View Abstract

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Abstract

TITLE: LIVER TEST ABNORMALITIES IN COVID-19 PATIENTS MAY NOT BE RELATED TO CYTOKINE STORM

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ABSTRACT BODY:

Abstract Body: Introduction: A recent systematic review reported a pooled prevalence of liver test abnormalities of 19% (range 1-53%) in COVID-19 patients. However, it is not clear whether the pathogenesis of liver test abnormalities could be due to direct action of SARS-Cov-2, hypoxia-associated metabolic derangements, drug-induced liver injury or cytokine storm related inflammation.

Objectives: To explore the clinical significance of liver test abnormalities in COVID-19 patients and to evaluate the levels of cytokines in patients with and without liver test abnormalities

Material and methods: We included 143 COVID-19 patients hospitalized in a single University Hospital, confirmed by quantitative reverse transcription PCR and 53 non COVID-19 healthy controls (HC) (mainly hospital staff) confirmed by a negative rapid serological. COVID-19 severity were stratified in mild, moderate and severe based on the presence of pneumonia and O2 saturation<94%. Abnormal liver tests was defined as the elevation over the upper limit of normal of total bilirubin (>1mg/dl), alanine aminotransferase (>31 UI/L) or alkaline phosphatase (>104 UI/L).
Blood samples were collected on the day of hospital admission in COVID-19 and at the time of evaluation on HC. 27 cytokines pro and antiinflammatory (Bio-Plex Pro™, Bio- Rad) were measured.
A multivariate logistic regression model was performed to analyze the relationship between liver test abnormality and the severity of COVID-19, in which the following variables were included: age> 60 years, sex, BMI>30, pneumonia, use of drugs (antibiotics, anti-inflammatories, antivirals), ferritin>300µg/l and fibrinogen>400 mg/dl.

Results: The mean age of the COVID-19 patients was 54 +/- 15 years, (F=50%) and HC was 52 +/- 8, (F= 62%). None of the patients had history of liver disease.
84 COVID-19 (59%; 95% CI 41-67) had abnormal liver test on admission and in 17 (32%; 95% CI 20-46) of HC (p=0.001). 57% of COVID-19 patients had a AST/ ALT ratio> 1.
There was a significant association between COVID-19 liver tests abnormalities and the following: BMI> 30 (p = 0.02), the presence of pneumonia (p = 0.001), O2 saturation <94% (p= 0.001) and the severity (p = 0.001).
In the multivariate analysis, liver tests abnormalities were associated with COVID-19 severity (OR 4.68 (95% CI 1.21-18.16); p = 0.03).
Significantly higher levels of the following cytokines were observed on admission in COVID-19 patients compared to HC: IL-1ra, IL-2, IL-6, IL-7, IL-8, IL- 13, IP-10, and PDGF-bb.
There were no significant differences in COVID-19 with and without liver tests abnormalities, on the levels of the 27 cytokines analyzed.

Conclusions: Liver tests abnormalities in COVID-19 patients were associated with the severity of the disease. Cytokine mediated inflammation may not play an important role in the pathogenesis of liver tests abnormalities.

	TOTAL (n=143)	Normal liver test (n=59)	Abnormal liver test (n=84)	Helathy controls (n=53)	p*
All patients					
Age, mean +/- sd, y		52 +/- 17	55 +/- 14	52 +/-8	0,28
Age 18-30, No. (%)		6 (10,67)	5 (5,95)	0 (0)	
Age 30-60, No. (%)		35 (59,32)	49 (58,33)	46 (86,79)	
Age 60-80, No. (%)		14 (23,73)	27 (32,14)	7 (13,21)	
Age>80, No. (%)		4 (6,78)	3 (3,57)	0(0)	0,5
Sex, No.(%)					
Female		34 (57,63)	37 (44,05)	33 (62,26)	
Male		25 (42,37)	47 (55,95)	20 (37,74)	0,11
Body Mass Index (BMI)					
BMI, median (IQR), kg/m^2		28 (25-31)	30 (27-35)	26,96 (23,80-31,56)	0,006
BMI>30 kg/m^2, No.(%)		19 (32,20)	44 (52,38)	17 (32,08)	0,017
0,21 Oxygen saturation, median (IQR)		97 (96-98)	95 (91,5-97)	NA	0,000
Oxygen saturation<94% at FIO, 21%, No (%)		9 (15,25)	34 (40,48)	NA	0,001
Pneumonia, No (%)		30 (50,85)	65 (77,38)	NA	0,001
Mild Covid (%)		29 (49,15)	19 (22,62)	NA	
Moderate (%)		21 (35,59)	32 (38,10)	NA	
Severe (%)		9 (15,25)	33 (39,29)	NA	0,001
Erythrosedimentation rate, median (IQR), s		28 (9-57)	33 (17-54)	NA	0,49
CRP, median (IQR), mg/L		2,34 (0,59-4,85)	3,44 (1,57-6,57)	NA	0,06
Ferritin, median (IQR), µg/L		300 (102-555)	584,35 (251- 1115,45)	NA	0,0003
>300		29 (49,15)	58 (69,05)	NA	0,02
Fibrinogen, median (IQR), mg/dL		465,5 (340-577)	551 (456-622)	NA	0,01
Albumin, median (IQR), g/dl		4 (3,6-4,4)	3,85 (3,59-4,2)	NA	0,22
D-dimer, median (IQR), µg/mL		0,38 (0,27-0,96)	0,53 (0,4-0,75)	NA	0,06
White blood cell count, median (IQR), cells/µL		5760 (4520-9000)	5805 (4710-8160)		0,72
Neutrophil count, median (IQR), cells/µL		3770 (2250-5560)	3810 (2685-5650)	257 (216-297)	0,58
Lymphocyte count, median (IQR), cells/µL		1565 (1100-2020)	1460 (1030- 1945)	34,5 (29,5- 43)	0,46

*Comparison between normal and abnormal liver test

CYTOKINE pg/ml (IQR)	TOTAL (n=143)	Normal liver test (n=59)	Abnormal liver test (n=84)	Healthy controls (n=53)	p	p*
IL-1b		0,89 (0,53-1,56)	1,12 (0,62-2,03)	1,62 (0,91-2,08)	0,01	0,06
IL-1ra		343,07 (204,76-510,77)	393,48 (289,81-663,52)	0 (0-59,18)	0,0001	0,86
IL-2		0,78 (0-2)	0,54 (0-2)	0 (0-0,19)	0,0001	0,23
IL-4		2,11 (1,39-4,05)	2,13 (1,2-4,45)	4,95 (3,25-6,75)	0,0001	0,34
IL-5		0 (0-2,34)	0 (0-2,34)	0 (0-6,18)	0,93	0,77
IL-6		4,07 (0,96-10,36)	4,05 (1,37-10,43)	0 (0-0,55)	0,0001	0,46
IL-7		24,68 (18,18-70,74)	29,69 (17,51-70,74)	18,18 (12,99-29,58)	0,0008	0,65
IL-8		6 (2,85-9,94)	7,17 (3,9-11,69)	4,49 (2,37-6,31)	0,0014	0,28
IL-9		152,51 (101,9-212,92)	146,13 (105,79-217,23)	467,09 (415,6-492,57)	0,0001	0,41
IL-10		0 (0-1,65)	0 (0-1,27)	0 (0-0)	0,0004	0,54
IL-12(p70)		0 (0,32-1,2)	0 (0,19-1,2)	0,68 (0,18-2,38)	0,09	0,9
IL-13		2,12 (1,68-2,97)	2,76 (1,68-3,69)	1,07 (0,09-1,8)	0,0001	0,56
IL-17		10,09 (7,01-14,76)	9,22 (7,12-14,84)	11,52 (7,44-14,56)	0,82	0,58
Eotaxin		74,25 (54,65-99,33)	78,44 (54,49-112,04)	72,6 (54,85-92,67)	0,76	0,77
FGF ba1c		5,26 (0-39,28)	9,25 (0-44,35)	53,4 (40,71-61,77)	0,0001	0,08
G-CSF		67,34 (44,37-85,25)	71,14 (48,06-100,35)	71,17 (52,19-97,13)	0,61	0,27
IP-10		2413,25 (1087,41-3931,1)	2658,66 (1180,84-4122,17)	682,31 (522,02-965,84)	0,0001	0,42
MCP-1(MCAF)		25,83 (15,23-48,12)	25,07 (16,66-45,87)	25,64 (16,84-34,73)	0,87	0,74
MIP-1α		1,4 (0,91-2,22)	1,79 (1,22-2,36)	1,65 (0,98-2,22)	0,32	0,07
MIP-1β		90,16 (73,97-104,66)	85,55 (70,18-108,29)	285,05 (264,55-313,19)	0,0001	0,33
PDGF-bb		2458,51 (1492,53-3456,68)	2448,51 (1584,56-3616,56)	1770,4 (1399,9-2064,35)	0,0003	0,71
RANTES		12971,2 (9547,51-14933,89)	12113,1 (9801,14-15839,7)	13540 (11148,55-16150,66)	0,3	0,89
TNF-α		45,15 (35,17-64,88)	48,5 (33,09-67,32)	52,75 (40,86-64,41)	0,8	0,78

* Comparison between normal and abnormal liver test

DISCLOSURE

The following authors have completed their 2022 DDW disclosure: Maria Piskorz: Disclosure completed | Esteban Gonzalez Ballerga: Disclosure completed | Ana Pisarevsky: Disclosure completed | Patrica Vega: Disclosure completed | Guillermina Ludueña: Disclosure completed | Fabiana Lopez Mingorance: Disclosure completed | Juan Olmos: Disclosure completed | Juan Sorda: Disclosure completed | JORGE DARUICH: Disclosure completed | Jorge Olmos: Disclosure completed