

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULTAD DE MEDICINA
PROGRAMA DE POSGRADO: CIENCIAS EN GASTRENTEROLOGIA Y
HEPATOLOGIA

Manifestaciones hepáticas de COVID-19

Ysela Ysabel Picón Pérez

Tesis de Maestría

Porto Alegre
2021

CIP - Catalogação na Publicação

Picón Perez, Ysela Ysabel
Manifestaciones hepáticas de COVID-19 / Ysela
Ysabel Picón Perez. -- 2020.
69 f.
Orientador: Mário Reis Álvares-da-Silva.

Coorientador: Dvora Joveleviths.

Dissertação (Mestrado) -- Universidade Federal do
Rio Grande do Sul, Faculdade de Medicina, Programa de
Pós-Graduação em Ciências em Gastroenterologia e
Hepatologia, Porto Alegre, BR-RS, 2020.

1. Hígado. 2. COVID-19. 3. COVID-19 severa. 4.
Enzimas hepáticas alteradas. I. Reis Álvares-da-Silva,
Mário, orient. II. Joveleviths, Dvora, coorient. III.
Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os
dados fornecidos pelo(a) autor(a).

Ysela Ysabel Picón Pérez

Manifestaciones hepáticas de COVID-19

Tesis de maestría presentada al Programa de Posgrado: Ciencias en Gastreenterología y Hepatología de la Universidade Federal do Rio Grande do Sul, como requisito parcial para obtención del título de maestro.

Orientador: Prof. Mario Reis Alvares-da-Silva

Co-orientadora: Profa. Dvora Joveleviths

Porto Alegre, Brasil
2021

AGRADECIMIENTOS

A mis queridos asesores, por ser parte de mi crecimiento profesional y personal; a mi asesor Dr. Mario Reis Alvares-da-Silva, quien con sus conocimientos, consideración y entusiasmo me guiaron en el proceso para alcanzar las metas deseadas; a mi asesora, Dra. Dvora Joveleviths, por su disposición de tiempo, su dedicación en cada etapa del proyecto, así como sus observaciones constructivas, las cuales me llevaban a reflexionar y mejorar cada día. La asesoría de ambos fue fundamental en mi formación, ambos se complementan y me inspiran a ser una mejor profesional cada día.

A los docentes que contribuyeron en cada curso, con las herramientas para desarrollar el proyecto, con especial consideración al Dr. Edison Capp, desde los cursos básicos hasta estadística, en cada clase con sus consejos motivadores.

A la CAPES, por el auxilio financiero, para realizar las actividades de investigación, y HCPA, por la accesibilidad a las historias clínicas.

A Gabriel Tayguara, Nelson Suarez y Matheus Michalczuck, por el apoyo y el compañerismo. A Larisa Longo y Melisa Keingeski por la colaboración durante el proceso.

A toda mi familia y amigos por su apoyo y cariño, quienes están lejos y tan cerca a la vez, cómplices en este camino.

TABLA DE CONTENIDO

RESUMEN	7
RESUMO.....	9
ABSTRACT.....	11
LISTA DE ABREVIATURAS	12
1. INTRODUCCIÓN	15
2. REVISIÓN BIBLIOGRÁFICA	17
2.1. COVID-19	17
2.2. COVID-19 SEVERA.....	17
2.3. MANIFESTACIONES HEPÁTICAS DE COVID-19	18
2.3.1. Prevalencia de alteraciones hepáticas.....	19
2.3.2. Causas de enzimas hepáticas alteradas	19
2.4. PRONÓSTICO DE TRANSAMINASAS ALTERADAS	27
3. JUSTIFICACIÓN.....	28
4. PREGUNTA DE LA INVESTIGACIÓN.....	29
5. HIPOTESIS.....	30
6. OBJETIVOS.....	31
6.1. GENERAL	31
6.2. ESPECÍFICOS	31
7. ARTICULO ORIGINAL	32
8. CONCLUSIONES	62
9. CONSIDERACIONES FINALES	63
10. PERSPECTIVAS.....	65

11. REFERENCIAS..... 66

RESUMEN

COVID-19 es una enfermedad multisistémica, que cursa principalmente con manifestaciones respiratorias. Las alteraciones hepáticas son frecuentes, pero con impacto variable, este estudio tiene el objetivo de evaluar la prevalencia de la afectación hepática en la admisión, así como evaluar su asociación con la severidad y mortalidad en pacientes hospitalizados con COVID-19.

Fueron formados dos grupos: el grupo transaminasas alteradas (TALT) y el grupo severidad de la COVID-19 (SC19). El grupo TALT basados en AST y/o ALT \geq 41 U/l, fue dividido en positivo y negativo; el grupo SC19, basado en PaO₂/FiO₂ $<$ 300 mmHg, fue dividido en severa y no severa. Entre cada subgrupo fueron comparadas: las características clínicas, exámenes de laboratorio y desenlaces finales. Los pacientes TALT positivos eran más jóvenes ($p=0.001$), con menor prevalencia de pacientes de diabetes mellitus e hipertensión, aunque la mayoría presentó hepatopatía previa ($p=0.017$), con marcadores inflamatorios más elevados, mayor proporción de COVID-19 severa ($p<0.001$) y estancia hospitalaria más prolongada ($p=0.009$). Análisis multivariado, mostró que el sexo masculino ($p=0.007$), la presencia de hepatopatía previa ($p=0.015$) y bilirrubina total aumentada ($p<0.001$) fueron factores independientes de transaminasas alteradas en la admisión. En el grupo SC19, los factores pronósticos fueron: edad mayor de 60 años ($p=0.001$), diabetes mellitus ($p=0.001$) y linfopenia ($p<0.001$), así como leucocitos ($p<0.001$), proteína c reactiva ($p<0.001$) y dímero D aumentados ($p<0.001$). La prevalencia de las transaminasas alteradas fue superior al 50% ($p=0.001$) y se correlacionó con la severidad de la enfermedad ($p=0.004$). Los pacientes mayores de 60 años tuvieron un riesgo aumentado de mortalidad ($p<0.001$). En conclusión, los pacientes con COVID-19 tienen una alta prevalencia de transaminasas alteradas en la admisión,

que se correlacionan con la severidad de la enfermedad y podrían ser consideradas como marcadores pronósticos para estratificar su riesgo.

Palabras-clave: Hígado, COVID-19, COVID-19 severa, enzimas hepáticas alteradas.

RESUMO

COVID-19 é uma doença multissistêmica que cursa principalmente com manifestações respiratórias. Uma vez que anormalidades hepáticas são comuns na doença aguda, mas com impacto variável, este estudo visa avaliar a prevalência do envolvimento hepático na admissão sobre a severidade e mortalidade da COVID-19 em pacientes hospitalizados.

Foram formados dois grupos: o grupo transaminases alteradas (TALT) e o grupo severidade da COVID-19 (SC19). O grupo TALT, baseado em AST e/ou ALT \geq 41U/l, foi dividido positivo e negativo; o grupo SC19, baseado no PaO₂/FiO₂ < 300 mmHg, foi dividido em severa e não severa. Entre cada subgrupo as características clínicas, exames de laboratório e desfechos foram comparadas. Los pacientes TALT positivos eram mais novos ($p=0,001$), com menor prevalência de diabetes e hipertensão, entretanto com presença de doença hepática prévia ($p=0,017$), marcadores inflamatórios mais altos, maior proporção de COVID-19 severa e permanência hospitalar mais longa ($p=0,009$). Análise multivariada mostrou que o sexo masculino ($p=0,007$), a presença de hepatopatia prévia ($p=0,015$) e a bilirrubina total elevada foram fatores independentes para transaminases alteradas ($p<0,001$). No grupo SC19, os fatores prognósticos foram: idade acima de 60 anos ($p=0,001$), diabetes mellitus ($p=0,001$) e linfopenia ($p<0,001$), assim como leucócitos ($p<0,001$), proteína c reativa ($p<0,001$) e dímero D aumentados ($p<0,001$). A prevalência de transaminases elevadas foi superior a 50% ($p = 0,001$) e correlacionou-se com a severidade da doença ($p=0,004$). Os pacientes acima de 60 anos tiveram risco aumentado de mortalidade ($p<0,001$). Em conclusão, pacientes com COVID-19 têm alta prevalência de transaminases elevadas na admissão, que se correlacionam à

severidade da doença e poderiam ser consideradas marcadores prognósticos para estratificar seu risco.

Palavras-chave: Fígado, SARS-CoV-2, COVID-19, COVID-19 severa, enzimas hepáticas alteradas.

ABSTRACT

COVID-19 is a multisystemic disease, primarily presenting with respiratory manifestations. As liver abnormalities are frequent but lead to uncertain outcomes, the objective of this study is to determine the prevalence of liver involvement as well as evaluate its effects on severity and mortality in hospitalized patients with COVID-19.

Two groups were performed: the altered transaminase group (TALT) and the COVID-19 severity group (SC19). The TALT group, based on AST and/or ALT \geq 41 U/l, was divided into severe and no severe. Clinical characteristics, laboratory and outcomes were compared. TALT positive patients were younger patients ($p=0.001$), with less diabetes and hypertension, although most presented previous liver disease ($p=0.017$), higher inflammatory markers and number of severe COVID-19 cases, with longer hospital stay ($p=0.009$) in comparison to TALT negative patients. Multivariate analysis showed that male gender ($p=0.007$), the presence of previous liver disease ($p=0.015$) and high total bilirubin ($p<0.001$) were independent factors for altered transaminases. In the SC19 group, the independent prognostic factors for severe COVID-19 were age over 60 years ($p=0.001$), diabetes mellitus ($p=0.001$) and lymphopenia ($p<0.001$), as well as higher leukocytes ($p<0.001$), increased c-reactive protein ($p<0.001$) and increased D-dimer ($p<0.001$). The prevalence of elevated transaminases was greater than 50% ($p=0.001$) and correlated with disease severity ($p=0.004$). Patients over 60 years old had an increased risk of mortality ($p<0.001$). In conclusion, patients with COVID-19 have a high prevalence of altered transaminases on admission, which correlates with disease severity and could be considered as prognostic markers to stratify their risk.

Keywords: Liver, SARS-CoV-2, COVID-19, severe COVID-19, Altered transaminases.

LISTA DE ABREVIATURAS

ALT – Alanina aminotransferasa

AST – Aspartato aminotransferasa

CK – Creatina quinasa

COVID-19 – del inglés coronavirus disease-2019

DM – Diabetes mellitus

ECA2 – Enzima convertidora de angiotensina 2

FA – Fosfatasa alcalina

FNT alfa – Factor de necrosis tumoral alfa

GGT – Gamma-glutamil transferasa

INF gamma – Interferón gamma

HTA – Hipertensión arterial

IL2 – Interleucina 2

IL6 – Interleucina 6

IL10 – Interleucina 10

LDH – Lactato deshidrogenasa

MAFLD – Enfermedad de hígado graso asociado a disfunción metabólica

PCR – Proteína C reactiva

SARS-CoV-2 – del inglés severe acute respiratory syndrome coronavirus

SC19 – COVID-19 severa

TALT – Transaminasas alteradas

UCI – Unidad de cuidados intensivos

ÍNDICE DE FIGURAS

FIGURA 1 – SARS-CoV-2 y receptores ACE2	21
FIGURA 2 – Expresión de receptores en el hígado.....	21
FIGURA 3 – Espectro de alteraciones patológicas del tejido hepático.....	ERRO! INDICADOR NÃO DEFINIDO.
FIGURA 4 – Fisiopatología COVID-19.....	24

1. INTRODUCCIÓN

COVID-19 sorprendió al mundo y en marzo 2020 se convirtió en una pandemia, que ha afectado a más de 256, 966 237 millones de personas (casos confirmados) y de estos 5, 151 643 millones murieron por infección de SARS-CoV-2 (1), Latinoamérica es una de las regiones más afectadas por la pandemia, con datos clínicos escasos. La identificación oportuna de pacientes en riesgo de enfermedad severa o muerte en la admisión, así como una oportuna intervención e ingreso a la unidad de cuidados intensivos (UCI), podrían mejorar el pronóstico.

COVID-19 es una enfermedad inducida por el virus SARS-CoV-2, es multisistémica, sin embargo, afecta principalmente el sistema respiratorio, manifestándose con una variedad de síntomas: tos, fiebre, disnea, anosmia, ageusia; entre otros sistemas afectados tenemos el cardiovascular, renal, gastrointestinal y hepatobiliar. Esta enfermedad tiene un espectro heterogéneo desde asintomáticas hasta falla multiorgánica. (2)

En la COVID-19 severa (3), la función respiratoria está comprometida, desde hipoxemia, y en casos más severos progresa a síndrome respiratorio agudo, hasta la falla multiorgánica, con gran impacto en el desenlace de la enfermedad, presentando una alta mortalidad en los pacientes con falla orgánica (4). Existen factores que predisponen a la severidad como edad avanzada, sexo masculino, comorbilidades como la hipertensión, diabetes mellitus y enfermedades cardiovasculares. (5,6)

El hígado es un órgano vital, con rol importante en la actividad metabólica. Al ser afectado se manifiesta con alteración de las enzimas hepáticas, con diferentes

patrones: hepatocelular, colestásico o mixto. Las manifestaciones hepáticas durante el curso del COVID-19 es frecuente y la causa específica no está determinada, se le atribuye al propio virus SARS-CoV-2, alteraciones inmunológicas (respuesta inmune e hipoxia), hepatotoxicidad y enfermedades hepáticas pre-existentes.(7) El impacto del COVID-19 en el hígado es controversial y podrían, las transaminasas alteradas, ser factores pronósticos de COVID-19 severa. (8,9)

2. REVISIÓN BIBLIOGRÁFICA

2.1. COVID-19

SARS-CoV-2 es un virus ARN, la proteína S (*spike*) es parte de su estructura y se une a los receptores ECA2 (enzima convertidora de angiotensina 2), facilitando el ingreso a las células de los diferentes tejidos, como pulmón, corazón, riñón, tracto gastrointestinal, hígado.(10) Este virus produce COVID-19, enfermedad multisistémica, con afectación principalmente respiratoria, con síntomas variados y un espectro clínico heterogéneo: asintomático, leve, moderada, severa y crítica

- Asintomática: individuos con prueba virológica positiva sin síntomas.
- Leve: individuos con síntomas como fiebre, tos, astenia, vómitos, diarrea, anosmia, ageusia. No tienen disnea ni imágenes alteradas.
- Moderada: individuos con evidencia de enfermedad respiratoria baja durante evaluación clínica o imagen alterada. Quienes tienen saturación de oxígeno $\geq 94\%$ al aire libre a nivel del mar.
- Severa: individuos que tienen saturación de oxígeno $< 94\%$ al aire libre al nivel del mar o $PaO_2/FiO_2 < 300$, frecuencia respiratoria > 30 respiraciones/minuto, o infiltrado pulmonar $> 50\%$.
- Enfermedad crítica: individuos que presentan falla respiratoria, shock séptico, y/o múltiple disfunción orgánica.(3)

2.2. COVID-19 severa

Cuando el curso clínico progresa a COVID-19 severa puede llevar a falla multiorgánica y muerte. La mortalidad estimada puede alcanzar del 3-7%.(11) La alta mortalidad ha sido asociada con COVID-19 severa y la excesiva producción de citosinas pro-inflamatorias (tormenta inflamatoria)(12)

Pacientes con edad avanzada, comorbilidades como diabetes mellitus (DM), hipertensión arterial (HTA), enfermedad cardiovascular, obesidad, enfermedad renal crónica, tienen riesgo incrementado de progresar a COVID-19 severa .(13)

Pacientes con COVID-19 severa han asociado incremento de marcadores inflamatorios siendo reconocida como la principal la interleucina-6 (IL6). (14,15) Otros marcadores como la proteína C reactiva (PCR), el lactato deshidrogenasa (LDH) y linfopenia fueron considerados predictores de severidad.(16–21). Jafarzadeh *et al.*, reportaron que la linfopenia podría reforzar la excesiva respuesta inflamatoria (16) así como la PCR producida en el hígado podría incrementar la inflamación en este. En un meta-análisis por Kovalic *et al.*, encontraron asociación entre COVID-19 severa y elevaciones de aspartato aminotransferasas (AST), bilirrubina total, albumina disminuida, así como una tendencia de elevadas alanino aminotransferasas (ALT) entre los casos severos. También encontró asociación con leucocitosis, neutrofilia, linfopenia, elevada creatina quinasa (CK), elevada lactato deshidrogenasa (LDH) y elevado tiempo de protrombina.(22)

2.3. Manifestaciones hepáticas de COVID-19

La injuria del hígado se manifiesta con alteración de las pruebas hepáticas: la lesión hepatocitaria se manifiesta a través de alteración de las enzimas aspartato aminotransferasa (AST) y alanina aminotransferasa (ALT), el daño de la vía biliar se manifiesta con alteración de fosfatasa alcalina y gamma-glutamil transferasa (GGT), la alteración de la función secreción o síntesis se manifiesta por alteración de la Bilirrubina, el tiempo de protrombina, la albúmina respectivamente.

2.3.1. Prevalencia de alteraciones hepáticas

La incidencia de enzimas hepáticas alteradas es variable entre los diferentes estudios, 14 a 76.3% entre los pacientes con COVID-19 (8,23–27) , un rango amplio debido a los diferentes puntos de corte utilizados como referencias, en los diferentes estudios. En Latinoamérica, Mendizabal *et al.* en un estudio multicéntrico prospectivo con 1611 pacientes reportó la prevalencia de enzimas hepáticas alteradas en 45.2% , y demostró la asociación con la mortalidad y la severidad de la enfermedad (28). Por otro lado Marin *et al.*, en un estudio retrospectivo con 1100 pacientes mostraron que el 75% de los pacientes presentaron enzimas hepáticas alteradas en la admisión y asociación de éstas con la severidad de la enfermedad (29). Similares hallazgos fueron reportados en una revisión sistemática por Sharma *et al.*, de 12,882 pacientes, AST estuvo aumentada en 41.1% y ALT en 29.1%, demostrando asociación con la severidad de la enfermedad.(9) Las alteraciones de las transaminasas son generalmente leves.(30) o menos de 5 veces su límite superior (27,31,32). El patrón hepatocelular fue el predominante, las elevaciones de bilirrubina, FA y GGT fueron poco frecuentes. La elevación de bilirrubina fue reportada entre 6 - 7%, de FA entre 4.1- 5% y GGT alteradas entre 17.6-54%. (27,32,33)

2.3.2. Causas de enzimas hepáticas alteradas

Las alteraciones hepáticas con mecanismo fisiopatológico poco entendido, está asociado a muchos factores:

- **Infección citopática directa.**

El hígado expresa receptores de la enzima convertidora de angiotensina (ECA2) que permite el ingreso del virus a través de la proteína S (*spike*). (Figura 1), el colangiocito expresa una cantidad considerablemente superior 59.7% comparado

al hepatocito 2.6% (Figura 2). La cantidad de receptores que expresa el colangiocito es similar a la cantidad expresada por pneumocito tipo 2. (34) Sin embargo las elevaciones de las enzimas tienen un patrón hepatocelular, diferente a lo esperado por la cantidad de receptores que predomina en la vía biliar y se esperaría un aumento mayor de enzimas colestásicas.

Entre los hallazgos histológicos de pacientes infectados con SARS-CoV-2, en un meta-análisis con 164 pacientes, el más frecuente hallazgo *post mortem* fue la congestión centrolobulillar, además de leve a moderada esteatosis, predominantemente macrovesicular y centrolobulillar así como leve a moderado infiltrado en la zona periportal.(35) En otro meta-análisis realizado por Díaz *et al.* con 116 pacientes los hallazgos mas frecuentes en pacientes fallecidos fueron esteatosis hepática y trombosis vascular, encontrando 19% de microtrombos en el sinusoides hepático. También se encontraron inflamación lobulillar y portal sin embargo, no se encontraron hallazgos relacionados a la vía biliar. (36) Los hallazgos histológicos son inespecíficos y podrían ser atribuidos a causas secundarias como shock, diabetes mellitus u obesidad(37). Se mostró infección hepática directa, a través de partículas de SARS-CoV-2 sin membrana en citoplasma de hepatocitos en 2 pacientes con enzimas hepáticas alteradas sin confirmarse con PCR para ácidos nucleicos virales dejando la opción que podría deberse a otro origen.(38) Los hallazgos histopatológicos se muestran en la figura 3.

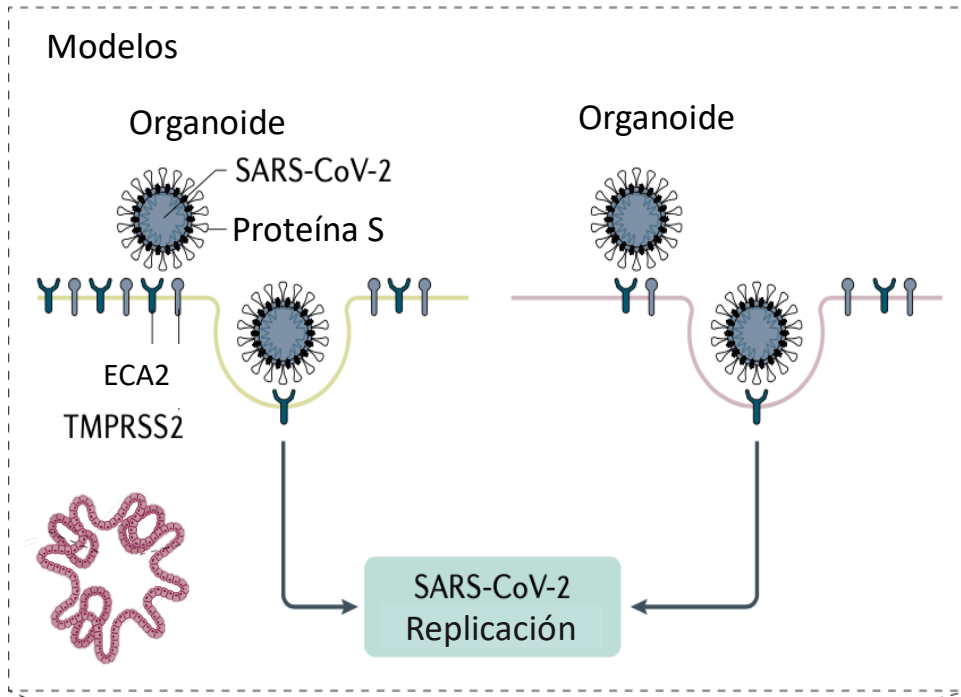


Figura 1 – SARS-CoV-2 y receptores ACE2. En modelos organoides los hepatocitos y los colangiocitos han mostrado la expresión necesaria de receptores para permitir el ingreso de SARS-CoV-2. Adaptado de (2).

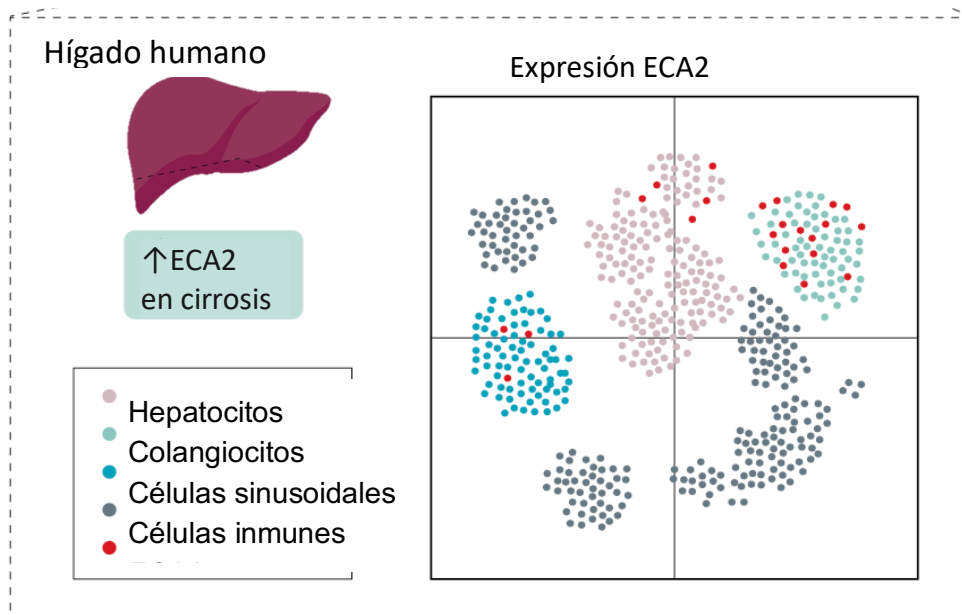


Figura 2 – Expresión de receptores en el hígado. Se muestra la variabilidad de expresión y distribución de los receptores ECA2 en los tipos de células del hígado. Los colangiocitos parecen tener mas grande concentración de receptores que los hepatocitos. Adaptado de (2).

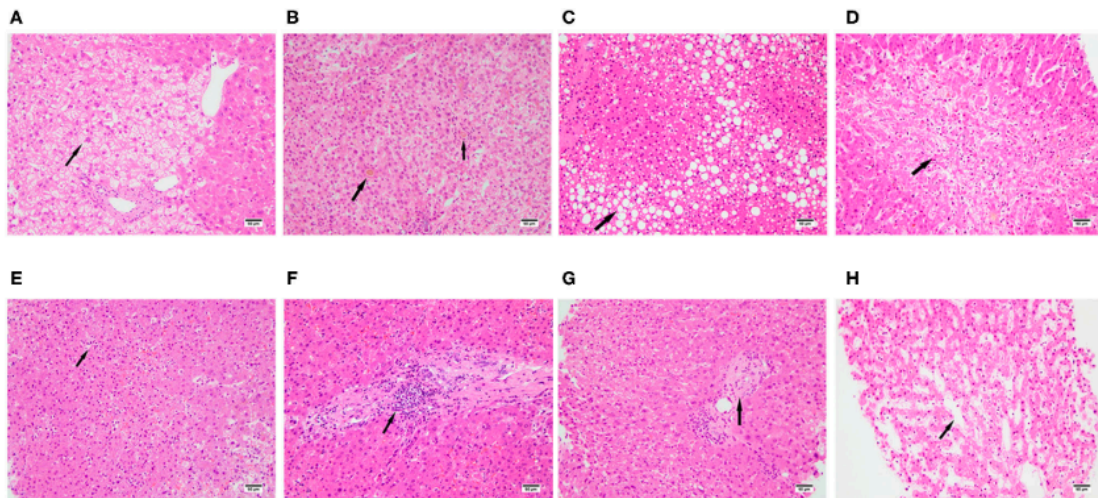


Figura 3 – Espectro de alteraciones patológicas del tejido hepático (en paciente con COVID-19 post mortem). A) Hepatocitos edematosos B) Colestasis C) Esteatosis D) Necrosis hepatocelular E) Inflamación lobulillar F) Inflamación portal G) Fibrosis H) Dilatación de los sinusoides, Bars = 50 um (A-D) Adaptado de (37)

- **Lesión inmunomediada.**

La alteración de las enzimas hepáticas podría estar asociado al proceso inflamatorio (lesión endotelial) e/o hipoxia (microtrombos y shock). La infección por SARS-CoV-2, genera una respuesta inflamatoria con liberación de citoquinas como interleucina 6, 2, 10 (IL6, IL2, IL10), factor de necrosis tumoral alfa (FNT alfa) e interferón gamma (IFN gamma), con la resolución de los casos leves, o puede ser una respuesta exagerada (tormenta inflamatoria) que puede llevar a falla multiorgánica y muerte.(38).

La tormenta inflamatoria es la hiperactivación de la inmunidad innata en el contexto de deplección de células T, característico de los casos severo de COVID-19 que están asociados a aumento de marcadores inflamatorios, una de las mas destacadas citosinas es la IL-6 así como también PCR y LDH.(12) Una respuesta

inflamatoria importante puede causar citopenias, daño del tejido hepático (aumento de transaminasa y LDH) y coagulopatía (Figura 4).

Los pacientes con COVID-19 severa presentan aumento de las enzimas hepáticas (33,39) y asocian incremento de marcadores inflamatorios (40,41), pudiendo estar relacionado a la tormenta inflamatoria que va a llevar a falla de órganos, manifestándose con la alteración de las enzimas hepáticas. Fu *et al.*, en un estudio multicéntrico, retrospectivo, mostró asociación de leucocitosis y PCR aumentada con enzimas hepáticas alteradas en pacientes con COVID-19.(25)

La IL6 podría tener un importante rol en dirigir al estado de hipercoagulabilidad tanto en el lecho hepático como sistémico, a través de daño inmunológico se produce injuria endotelial con incremento de expresión de niveles incrementado del factor *Von willebrand* en el lecho vascular del hígado, pudiendo producirse excesiva trombina que inhibe la fibrinólisis, como consecuencia deposición de microtrombos y disfunción microvascular (42). De 43 biopsias hepáticas realizadas en pacientes con COVID-19 fueron observados microtrombos en 23 (53%), encontrando asociación con incremento de transaminasas(43). Sin embargo, en otro estudio se evaluó la activación coagulación en los vasos intrahepáticos a través de marcadores como C4d (activación del complemento), C5d y CD61(activación de plaquetas) encontrándose en el 22%, 0% y 14.8% de las muestras respectivamente, demostrando escasa activación de los factores de la coagulación localmente y de la agregación plaquetaria. atribuyéndoles a los eventos vasculares en otros estudios probablemente a alteraciones de la coagulación sistémica. (44)

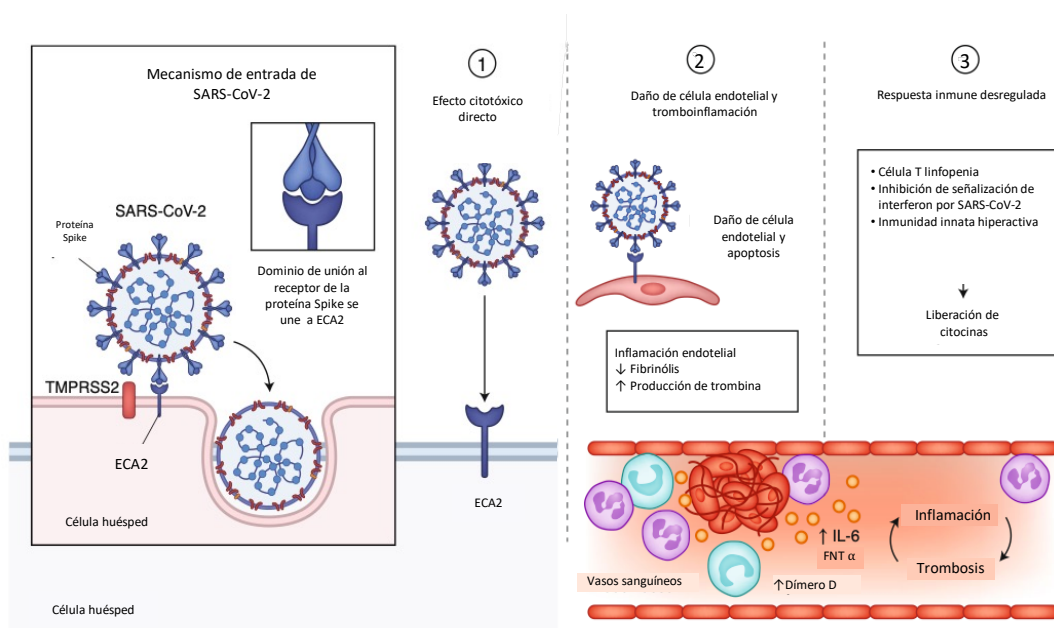


Figura 4 – Fisiopatología COVID-19. SARS-CoV-2 entra en las células a través de la interacción de la proteína S (spike) con el receptor de entrada ECA2. Mecanismo propuesto del daño celular por SARS-CoV-2: 1) Daño directo del Virus. 2) Daño de células endoteliales y tromboinflamación. 3) Respuesta inmune desregulada e inflamación excesiva causada por la inhibición de la señal del Interferón, depleción Células T, citosinas proinflamatorias (IL-6 y FNT alfa). ECA2 – Enzima convertidora de angiotensina 2. Adaptado de (42)

• Hepatotoxicidad

Enzimas hepáticas alteradas en la admisión en pacientes con COVID-19, podría ser causado por fármacos antes de la hospitalización, sin embargo, actualmente no hay un tratamiento específico por COVID-19. Descripción de tratamientos previos de la admisión es escasa, además condiciones pre-existentes tendrían influencia también en las alteraciones. Medicamentos usados previos a la admisión, como acetaminofén, antibióticos, corticoides, antivirales, en dosis no

establecidas e incluso medicamentos no autorizados como profilaxis como ivermectina, que son potencialmente hepatotóxicos.

Sólo los corticoides mostraron reducir la mortalidad (45). Durante la hospitalización son principalmente usados los antibióticos y los corticoides, en casos severos con sobreinfecciones, antibióticos de amplio espectro, antifúngicos, antivirales son utilizados, la combinación de estos podría causar daño hepático, además de los medicamentos en investigación. Un estudio por Cai *et al.*, mostró que el uso de lopinavir/ritonavir durante la hospitalización tuvo asociación con el aumento de enzimas hepáticas. (23) Así también Yip *et al.*, demostró que además de lopinavir/ritonavir, los corticoides estaban asociados con alteración de las enzimas hepáticas.(26) Por otro lado en otro estudio se reportó que no había diferencia con los fármacos antes de la admisión. (32)

- **Enfermedad hepática Pre-existente**

Las enfermedades hepáticas pre-existentes, tiene una variedad de subgrupos cada uno con sus propias características (enfermedad de hígado graso asociado a disfunción metabólica [MAFLD], virales, cirrosis) y con diferente prevalencia.

Si la enfermedad hepática pre-existente tiene un rol en el curso clínico es controversial. La prevalencia de hepatopatía previa es variable 6.8% - 21% entre los diferentes estudios.(8,25,28,46). Yadav *et al.*, en una revisión sistemática con 2115 pacientes reportó que la prevalencia de hepatopatía previa fue 4%, (virus de hepatitis B, fue la más frecuente). Hay estudios que sugieren que pacientes con hepatopatía crónica son mas susceptibles, y tienen incrementado riesgo de complicaciones y mortalidad (47–49). Por otro lado, hay estudios que no encontraron asociación (46,50). Que subgrupo es más susceptible, es desconocido.

Los pacientes con cirrosis tienen disfunción del sistema inmune, que pueden predisponer a mayor susceptibilidad a infecciones y generar una respuesta inflamatoria aberrante (51), se ha demostrado a través en modelos organoides, que los hígados con cirrosis tienen incrementada la expresión de receptores ACE2 comparado con un hígado no cirrótico(2)

En un estudio multicéntrico por Marjot *et al.*, se demostró que los pacientes con cirrosis descompensada tienen mayor riesgo de mortalidad comparados con aquellos sin cirrosis (32% vs 8%) (52). MAFLD, la más frecuente de las hepatopatías pre-existentes, tiene un perfil en común con pacientes con COVID-19 en riesgo: edad avanzada, diabetes mellitus, hipertensión arterial y riesgo cardiovascular, obesidad (13). Pacientes con MAFLD, presentan grado de inflamación crónica (IL 6 aumentada), que compromete el sistema inmune y causa disfunción endotelial microvascular (53). En una revisión sistemática por Heygi *et al.*, demostró que los pacientes con MAFLD fue asociado a un riesgo aumentado de COVID-19 severo comparado con aquellos que no tienen MAFLD.(54)

Si la hepatopatía pre-existente, podría interferir con los hallazgos encontrados: enzimas hepáticas alteradas, empeorando la función hepática, es controversial.

- **Otras causas en pacientes críticos**

Pacientes críticos con COVID-19, pueden presentar cambios hemodinámicos debido a shock, falla cardíaca e/o respiratoria y manifestarse como hepatitis hipóxica. Durante el shock hay caída de la presión arterial, se reduce la perfusión arterial del hígado, llegando a producir daño celular. Durante la falla cardíaca además de la caída de presión, puede presentarse congestión venosa hepática que podría predisponer a los hepatocitos a mayor hipoxia.(55)

2.4. Pronóstico de transaminasas alteradas

Es controversial el valor pronóstico de las transaminasas alteradas, algunos estudios demostraron, asociación con la severidad y complicaciones, (29) así como con la mortalidad. (56). En un estudio prospectivo multicéntrico con 1611 pacientes por Mendizabal et al. reportaron asociación de las transaminasas alteradas en la admisión con la severidad y mortalidad. Kovalic et al., en una revisión sistemática con 586 pacientes reportaron la asociación AST elevada con la severidad.(22). En otra revisión sistemática por Yip et al. con 1040 pacientes, reportaron que enzimas elevadas tuvieron mayor riesgo requerir ventilación mecánica, admisión en la UTI y mortalidad. (26) De acuerdo con estos resultados, una revisión sistemática por Sharma et al. con 12 882 pacientes, encontraron la prevalencia de AST aumentada en 41.1% y ALT en 29.1%, y la asociación de estas con la severidad de la enfermedad. (9) Por otro lado hay estudios que mostraron que no hay asociación con evolución clínica tórpida.(8,57).

3. JUSTIFICACIÓN

Latinoamérica es una de las regiones más afectadas por la pandemia de COVID-19 y de la cual los datos clínicos son escasos. COVID-19 va más allá del sistema respiratorio y tiene impacto en los diferentes sistemas, el hígado es afectado por esta enfermedad sin tener clara la fisiopatología, a la cual se le atribuye diferentes factores como lesión por propio virus, alteración inmunológica (respuesta inflamatoria e hipoxia), hepatotoxicidad y/o enfermedad hepática previa, causando dudas en la práctica clínica y manifestaciones hepáticas poco claras, expresadas con alteración de las enzimas hepáticas, con impacto en el curso clínico e resultados finales poco conocidos.

La finalidad de este estudio es determinar la prevalencia de las enzimas hepáticas alteradas así como determinar si hay asociación con evolución clínica y resultados finales em uma grande corte de um hospital geral no sul do Brasil.

4. PREGUNTA DE LA INVESTIGACIÓN

¿Las alteraciones de las enzimas hepáticas en la admisión están asociadas a mayor severidad, complicaciones y mortalidad, en casos de pacientes con COVID-19?

5. HIPOTESIS

Las alteraciones de las enzimas hepáticas en la admisión están asociadas a mayor severidad, complicaciones y mortalidad en casos de pacientes con COVID-19.

6. OBJETIVOS

6.1. General

- Evaluar las alteraciones de las enzimas hepáticas desde el punto de vista clínico en pacientes con COVID-19.

6.2. Específicos

- Determinar la prevalencia de las enzimas hepáticas alteradas en la admisión.
- Evaluar los parámetros inflamatorios como PCR, LDH, CK y leucocitos y compararlos entre los grupos.
- Correlacionar las alteraciones hepáticas con la evolución clínica, severidad de la enfermedad, mortalidad y estancia hospitalaria.

7. ARTICULO ORIGINAL

Titulo: “Minimal liver enzymes abnormalities at admission are related to severe COVID-19 clinical course in a large Brazilian cohort”

Author names and affiliations: Ysela Picon^{1,2}, Dvora Joveleviths^{1,3,4}, Mario Reis Alvares-da-Silva^{1,2,3,4}

¹Graduate Program: Sciences in Gastroenterology and Hepatology, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

²World Gastroenterology Organisation Porto Alegre Hepatology Training Center, Porto Alegre, Brazil

³School of Medicine, UFRGS, Porto Alegre, Brazil

⁴Gastroenterology and Hepatology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Corresponding author: Mario Reis Alvares-da-Silva, GI/Liver Unit Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 235, Porto Alegre, Brazil, 90035-903; marioreis@live.com.

Abstract

Background and aims: Coronavirus disease (COVID-19) is a multisystemic disease, primarily affecting the respiratory system. Liver involvement is frequent during the disease, but the impact on the clinical course and outcomes are controversial. The aim was to assess liver function at the admission and evaluate its effects on severity and mortality in hospitalized patients with COVID-19.

Methods: this is a retrospective study of hospitalized patients in a tertiary hospital in Brazil, with PCR confirmed SARS-CoV-2 infection between April and October 2020. 1080 out of 1229 patients had liver enzymes on admission and were divided in two cohorts, based on the presence or absence of abnormal aminotransferases. Demographic, clinical, laboratory, imaging, clinical severity, and mortality were evaluated. Patients were followed until discharge or death.

Results: Median age was 60 years and 51.5% were male. The more frequent comorbidities were hypertension (51.2%), diabetes (31.6%). Chronic liver disease and cirrhosis were present in 8.6% and 2.3%, respectively. Abnormal aminotransferases higher than 40 IU/L were present in 56.9% of patients [mild (1-2 times): 63.9%; moderate (2-5 times):29.8%; severe (>5 times):6.3%]. Patients with abnormal aminotransferases had a higher proportion of severe COVID-19 cases (59% vs 44%; $p<0.001$) than those with normal results. Male gender [RR 1.49, $p=0.007$], increased total bilirubin [RR 1.18, $p<0.001$] and chronic liver disease [RR 1.47, $p=0.015$] were predictors of abnormal aminotransferases on admission. Patients with abnormal aminotransferases had a higher risk of disease severity [RR 1.19; $p=0.004$]. Mortality was 23.6%, and patients above 60 years [RR 2.3, $p<0.001$] had higher risk of mortality as well as increased INR [RR 1.26, $p=0.01$] and/or D-dimer [RR1.05, $p<0.001$]. Our finds no showed association among abnormal aminotransferases and mortality.

Conclusions: Elevated aminotransferases are common in COVID-19 hospitalized patients and were independently correlated with severe COVID-19. Even mild AST or ALT abnormalities at admission may be a severity prognostic marker.

Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 surprised the world in the early 2020 and has become a challenge, remaining unpredictable until now. More than 296.496.809 cases of COVID-19 among them 5.462.631 deaths in the world were reported by WHO by January 2022. In Brazil, more than 600,000 deaths were reported. [1]

COVID-19 is a multisystemic disease, mainly affecting the respiratory system with a broad spectrum of disease, from mild to critical, with complications as pulmonary thromboembolism until multi-organ failure [2,3]. Liver is involved, and several studies reported a wide range of prevalence of abnormal liver enzymes [4–9]. The exact pathophysiology of liver damage is unknown, and it is attributed to multiple factors as: a) SARS-CoV-2 liver replication, b) systemic inflammatory response or hypoxia; c) hepatotoxic drugs, and d) pre-existing comorbidities [10]. Even liver biopsy available data showed variables histological changes, suggesting a multiple insult [11,12].

Varying levels of abnormal liver enzymes, most increased transaminases have been associated with disease severity, complications and mortality in some studies [13,14], although its impact on clinical course is still controversial [15]. Furthermore, very few studies in Latin America have addressed this issue.

The aim of present study was to evaluate the prevalence of abnormal liver enzymes on admission in patients with COVID-19 admitted a tertiary general hospital in South of Brazil, as well as assess its impact on in-hospital severity and mortality.

Patients and methods

Study design

This is a retrospective single-center cohort study analyzing patients admitted between April 1st and October 31, 2020, at a university hospital in Porto Alegre, Brazil. The study was approved by the Ethics Committee of the Hospital de Clinicas in Porto Alegre (Project N° 20200340). Patients were exempted from sign informed consent.

Patients' characteristics

Patients aged ≥ 18 years with nasopharyngeal or oropharyngeal swab samples RT-PCR SARS-CoV2 positive were enrolled and followed until discharge of hospital, or death.

Cohort characteristics

We collected from electronic medical records the following data: demographics, medical history, clinical characteristics, admission laboratory [complete blood count, C-reactive protein, creatine kinase, lactate dehydrogenase, D-dimer, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), creatinine, international normalized ratio (INR) and prothrombin time (PT)], radiological reports and medication history. COVID-19 therapy, including antibiotic, antivirals, steroids and others, were evaluated before admission. Lymphopenia was considered less than $1000 \times 10^3/uL$ [16]. Liver enzymes enabled to separate the cohort into two subgroups based on AST and/or ALT $\geq 41IU/L$: abnormal liver enzymes (ALE) and normal liver enzymes (NLE) [17]. Liver enzymes elevations on admission (AST and/or ALT), were categorized as mild (<2 times ULN), moderate (2-5 times ULN), and severe (>5 times ULN) as previously described elsewhere [6,9]

COVID-19 severity

Severe COVID-19 was defined as a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mmHg or organ failure (ventilatory support requirement, vasoactive drug, or renal substitute therapy with hemodialysis [18]). Patients were categorized in severe and no severe and compared.

Definitions of comorbidities

Chronic kidney disease and end-stage renal disease were defined as usual [19] and included as “kidney disease”. Coronary artery disease and congestive heart failure were grouped as “cardiovascular disease”. Chronic liver disease (CLD) was the presence of at least 6 months long history of liver damage before the admission. Liver steatosis was defined by liver image showing hepatic steatosis 3 months before or during hospitalization. MAFLD was defined according to published criteria. [20]

Outcomes

The main outcomes assessed were COVID-19 severity and mortality during hospitalization.

Statistical analysis

Categorical variables were reported as percentages and comparisons were made using chi-square test or Fisher’s exact test. Continuous variables were reported as median (minimum - maximum) or mean with standard deviation, comparisons were made with Student’s t test or Mann-Whitney U test, according to distribution (Shapiro - Wilk test). $P < 0.05$ was considered as statistical significance. To explore independent factor associated with severe disease and mortality was performed a univariate analysis including demographic, clinical and laboratory data. Significant variables were considered to perform a model of multivariate analysis using

Cox regression in mortality and Poisson regression in disease severity. In the same way were explored factors associated with abnormal liver enzymes. Multivariate analysis in each case was adjusted for age >60, sex, hypertension, T2DM and previous history of liver disease. Data analysis was performed with IBM SPSS Statistics, version 25.0. (IBM Corp., Armonk, N.Y., USA)

Results

Of 1,508 medical records referring to 1,454 patients, 1,229 were included as showed in a figure 1. Table 1 summarizes demographic and clinical data. Median age was of 60 years, most patients were male, and comorbidities were common, especially hypertension, obesity, and diabetes. Chronic liver disease was present in 106 (8.6%) patients. Among COVID-19 symptoms, dyspnea and fever were present in more than 50%. Chest imaging abnormalities were present in 882 (71.80%). Half of the included patients were admitted to the intensive care unit (ICU). Liver injury, defined as AST and/or ALT ≥ 2 x ULN, and total bilirubin ≥ 2 x ULN and/or $1.7 \geq$ INR), was present in only 1.3%. A significant number of patients received COVID-19 intended treatment before admission, as demonstrated.

Table 2 shows baseline laboratory on admission. Median AST and ALT were 40 and 36 UI, respectively, and median bilirubin was 0.5mg/dL. Canalicular enzymes were seldom requested. Inflammatory markers such as CRP and LDH were usually high, as well as d-dimer. During hospitalization, antibiotics and steroids were highly prescribed (Table 1). Investigational products were given to 126 (10.3%), including convalescent plasma therapy and baricitinib.

Characteristics of Patients with Abnormal Liver Enzyme

Of total 1,229 patients, 1,080 (87.9%) patients had record of AST and/or ALT available on admission, among whom 614 (56.9%) had abnormal liver enzymes (ALE group). Table 3 details the obtained results, comparing patients with normal and abnormal liver enzymes.

Patients with ALE were younger, male, and had a more frequent history of previous liver disease. It is noteworthy that inpatients with elevated liver AST and/or ALT, mild elevation was present in 63.8%, while 29.8% had moderate and 6.36% severe abnormalities. Table 4 displays a Poisson regression of factors associated with abnormal liver enzymes. Inflammatory markers were higher in ALE patients, as well as were a list of variables, including COVID-19 severity. However, in multivariable analysis only male gender, previous liver disease and bilirubin were significantly associated as independent risk factors of liver enzymes abnormalities. ALE patients presented a higher length of stay [9 days (0-94) vs 7.5 days (0 - 64), $p = 0.009$]

Characteristics of Patients with severe COVID-19

Of the total 1,229, 639 (51.9%) patients presented severe COVID-19. Compared with non-severe disease, they were older, male, and presented more comorbidities (Table 5)

A multivariate analysis confirmed that ALE, age above 60 years old, the presence of diabetes and some laboratory abnormalities, such as high CRP and d-dimer levels were independently related to the disease severity. (Figure 2)

Mortality

Factors associated with mortality are presented in table 6. After an adjusted multivariate analysis, age above 60, coagulation abnormalities and higher d-dimer levels were significantly associated with it.

Discussion

This study evaluated a large cohort of patients with COVID-19 admitted to a tertiary hospital, and demonstrated that even mild AST and ALT abnormalities are predictors of disease severity. Over half of our cohort (58.6%) presented abnormal liver enzymes on admission; this figure is within of wide range (14 - 81.7%) reported by others studies that observed abnormal liver enzymes on admission or during hospitalization. [21–29]. The results' variability is related to different liver enzymes cutoffs used and to the significant difference among studied populations. We considered AST and/or ALT ≥ 41 , as a marker of liver enzymes abnormality, in line with others studies. [7,23,25] Having this cutoff as reference we found that ALE on admission was significantly associated to the COVID-19 severity in a multivariate model. ALE on admission, may be a manifestation of liver and multisystemic COVID-19 involvement could lead clumsy evolution with adverse outcomes, as reported by other [7,32–34]. There are few previous studies in South America suggesting association between ALE and severity disease. A Brazilian multicenter study included 406 patients with COVID-19 and reported a prevalence of twice elevated AST and ALT levels (ALEx2) at admission of 14%. Adjusted for age and sex, in-hospital all-cause mortality was higher in this group than inpatients with lower enzymes [30]. In the present study we found 29.8% of patients with ALEx2 at admission, but they did not correlate to COVID-19 severity or mortality. One smaller Latin American study included 298 patients and demonstrated that ALEx2 on admission was independently associated with 1-week mortality. In addition, patients without ALEx2 at admission who developed 1-week de novo-ALEx2 (39.8%) presented a higher mortality during the second week[31]. Cai *et al.*, reported 76.3% of liver enzymes increment during hospitalization in COVID-19 patients, and found association with Lopinavir/Ritonavir [7]. In the present study, only 15.87% of patients presented de novo AST and/or ALT abnormalities during the hospital stay without association to severity and mortality. However, a little sample size in the sub-analysis limits ours results.

Severe COVID-19 (SC-19) patients were older (> 60 years old), presented more comorbidities and higher inflammatory markers, such as leukocytes, CRP, LDH and CPK with lower lymphocytes similar to some other reports.[41–44] We found higher levels of inflammatory markers in ALE patients, suggesting SARS-CoV-2 induced inflammatory response could be related to liver injury as inflammatory reaction could lead to cytokine storm which is a key in the severe disease, [39,40]. We also found increased D-dimer as risk factor of SC19, the same described by some other authors[38,41], and could be unchained by inflammatory response. We found association among D-dimer and ALE in univariate, although it lost significance in the multivariate analyze. D-dimer is a hemostatic biomarker, higher levels of D-dimer indicate that there is fibrin generation and fibrinolysis, in patients with COVID-19 could be extrahepatic origin.[42]

In this study, male gender, CLD and increased total bilirubin were predictors of ALE at admission. Previous studies reported ACE2 receptors are mediated by androgens, being higher in men [5]. CLD was reported in 8.6%, similar to the prevalence reported by Hao et al. [24] but higher than the results of a systematic review (3.6%)[44]. Some reports suggest CLD increases the risk of complications or mortality. However, we did not find any association here, the same reported in some studies [44,45], including a meta-analysis of 8,800 patients[45]. On the other hand, a recent Brazilian study with 1,034 COVID-19 patients showed that CLD is linked to the mortality. [46]. Moreover, patients with CLD could present higher expression of ACE2 receptor and could be more susceptible to the virus [10], and Child-Pugh C cirrhotics have an increased risk of complications and mortality[47,48]. We found that ALE on admission was associated with SC-19 despite having less diabetes, hypertension and chronic kidney disease, supporting the prognostic role of liver enzymes. In addition, ALE patients had longer hospital stay, as we demonstrated here in agreement some studies. [49] A multicenter retrospective study with 1765 patients in Hubei province, in China, reported an increased

mortality risk in cases of elevated AST (above 34 U/L) [50], although we did not find it, in line with some other studies. [24] [15] In the present study, 23.6% of patients died, and patient aged above 60 years had a higher risk of death [39] These findings are consistent with several studies [14,51,52] including a Brazilian one [46]. This finding may be related to the physiological changes of aging. Furthermore, patients with abnormal coagulation with increased INR and elevated D-dimer at admission also have an increased risk of mortality[41]. Coagulation disorders might be related to inflammatory storm as well. [53].

This study has some strengths and limitations that should be considered. So far, this is the largest single centered study in Brazil, conducted at a high-volume University tertiary hospital, and it is the first solely reporting results from the South Brazil. On the other hand, it was retrospective, and some data could be incomplete or not recorded, such as medications, alcohol consumption, body mass index, and canalicular enzymes at admission.

In conclusion, we demonstrated in a large Brazilian cohort that prevalence of abnormal AST and/or ALT on admission is high (more than 50%) and that mild AST and/or ALT abnormalities are predictors of high-risk severe COVID-19. Thus, AST and ALT should be determined on admission and, in case of abnormalities, a careful observation of clinical course is advocated.

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALB: albumin; AHT: arterial hypertension, ALP: alkaline phosphatase, COVID-19: coronavirus disease-2019, CI: confidence interval, CK: Creatine kinase, CRP: c-reactive protein, CLD: chronic liver disease, DM: diabetes mellitus, FLD: fatty liver disease, ICU: intensive care unit, LDH: lactic dehydrogenase, LYM: lymphocyte, NEUT: neutrophil, OR: odds ratio,RR: relative risk, SARS-CoV-2: severe acute respiratory syndrome coronavirus,SD: standard deviation, TB: Total bilirubin.

Acknowledgments: Not applicable

Conflicts of interest: None.

REFERENCE

- [1] WHO Coronavirus Disease (COVID-19) Dashboard 2022. <https://covid19.who.int> (accessed January 5, 2022).
- [2] Martines RB, Ritter JM, Matkovic E, Gary J, Bollweg BC, Bullock H, et al. Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, united states. *Emerg Infect Dis* 2020;26:2005–15. <https://doi.org/10.3201/eid2609.202095>.
- [3] Thakur V, Ratho RK, Kumar P, Bhatia SK, Bora I, Mohi GK, et al. Multi-organ involvement in covid-19: Beyond pulmonary manifestations. *J Clin Med* 2021;10:1–19. <https://doi.org/10.3390/jcm10030446>.
- [4] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5:428–30. [https://doi.org/10.1016/S2468-1253\(20\)30057-1](https://doi.org/10.1016/S2468-1253(20)30057-1).
- [5] Harapan H, Fajar JK, Supriono S, Soegiarto G, Wulandari L, Seratin F, et al. The prevalence, predictors and outcomes of acute liver injury among patients with COVID-19: A systematic review and meta-analysis. *Rev Med Virol* 2021:1–8. <https://doi.org/10.1002/rmv.2304>.
- [6] Mendizabal M, Piñero F, Ridruejo E, Anders M, Silveyra MD, Torre A, et al. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. *Ann Hepatol* 2021;21:100298. <https://doi.org/10.1016/j.aohep.2020.100298>.
- [7] Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. *J Hepatol* 2020;73:566–74. <https://doi.org/10.1016/j.jhep.2020.04.006>.

- [8] Medetalibeyoglu A, Catma Y, Senkal N, Ormeci A, Cavus B, Kose M, et al. The effect of liver test abnormalities on the prognosis of COVID-19. *Ann Hepatol* 2020;19:614–21. <https://doi.org/10.1016/j.aohep.2020.08.068>.
- [9] Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020;72:807–17. <https://doi.org/10.1002/hep.31404>.
- [10] Marjot T, Webb GJ, Barritt AS, Moon AM, Stamataki Z, Wong VW, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021;18:348–64. <https://doi.org/10.1038/s41575-021-00426-4>.
- [11] Lagana SM, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol an Off J United States Can Acad Pathol Inc* 2020;33:2147–55. <https://doi.org/10.1038/s41379-020-00649-x>.
- [12] Vishwajeet V, Purohit A, Kumar D, Vijayvergia P, Tripathi S, Kanchan T, et al. Evaluation of liver histopathological findings of COVID-19 by minimally invasive autopsies. *J Clin Exp Hepatol* 2021. <https://doi.org/10.1016/j.jceh.2021.07.004>.
- [13] Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients – A systematic review and meta-analysis. *Ann Hepatol* 2021;21:100273. <https://doi.org/10.1016/j.aohep.2020.10.001>.
- [14] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for

- mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- [15] Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* 2020;92:797–806. <https://doi.org/10.1002/jmv.25783>.
- [16] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- [17] Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. vol. 10. 2016. <https://doi.org/10.1007/s12072-015-9675-4>.
- [18] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Disponible en: <https://covid19treatmentguidelines.nih.gov/>. *Natl Inst Heal* 2020;2019:130.
- [19] Andrassy KM. Comments on “KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.” *Kidney Int* 2013;84:622–3. <https://doi.org/10.1038/ki.2013.243>.
- [20] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020;73:202–9. <https://doi.org/10.1016/j.jhep.2020.03.039>.
- [21] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges.

- Lancet Gastroenterol Hepatol 2020;5:428–30. [https://doi.org/10.1016/S2468-1253\(20\)30057-1](https://doi.org/10.1016/S2468-1253(20)30057-1).
- [22] Harapan H, Karunia J, Supriono F, Soegiarto G, Wulandari L, Seratin F, et al. The prevalence, predictors and outcomes of acute liver injury among patients with COVID - 19: A systematic review and meta - analysis 2021:1–8. <https://doi.org/10.1002/rmv.2304>.
- [23] Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, et al. Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. *Hepatology* 2021;73:1509–20. <https://doi.org/10.1002/hep.31446>.
- [24] Hao S-R, Zhang S-Y, Lian J-S, Jin X, Ye C-Y, Cai H, et al. Liver Enzyme Elevation in Coronavirus Disease 2019. *Am J Gastroenterol* 2020; Publish Ah:1075–83.
- [25] Yip TCF, Lui GCY, Wong VWS, Chow VCY, Ho THY, Li TCM, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut* 2021;70:733–42. <https://doi.org/10.1136/gutjnl-2020-321726>.
- [26] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. 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;8:475–81. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5).
- [27] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13. <https://doi.org/10.1016/S0140->

6736(20)30211-7.

- [28] Hamid S, Alvares Da Silva MR, Burak KW, Chen T, Drenth JPH, Esmat G, et al. WGO Guidance for the Care of Patients with COVID-19 and Liver Disease. *J Clin Gastroenterol* 2021;55:1–11. <https://doi.org/10.1097/MCG.0000000000001459>.
- [29] Marín Dueñas I, Vega J, Carrillo-Ng H, Veramendi-Schult I, Zavaleta Alva R, Vásquez L, et al. P-27 Alteration in Liver Function Tests Among Patients Hospitalized for Covid-19: a Multicentric Study in Peru. *Ann Hepatol* 2021;24:100391. <https://doi.org/10.1016/j.aohep.2021.100391>.
- [30] Pozzobon FM, Perazzo H, Bozza FA, Rodrigues RS, de Mello Perez R, Chindamo MC. Liver injury predicts overall mortality in severe COVID-19: a prospective multicenter study in Brazil. *Hepatol Int* 2021;15:493–501. <https://doi.org/10.1007/s12072-021-10141-6>.
- [31] Balderramo D, Mattos AZ, Mulqui V, Chiesa T, Plácido-Damián Z, Abarca J, et al. Abnormal Liver Tests during Hospitalization Predict Mortality in Patients with COVID-19: A Multicenter Study from South America. *Can J Gastroenterol Hepatol* 2021;2021. <https://doi.org/10.1155/2021/1622533>.
- [32] Piano S, Dalbeni A, Vettore E, Benfaremo D, Mattioli M, Gambino CG, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. *Liver Int* 2020;40:2394–406. <https://doi.org/10.1111/liv.14565>.
- [33] Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated Liver Biochemistries in Hospitalized Chinese Patients With Severe COVID-19: Systematic Review and Meta-analysis. *Hepatology* 2021;73:1521–30. <https://doi.org/10.1002/hep.31472>.

- [34] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. *BMJ* 2020;369. <https://doi.org/10.1136/bmj.m1966>.
- [35] Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: A multicenter study of clinical features. *Am J Respir Crit Care Med* 2020;201:1380–8. <https://doi.org/10.1164/rccm.202002-0445OC>.
- [36] Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5:16–8. <https://doi.org/10.1038/s41392-020-0148-4>.
- [37] Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, et al. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. *Hepatology* 2020;72:389–98. <https://doi.org/10.1002/hep.31301>.
- [38] Hariyanto TI, Japar KV, Kwenandar F, Damay V, Siregar JI, Lugito NPH, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. *Am J Emerg Med* 2021;41:110–9. <https://doi.org/10.1016/j.ajem.2020.12.076>.
- [39] Xu G, Ye M, Zhao J, Liu F, Ma W. New view on older adults with COVID-19: comments on “SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes.” *GeroScience* 2020;42:1225–7. <https://doi.org/10.1007/s11357-020-00232-x>.
- [40] Marie D, Valle D, Kim-schulze S, Huang H, Beckmann ND, Nirenberg S, et al.

COVID-19 severity and survival. *Nat Med* 2019;26.

- [41] Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. *J Intensive Care* 2020;8:1–11. <https://doi.org/10.1186/s40560-020-00466-z>.
- [42] Ibañez C, Perdomo J, Calvo A, Ferrando C, Reverter JC, Tassies D, et al. High D dimers and low global fibrinolysis coexist in COVID19 patients: what is going on in there? *J Thromb Thrombolysis* 2021;51:308–12. <https://doi.org/10.1007/s11239-020-02226-0>.
- [43] Santana MF, Guerra MT, Hundt MA, Ciarleglio MM, Pinto RA de A, Dutra BG, et al. Correlation Between Clinical and Pathological Findings of Liver Injury in 27 Patients With Lethal COVID-19 Infections in Brazil. *Hepatol Commun* 2021;0:1–11. <https://doi.org/10.1002/hep4.1820>.
- [44] Kulkarni A V, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020;52:584–99. <https://doi.org/10.1111/apt.15916>.
- [45] Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. *Ann Hepatol* 2021;21:100273. <https://doi.org/10.1016/j.aohep.2020.10.001>.
- [46] Konstantyner T, Martins C, Lupi C, Yashiro S, Sanchez N. Baseline factors associated with death in a COVID-19 hospital cohort ., *Rev Saude Publica* 2021:1–5. <https://doi.org/https://doi.org/10.11606/s1518-8787.2021055003684> Copyright:

- [47] Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2021;19:1469-1479.e19.
<https://doi.org/10.1016/j.cgh.2020.09.027>.
- [48] Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021;74:567–77.
<https://doi.org/10.1016/j.jhep.2020.09.024>.
- [49] Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020;18:1561–6.
<https://doi.org/10.1016/j.cgh.2020.04.002>.
- [50] Liu X, Zhu L, Lu T, Liu X, Jiao D, Tang X, et al. Epidemiologic Characteristics of and Prognostic Factors for COVID-19 Among Hospitalized Patients: Updated Implications From Hubei Province, China. *Front Public Heal* 2021;9:1–10.
<https://doi.org/10.3389/fpubh.2021.726491>.
- [51] Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020;80:639–45. <https://doi.org/10.1016/j.jinf.2020.03.019>.
- [52] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934–43.
<https://doi.org/10.1001/jamainternmed.2020.0994>.

[53] RJ J, Ari M. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8:e46–7. [https://doi.org/10.1016/S2213-2600\(20\)30216-2](https://doi.org/10.1016/S2213-2600(20)30216-2).

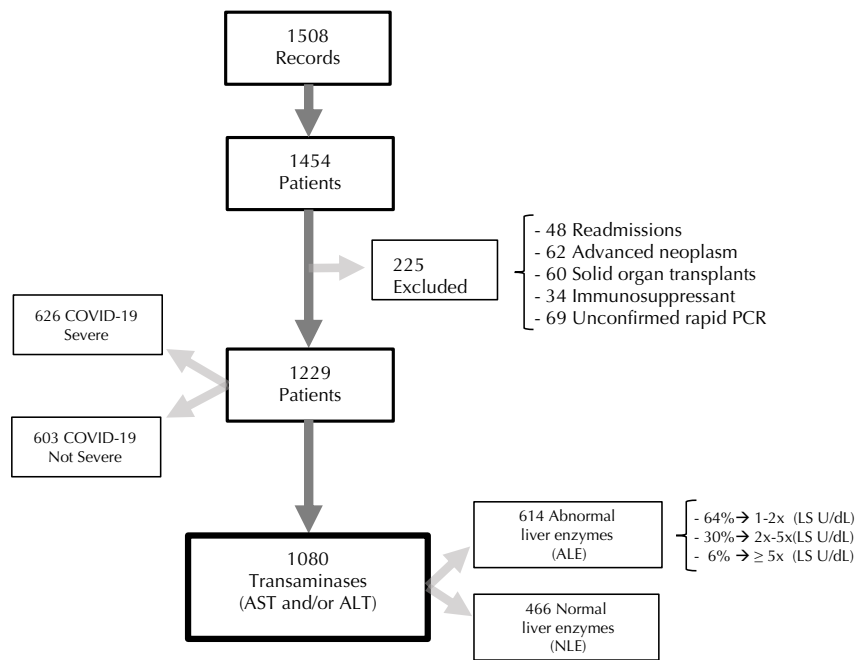


Figure 1: Patient's inclusion scheme.

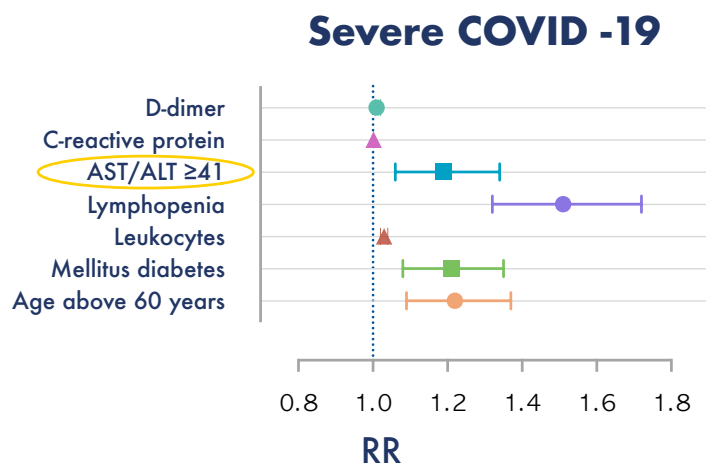


Figure 2: Factors associated with severe COVID-19.

Table 1. Demographics characteristics of patients with COVID-19

Study population: 1229 patients with COVID-19	n	Nº (%)
Age, median (minimum - maximum)	1229	60 (18-102)
Age above 60	1229	615 (50)
Age below 60	1229	614 (50)
Gender		
Male	1229	633 (51.5)
Female	1229	596 (48.5)
Comorbidities		
Hypertension	1227	629 (51.2)
Diabetes	1227	388 (31.6)
Obesity	981	428 (34.8)
Cardiovascular disease	1227	209 (17)
Kidney chronic disease	1227	97 (7.9)
Chronic liver disease	194	106(8.6)
MAFLD	171	47 (3.8)
Cirrhosis	1227	28 (2.3)
Clinical symptoms		
Dyspnea	1208	781(63.5)
Fever	1208	653 (53.1)
Cough	1208	191 (15.5)
Myalgia	1208	270 (22.0)
Diarrhea	1208	218 (17.7)
Abdominal pain	1208	51 (4.1)
Nausea and vomiting	1208	140 (11.4)
Anorexia	1208	107 (8.7)
Anosmia	1208	166 (13.5)
Ageusia	1208	100 (8.1)
Chest imaging		
Ground glass pattern	1164	883 (71.8)
Unilateral consolidation pattern	1164	47 (3.8)
Bilateral consolidation pattern	1164	54 (4.4)
No lesions	1164	180 (14.6)
Complications		
Liver injury	1080	16 (1.3%)
Pulmonary thromboembolism	263	77 (6.3)
Extrapulmonary thrombosis	263	39 (3.2)
Severe COVID-19	1229	639 (52.0)
Oxygen support	1229	952 (77.5)
ICU admission	1229	615 (50.0)
Mechanical ventilation	1229	441 (35.9)
Hemodialysis support	1229	203 (16.5)

Vasoactive drugs support	1229	437 (35.6)
ECMO support	1229	11 (0.9)
Scores ICU		
APACHE	561	11 (0 - 33)
SAPS3	555	58 (27 - 145)
SOFA	477	5 (1 - 16)
Treatment before admission		
Antibiotic therapy	810	492 (40)
Antiviral therapy	810	64 (5.2)
Steroids therapy	810	124 (10.1)
Others therapies	810	26 (2.1)
Treatment in hospital		
Antibiotics	1229	1016 (82.7)
Antiviral therapy	1229	167 (13.6)
Steroids	1229	785 (63.9)
Other	1229	264 (21.5)
Hospital stay		
Emergency	1229	0 (0-5)
Hospitalization	1229	5 (0 - 169)
ICU	1229	10 (0 - 94)
Total hospital stay	1229	8 (0 - 176)
Clinical evolution		
Discharge	1229	802 (65.3)
Transfer	1229	137 (11.1)
Death	1229	290 (23.6)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; MAFLD, metabolic dysfunction associated fatty liver disease;

Table 2. Admission laboratory test of patients with COVID-19.

Tests in study population	reference values	N° patients tested	Value, median (minimum-maximum)
Hematology			
WBC (x 10 ⁹ /L)		1196	7.78 (1.47 - 40.01)
Neutrophils (x 10 ⁹ /L)		1192	6.05 (0.24 - 35.21)
Lymphocytes (x 10 ⁹ /L)		1192	0.90 (0.04 - 9.44)
Lymphopenia (<1000)		687	0.65 (0.04 - 0.99)
Platelets (x 10 ⁹ /L)	150 - 450	1188	211 (9 - 722)
Biochemical			
AST at admission (U/L)	<41	1074	40 (8 - 1992)
ALT at admission (U/L)	<41	1082	36 (5 - 1665)
AST ALT ≥41 at admission			
AST		604	57 (19 - 1992)
ALT		613	56 (6 - 1665)
AST Highest hospitalization (U/L)		1126	43 (8 -27 087)
ALT Highest hospitalization (U/L)		1131	42 (5 - 5588)
Total bilirubin (mg/dL)	0.3 - 1.2	1027	0.5 (0.3 - 6.1)
TB >1.2 (mg/dL)		61	1.8 (1.3 - 6.1)
ALP (U/L)	40 - 150	88	95.5 (38 - 564)
GGT (U/L)	<59	46	95 (10 -1163)
Albumin (g/dL)	3.5 - 5.2	150	3.18 (±0.69)
Creatinine (mg/dL)		1183	0.97 (0.37 - 16.85)
Inflammation			
CRP (mg/L)	< 5	1086	103.8 (1 - 487)
LDH (U/L)	15-220	956	374.5 (1.80 - 9 920)
CK (U/L)		953	98 (4.7 - 18 178)
Coagulation			
TP (s)	13		
INR	1	1052	1.09 (1 - 6.22)
D-dimer (ug/mL)	≤0.5	1040	1.05 (0.19 - 20)

Abbreviations: ALT, alanine aminotransferase; ALP, alkalina phosphatase; AST, aspartate aminotransferase; CK, creatine kinasa; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC: White blood cells.

Table 3. Clinical characteristics, laboratory on admission, among patients with abnormal liver enzymes and normal liver enzymes and among severe and no severe COVID-19

Clinical characteristics	n	All patients			p-value ^a	All patients with liver enzymes			p-value ^a
		COVID-19, No (%)	No severe COVID-19 (NSC19) (n=590)	Severe COVID-19 (SC19) (n=639)		Liver enzymes (n=1080)	Normal liver enzymes (NLE) (n=466)	Abnormal liver enzymes (ALE) (n=614)	
Age, median (minimum - maximum)	1229	60 (18-102)	54 (18-95)	63 (19 - 102)	<0.001	59 (19 - 102)	62.5 (19 - 102)	57 (19 - 94)	0.001
Age above 60	1229	615 (50)	238 (40.3)	377 (59.0)*		538 (49.8)	265 (56.9)*	273 (44.5)	
Age below 60	1229	614 (50)	352 (59.7)*	262 (41.0)	<0.001	542 (50.2)	201 (43.1)	341 (55.5)*	<0.001
Gender									
Male	1229	633 (51.5)	279 (47.3)	354 (55.4)*		559 (51.8)	210 (45.1)	349 (56.8)*	
Female	1229	596 (48.5)	311 (52.7)*	285 (44.6)	0.005	521 (48.2)	256 (54.9)*	265 (43.2)	<0.001
Comorbidities									
Hypertension	1227	629 (51.2)	257 (43.6)	372 (58.4)*	<0.001	561 (52.0)	259 (55.6)*	302 (49.2)	0.046
Diabetes	1227	388 (31.6)	142 (24.1)	246 (38.6)*	<0.001	339 (31.4)	177 (38.0)*	162 (26.4)	<0.001
Kidney chronic disease	1227	97 (7.9)	40 (6.8)	57 (8.9)	0.193	77 (7.1)	48 (10.3)*	29 (4.7)	0.001
Chronic liver disease	194	106(8.6)	48 (52.7)	58 (56.3)	0.724	91 (8.42)	33 (45.8)	58 (65.9)*	0.017
MAFLD	171	47 (3.8)	26 (31.0)	21 (24.1)	0.408	42 (3.9)	14 (22.6)	28 (36.4)	0.116
Cirrhosis	1227	28 (2.3)	10 (1.7)	18 (2.8)	0.257	21 (1.94)	6 (1.3)	15 (2.4)	0.253
Complications									
Pulmonary embolism	263	77 (6.3)	15 (18.8)	62 (33.9)*	0.02	69 (6.39)	25 (27.8)	44 (29.1)	0.937
Extrapulmonary thromboembolism	263	39 (3.2)	1 (7.7)	38 (46.3)*	0.02	36 (3.33)	9 (42.9)	27 (42.9)	1.00
Severe COVID-19						569 (100)	207 (44.4)	362 (59.0)	<0.001
Clinical evolution									
Discharge	1229	802 (65.3)	532 (90.2)*	270 (42.3)		705 (65.3)	326 (70.0)*	379 (61.7)	
Dead	1229	290 (23.6)	0 (0.00)	290 (45.4)*		250 (23.1)	87 (18.7)	163 (26.5)*	
Transfer	1229	137 (11.1)	58 (9.8)	79 (12.4)	0.001*	125 (11.6)	53 (11.4)	72 (11.7)	0.007
Laboratory findings, value, median (minimum - maximum)									
Hematology									
WBC (x 10 ⁹ /L)	1196	7.78 (1.47 - 40.01)	6.75 (1.81 - 34.51)	9.03 (1.47 - 40.01)	<0.001	7.81 (1.81 - 40.01)	7.43 (2.06 - 34.97)	8.22 (1.81 - 40.1)	<0.001
Neutrophils (x 10 ⁹ /L)	1192	6.05 (0.24 - 35.21)	4.91 (0.24 - 29.64)	7.37 (0.53 - 35.21)	<0.001	6.11 (0.24 - 35.21)	5.57 (0.45 - 26.93)	6.52 (0.24 - 35.1)	<0.001
Lymphocytes (x 10 ⁹ /L)	1192	0.90 (0.04 - 9.44)	1.11 (0.07 - 9.50)	0.75 (0.04 - 6.69)	<0.001	0.55 (0.04 - 9.5)	0.95 (0.13 - 4.02)	0.87 (0.04 - 9.5)	0.096
Lymphopenia (<1000)	687	0.65 (0.04 - 0.99)	0.71 (0.06 - 0.99)	0.5 (0.04 - 0.9)	<0.001	0.63 (0.04-0.99)	0.64 (0.13 - 0.99)	0.62 (0.04 -0.99)	0.548
Platelets (x 10 ⁹ /L)	1188	211 (9 - 722)	204 (20 - 722)	218 (9 - 685)	0.179	213 (9 - 713)	209.5 (22 - 643)	217 (9 - 713)	0.254

Biochemical									
AST admission (U/L)	1074	40 (8 - 1992)	35.5 (8 - 314)	44 (9 - 1992)	<0.001	52.5 (22 - 581)	27 (8 - 40)	57 (19 - 1992)	<0.001
ALT admission (U/L)	1082	36 (5 - 1665)	35 (5 - 518)	37 (6 - 1665)	0.095	51.5 (6 - 518)	22 (5 - 40)	56 (6 - 1665)	<0.001
Total bilirubin (mg/dL)	1027	0.5 (0.3 - 6.1)	0.5 (0.3 - 6.10)	0.5 (0.3 - 5.80)	0.017	0.6 (0.3 - 2.4)	0.4 (0.3 - 2.8)	0.5 (0.3 - 6.1)	<0.001
TB > 1.2 (mg/dL) No (%)						59 (5.9)	12 (2.8)	47 (8.1)	0.001
ALP (U/L)	88	95.5 (38 - 564)	90 (45 - 564)	96.5 (38 - 492)	0.729	93 (45 - 492)	84 (38 - 492)	117 (45 - 564)	0.003
GGT (U/L)	46	95 (10 -1163)	109 (10 -744)	80 (26 - 1163)	0.991	134 (18 - 1163)	53 (10 - 1163)	159 (17 - 144)	0.015
Albumin (g/dL)	150	3.18 (±0.69)	3.55 (±0.59)	2.88 (±0.64)	<0.001 ^b	3.20 (± 0.70)	3.4 (± 0.63)	3.07 (±0.74)	0.023 ^b
AST ALT ≥41 No (%)	614	614 (100)	252 (49.3)	362 (63.6)	<0.001				
AST≥41 (U/L)	604	57 (19 - 1992)	53 (23 - 314)	59 (19 - 1992)	<0.001				
ALT≥41 (U/L)	613	56 (6 - 1665)	59 (6-518)	52 (11 - 1665)	0.001				
Inflammation									
CRP (mg/L)	1086	103.8 (1 - 487)	65.7 (1 - 374.1)	140 (1 - 487)	<0.001	105.8 (1 - 487)	89.1 (1 - 487)	120.35 (1 - 444)	<0.001
LDH (U/L)	956	374.5 (1.80 - 9 920)	307 (1.98 - 1018)	464 (1.80 - 9920)	<0.001	374 (1.80 - 9920)	296 (1.88 - 999)	448 (3.17 - 9 920)	<0.001
CK (U/L)	953	98 (4.7 - 18 178)	83 (8 - 10 203)	117 (4.70 - 18 178)	<0.001	101 (4.70 - 16 981)	80 (4.7 - 1487)	121 (8.45 - 16 972)	<0.001
Coagulation									
INR	1052	1.09 (1 - 6.22)	1.06 (1-3)	1.13 (1 - 6.22)	<0.001	1.09 (1 - 6.22)	1.08 (1 - 3.14)	1.10 (1 - 6.00)	0.032
D-dimer (ug/mL)	1040	1.05 (0.19 - 20)	0.76 (0.19 - 20)	1.45 (0.19 - 20)	<0.001	1.03 (0.19 - 20)	0.9 (0.19 - 20.0)	1.15 (0.19 - 20.0)	<0.001
Hospital stay									
Total stay	1229	8 (0 -176)	5 (0 - 64)	14 (0 - 176)	<0.001	8 (0 - 94)	7.5 (0 - 64)	9 (0 - 94)	0.009

Abbreviations: ALT, alanine aminotransferase; ALP, alkalina phosphatase; AST, aspartate aminotransferase; CK, creatine kinasa; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; MAFLD, metabolic dysfunction associated fatty liver disease; SOFA, sequential organ failure asseszment; WBC: White blood cells.

^a:Chi-square test was used for comparisons of categorical variables, and Mann-Whitney U test was used for comparisons of continuos asimmetric variables.

^b: Srudent's T-test was used for comparisons of continuos simmetriv variables

*: adjusted residuals

Table 4. Poisson Regression of factor associates with abnormal liver enzymes

Patient characteristics and findings	Univariate			Multivariate		
	RR	(95% CI)	<i>p</i> - value	RR	(95% CI)	<i>p</i> - value
Clinical characteristics and comorbidities						
Male gender	1.23	(1.10 - 1.37)	<.001	1.49	(1.12 - 1.99)	0.007
Chronic liver disease	1.51	(1.10 - 2.06)	0.01	1.47	(1.08 - 2.01)	0.015
Severe COVID-19	1.29	(1.16 - 1.44)	<.001			
Laboratory findings						
Hematology						
White blood cells (x 10 ⁹ /L)	1.02	(1.01 - 1.03)	<.001			
Total bilirubin (mg/dL)	1.27	(1.17 - 1.37)	<.001	1.18	(1.09 - 1.27)	<.001
Inflammatory markers						
CRP (mg/dL)	1.001	(1.001 - 1.002)	<.001			
LDH (U/L)	1.00	(1.00 - 1.00)	0.001			
CK (U/L)	1.00	(1.00 - 1.00)	<.001			
Coagulation						
INR	1.14	(1.07 - 1.21)	<.001			
D-dimer (ug/mL)	1.02	(1.02 - 1.01)	<.001			

Abbreviations: CK, creatine kinase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC: White blood cells.

Table 5. Poisson Regression of factor associates with severe COVID-19

Patient characteristics and findings	Univariate			Multivariate		
	RR	(95% CI)	<i>p</i> - value	RR	(95% CI)	<i>p</i> - value
Clinical characteristics						
Age above 60 years	1.44	(1.29 - 1.61)	<.001	1.22	(1.09 - 1.37)	0.001
Male gender	1.17	(1.05 - 1.30)	0.005			
Comorbidities						
Diabetes	1.36	(1.23 - 1.51)	<.001	1.21	(1.08 - 1.35)	0.001
Hypertension	1.34	(1.20 - 1.49)	<.001			
Complications						
Pulmonary tromboembolism	1.24	(1.06 - 1.44)	0.006			
Laboratory findings						
Hematology						
White blood cells (x 10 ⁹ /L)	1.04	(1.03 - 1.05)	<.001	1.03	(1.02 - 1.04)	<0.001
Lymphopenia (<1000 x 10 ⁹ /L)	1.69	(1.49 - 1.92)	<.001	1.51	(1.32 - 1.72)	<0.001
Biochemical						
AST and/or ALT ≥41 (U/L)	1.33	(1.18 - 1.50)	<.001	1.19	(1.06 - 1.34)	0.004
Total bilirubin (mg/dL)	1.16	(1.05 - 1.28)	0.003			
Inflammatory markers						
CRP (mg/dL)	1.003	(1.003 - 1.004)	<.001	1.002	(1.001 - 1.002)	<0.001
LDH (U/L)	1.00	(1.00 - 1.00)	<.001			
CK (U/L)	1.00	(1.00 - 1.00)	<.001			
Coagulation						
INR	1.28	(1.19 - 1.37)	<.001			
D-dimer (ug/mL)	1.04	(1.04 - 1.05)	<.001	1.01	(1.006 - 1.021)	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC: White blood cells.

Table 6. Cox Regression of factor associates with mortality in patients with COVID-19

Patient characteristics and findings	Univariate			Multivariate		
	HR	(95% CI)	<i>p</i> - value	HR	(95% CI)	<i>p</i> - value
Clinical characteristics						
Age above 60 years	2.62	(2.00 - 3.42)	<.001	2.3 4	(1.73 - 3.16)	<.001
Male gender	0.92	(0.73 - 1.16)	0.5			
Comorbidities						
Diabetes	1.21	(0.96 - 1.53)	0.11			
Hypertension	1.16	(0.92 - 1.47)	0.22			
Chronic liver disease	1.15	(0.67 - 1.97)	0.62			
Complications						
Severe COVID-19	34.1 5	(9.76 - 119.28)	<.001			
Pulmonary tromboembolism	1.12	(0.73 - 1.73)	0.59			
Laboratory findings						
Hemalogy						
White blood cells (x 10 ⁹ /L)	1.04	(1.03 - 1.06)	<.001			
Lymphopenia (<1000 x 10 ⁹ /L)	1.38	(1.05 - 1.81)	0.02			
Biochemical						
AST (U/L)	1.00	(1.00 - 1.00)	0.033			
ALT (U/L)	1.00	(1.00 - 1.00)	0.08			
AST ≥41 (U/L)	1.20	(0.93 - 1.55)	0.17			
ALT ≥41 (U/L)	0.84	(0.65 - 1.08)	0.18			
AST and/or ALT ≥41 (U/L)	1.12	(0.86 - 1.45)	0.40			
AST Highest hospitalization (U/L)	1.00	(1.00 - 1.00)	0.19			
ALT Highest hospitalization (U/L)	1.00	(1.00 - 1.00)	0.56			
Total bilirubin (mg/dL)	1.18	(0.94 - 1.49)	0.18			
Inflammatory markers						
CRP (mg/dL)	1.00	(1.00 - 1.00)	0.002			
LDH (U/L)	1.00	(1.00 - 1.00)	0.48			
CK (U/L)	1.00	(1.00 - 1.00)	0.49			
Coagulation						
INR	1.06	(1.04 - 1.08)	<.001	1.2 6	(1.05 - 1.52)	0.013
D-dimer (ug/mL)	1.05	(1.04 - 1.08)	<.001	1.0 5	(1.03 - 1.07)	<.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC: White blood cells.

8. CONCLUSIONES

- Las manifestaciones hepáticas son frecuentes y son las transaminasas alteradas las más relevantes.
- Las transaminasas alteradas tienen una prevalencia de más del 50%, siendo predominantemente leves.
- Los parámetros inflamatorios están más elevados en el grupo de las transaminasas alteradas sin llegar a correlacionarse.
- Las transaminasas alteradas se correlacionan con la severidad de la enfermedad, podrían ser considerados marcadores pronósticos en la práctica clínica para estratificar el riesgo del paciente en la admisión y contribuir con un mejor pronóstico.

9. CONSIDERACIONES FINALES

Como consideraciones finales, vamos a citar los puntos positivos y algunas limitaciones del presente estudio.

- Este estudio cuenta con una muestra amplia (1229 pacientes), registrados en un base de datos detallada, dándole la capacidad a nuestros hallazgos de representar una verdadera relación entre las enzimas hepáticas alteradas y la severidad de la enfermedad. (validez interna). Latinoamérica es una de las regiones más afectadas, y pocos estudios sobre el impacto de COVID-19 en el hígado han sido publicados, este sería sólo la cuarta publicación con una población de más de 1000 pacientes en Latinoamérica, y la segunda en Brasil con más de 1000 pacientes.
- Dentro de las limitaciones tenemos que es un estudio retrospectivo con algunos datos incompletos o no registrados en las historias clínicas como peso, el consumo de alcohol fue registrado como antecedente sin especificar la cantidad; la FA, GGT y albumina no fueron evaluadas a pesar de haber reportes con alteraciones importantes de GGT durante el curso clínico, así como reportes de colangiopatía prolongada importante como consecuencia de COVID-19, esto se debe a que fueron solicitadas en menos del 10% de la muestra. Se contó con algunas ecografías abdominales y tomografías de tórax con alguna parte de hígado para evaluar esteatosis hepática, que, junto con el peso, diabetes son importantes para estimar la prevalencia de MAFLD, pudiendo ser subestimada la prevalencia de esta; así también el tratamiento antes de la hospitalización podría causar alteraciones hepáticas y sólo se encontraron registros parciales.

- Algunos pacientes fueron incluidos en protocolos de investigación de tratamiento, cuyos resultados están pendientes y podrían haber afectado alguno de los resultados.
- Se evaluaron las transaminasas en la admisión, está pendiente el análisis de la variación de estas durante la hospitalización, así como el valor máximo de las transaminasas alcanzadas durante el periodo de hospitalización que podrían traer otras informaciones.
- No contamos con biopsias hepáticas, limitándose la correlación clínico patológica, uno de los objetivos del estudio considerados al inicio: realizar biopsia a los casos de COVID-19 severa con mala evolución y fallecieron, no fue posible concretarlo por diversos factores tanto logísticos como éticos.

10. PERSPECTIVAS

- Múltiples variantes de SARS-CoV-2 están circulando actualmente en el mundo; la variante predominante en Brasil al inicio del 2021 fue P.1, durante el periodo de Febrero – Abril, el numero de casos de pacientes con COVID-19 y las complicaciones hepáticas aumentaron. En el Hospital de Clínicas de Porto Alegre fueron hospitalizados más de 1000 casos de pacientes COVID-19 en sólo 3 meses llegando a saturar la capacidad del hospital. Si la variante P.1 de SARS-CoV-2 podría asociar cambios en la morbilidad y mortalidad es lo que se va evaluar en una segunda fase.
- Con este estudio obtuvimos el perfil del paciente que tiene enzimas hepáticas alteradas en la admisión y los factores asociados a un riesgo aumentado de presentarlas. Teniendo como base estos resultados podremos compararlos con los del segundo periodo, responderemos preguntas como si el perfil del paciente ha cambiado, si las alteraciones hepáticas tienen una mayor prevalencia y evaluaremos el impacto en el curso clínico y desenlaces finales.
- El protocolo de investigación aprobado para realizar el presente estudio tiene autorización para utilizar muestras serológicas de la población considerada; dichas muestras se encuentran almacenadas en el BIOBANCO de COVID-19 del Hospital de Clínicas de Porto Alegre. En una segunda fase se evaluarán los marcadores inflamatorios (interleucinas) de ambas poblaciones (primer y segundo periodo) para compararlos y determinar si la inflamación es mayor entre los pacientes con COVID-19 severa y si existe correlación con la alteración de las transaminasas.

11. REFERENCIAS BIBLIOGRÁFICAS

1. WHO. WHO Corononavirus (COVID-19) Dashboard [Internet]. [cited 2021 Nov 22]. Available from: <https://covid19.who.int>
2. Marjot T, Webb GJ, Barritt AS, Moon AM, Stamataki Z, Wong VW, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol*. 2021;18(5):348–64.
3. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Disponible en: <https://covid19treatmentguidelines.nih.gov/>. Natl Inst Heal [Internet]. 2020;2019:130. Available from: <https://www.covid19treatmentguidelines.nih.gov/>
4. Xie P, Ma W, Tang H, Liu D. Severe COVID-19: A Review of Recent Progress With a Look Toward the Future. *Front Public Heal*. 2020;8(May):1–7.
5. Li J, He X, Yuan Yuan, Zhang W, Li X, Zhang Y, et al. Meta-analysis investigating the relationship between clinical features, outcomes, and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. *Am J Infect Control* [Internet]. 2021;49(1):82–9. Available from: <https://doi.org/10.1016/j.ajic.2020.06.008>
6. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology*. 2021;64(1):36–47.
7. Moreira JL de S, Barbosa SM de S, Gonçalves Júnior J. Pathophysiology and molecular mechanisms of liver injury in severe forms of COVID-19: An integrative review. *Clin Res Hepatol Gastroenterol*. 2021;45(6):101752.
8. Hao S-R, Zhang S-Y, Lian J-S, Jin X, Ye C-Y, Cai H, et al. Liver Enzyme Elevation in Coronavirus Disease 2019. *Am J Gastroenterol*. 2020;Publish Ah:1075–83.
9. Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. *Ann Hepatol*. 2021;21:100273.
10. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. *Hypertens Res*. 2020;43(7):648–54.
11. WHO. COVID-19 weekly epidemiological update. *World Heal Organ* [Internet]. 2021;(58):1–23. Available from: <https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update>
12. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. *Front Immunol*. 2020;11(June):1–4.
13. Li X, Zhong X, Wang Y, Zeng X, Luo T, Liu Q. Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis. *PLoS One*. 2021;16(5):e0250602.
14. Effenberger M, Grandner C, Grabherr F, Griesmacher A, Ploner T, Hartig F, et al. Systemic inflammation as fuel for acute liver injury in COVID-19. *Dig Liver Dis* [Internet]. 2021;53(2):158–65. Available from: <https://doi.org/10.1016/j.dld.2020.08.004>
15. Marie D, Valle D, Kim-schulze S, Huang H, Beckmann ND, Nirenberg S, et al. COVID-19 severity and survival. *Nat Med* [Internet]. 2019;26(October). Available from: <http://dx.doi.org/10.1038/s41591-020-1051-9>
16. Jafarzadeh A, Jafarzadeh S, Nozari P, Mokhtari P, Nemati M. Lymphopenia an

- important immunological abnormality in patients with COVID-19: Possible mechanisms. *Scand J Immunol*. 2021;93(2):1–16.
17. Lu JY, Anand H, Frager SZ, Hou W, Duong TQ. Longitudinal progression of clinical variables associated with graded liver injury in COVID-19 patients. *Hepatology*. 2021;15(4):1018–26.
 18. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - J Am Med Assoc*. 2020;323(11):1061–9.
 19. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med*. 2020;180(8):1081–9.
 20. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol [Internet]*. 2020;146(1):110–8. Available from: <https://doi.org/10.1016/j.jaci.2020.04.006>
 21. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis*. 2020;14:1–14.
 22. Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated Liver Biochemistries in Hospitalized Chinese Patients With Severe COVID-19: Systematic Review and Meta-analysis. *Hepatology*. 2021 Apr;73(4):1521–30.
 23. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. *J Hepatol [Internet]*. 2020;73(3):566–74. Available from: <https://doi.org/10.1016/j.jhep.2020.04.006>
 24. Harapan H, Fajar JK, Supriyono S, Soegiarto G, Wulandari L, Seratin F, et al. The prevalence, predictors and outcomes of acute liver injury among patients with COVID-19: A systematic review and meta-analysis. *Rev Med Virol*. 2021;(August):1–8.
 25. Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, et al. Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. *Hepatology*. 2021;73(4):1509–20.
 26. Yip TCF, Lui GCY, Wong VWS, Chow VCY, Ho THY, Li TCM, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut*. 2021;70(4):733–42.
 27. 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 Off J Int Assoc Study Liver*. 2020 Sep;40(9):2095–103.
 28. Mendizabal M, Piñero F, Ridruejo E, Anders M, Silveyra MD, Torre A, et al. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. *Ann Hepatol*. 2021;21:100298.
 29. Marín Dueñas I, Vega J, Carrillo-Ng H, Veramendi-Schult I, Zavaleta Alva R, Vásquez L, et al. P-27 Alteration in Liver Function Tests Among Patients Hospitalized for Covid-19: a Multicentric Study in Peru. *Ann Hepatol*. 2021;24(2):100391.
 30. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology*. 2020;72(3):807–17.
 31. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al.

- Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA - J Am Med Assoc.* 2020;323(20):2052–9.
32. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* [Internet]. 2020;18(7):1561–6. Available from: <https://doi.org/10.1016/j.cgh.2020.04.002>
 33. Wu Y, Li H, Guo X, Yoshida EM, Mendez-Sanchez N, Levi Sandri GB, et al. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. *Hepatol Int.* 2020 Sep;14(5):621–37.
 34. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bioRxiv.* 2020;
 35. Caramaschi S, Kapp ME, Miller SE, Eisenberg R, Johnson J, Epperly G, et al. Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. *Mod Pathol.* 2021;34(9):1614–33.
 36. Diaz, Luis, Idalsoaga, Francisco, Cannistra, Macarena et al. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7789052/pdf/WJG-26-7693.pdf>. *World J Gastroenterol.* 2020;26(48):7693–706.
 37. Chu H, Peng L, Hu L, Zhu Y, Zhao J, Su H, et al. Liver Histopathological Analysis of 24 Postmortem Findings of Patients With COVID-19 in China. *Front Med.* 2021;8(October):1–9.
 38. Bertolini A, van de Peppel IP, Bodewes FAJA, Moshage H, Fantin A, Farinati F, et al. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. *Hepatology.* 2020 Nov;72(5):1864–72.
 39. Parohan M, Yaghoubi S, Seraji A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies. *Hepatol Res.* 2020;50(8):924–35.
 40. Ghazavi A, Ganji A, Keshavarzian N, Rabiemajd S, Mosayebi G. Cytokine profile and disease severity in patients with COVID-19. *Cytokine* [Internet]. 2021;137(June 2020):155323. Available from: <https://doi.org/10.1016/j.cyto.2020.155323>
 41. Chuan Qin, Zhou L, Hu Z, Zhang S. Dysregulation of immune response in patients with COVID-19 in Wuhan, China Chuan. *J Chem Inf Model.* 2020;53(9):1689–99.
 42. Gupta A, Madhavan M V., Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* 2020;26(7):1017–32.
 43. Kondo R, Kawaguchi N, McConnell MJ, Sonzogni A, Licini L, Valle C, et al. Pathological characteristics of liver sinusoidal thrombosis in COVID-19 patients: A series of 43 cases. *Hepatol Res.* 2021;51(9):1000–6.
 44. Santana MF, Guerra MT, Hundt MA, Ciarleglio MM, Pinto RA de A, Dutra BG, et al. Correlation Between Clinical and Pathological Findings of Liver Injury in 27 Patients With Lethal COVID-19 Infections in Brazil. *Hepatol Commun.* 2021;0(0):1–11.
 45. Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. *Intensive Care Med.* 2021;47(5):521–37.
 46. Kulkarni A V, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther.* 2020 Aug;52(4):584–99.

47. CDC. Coronavirus disease 2019: people with certain medical conditions. [Internet]. 2021 [cited 2021 Nov 1]. Available from: susceptibility to infections developing intense inflammatory response.
48. Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* [Internet]. 2021;19(7):1469-1479.e19. Available from: <https://doi.org/10.1016/j.cgh.2020.09.027>
49. Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol*. 2020 Nov;73(5):1063–71.
50. Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients – A systematic review and meta-analysis. *Ann Hepatol* [Internet]. 2021;21:100273. Available from: <https://doi.org/10.1016/j.aohep.2020.10.001>
51. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. *J Hepatol*. 2014;61(6):1385–96.
52. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* [Internet]. 2021;74(3):567–77. Available from: <https://doi.org/10.1016/j.jhep.2020.09.024>
53. Dongiovanni P, Meroni M, Longo M, Fracanzani AL. MAFLD in COVID-19 patients: an insidious enemy. Vol. 14, *Expert review of gastroenterology & hepatology*. England; 2020. p. 867–72.
54. Hegyi PJ, Váncsa S, Ocskay K, Dembrovszky F, Kiss S, Farkas N, et al. Metabolic Associated Fatty Liver Disease Is Associated With an Increased Risk of Severe COVID-19: A Systematic Review With Meta-Analysis. Vol. 8, *Frontiers in medicine*. 2021. p. 626425.
55. Kavoliuniene Ausra, Vaitiekiene Audrone CG. Congestive hepatopathy and hypoxic hepatitis in heart failure: A cardiologist's point of view. 1384;1–9.
56. Yadav DK, Singh A, Zhang Q, Bai X, Zhang W, Yadav RK, et al. Involvement of liver in COVID-19: systematic review and meta-analysis. Vol. 70, *Gut*. 2021. p. 807–9.
57. Li X, Xu S, Yu M, Wang K, Tao Y. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. 1384;1–12.