L: 94%; 21-31.5 μmol/L: 6%
Cao <i>et al</i> ^[31]	NR	All patients: 30.63 ± 18.85; Non-severe: 27.98 ± 25.8; Severe: 44.13 ± 36.26	NR	All patients: 31.35 ± 20.36; Non-severe: 28.89 ± 31.83; Severe: 43.87 ± 47.8	NR	NR
Chen N <i>et al</i> ^[9]	35%	All patients: 34 (26-48)	28%	All patients: 39 (21-55)	18%	All patients: 15.1 ± 7.6
Richardson <i>et al</i> ^[10]	58.4%	All patients: 46 (31-71)	39%	All patients: 33 (21-55)	NR	NR
Zhang <i>et al</i> ^[10]	NR	All patients: 29 (22-49); Non-severe: 27 (20-38); Severe: 51 (29-78)	NR	All patients: 23 (16-39); Non-severe: 22 (14-33); Severe: 32 (22-57)	NR	All patients: 10 (8-14.2); Non-severe: 9.6 (7.9-13.8); Severe: 11.4 (8.6-17.4)
Bhatraju <i>et al</i> ^[11]	41%	NR	32%	NR	NR	0.6 (0.5-0.7)
Zhou <i>et al</i> ^[8]	NR	NR	All patients: 31% Survivor: 24%; Non-survivor: 48%	All patients: 30 (17-46); Survivor: 27 (15-40); Non-survivor: 40 (24-51)	NR	NR
Pan <i>et al</i> ^[15]	NR	All patients: 35.6 ± 59.6	NR	All patients: 35.8 ± 48.5	NR	All patients: 13.3 ± 10.2
Wang <i>et al</i> ^[7]	NR	All patients: 31 (24-51); Non-ICU: 29 (21-38); ICU: 52 (30-70)	NR	All patients: 24 (16-40); Non-ICU: 23 (15-36); ICU: 35 (19-57)	NR	All patients: 9.8 (8.4-14.1); Non-ICU: 9.3 (8.2-12.8); ICU: 11.55 (9.6-18.6)
Fu <i>et al</i> ^[16]	NR	Common: 16 (20-35); Severe: 29 (23-54); Critical ill: 49 (35-80)	NR	Common: 22 (14-35); Severe: 23 (15-36); Critical ill: 33 (19-61)	NR	² Common: 10.4 (7.5-14.7) Severe: 10.9 (8.0-16.2); Critical ill: 12.6 (10.5-17)
Chen <i>et al</i> ^[17]	All patients: 31%; Deaths: 52%;	All patients: 16 (22-46);	All patients: 22%; Deaths: 27%;	All patients: 23 (15-38);	NR	All patients: 9.6 (6.7-13.5);

Recovered: 16%	Recovered: 25 (20-33.3); Deaths: 45 (31-67)	Recovered: 19%	Recovered: 20 (14.2-32); Deaths: 28 (18-57)	Recovered: 8.4 (5.8-11.2); Deaths: 12.6 (9.4-16.7)
----------------	---	----------------	---	--

¹Data is mean ± SD or median.

²Values on admission. ALT: Alanine transaminase; AST: Aspartate transaminase; NR: Not report; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; ULN: Upper limit of normal.

were not as high as supposed, with AST, ALT and bilirubin serum levels averaging 72 U/L (IQR: 30-71), 26 U/L (IQR: 18.5-47.5) and 13.6 µmol/L (IQR: 10-22.9) on admission, respectively, and 74.5 U/L (IQR: 35.5-184), 30.5 U/L (IQR: 22-102.5) and 26 µmol/L (IQR: 18.5-47.5) 24 h before death. Moreover, the authors also compared COVID-19 patients with 119 patients with community-acquired pneumonia due to other etiologies and did not observe significant differences in aminotransferase serum levels^[10].

Although uncommon, there have been published reports of significant elevation in liver enzymes, such as the elevations described among 99 COVID-19 patients in the study by Chen *et al*^[9], with one case (1%) presenting an ALT of 7590 U/L and an AST of 1145 U/L^[9].

According to the studies published so far, liver enzyme serum levels are not very elevated during SARS-CoV-2 infection; most often they are below twice the ULN. These findings suggest that hepatocyte necrosis on the hepatic parenchyma is discrete and that liver injury does not seem to be very relevant. Likewise, serum levels appear to increase according to the progression time of the disease COVID-19 severity. To date, rare cases of high elevations of liver enzymes have been described during COVID-19.

HISTOPATHOLOGICAL FINDINGS

Therefore, the evidence shows that liver injury has little clinical relevance in the course of COVID-19 disease. Nevertheless, liver failure is a rare complication in severe cases, even though hypoxia and shock may contribute to hepatocyte damage. On the other hand, reports of acute respiratory failure, heart failure, acute cardiac injury, acute kidney injury and shock predominate in many studies as more frequent complications and causes of death^[5-8,10,13,17,18].

Little is known about how hepatocytes are damaged during SARS-CoV-2 infection. However, years ago, evaluation of three patients with SARS-CoV confirmed the presence of coronavirus in liver tissue by RT-PCR, but the virus was present in low titles because no viral inclusions were observed ultrastructurally^[20,21].

Additionally, postmortem histopathological studies show discrete changes in the hepatic parenchyma, and these findings may have multifactorial causes related to the viral mode of action, inflammatory response, adjacent repercussions of systemic

hemodynamic alterations, coagulation disorders or drug induced liver injury (DILI)^[22-24].

In a study developed in Milan with 48 liver biopsies from postmortem COVID-19 patients, vascular changes in the portal vein were observed, with an increased number of portal branches, terminal vessel dilations, and thrombi found in portal and sinusoidal vessels. The inflammatory alterations were discrete, with mild portal and lobular infiltrates. The authors suggested that histopathological findings in COVID-19 are suggestive of changes in the intrahepatic blood vessel network secondary to systemic alterations induced by SARS-CoV-2 that could indicate that they are a target, in addition to the lung parenchyma or cardiovascular system. However, they conclude that liver failure is not a major concern in COVID-19 cases, and this organ is not a significant inflammatory injury target^[23].

Moreover, some authors suggest that liver injury in COVID-19 may be triggered by viral replication itself within hepatocytes, since SARS-CoV-2 binds cells through the angiotensin-2-converting enzyme, especially in bile epithelium cells^[23]. Nevertheless, the low serum aminotransferase levels observed in COVID-19 patients do not suggest that the exacerbated inflammatory response or direct viral injury to hepatocytes is relevant. The pattern of the aminotransferase curve during SARS-CoV-2 infection is different from those observed in hepatitis associated with other epidemic viruses that induce frequent and intense LFT elevations due to diffuse parenchymal necrosis, as found, for example, in patients with dengue or yellow fever^[25-26]. In fact, the liver injury found in COVID-19 looks that one observed in other viruses, such as SARS, MERS and influenza^[29-31].

Lastly, the liver histopathological findings observed in most patients with COVID-19 are suggestive of vascular abnormalities possibly resulting from increased arterial flow to the liver secondary to cardiac distress and thrombotic phenomena in the portal and sinusoidal vessels^[23]. Nonetheless, eventually in some patients might be the involvement of some drug, as antibiotics or antivirals, in the induction of liver injury.

OTHER CAUSES OF LIVER INJURY IN SARS-CoV-2

Other factors may be involved in hepatic enzyme alterations. Several medications used to treat COVID-19, mainly antivirals such as lopinavir/ritonavir and remdesivir, chloroquine and hydroxychloroquine antimalarials, antibiotics including azithromycin, or immune-modulators such as tocilizumab, may lead to DILI. Therefore, physicians should be aware of the LFT profile in response to drug use to help attribute liver injury to the natural history of infection^[19,32-39].

Antivirals such as lopinavir/ritonavir and remdesivir that have been recently used for COVID-19 may be associated with liver injuries. DILI from lopinavir/ritonavir has been reported in 2%-10% of patients^[32]. Cai *et al*^[19] published a trial in which 417 patients using lopinavir/ritonavir presented a higher risk for developing liver injury [OR of 4.44 ($P < 0.01$)] and higher levels of bilirubin and gammaGT during hospitalization ($P < 0.004$)^[19].

The use of antimicrobials and antibiotics, frequently prescribed for suspicious or confirmed very ill COVID-10 patients, is considered a frequent etiology of DILI^[33].

In the reviewed papers, antivirals and antimicrobials were often prescribed to COVID-19 patients, ranging from 21% to 93% and 58% to 100%, respectively and many times they were used simultaneously^[5-11,13,17]. Liver enzymes abnormalities were often seen, even in the trials that less frequently used antiviral treatment^[6,8,11]. In Zhou *et al*^[8] trial, lopinavir/ritonavir was used in around 20% of the patients either they survive or not, and ALT abnormalities was observed in 24% and 48% respectively^[8]. There is also a wide variability in antivirals prescribed to patients, such as oseltamivir, remdesivir, lopinavir/ritonavir and ganciclovir. The same is also observed with the use of antimicrobials, either alone or in combination with antivirals and other drugs. This does not allow us to establish a clear causality relationship or even the amount of importance to the use of this drugs and the liver injury. Besides it the histopathological findings do not suggest a DILI pattern^[23].

Hydroxychloroquine (HCQ) has been used, though still off-label, in several countries, despite the limited number of studies published so far and divergent opinions regarding its efficacy. Although hepatotoxicity in users of HCQ is uncommon, LFTs and severe liver dysfunction have been documented^[37-40].

Makin *et al*^[40] reported two cases of patients with rheumatological disease who, after 2 wk of using 400 mg of HCQ daily, were admitted with fulminant hepatitis; one required a liver transplant, and both patients died^[40]. Recently, Falcão *et al*^[37] reported

an increase in LFTs in very sick COVID-19 patients on drug treatment, with return to normal levels once the drugs were halted^[37].

The mechanisms of hepatic injury related to HCQ are poorly established, and toxicity may be due to reactive metabolites and oxidative stress induced by this drug or an idiosyncratic toxic or synergistic effect associated with inflammatory processes induced by the infection itself^[41-43].

More recently, azithromycin in association with HCQ has become a therapeutic option for COVID-19 patients^[44,45]. Biliary and hepatocellular injury have been associated with azithromycin use^[34-36]. Another report with 18 patients presenting with azithromycin-induced DILI described a wide range of histopathological abnormalities, including hepatitis, veno-occlusive changes and/or central venulitis acute cholestasis and cholestatic hepatitis^[35].

Due to the significantly increased use of HCQ and azithromycin during COVID-19 disease treatment, liver toxicity related to these drugs must be considered, and liver abnormalities should not be solely attributable to SARS-CoV-2 infection itself; the high risk of DILI seen in these scenarios should not be neglected. If DILI is suspected, COVID-19 drugs should be promptly halted.

Additionally, it is highly difficult to establish a causality relationship between a specific drug and liver injury during COVID-19 infection, because most of the times they are used as combination of antimalarials, antivirals, antimicrobials, anticoagulants and sometimes vasoactive drugs. It is also worth remembering that the most severe cases, which do not present favorable evolution, are those where more drugs are administered in the fight against the disease.

CONCLUSION

Despite the common descriptions of liver enzyme abnormalities observed in COVID-19 patients, the frequency, intensity and impact of liver injury are discrete and of little clinical significance regarding morbidity or mortality of this disease. A better understanding of the natural history of liver involvement may be addressed in the near future with well-designed prospective studies regarding viral and immunologic research.

REFERENCES

- 1 **Ashour HM**, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. *Pathogens* 2020; 9 [PMID: 32143502 DOI: 10.3390/pathogens9030186]
- 2 **World Health Organization**. Coronavirus disease 2019 (COVID-19) Situation Report. World Health Organization, 2020. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
- 3 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]
- 4 **Mizumoto K**, Chowell G. Estimating Risk for Death from Coronavirus Disease, China, January-February 2020. *Emerg Infect Dis* 2020; 26: 1251-1256 [PMID: 32168464 DOI: 10.3201/eid2606.200233]
- 5 **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]
- 6 **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]
- 7 **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 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
- 8 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]
- 9 **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]

- 10 **Zhang G**, Hu C, Luo L, Fang F, Chen Y, Li J, Peng Z, Pan H. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol* 2020; **127**: 104364 [PMID: [32311650](#) DOI: [10.1016/j.jcv.2020.104364](#)]
- 11 **Bhatraju PK**, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S, Mikacenic C. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med* 2020; **382**: 2012-2022 [PMID: [32227758](#) DOI: [10.1056/NEJMoa2004500](#)]
- 12 **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](#)]
- 13 **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 [PMID: [32239796](#) DOI: [10.1111/liv.14455](#)]
- 14 **Cao WL**, Shi L, Chen L, Xu XM, ZW. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. *medRxiv* 2020 [DOI: [10.1101/2020.02.23.20026963](#)]
- 15 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: [32287140](#) DOI: [10.14309/ajg.0000000000000620](#)]
- 16 **Fu L**, Fei J, Xu S, Xiang HX, Xiang Y, Tan ZX, Li MD, Liu FF, Li Y, Han MF, Li XY, Zhao H, Xu DX. Acute liver injury and its association with death risk of patients with COVID-19: a hospital-based prospective case-cohort study. *medRxiv* 2020 [DOI: [10.1101/2020.04.02.20050997](#)]
- 17 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: [32217556](#) DOI: [10.1136/bmj.m1091](#)]
- 18 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; and 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 [PMID: [32320003](#) DOI: [10.1001/jama.2020.6775](#)]
- 19 **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 [PMID: [32298767](#) DOI: [10.1016/j.jhep.2020.04.006](#)]
- 20 **Li X**, Wang L, Yan S, Yang F, Xiang L, Zhu J, Shen B, Gong Z. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. *Int J Infect Dis* 2020; **94**: 128-132 [PMID: [32251805](#) DOI: [10.1016/j.ijid.2020.03.053](#)]
- 21 **Chau TN**, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, Choi KW, Tso YK, Lau T, Lai ST, Lai CL. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology* 2004; **39**: 302-310 [PMID: [14767982](#) DOI: [10.1002/hep.20111](#)]
- 22 **Tian S**, Xiong Y, Liu H, Niu L, Guo J, Liao M, Xiao SY. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol* 2020; **33**: 1007-1014 [PMID: [32291399](#) DOI: [10.1038/s41379-020-0536-x](#)]
- 23 **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. Preprints 2020. [DOI: [10.20944/preprints202004.0438.v1](#)]
- 24 **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](#)]
- 25 **Souza LJ**, Alves JG, Nogueira RM, Gicovate Neto C, Bastos DA, Siqueira EW, Souto Filho JT, Cezário Tde A, Soares CE, Carneiro Rda C. Aminotransferase changes and acute hepatitis in patients with dengue fever: analysis of 1,585 cases. *Braz J Infect Dis* 2004; **8**: 156-163 [PMID: [15361994](#) DOI: [10.1590/S1413-86702004000200006](#)]
- 26 **Samanta J**, Sharma V. Dengue and its effects on liver. *World J Clin Cases* 2015; **3**: 125-131 [PMID: [25685758](#) DOI: [10.12998/wjcc.v3.i2.125](#)]
- 27 **Escosteguy CC**, Pereira AGL, Marques MRVE, de Araujo Lima TR, Galliez RM, Medronho AR. Yellow fever: Profile of cases and factors associated with death in a hospital in the State of Rio de Janeiro, 2017-2018. *Rev Saude Publica* 2019; **53**: 1-12 [DOI: [10.11606/s1518-8787.2019053001434](#)]
- 28 **Costa DS**, Moita LA, Alves EH, Sales AC, Rodrigues RR, Galeno JG, Gomes TN, Ferreira GP, Vasconcelos D. Dengue Virus and Yellow Fever Virus Damage the Liver: A Systematic Review About the Histopathological Profiles. *J Gastroenterol Hepatol Res* 2019; **8**: 2864-2870 [DOI: [10.17554/j.issn.2224-3992.2019.07.823](#)]
- 29 **Chang HL**, Chen KT, Lai SK, Kuo HW, Su IJ, Lin RS, Sung FC. Hematological and biochemical factors predicting SARS fatality in Taiwan. *J Formos Med Assoc* 2006; **105**: 439-450 [PMID: [16801031](#) DOI: [10.1515/eclm-2020-0369](#)]
- 30 **Saad M**, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M, Al Nakhli D, Al Aidaroos AY, Al Sherbeeni N, Al-Khashan HI, Memish ZA, Albarrak AM. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014; **29**: 301-306 [PMID: [25303830](#) DOI: [10.1016/j.ijid.2014.09.003](#)]
- 31 **Cao B**, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, Liang ZA, Liang L, Zhang SJ, Zhang B, Gu L, Lu LH, Wang DY, Wang C; National Influenza A Pandemic (H1N1) 2009 Clinical Investigation Group of China. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009; **361**: 2507-2517 [PMID: [20007555](#) DOI: [10.1056/NEJMoa0906612](#)]

- 32 **Sanders JM**, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020 [PMID: 32282022 DOI: 10.1001/jama.2020.6019]
- 33 **Licata A**. Adverse drug reactions and organ damage: The liver. *Eur J Intern Med* 2016; **28**: 9-16 [PMID: 26827101 DOI: 10.1016/j.ejim.2015.12.017]
- 34 **Ellison CA**, Blackwell SB. Acute Hepatocellular Injury Associated With Azithromycin. *J Pharm Pract* 2020 [PMID: 31928122 DOI: 10.1177/0897190019894428]
- 35 **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]
- 36 **Chalasani N**, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, Watkins PB, Navarro V, Barnhart H, Gu J, Serrano J; United States Drug Induced Liver Injury Network. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. *Gastroenterology* 2015; **148**: 1340-52.e7 [PMID: 25754159 DOI: 10.1053/j.gastro.2015.03.006]
- 37 **Falcão MB**, Pamplona de Góes Cavalcanti L, Filgueiras Filho NM, Antunes de Brito CA. Case Report: Hepatotoxicity Associated with the Use of Hydroxychloroquine in a Patient with COVID-19. *Am J Trop Med Hyg* 2020; **102**: 1214-1216 [PMID: 32314698 DOI: 10.4269/ajtmh.20-0276]
- 38 **Abdel Galil SM**. Hydroxychloroquine-induced toxic hepatitis in a patient with systemic lupus erythematosus: a case report. *Lupus* 2015; **24**: 638-640 [PMID: 25424894 DOI: 10.1177/0961203314561667]
- 39 **Giner Galvañ V**, Oltra MR, Rueda D, Esteban MJ, Redón J. Severe acute hepatitis related to hydroxychloroquine in a woman with mixed connective tissue disease. *Clin Rheumatol* 2007; **26**: 971-972 [PMID: 16575495 DOI: 10.1007/s10067-006-0218-1]
- 40 **Makin AJ**, Wendon J, Fitt S, Portmann BC, Williams R. Fulminant hepatic failure secondary to hydroxychloroquine. *Gut* 1994; **35**: 569-570 [PMID: 8175002 DOI: 10.1136/gut.35.4.569]
- 41 **Wei CH**, Penunuri A, Karpouzias G, Fleishman W, Datta A, French SW. Troxois necrosis, a novel mechanism for drug-induced hepatitis secondary to immunomodulatory therapy. *Exp Mol Pathol* 2015; **99**: 341-343 [PMID: 26297838 DOI: 10.1016/j.yexmp.2015.08.006]
- 42 **Jamshidzadeh A**, Heidari R, Abazari F, Ramezani M, Khodaei F, Ommati MM, Ayarzadeh M, Firuzi R, Saeedi A, Azarpira N, Najibi A. Antimalarial drugs-induced hepatic injury in rats and the protective role of carnosine. *Pharm Sci* 2016; **22**: 170-180 [DOI: 10.15171/PS.2016.27]
- 43 **Niknahad H**, Heidari R, Firuzi R, Abazari F, Ramezani M, Azarpira N, Hosseinzadeh M, Najibi A, Saeedi A. Concurrent Inflammation Augments Antimalarial Drugs-Induced Liver Injury in Rats. *Adv Pharm Bull* 2016; **6**: 617-625 [PMID: 28101469 DOI: 10.15171/apb.2016.076]
- 44 **Andreani J**, Le Bideau M, Duflot I, Jardot P, Rolland C, Boxberger M, Wurtz N, Rolain JM, Colson P, La Scola B, Raoult D. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. *Microb Pathog* 2020; **145**: 104228 [PMID: 32344177 DOI: 10.1016/j.micpath.2020.104228]
- 45 **Gautret P**, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, Mailhe M, Doudier B, Aubry C, Amrane S, Seng P, Hocquart M, Eldin C, Finance J, Vieira VE, Tissot-Dupont HT, Honoré S, Stein A, Million M, Colson P, La Scola B, Veit V, Jacquier A, Deharo JC, Drancourt M, Fournier PE, Rolain JM, Brouqui P, Raoult D. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis* 2020; **34**: 101663 [PMID: 32289548 DOI: 10.1016/j.tmaid.2020.101663]



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

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

<https://www.wjgnet.com>

