Alcohol Prevention Day

14 Maggio 2021

Istituto Superiore di Sanità, Aula Pocchiari
Roma, Viale Regina Elena 299

APRILE MESE DI PREVENZIONE ALCOLOGICA

organizzato da:

Osservatorio Nazionale Alcol
Centro Nazionale Dipendenze e Doping

WHO Collaborating Centre
for Research and Health Promotion on Alcohol and
Alcohol-related Health Problems

In collaborazione con:

Ministero della Salute

e con:
Società Italiana di Alcologia - SIA
Associazione Italiana Club Alcologici Territoriali - AICAT
Eurocare

Gianni Testino

SC Patologia delle Dipendenze ed Epatologia
Centro Alcologico Regionale
ASL3 Liguria
IRCCS Ospedale Policlinico San Martino, Genova

Società Italiana di Alcologia (SIA)

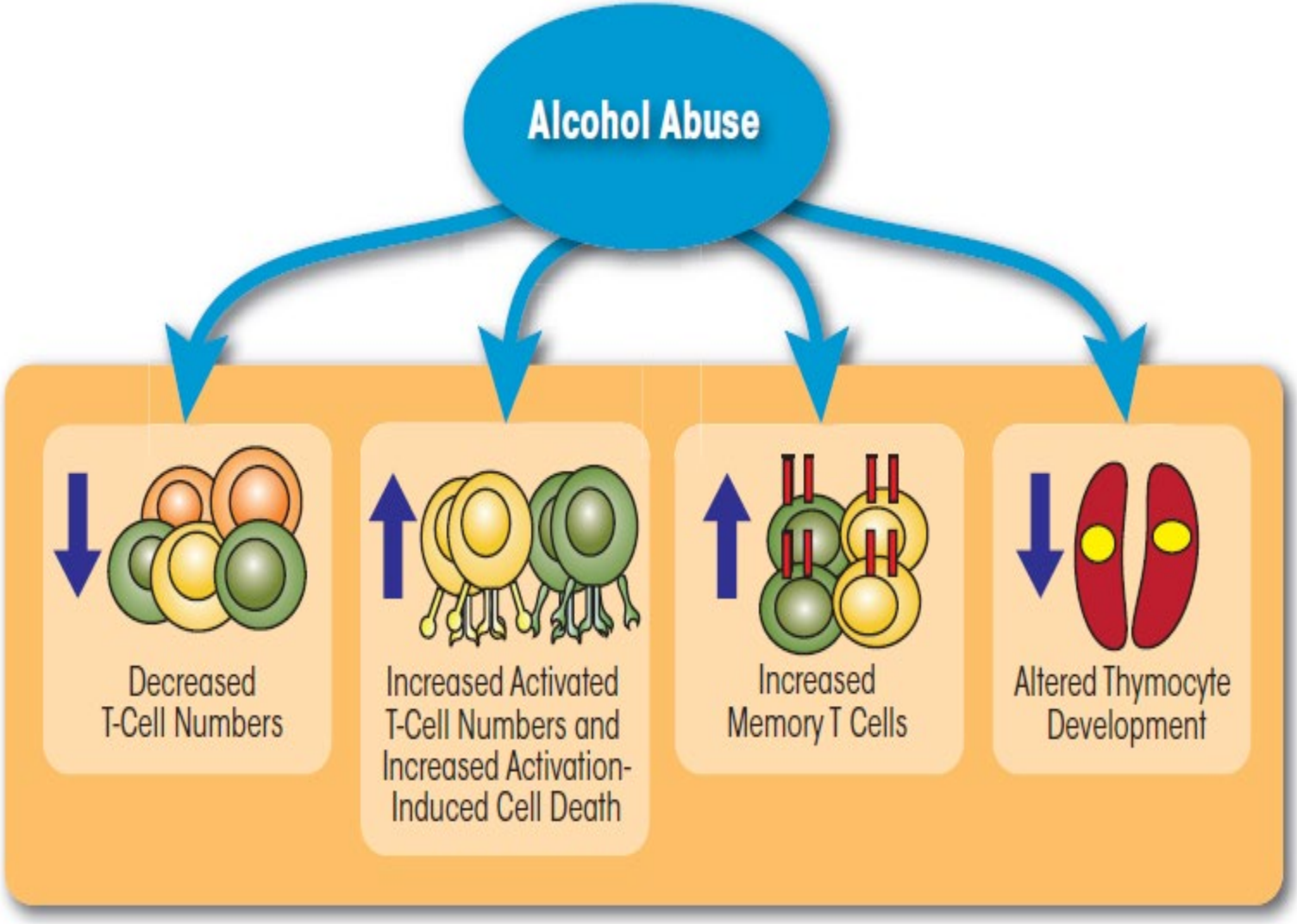
Impatto del Covid-19 su Disturbi da Uso di Alcol ed Epatopatie: le linee guida SIA

Alcohol's Effect on Host Defense

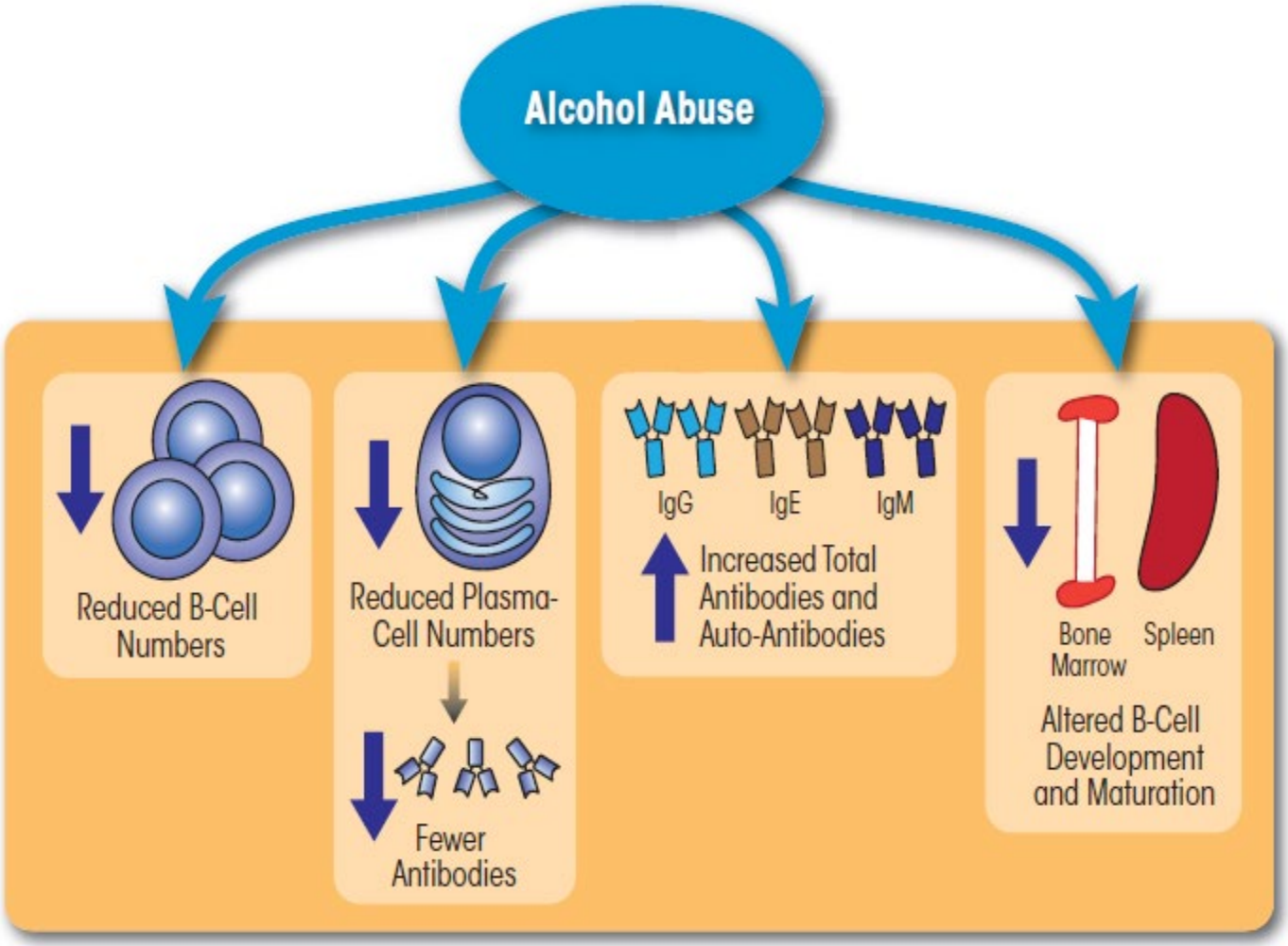
Gyongyi Szabo, M.D., Ph.D., and Banishree Saha, Ph.D.

Alcohol affects many organs, including the immune system, with even moderate amounts of alcohol influencing immune responses. Although alcohol can alter the actions of all cell populations involved in the innate and adaptive immune responses, the effect in many cases is a subclinical immunosuppression that becomes clinically relevant only after a secondary insult (e.g., bacterial or viral infection or other tissue damage). Alcohol's specific effects on the innate immune system depend on the pattern of alcohol exposure, with acute alcohol inhibiting and chronic alcohol accelerating inflammatory responses. The proinflammatory effects of chronic alcohol play a major role in the pathogenesis of alcoholic liver disease and pancreatitis, but also affect numerous other organs and tissues. In addition to promoting proinflammatory immune responses, alcohol also impairs anti-inflammatory cytokines. Chronic alcohol exposure also interferes with the normal functioning of all aspects of the adaptive immune response, including both cell-mediated and humoral responses. All of these effects enhance the susceptibility of chronic alcoholics to viral and bacterial infections and to sterile inflammation.

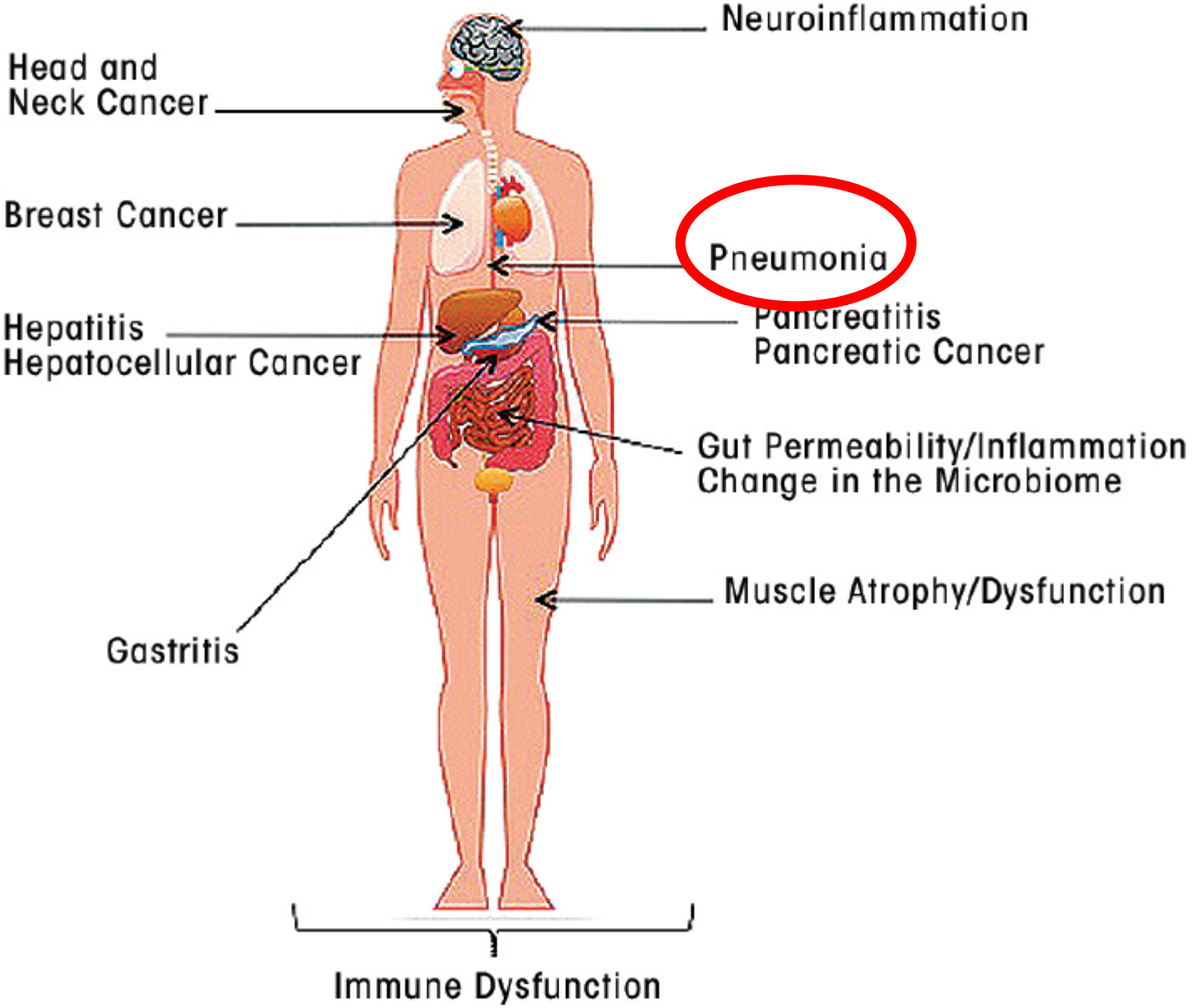
Szabo and Saha, Alcohol Res 2015



Pasala et al, Alcohol Res 2015



Pasala et al, Alcohol Res 2015



Szabo and Saha, Alcohol Res 2015

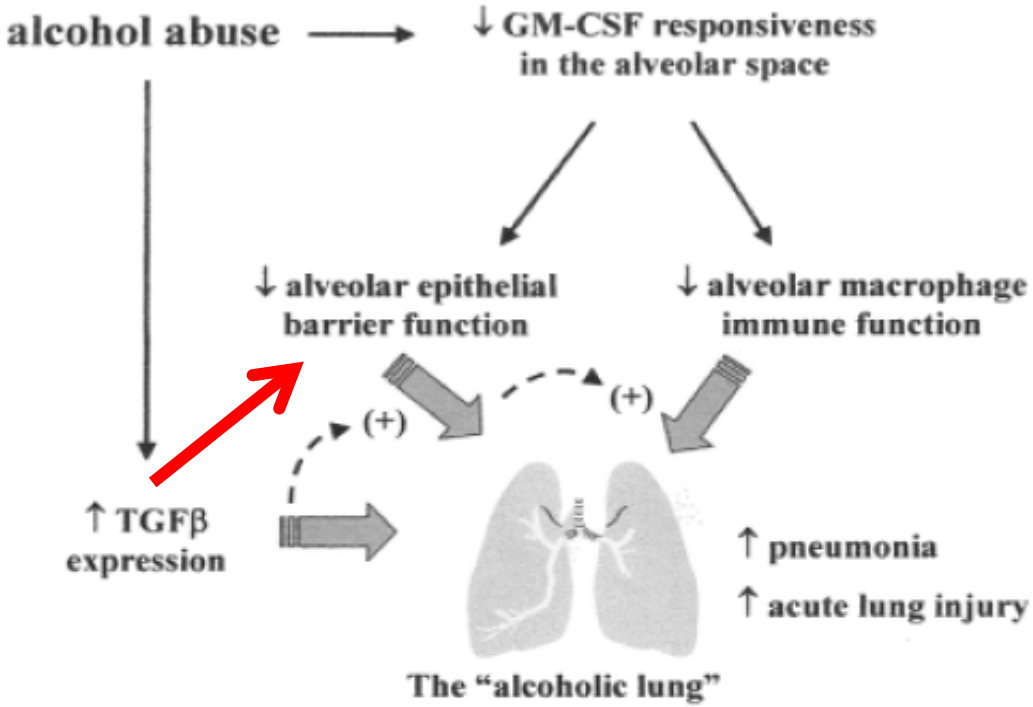
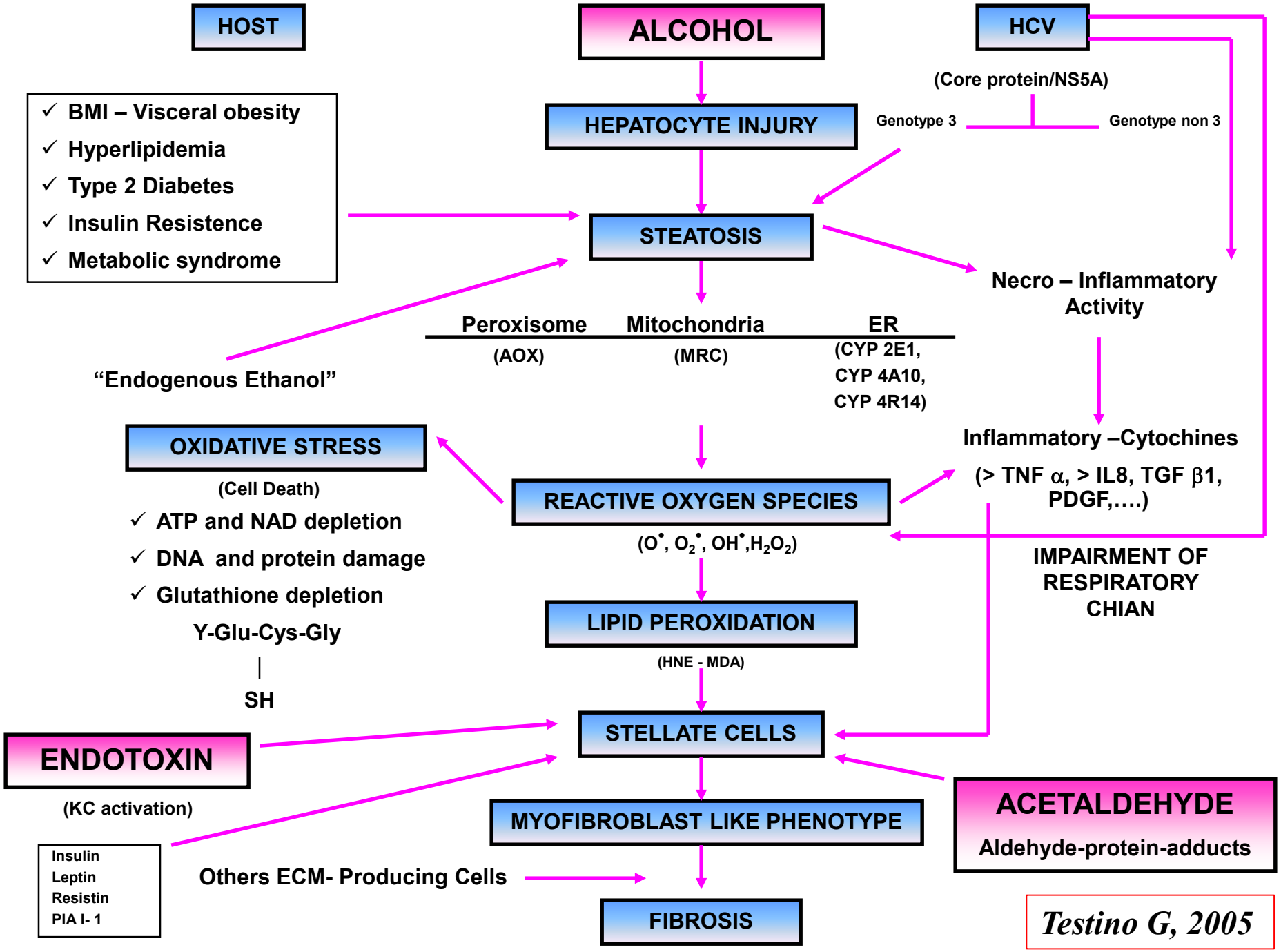


Fig. 2. Schematic representation of the mechanisms by which chronic alcohol abuse renders individuals susceptible to both pneumonia and acute lung injury. Decreased responsiveness to granulocyte/macrophage colony-stimulating factor (GM-CSF) leads to alveolar epithelial barrier dysfunction as well as to markedly dampened alveolar macrophage immune function. In parallel, aberrant expression and activation of transforming growth factor β (TGFβ) exacerbates the epithelial and macrophage dysfunction. The net result is that the "alcoholic lung" is vulnerable to both pneumonia and acute lung injury.

Bechara et al, Alcohol Clin Exp Res 2006 (DOI: 10.1111/j.1530-0277.2006.00084.x)


HOST
ALCOHOL
HCV
(Core protein/NS5A)
Genotype 3
Genotype non 3
✓ BMI – Visceral obesity
✓ Hyperlipidemia
✓ Type 2 Diabetes
✓ Insulin Resistence
✓ Metabolic syndrome
HEPATOCYTE INJURY
STEATOSIS
Necro – Inflammatory Activity
Peroxisome
(AOX)
Mitochondria
(MRC)
ER
(CYP 2E1, CYP 4A10, CYP 4R14)
"Endogenous Ethanol"
OXIDATIVE STRESS
(Cell Death)
✓ ATP and NAD depletion
✓ DNA and protein damage
✓ Glutathione depletion
Y-Glu-Cys-Gly
|
SH
REACTIVE OXYGEN SPECIES
($O^{\bullet}$, $O_2^{\bullet}$, $OH^{\bullet}$,H_2O_2)
Inflammatory –Cytochines
(> TNF α, > IL8, TGF β1, PDGF,….)
IMPAIRMENT OF RESPIRATORY CHIAN
LIPID PEROXIDATION
(HNE - MDA)
ENDOTOXIN
(KC activation)
STELLATE CELLS
ACETALDEHYDE
Aldehyde-protein-adducts
Insulin
Leptin
Resistin
PIA I- 1
MYOFIBROBLAST LIKE PHENOTYPE
Others ECM- Producing Cells
FIBROSIS
Testino G, 2005

ETANOLO, EPATOPATIA CRONICA, RISCHIO INFETTIVOLOGICO

Compromissione attività immunitaria innata

Compromissione attività immunitaria acquisita

Sovrapposizione infezione batterica su virale

Interazione con vaccini

Steatosi/steatoepatite aumenta espressione ACE2

Testino G, APD 2021

PREVALENCE OF ALCOHOL RELATED LIVER DISEASE IN HAZARDOUS DRINKERS

Systematic Review – 15 studies – 3,474 partecipants

15% normal histological appearance

27% steatosis

24% steatohepatis

27% fibrosis without cirrhosis

26% cirrhosis

Parker R et al, J Hepatol 2019; 71: 586-93; doi: 10.1016/j.jhep.2019.05.020

ASYMPTOMATIC ELEVATED LIVER BIOCHEMISTRIES

AST/ALT	14-76%
GGT	50%
Bilirubin	10%

Guan et al, N Engl J Med 2020
Fan et al, Clin Gastroenterol Hepatol 2020
Cai et al, J Hepatol 2020

AST > 40 IU/L

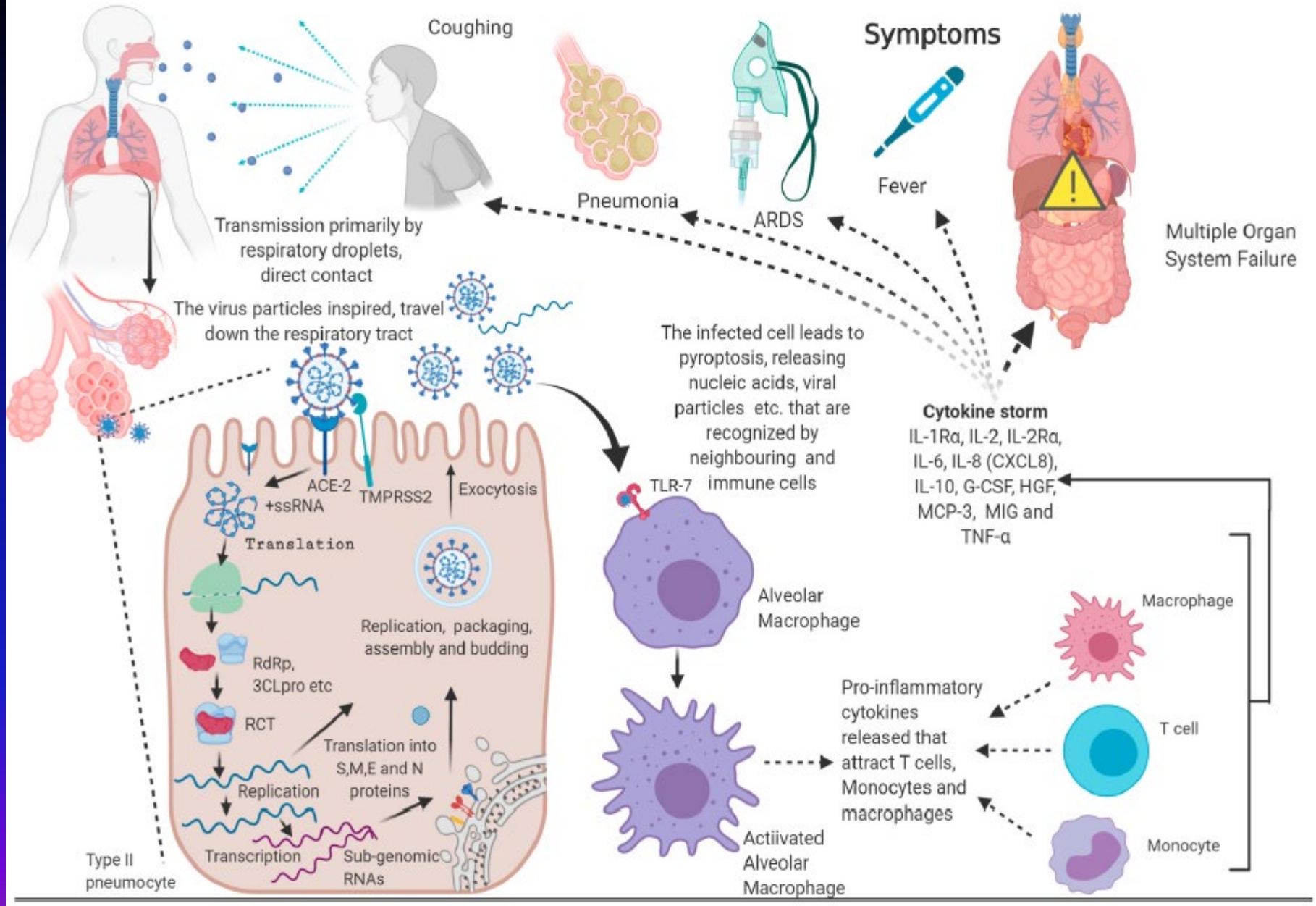
16% recovered
52% patients who died

(rarely exceed 3 times the upper limit of normal)

Chen et al, BMJ 2020
Hamid et al, J Clin Gastroenterol 2021

Acute on Chronic Liver Failure (ACLF)

In 2 retrospective studies, ACLF was reported in 12% and 28% of patients with baseline compensated cirrhosis.
COVID-19 was associated with liver injury and increased 30-day mortality in both studies.
Sarin et al, Hepatol Int 2020
Iavarone H, J Hepatol 2020



Chug et al, Eur J Pharmachol 2021

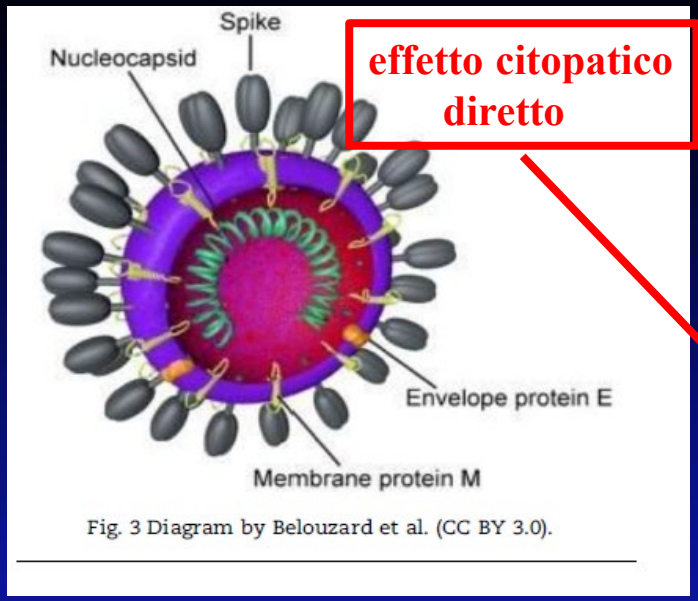


Fig. 3 Diagram by Belouzard et al. (CC BY 3.0).

effetto citopatico diretto

Aggravamento eventuale danno pre-esistente

Riattivazione HBV (tocilizumab, baricitinib, …)

ACE2

Reazione immunitaria incontrollata

disturbo da uso di alcol
sindrome metabolica

Danno da farmaci

ACE2

Ipossia

> Recettori

Eventi tromboembolici

Testino G et al, 2021 (submitted)

Mild but prolonged elevation of serum angiotensin converting enzyme (ACE) activity in alcoholics

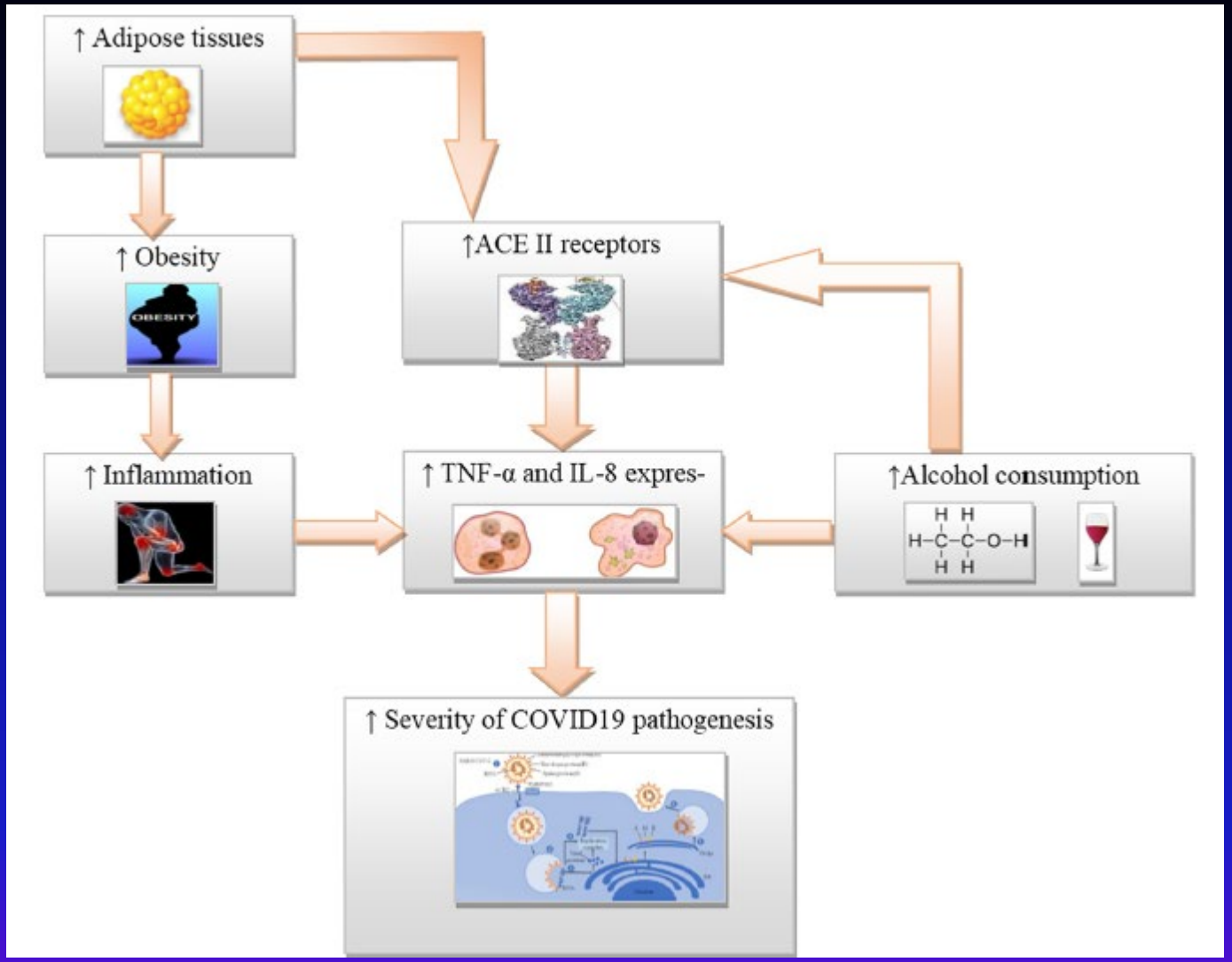
F Okuno, M Arai, H Ishii, Y Shigeta, Y Ebihara, S Takagi, M Tsuchiya

PMID: 3028446 (1996)

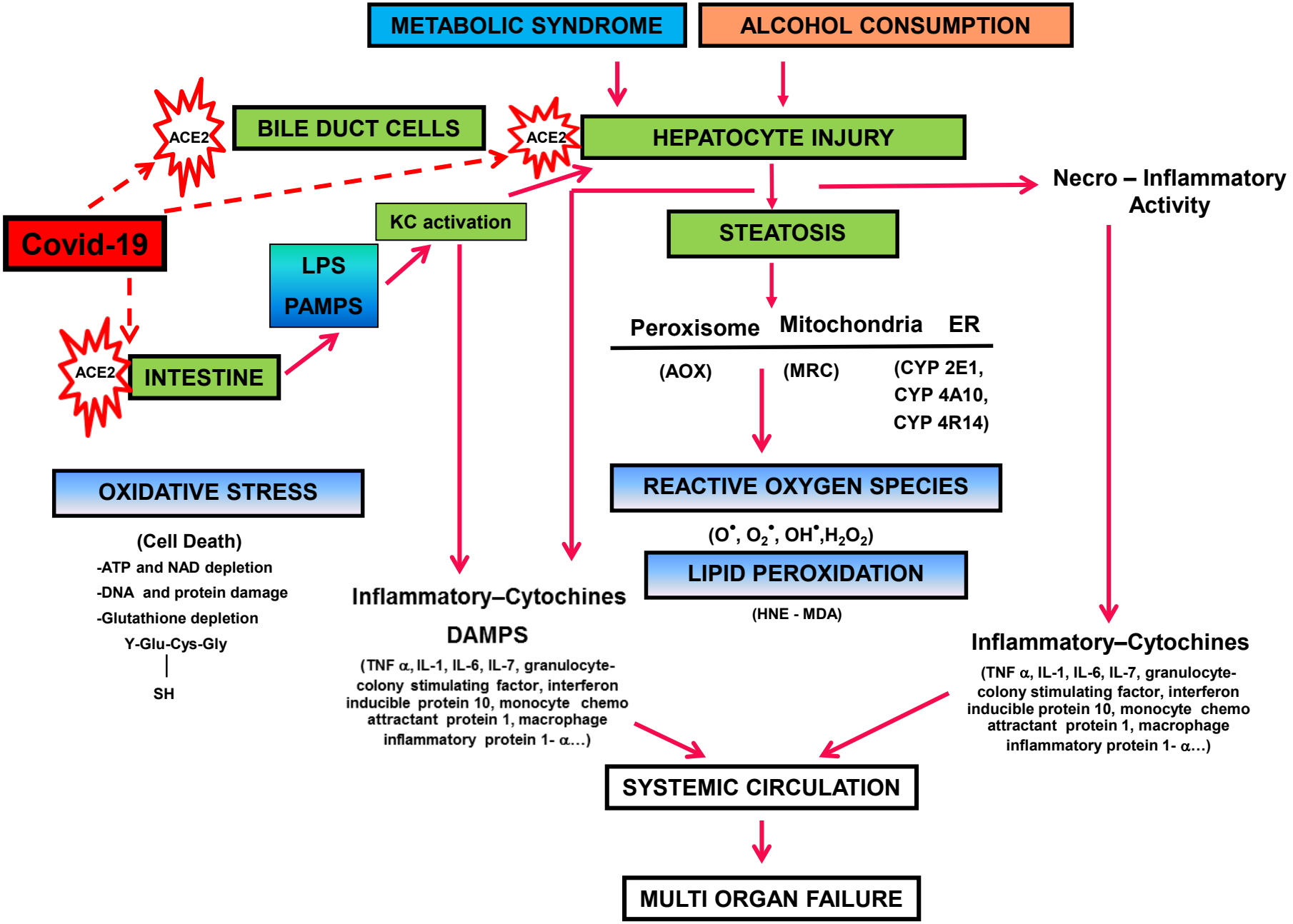
DOI: 10.1016/0741-8329(86)90053-4

Abstract

Serum activity of angiotensin converting enzyme (ACE) was serially measured in 47 hospitalized chronic alcoholics with liver disease. Compared to healthy controls, ACE activity, on admission, in the serum of alcoholics was significantly elevated (42.5 +/- 16.6 U/ml vs. 32.4 +/- 9.6 U/ml; p less than 0.005). About 36% of the patients had an elevated ACE level exceeding an upper normal value of 42 U/ml (mean +/- SD). In contrast to the rapid normalization of such enzymes as aspartate transaminase (AST), alanine transaminase (ALT) and lactic dehydrogenase (LDH) which represent parenchymal liver cell injury, the activity of ACE remained elevated over a period of 4 weeks even with abstinence. The serum level of ACE was significantly correlated with levels of alkaline phosphatase, gamma-glutamyltranspeptidase and monoamine oxidase, but not with those of AST, ALT and LDH. These data suggest increased ACE activity in alcoholics may be related to the influence of chronic consumption of alcohol on hepatic nonparenchymal systems.



Bilal et al, Medical Hypotheses 2020 (DOI: 10.1016/j.mehy.2020.110272)
Prins and Olinga, Liver Int 2020 (DOI: 10.1111/LIV.14484)



G Testino, Eur Gastroenterol Hepatol 2021; 33(3): 451-452; doi: 10.1097/MEG.0000000000001809

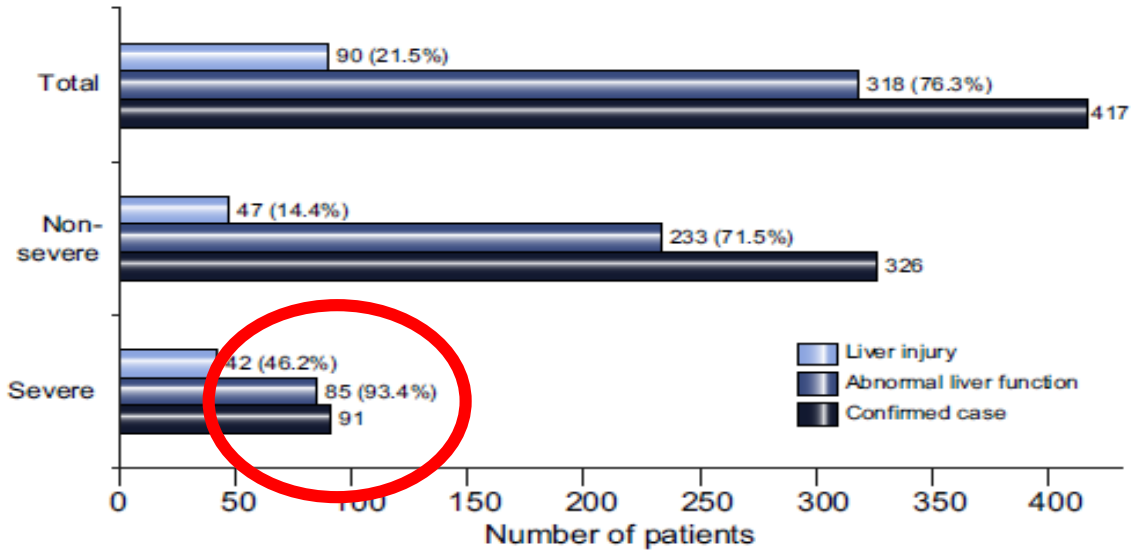
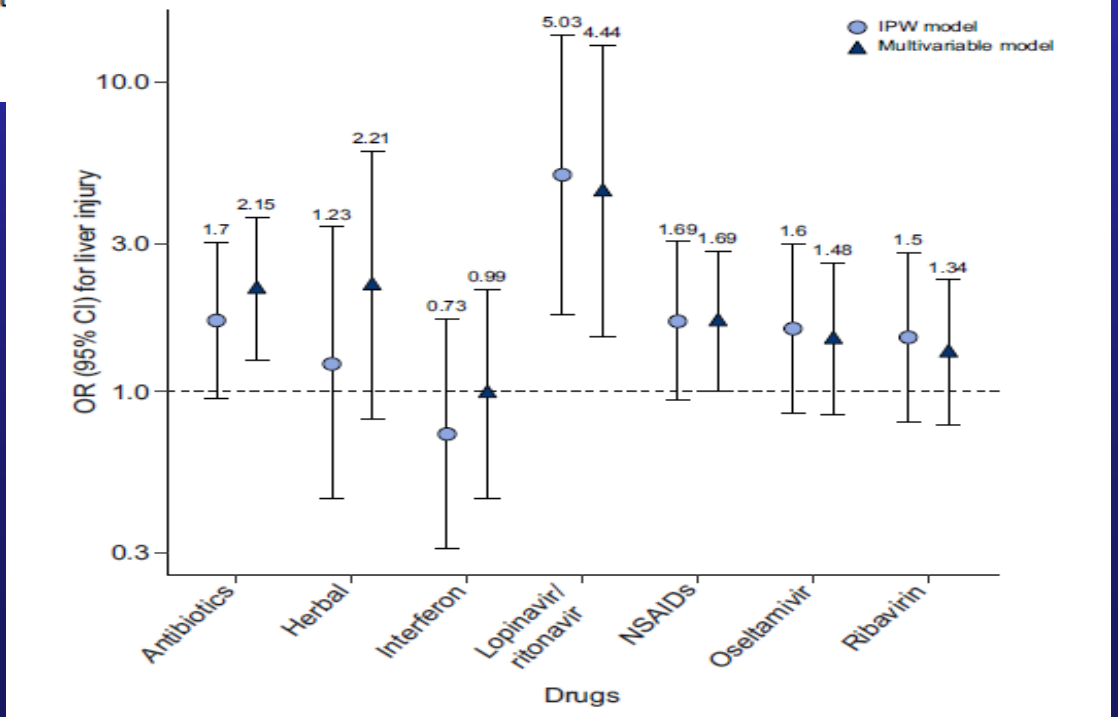


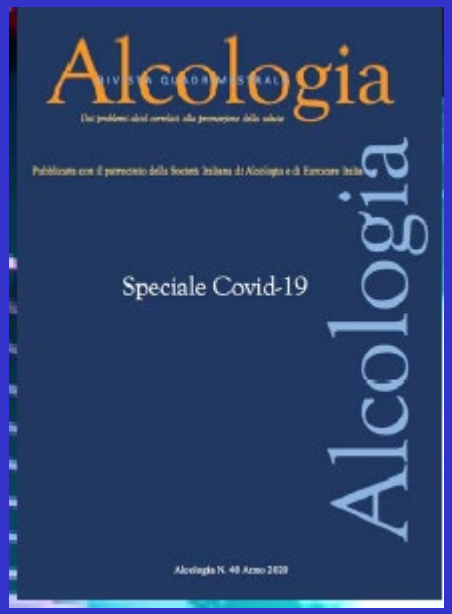
Fig. 1. Liver test abnormality during hospitalization in patients with COVID-19 by severity of disease. (Bars represent

Severe Covid-19 vs Non Severe:

	Liver injury	Abnormal function
Severe	**46.2%**	**93.4%**
Non Severe	**14.4%**	**71.5%**



Cai et al, J Hepatol 2020



Recommendations for the management of Alcohol Use Disorder (AUD) patient during and post COVID-19 pandemic (I)

1. *Asymptomatic patients*:

-the patient must stay at home (?)
-a telephone call evaluation may be carried out at least once a week for a rapid check of the clinical condition regarding alcohol use
-do not discontinue adversative, anti-craving, or psychotropic drugs
-alert peers and family members of AUD patients that their social isolation may increases the risk for relapse to alcohol use
-employ e-group treatment where the majority of the participants had access to technology, while for those living in poor conditions maintain monitoring of clinical conditions through telephone calls

Società Italiana di Alcologia – Osservatorio Alcol Istituto Superiore di Sanità; 2020 (https://www.epicentro.iss.it/coronavirus/sars-cov-2-dipendenze-alcol-raccomandazioni-sia)

Recommendations for the management of AUD patient during and post COVID-19 pandemic (II)

2. *Symptomatic patients*:

-do not visit patients, and in accordance with specialists (experts in infection diseases, internal medicine or pneumologists), hospitalization in a COVID-19 area may be necessary

-telemedicine (phone calls, e-mail or video calls) should be encouraged

-if the patient enters in a COVID-19 clinical pharmacological trial with hydroxychloroquine, anti-virals, corticosteroids, and low molecular weight heparin, a careful evaluation of the discontinuation of adversative / anti-craving drugs or re-modulation of the dosage or substitution of the psychotropic drugs due to the drug interactions and / or worsening of symptoms may be planned

-in patients treated with psychotropic drugs and hydroxychloroquine or anti-virals, frequent blood samples of ALT and bilirubin levels need to be taken: if ALT is >3-5 times higher than normal and bilirubin levels are beyond the limits, psychotropic drugs (i.e. anti-depressants) need to be discontinued

-consider that, due to more susceptibility in AUD patients to infections in general, use of corticosteroid may be used only in case of severe form of SARS-CoV-2 infections needing an oxygen support preferably in hospitalized patients

Recommendations for the management of AUD patient during and post COVID-19 pandemic (III)

3. *Patients with alcoholic liver disease (ALD)*:

-patients with compensated ALD should postpone medical visits and routine laboratory controls, and telemedicine (phone calls, e-mail or video calls) should be encouraged limiting out-patient visits to those with high MELD (score >20);

-patients should be encouraged to receive pneumococcus and influenza vaccinations

-*treatment for alcoholic liver cirrhosis-associated complications* (portal hypertension, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis and gastrointestinal bleeding) *should be continued* (when it is possible such as for paracentesis, in a Day Hospital/Day Service setting), and when patients need hospitalization, this may be done in a non-COVID ward after the performance of the SARS-CoV-2 testing

-in hospitalized patients, video-calls with family members may be planned

Recommendations for the management of AUD patient during and post COVID-19 pandemic (IV)

4. *Patients awaiting liver transplantation (LT)*:

-in LT-ICU the main measures of standard of care may be: a) the exclusion of SARS-CoV-2 positive donors and recipients; b) positive professional staff may stay at home; c) apply infection control measures in order to minimize the risk of spread; d) a physical separation in two sectors (the so called "clean" and "dirty" areas) in the LT-ICU with a strict monitoring of no cross-traffic

-LT in patients resulted positive for SARS-CoV-2 infection may be postponed after resolution of the infection

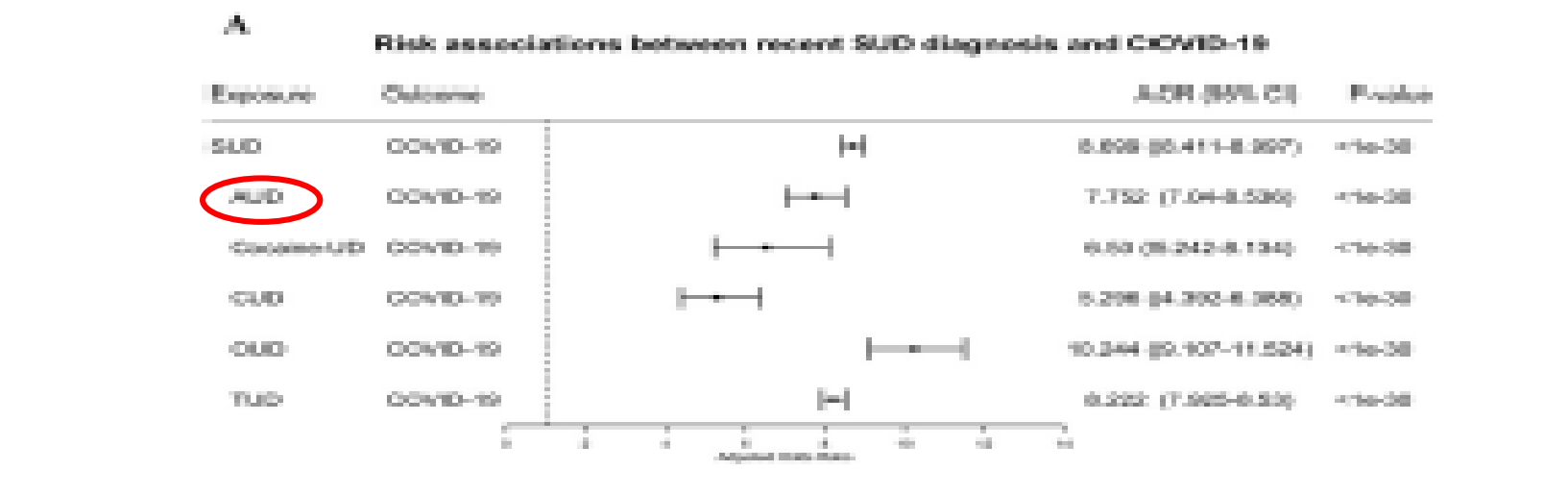
-even though the 6 months rule remains a valid criterion for LT for AUD patients, in selected patients (poor short-term prognosis with MELD score >20, high motivation to abstain, deep consciousness of his/her drinking status of the disease, the presence of a solid psycho-social and family supports) 3 months of abstinence may be adequate

-in selected patients affected by a severe acute alcoholic hepatitis not responder to corticosteroid therapy, acute LT may be considered appropriate after an accurate evaluation of a multidisciplinary professional group

-post-LT immune-suppression regimens should not be changed, however, in patients diagnosed with COVID-19, reduction of doses should be considered

SUBSTANCE USE DISORDERS AND COVID-19 RISK

Alcohol Use Disorder (AUD); Opioid Use Disorder (OUD); Cannabis Use Disorder (CUD) Tobacco Use Disorder (TUD), Cocaine Use Disorder (Cocaine-UD)



OUD	**10.244**
AUD	**7.752**
Cocaine-UD	**6.530**
CUD	**5.296**

adjusted odd ratio

…worse outcomes (death: 9.6%, hospitalization: 41%) than general population (death: 6.6%, hospitalization 30.15%) …

Wang et al, Molecular Psichiatry 2021

COVID-19 AL 31 DICEMBRE 2020
confronto pazienti del Centro Alcologico Regionale Ligure con popolazione generale

Regione Liguria

1509.000 abitanti

91.780 Covid-19 positivi 6%

3905 Deceduti 4.2%

Centro Alcologico Regionale

314 AUD (DSM5 moderato/severo)

25/314 7.89%

13/25 ricoverati (52%)

-7 Ricoverati non deceduti

-4 Ricoverati deceduti (16%)

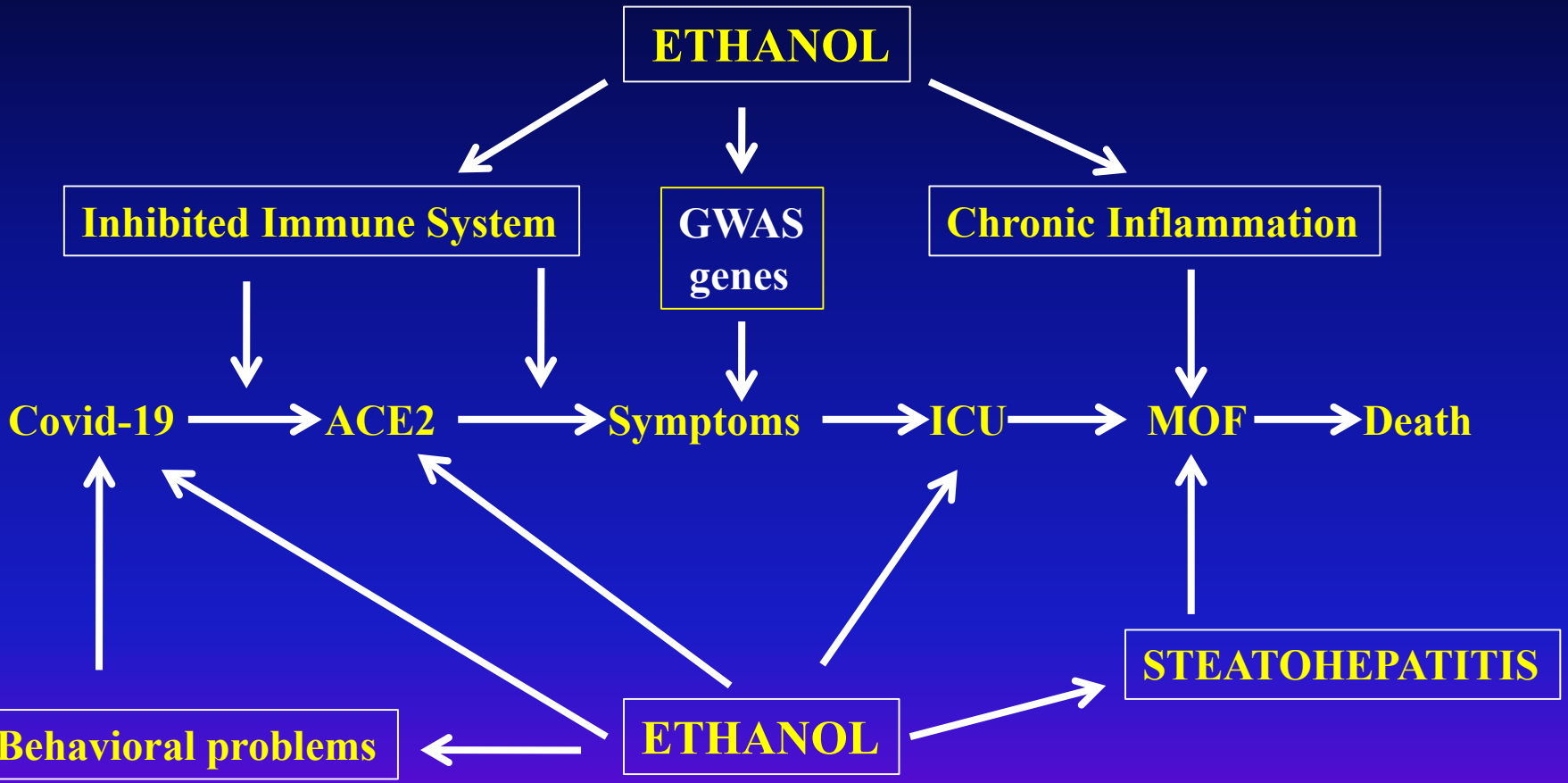
6 a casa (eparina/steroidi)

8 paracetamolo

>15% casi di DUA – DSM5 severo
20% di ricadute

Testino G, APD 2021

ALCOHOL USE DISORDERS PATIENTS
A FRAIL PATIENT



ICU: intensive care unit
MOF: multiorgan failure

Testino G, 2021

Disturbo da Uso di Alcol (DUA) e Vaccino anti-SARS-CoV-2

20-30% maschi e 10-20% femmine con DUA (DSM-5) – Vaccinazione di massa

Inibizione/alterazione sistema immunitario (innato/ acquisito)

Bailey, 2021

Inibizione presentazione antigenica da parte delle cellule dendritiche

Eken et al, 2011

Componente T recupera piena funzione dopo 30 giorni di astensione

Pasala et al, 2005

Riduzione risposta già dimostrata per vaccino anti-influenzale, anti-HBV, anti M. Tubercolosis…

De Maria et al, 2001; Pasala et al 2005; Braithwaite and Bryant, 2010; Iversen et al, 2021

Disturbo da Uso di Alcol e Vaccino anti-SARS-CoV-2

20-30% maschi e 10-20% femmine con DUA – Vaccinazione di massa

VACCINO ? ETANOLO ? VACCINO/ETANOLO?

Trombocitopenia con recupero dopo 7-15 giorni di astensione

Silczuk et al, 2020

Fenomeni trombo-embolici (anche in sede vascolare cerebrale)

Zoller et al, 2015

Fenomeni di Coagulazione Intravascolare Disseminata

Singh et al, 2020

Produzione auto-anticorpale

Mandyam et al, 2017

DISORDINE DA USO DI ALCOL

paziente «fragile»: mandatoria vaccinazione anti Covid- 19

CONSUMO DI ALCOL
per principio di precauzione !!

↓

Identificazione di consumo rischioso/dannoso

Astensione alcol per circa 30 giorni
o comunque riduzione a livelli di consumo a basso rischio

Testino G, APD 2021


Grazie