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MEDICAL INTERNET NEWS

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Original Research | 30 August 2022

The Association of Baseline Plasma SARS-CoV-2 Nucleocapsid Antigen Level and Outcomes in Patients Hospitalized With COVID-19 FREE

ACTIV-3/TICO Study Group*

Author, Article, and Disclosure Information

https://doi.org/10.7326/M22-0924

Results:

Plasma antigen was below the level of quantification in 5% of participants at enrollment, and 1000 ng/L or greater in 57%. Baseline pulmonary severity of illness was strongly associated with plasma antigen level, with mean plasma antigen level 3.10-fold higher among those requiring noninvasive ventilation or high-flow nasal cannula compared with room air (95% CI, 2.22 to 4.34). Plasma antigen level was higher in those who lacked antispike antibodies (6.42 fold; CI, 5.37 to 7.66) and in those with the Delta variant (1.73 fold; CI, 1.41 to 2.13). Additional factors associated with higher baseline antigen level included male sex, shorter time since hospital admission, decreased days of remdesivir, and renal impairment. In contrast, race, ethnicity, body mass index, and immunocompromising conditions were not associated with plasma antigen levels. Plasma antigen level of 1000 ng/L or greater was associated with a markedly higher odds of worsened pulmonary status at day 5 (odds ratio, 5.06 [CI, 3.41 to 7.50]) and longer time to hospital discharge (median, 7 vs. 4 days; subhazard ratio, 0.51 [CI, 0.45 to 0.57]), with subhazard ratios similar across all levels of baseline pulmonary severity.

Limitations:

Plasma samples were drawn at enrollment, not hospital presentation. No point-of-care test to measure plasma antigen is currently available.

Conclusion:

Elevated plasma antigen is highly associated with both severity of pulmonary illness and clinically important patient outcomes. Multiple clinical and viral factors are associated with plasma antigen level at presentation. These data support a potential role of ongoing viral replication in the pathogenesis of SARS-CoV-2 in hospitalized patients.

NEWS RELEASE 24-AUG-2022

Whole blood RNA profiling of severe COVID-19 cases

Researchers from Osaka University evaluate RNA profiles in the blood to shed light on the signaling pathways underlying the pathogenesis of COVID-19

Peer-Reviewed Publication

Osaka, Japan – Just as a recipe contains the instructions needed to make a dish, messenger ribonucleic acid (mRNA) sequences in the body contain the information needed to make proteins. Changes in the expression of specific mRNAs and short RNA sequences known as microRNAs, which can act to suppress protein synthesis, may accompany disease. Recently, researchers in Japan have uncovered changes in mRNA and microRNA expression patterns that occur in the blood during severe COVID-19 infection.

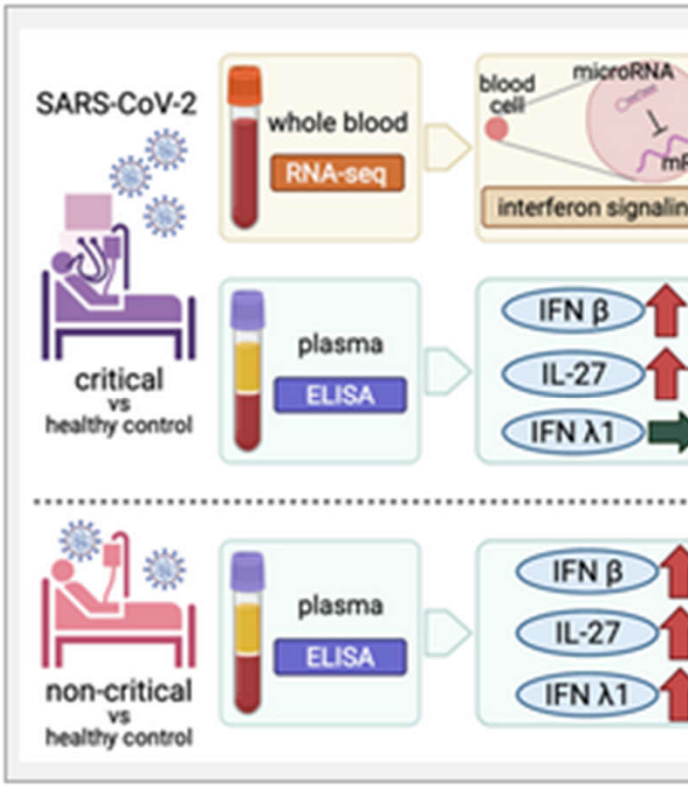
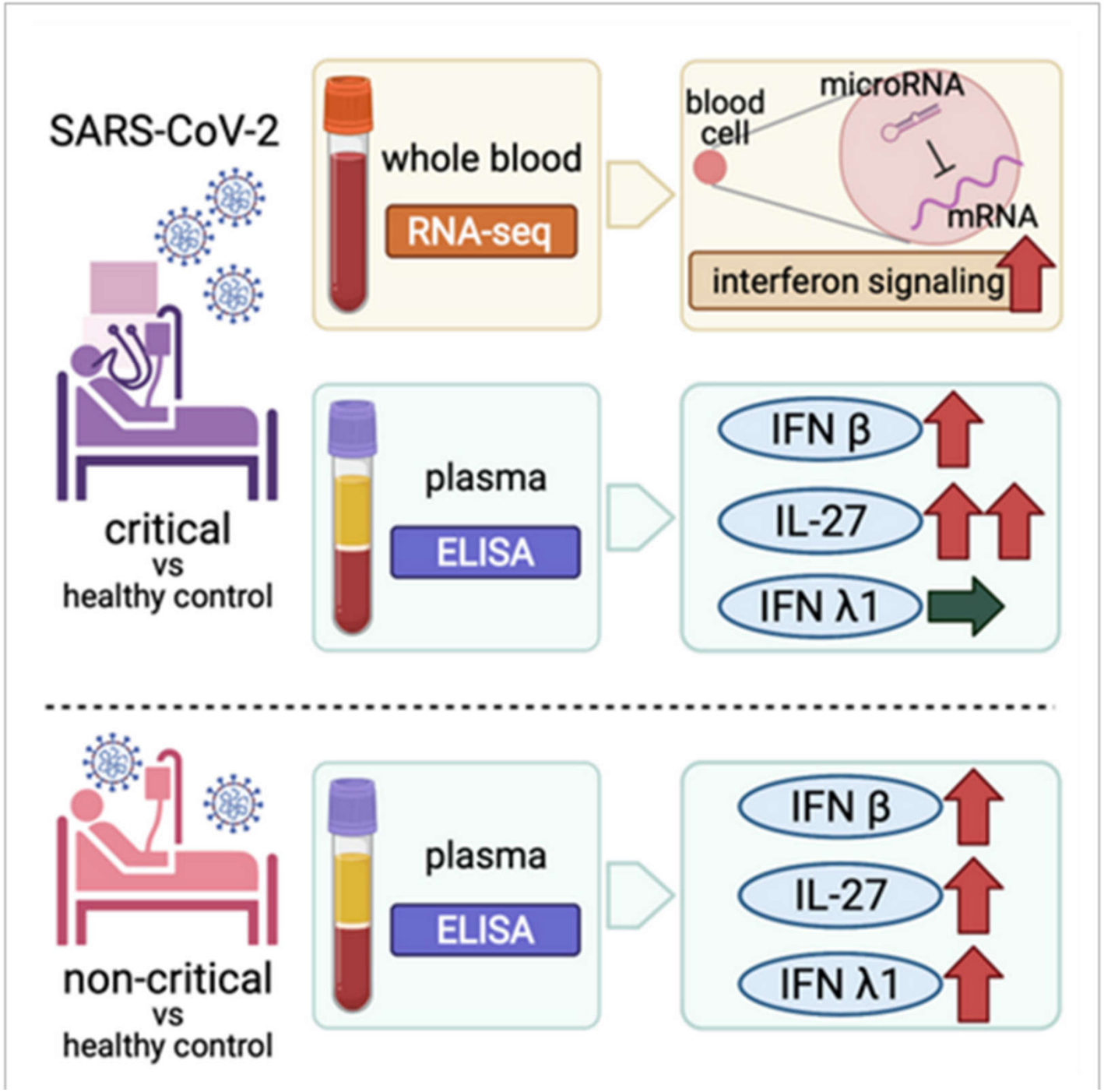


IMAGE: OUTLINE OF THIS STUDY view more

CREDIT: 2022 YUKI TOGAMI ET AL., SIGNIFICA
OF INTERFERON SIGNALING BASED ON MRNA
MICRORNA INTEGRATION AND PLASMA PROT
ANALYSES IN CRITICALLY ILL COVID-19 PATIEN
MOLECULAR THERAPY-NUCLEIC ACIDS

In a new study published in *Molecular Therapy Nucleic Acids*, researchers led by Osaka University comprehensively analyzed the mRNA and microRNA profiles of whole blood samples from patients with severe COVID-19 using a technique known as RNA-sequencing. RNA-sequencing allows for the evaluation of all of the RNA content expre within a population of cells.


SARS-CoV-2
critical
vs
healthy control
whole blood
RNA-seq
blood cell
microRNA
mRNA
interferon signaling
plasma
ELISA
IFN β
IL-27
IFN λ1
non-critical
vs
healthy control
plasma
ELISA
IFN β
IL-27
IFN λ1

MAYO CLINIC Mayo Clinic Proceedings

ORIGINAL ARTICLE | VOLUME 97, ISSUE 8, P1483-1492, AUGUST 01, 2022

Effectiveness and Safety of Clopidogrel vs Aspirin in Elderly Patients With Ischemic Stroke

Hsin-Yi Huang, MS, BCCCP • Shin-Yi Lin, MS • Aaron J. Katz, PharmD, PhD • ... Fang-Ju Lin, PhD • Chi-Chuan Wang, PhD • Chung-Hsuen Wu, PhD • Show all authors

DOI: https://doi.org/10.1016/j.mayocp.2022.01.033 •

Results

A total of 15,045 patients were included in the study, 1979 of whom used clopidogrel and 13,066 who used aspirin following hospitalization for primary acute ischemic stroke. Clopidogrel use was associated with significantly lower risk of recurrent acute ischemic stroke (hazard ratio [HR], 0.89; 95% CI, 0.83 to 0.96; *P*=.002), composite cardiovascular events (HR, 0.88; 95% CI, 0.82 to 0.95; *P*<.001), intracranial hemorrhage (HR, 0.71; 95% CI, 0.56 to 0.90; *P*=.005), and composite major bleeding events (HR, 0.89; 95% CI, 0.80 to 0.99; *P*=.04) compared with aspirin use.

Conclusion

In patients aged 80 years or older with primary acute ischemic stroke, clopidogrel users had lower risks of recurrent stroke and the composite cardiovascular events compared with aspirin users. Clopidogrel users also had lower risks of intracranial hemorrhage and the composite major bleeding events compared with aspirin users.

General Thoracic and Cardiovascular Surgery
https://doi.org/10.1007/s11748-022-01868-6

ORIGINAL ARTICLE

Impact of accurate diagnosis of interstitial lung diseases on postoperative outcomes in lung cancer

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Received: 24 May 2022 / Accepted: 15 August 2022

Abstract

Objective The prognostic impact of interstitial lung disease (ILD) subclassification based on both high-resolution computed tomography (HRCT) scan findings and histopathological findings is unknown.

Methods We retrospectively analyzed 104 patients who were diagnosed with clinical ILD according to HRCT scan findings and who underwent lung cancer surgery. Via an expert multidisciplinary discussion, we re-classified HRCT scan findings and validated the histopathological patterns of ILDs in lung specimens.

Results There were several mismatches between HRCT scan findings and histological patterns. Moreover, 87 (83.7%) and 6 (5.8%) patients were diagnosed with definitive ILD and pathological non-ILD, respectively. Finally, 82 patients with idiopathic interstitial pneumonias (IIPs) were divided into the idiopathic pulmonary fibrosis (IPF) ($n=61$) group and the other group ($n=21$). The 5-year overall survival rate of the IPF group was significantly lower than that of the other group (22.8% vs 67.9%; $p=0.011$). Sub-classification of IIPs was found to be an independent prognostic factor for overall survival in patients with lung cancer.

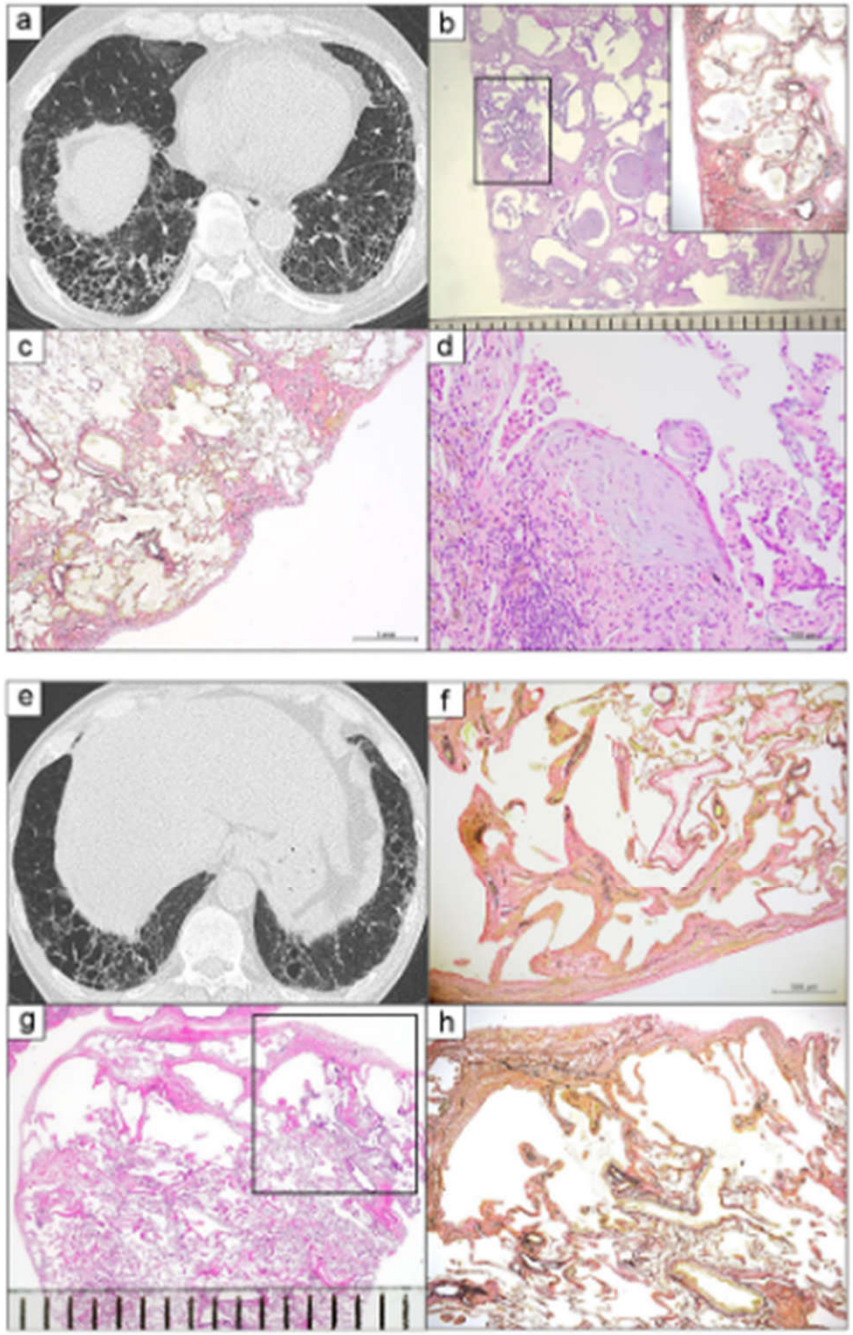

Fig. 2 Comparison of HRCT scan findings and histopathological patterns between patients diagnosed with IIP and those with pathological non-ILD. **a**–**d**. An IIP case. **a** The UIP pattern on HRCT: presence of honeycombing with sub-pleural and basal predominance. **b** Panoramatic view (scale bar: 1 mm) and low-magnification photograph (box) (Elastica van Gieson staining) showing dense fibrosis with architectural distortion in the form of honeycomb change. **c** Low-magnification photomicrograph showing predominant sub-pleural and para-septal distribution of fibrosis (scale bar: 1 mm, **H** & **E**). **d** Higher-magnification photomicrograph showing fibroblast foci (scale bar: 100 µm, **H** & **E**).**e**–**h**. A pathological non-ILD case. **e** Indeterminate UIP pattern on HRCT: multiple thin-walled cysts in the lower lobe. **f** High magnification photomicrograph showing mild fibrosis with centriacinar emphysema in the background (scale bar: 500 µm, Elastica van Gieson stain). **g** Panoramatic view (scale bar: 1 mm) and **h** low-magnification photomicrograph (box in Fig. 4 g) (Elastica van Gieson staining) showing a fibrous wall of bronchiolocentric cysts. *HRCT*: high-resolution computed tomography, *IIP*: idiopathic interstitial pneumonia, *ILD*: interstitial lung disease, *UIP*: usual interstitial pneumonia

Table 1 Characteristics between the IIP and other groups

	IIP ($n=82$)	Pathological non-ILD ($n=6$)	p value*	ILD with a known cause ($n=5$)	p value**
Male sex	73 (89.0)	4 (66.7)	0.110	0	<0.001
Smoking history, yes	79 (96.3)	6 (100)	0.634	2 (40.0)	<0.001
Tobacco, pack-years	50.7±32.8	69.4±34.2	0.183	13.4±21.0	0.014
KL-6 level (U/mL)	641.4±371.7	521.3±298.3	0.442	916.2±443.1	0.116
SP-D level (ng/mL)	150.1±93.5	106.9±64.2	0.271	129.8±38.7	0.632
Pulmonary function					
VC%pred (%)	98.6±18.6	108.1±22.4	0.235	101.8±20.3	0.708
DLco%pred (%)	73.8±20.7	72.0±28.8	0.842	61.9±22.5	0.216
FEV_1/FVC (%)	75.5±8.4	60.3±8.1	<0.001	78.8±7.9	0.396
HRCT pattern			<0.001		<0.001
UIP	47 (57.3)	0		1 (20.0)	
Probable UIP	18 (22.0)	0		0	
Indeterminate UIP	13 (15.9)	6 (100)		1 (20.0)	
Alternative diagnosis	4 (4.9)	0		3 (60.0)	
Surgical procedure			0.569		0.707
Pneumonectomy	1 (1.2)	0		0	
Lobectomy	61 (74.4)	6 (100)		3 (60.0)	
Segmentectomy	4 (4.9)	0		0	
Partial resection	16 (19.5)	0		2 (40.0)	
Clinical staging			0.684		0.368
I	41 (50.0)	2 (33.3)		4 (80.0)	
II	24 (29.3)	2 (33.3)		1 (20.0)	
III	17 (20.7)	2 (33.3)		0	
Pathologic staging			0.425		0.516
I	41 (50.0)	2 (33.3)		4 (80.0)	
II	17 (20.7)	3 (50.0)		1 (20.0)	
III	22 (26.8)	1 (16.7)		0	
IV	2 (2.4)	0		0	
AE from any cause	24 (29.3)	0	0.120	1 (20.0)	0.657
Postoperative AE	13 (15.9)	0	0.291	0	0.334
Adjuvant therapy			0.906		0.838
Carboplatin-based	8 (9.8)	1 (16.7)		0	
Cisplatin-based	1 (1.2)	0		0	
Other	3 (3.7)	0		0	

Conclusion

An accurate, detailed diagnosis of IIP/IPF according to both HRCT scan findings and histopathological patterns is important for providing an appropriate treatment among patients with lung cancer.

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DOI: 10.1111/liv.15253

Liver INTERNATIONAL

REVIEW

Hepatocellular carcinoma: The virus or the liver?

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Abstract

Hepatocellular carcinoma (HCC) represents a major public health problem being one of the most common causes of cancer-related deaths worldwide. Hepatitis B (HBV) and C viruses have been classified as oncoviruses and are responsible for the majority of HCC cases, while the role of hepatitis D virus (HDV) in liver carcinogenesis has not been elucidated. HDV/HBV coinfection is related to more severe liver damage than HBV mono-infection and recent studies suggest that HDV/HBV patients are at increased risk of developing HCC compared to HBV mono-infected patients. HBV is known to promote hepatocarcinogenesis via DNA integration into host DNA, disruption of molecular pathways by regulatory HBV x (HBx) protein and excessive oxidative stress. Recently, several molecular mechanisms have been proposed to clarify the pathogenesis of HDV-related HCC including activation of signalling pathways by specific HDV antigens, epigenetic dysregulation and altered gene expression. Alongside, ongoing chronic inflammation and impaired immune responses have also been suggested to facilitate carcinogenesis. Finally, cellular senescence seems to play an important role in chronic viral infection and inflammation leading to hepatocarcinogenesis. In this review, we summarize the current literature on the impact of HDV in HCC development and discuss the potential interplay between HBV, HDV and neighbouring liver tissue in liver carcinogenesis.

Key points

- Patients with hepatitis D (HDV) and hepatitis B virus (HBV) coinfection are at increased risk of developing hepatocellular carcinoma (HCC)
- HBV infection promotes HCC development through integration to host DNA, dysregulation of cellular processes by HBV protein x (HBx) and oxidative stress
- HDV can lead to HCC through silencing of tumour suppressor genes, increased cell proliferation, genomic instability and excessive inflammation
- Chronic liver inflammation and hepatocellular senescence facilitate HCC development regardless of the cause

1st author, year	Sample	Major findings
Goto, 2000[61]	Cell lines	LHDAg activated the SRF- and SRE-dependent signal transduction pathway
Goto, 2003[62]	Cell lines	HBx and LHDAg synergically activate the SRE pathway
Choi, 2007[68]	Cell lines	LHDAg activated the TGF-β and the c-Jun pathway
Liao, 2009[74]	Cell lines	HDAgs upregulate the clusterin gene
Park, 2009[70]	Cell lines	LHDAg modulates NF-κB signalling pathway via TNF
Williams, 2012[69]	Cell lines	LHDAg modulates NF-κB signalling pathway and STAT-3 via oxidative stress
Benegiamo, 2013[80]	Cell lines	HDAgs upregulate DNMT3 expression and hypermethylation of the E2F1 gene through STAT3 pathway
Chen, 2018[77]	Cell lines	SHDAg downregulates GSTP1 production leading to increased ROS production
Diaz, 2018[81]	Human liver tissue	Upregulation of genes involved in genome instability in HDV-related hepatocellular carcinoma specimens

Abbreviations: DNMT3, DNA (cytosine-5)-methyltransferase 3; GSTP1, Glutathione S-Transferase Pi 1; HBx, hepatitis B virus x protein; HDAgs, HDV antigens; LHDAg, large HDV antigen; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SHDAg, small HDV antigen; SRE, serum response element; SRF, serum response factor; STAT-3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor β; TNF, tumour necrosis factor.

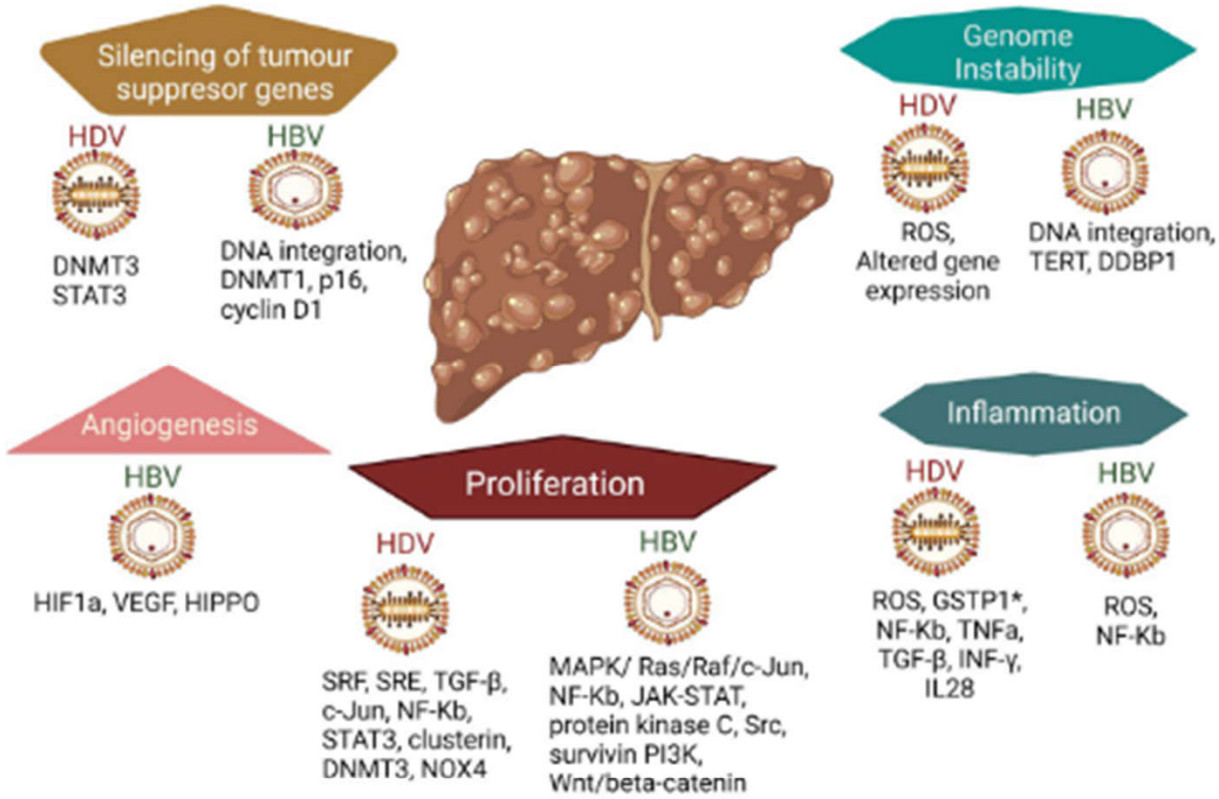

FIGURE 1 Molecular mechanisms involved in hepatitis B (HBV)- and hepatitis D virus (HDV)-related hepatocarcinogenesis. All factors/pathways are upregulated, except for those indicated by asterisk (*) which are downregulated. The figure was created with BioRender.com. DNMT3, DNA (cytosine-5)-methyltransferase 3; STAT3, signal transducer and activator of transcription; DNMT1, DNA (cytosine-5)-methyltransferase 1; SRF, serum response factor; SRE; serum response element; TGF-β, transforming growth factor β; NF-κB, nuclear factor kappa B; NOX4, NADPH oxidase 4; MAPK, Mitogen-activated protein kinase; ROS, reactive oxygen species; TERT, telomerase reverse transcriptase DDBP1, DNA damage-binding protein 1; GSTP1, Glutathione S-transferase Pi 1; TNF, tumour necrosis factor; IL28, interleukin 28; HIF1a, hypoxia inducible factor 1a; VEGF, vascular endothelial growth factor

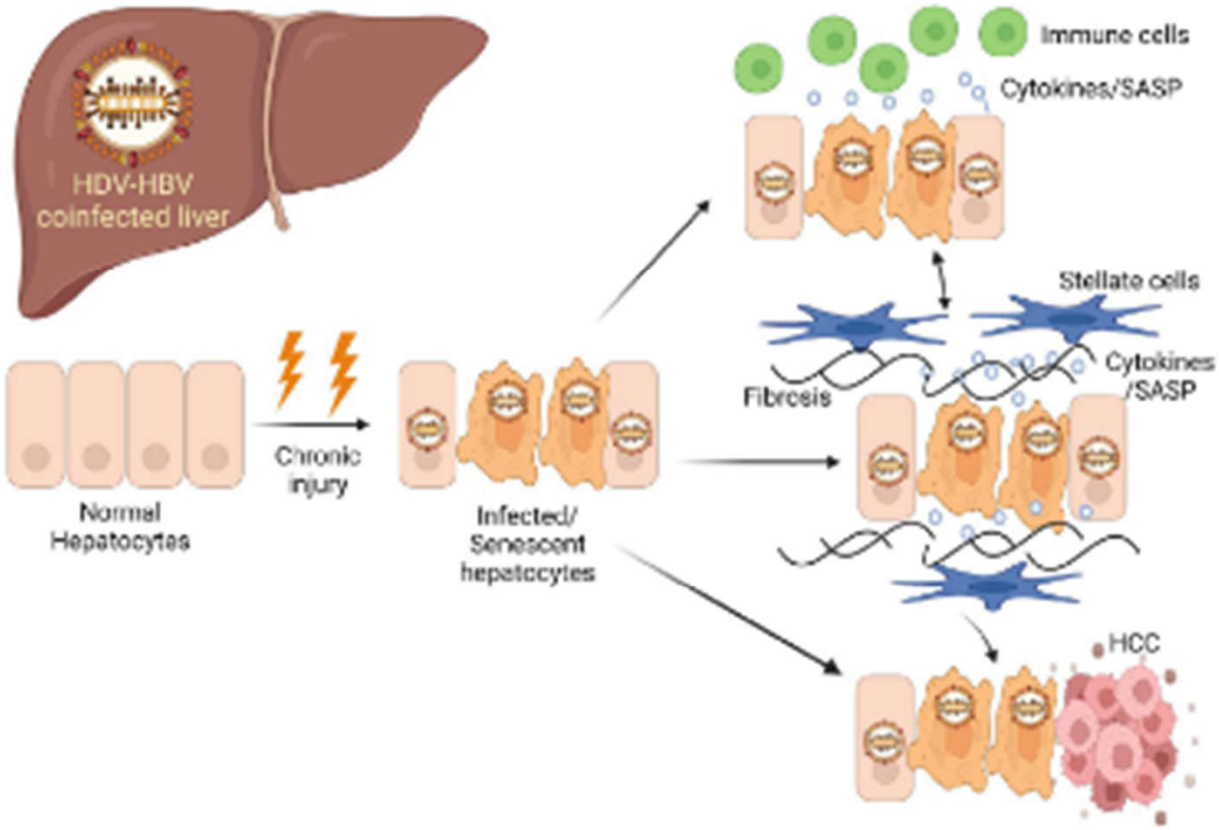

FIGURE 2 Mechanisms involved in chronic liver injury in patients with chronic hepatitis D (HDV) and B virus (HBV) coinfection which can promote hepatocarcinogenesis. The figure was created with BioRender.com. HCC, hepatocellular carcinoma; SASP, senescence-associated secretory phenotype

6 | CONCLUSIONS

HDV infection is a major public health issue affecting millions of patients worldwide, with severe clinical complications including decompensated cirrhosis and HCC. Several recent in vitro studies have attempted to shred light to the pathogenesis of HDV-related HCC, but the exact molecular pathways remain to be elucidated. Because of the specific nature of this defective virus, it could be assumed that both chronic HDV and HBV infection as well as the damaged neighbouring liver tissue and impaired immune responses contribute to HCC development. It is well known that HBV can trigger hepatocarcinogenesis through several direct mechanisms. On the other hand, HDV seems to be able to induce hepatocarcinogenesis either directly through different molecular mechanisms including silencing of tumour suppressor genes and genomic instability or indirectly through excessive inflammation, increased cell proliferation and hepatocellular senescence that facilitate HCC development regardless of the cause. In any case, there is still an unmet medical need for more studies, in order to clarify the exact role of HDV in liver carcinogenesis and identify molecular pathways that could serve as potential therapeutic targets.

CONFLICT OF INTEREST

NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polypill Strategy in Secondary Cardiovascular Prevention

Jose M. Castellano, M.D., Ph.D., Stuart J. Pocock, Ph.D., Deepak L. Bhatt, M.D., M.P.H., Antonio J. Quesada, Ph.D., Ruth Owen, M.Sc., Antonio Fernandez-Ortiz, M.D., Ph.D., Pedro L. Sanchez, M.D., Ph.D., Francisco Marin Ortuño, M.D., Ph.D., Jose M. Vazquez Rodriguez, M.D., Alexandra Domingo-Fernández, B.Sc., Iñigo Lozano, M.D., Maria C. Roncaglioni, M.Sc., et al., for the SECURE Investigators*

August 26, 2022
DOI: 10.1056/NEJMoa2208275

Abstract

BACKGROUND A polypill that includes key medications associated with improved outcomes (aspirin, angiotensin-converting–enzyme [ACE] inhibitor, and statin) has been proposed as a simple approach to the secondary prevention of cardiovascular death and complications after myocardial infarction.

METHODS In this phase 3, randomized, controlled clinical trial, we assigned patients with myocardial infarction within the previous 6 months to a polypill-based strategy or usual care. The polypill treatment consisted of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The primary composite outcome was cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization. The key secondary end point was a composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke.

RESULTS A total of 2499 patients underwent randomization and were followed for a median of 36 months. A primary-outcome event occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% confidence interval [CI], 0.60 to 0.96; P=0.02). A key secondary-outcome event occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P=0.005). The results were consistent across prespecified subgroups. Medication adherence as reported by the patients was higher in the polypill group than in the usual-care group. Adverse events were similar between groups.

CONCLUSIONS Treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events than usual care. (Funded by the European Union Horizon 2020; SECURE ClinicalTrials.gov number, NCT02596126; EudraCT number, 2015-002868-17.)

THE END