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ORIGINAL RESEARCH
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COVCOG 2: Cognitive and Memory Deficits in Long COVID: A Second Publication From the COVID and Cognition Study

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COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been often characterized as a respiratory disease. However, it is increasingly being understood as an infection that impacts multiple systems, and many patients report neurological symptoms. Indeed, there is accumulating evidence for neural damage in some individuals, with recent studies suggesting loss of gray matter in multiple regions, particularly in the left hemisphere. There are several mechanisms by which the COVID-19 infection may lead to neurological symptoms and structural and functional changes in the brain, and cognitive problems are one of the most commonly reported symptoms in those experiencing Long COVID – the chronic illness following the COVID-19 infection that affects between 10 and 25% of patients. However, there is yet little research testing cognition in Long COVID. The COVID and Cognition Study is a cross-sectional/longitudinal study aiming to understand cognitive problems in Long COVID. The first paper from the study explored the characteristics of our sample of 181 individuals who had experienced the COVID-19 infection, and 185 who had not, and the factors that predicted ongoing symptoms and self-reported cognitive deficits. In this second paper from the study, we assess this sample on tests of memory, language, and executive function. We hypothesize that performance on "objective" cognitive tests will reflect self-reported cognitive symptoms. We further hypothesize that some symptom profiles may be more predictive of cognitive performance than others, perhaps giving some information about the mechanism. We found a consistent pattern of memory deficits in those that had experienced the COVID-19 infection, with deficits increasing with the severity of self-reported ongoing symptoms. Fatigue/Mixed symptoms during the initial illness and ongoing neurological symptoms were predictive of cognitive performance.

Keywords: Long COVID, cognition, neurological, memory, executive functions, language, COVID-19, symptoms

Olivares and Arboix, 2009).

Summary

In this second investigation of the first baseline session of the COVID and Cognition study, we explored whether those who had experienced the COVID-19 infection showed measurable differences in assessments of cognitive performance. We found a consistent association between the COVID-19 infection and reduced memory performance, with those with ongoing symptoms being less accurate and slower in a test of verbal memory, but (once demographics and multiple comparisons were accounted for) there were no significant group effects in any other cognitive domain. When considering the nature of symptoms experienced, Fatigue/Mixed and Dermatological symptoms during the initial 3 weeks of illness were associated with reduced memory performance and slower reaction times on Executive Function Performance and Reaction Time tasks, respectively. Neurological symptoms during the ongoing illness were associated with performance in the Executive Function tasks, while the same symptoms experienced at the time of test predicted variance in memory. These were the most robust findings, with a conservative correction for multiple comparisons, suggesting that other identified associations may be worthy of further investigation.

In combination with previous evidence for cognitive dysfunction (e.g., Hampshire et al., 2021) and neural damage following the COVID-19 infection (Douaud et al., 2021), these findings are concerning and suggest that COVID-19 is an illness that may be associated with considerable cognitive and neurological sequelae of unknown longevity. This is particularly concerning given the potential for these changes to translate into greater vulnerability to neurodegeneration. These findings should be of note to policymakers, both in the context of post-COVID support provision and in the nature of the response to the ongoing pandemic. It is yet to be seen whether the proportion of infections that translate into Long COVID remains similar in the face of changes in both population immunity (*via* both vaccination and previous infection) and disease variants. However, if the current patterns persist, the long-term societal impacts of unmitigated spread may be considerable. In terms of follow-up support for patients, we reported in our previous publication (Guo et al., 2022) that a large proportion of our sample reported difficulty in getting support from medical professionals, and one reason for this may be a reluctance to consider self-reported cognitive deficits as a concrete indicator (rather than, for example, a component of general fatigue). It is thus notable that, in this study, self-reported memory issues were associated with measurable reductions in memory ability and that these are linked with other neurological symptoms. This suggests that neurological and neuropsychological assessment should be made more widely available to patients with Long COVID reporting cognitive deficits.

The COVID and Cognition participants were followed up multiple times following this assessment, and future publications with this cohort will prove informative as to the likely progression in symptoms and cognitive performance over time. However, given the associations shown in our previous publication with the number of weeks since infection (Guo et al., 2022), it seems likely that a considerable proportion of individuals may show stable cognitive symptoms over many months.

CORRESPONDENCE

Molnupiravir for Covid-19 in Nonhospitalized Patients

TO THE EDITOR: In their report on the MOVe-OUT trial, Jayk Bernal et al. (Feb. 10 issue)[1] present improbable statistical results. Overestimated treatment effects in interim analyses are well understood.[2] Much less common is a reversal of the treatment effect from the interim analysis to the next analysis. Initially, a planned interim analysis from Merck showed an efficacy of approximately 50% with respect to the primary outcome of hospitalization for any cause or death through day 29, with a primary outcome event occurring in 28 of 385 participants who received molnupiravir and in 53 of 377 participants who received placebo.[1,3] The efficacy later decreased to approximately 30% (a primary outcome event occurred in 48 of 709 participants who received molnupiravir and in 68 of 699 participants who received placebo).[1]

This difference was driven by an increased benefit with placebo in the post–interim analysis phase, with a primary outcome event occurring in 20 of 324 participants who received molnupiravir and in 15 of 322 participants who received placebo. The disparity between these periods is so large that the difference is statistically implausible. Furthermore, at a key Food and Drug Administration advisory meeting for emergency use authorization for molnupiravir,[3] researchers from Merck presented data across 10 countries. In the primary analysis, point estimates of absolute risk differences varied from −19.6 percentage points in Brazil to 9.1 percentage points in Guatemala, with mutually exclusive confidence intervals.

Kristian Thorlund, Ph.D.
McMaster University

This letter was published on March 16, 2022, at NEJM.org.

1. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2022;386:509-20.
2. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010;303:1180-7.
3. Curtis S, Hazuda D, Blanchard K, et al. Molnupiravir. Presented at the virtual FDA Antimicrobial Drugs Advisory Committee Meeting, November 30, 2021:slide 88 (https://www.fda.gov/media/154472/download).

DOI: 10.1056/NEJMc2201612

TO THE EDITOR: In the trial conducted by Jayk Bernal et al., according to the results of the subgroup analysis of SARS-CoV-2 nucleocapsid antibody status at baseline, a benefit was observed only in the participants with negative status, among whom the adjusted risk difference was −5.1 percentage points (95% confidence interval [CI], −8.8 to −1.6); the adjusted risk difference among those with positive status was 2.3 (95% CI, −1.7 to 7.1). The data from the participants with positive status corresponds to 21% of the trial sample, which is unlikely to include participants with a reinfection given the state of the pandemic when the trial was conducted.[1] Therefore, we could hypothesize that the participants who already had antibody production at the time of diagnosis[2] either had received a diagnosis at a later stage of the infection than those with negative status or had an early immune response.[3] The importance of early treatment was considered in investigations such as the Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial.[4] Do only persons who have not started to mount an

Circulation:
Cardiovascular Imaging

RESEARCH ARTICLE

Full Text

Breast Arterial Calcification: a Novel Cardiovascular Risk Enhancer Among Postmenopausal Women

Carlos Iribarren, Malini Chandra, Catherine Lee, Gabriela Sanchez, Danny L. Sam, Farima Faith Azamian, Hyo-Min Cho, Huanjun Ding, Nathan D. Wong and Sabee Molloi

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Circulation: Cardiovascular Imaging. 2022;15

Background:

Breast arterial calcification (BAC), a common incidental finding in mammography, has been shown to be associated with angiographic coronary artery disease and cardiovascular disease (CVD) outcomes. We aimed to (1) examine the association of BAC presence and quantity with hard atherosclerotic CVD (ASCVD) and global CVD; (2) ascertain model calibration, discrimination and reclassification of ASCVD risk; (3) assess the joint effect of BAC presence and 10-year pooled cohorts equations risk on ASCVD.

Methods:

A cohort study of 5059 women aged 60-79 years recruited after attending mammography screening between October 2012 and February 2015 was conducted in a large health plan in Northern California, United States. BAC status (presence versus absence) and quantity (calcium mass mg) was determined using digital mammograms. Prespecified end points were incident hard ASCVD and a composite of global CVD.

Results:

Twenty-six percent of women had BAC >0 mg. After a mean (SD) follow-up of 6.5 (1.6) years, we ascertained 155 (3.0%) ASCVD events and 427 (8.4%) global CVD events. In Cox regression adjusted for traditional CVD risk factors, BAC presence was associated with a 1.51 (95% CI, 1.08–2.11; *P*=0.02) increased hazard of ASCVD and a 1.23 (95% CI, 1.002–1.52; *P*=0.04) increased hazard of global CVD. While there was no evidence of dose-response association with ASCVD, a threshold effect was found for global CVD at very high BAC burden (95th percentile when BAC present). BAC status provided additional risk stratification of the pooled cohorts equations risk. We noted improvements in model calibration and reclassification of ASCVD: the overall net reclassification improvement was 0.12 (95% CI, 0.03–0.14; *P*=0.01) and the bias-corrected clinical-net reclassification improvement was 0.11 (95% CI, 0.01–0.22; *P*=0.04) after adding BAC status.

Conclusions:

Our results indicate that BAC has potential utility for primary CVD prevention and, therefore, support the notion that BAC ought to be considered a risk-enhancing factor for ASCVD among postmenopausal women.

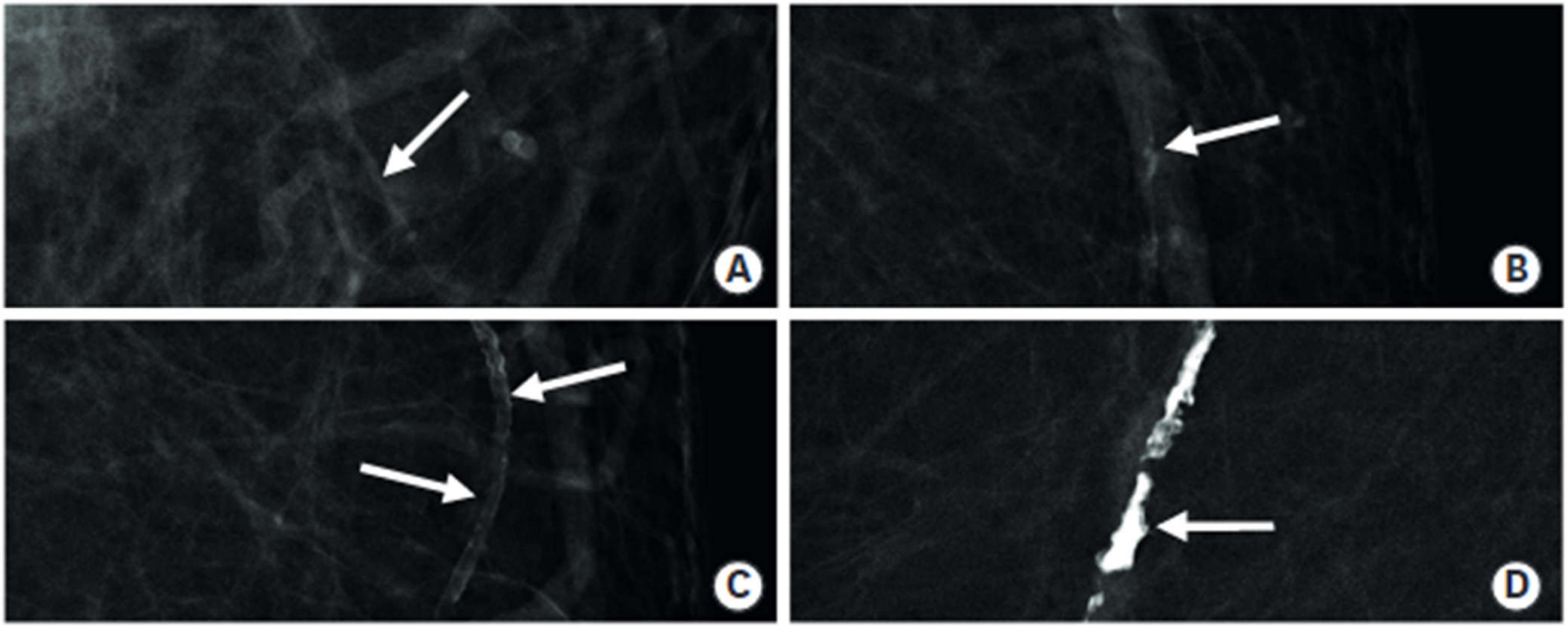

Figure 1. Scoring system of breast arterial calcification (BAC) density. The calcification density of the vessel in the densest segment is scored using 4-step scale. White arrow indicates calcification segment. (A) 0, none, (B) 1, vessel wall calcification with clear visualization of the lumen and/or single wall calcination, (C) 2, vessel wall calcification with clouding of the lumen, (D) 3, dense vessel wall calcification without visualization of the lumen.

Table 2. Association of breast arterial calcification with coronary atherosclerosis

Author, year	n	Age	Modality	Conclusion
Moshyedi, 1995[8]	182	39–92	CA	BAC in women aged less than 59 years may indicate an additional risk factor for CAD, particularly in diabetic patients.
Henkin, 2003[9]	319	50–70	CA	The presence of BAC does not differentiate between patients with angiographic evidence of CAD and those with angiographically normal coronary arteries.
Topal, 2007[10]	123	> 40	CA	There was a significant increase in the frequency of BAC among subjects with more than two vessels with stenosis.
Fiuza Ferreira, 2007[11]	131	42–81	CA	A strong association exists between intramammary arterial calcifications and CAD (adjusted OR: 4.6).
Penugonda, 2010[12]	94	66.7 (mean)	CA	BAC was not positively associated with cardiovascular risk factors, documented CAD, or acute cardiovascular events, suggesting that BAC is not a useful predictor of CAD in intermediate-to high-risk patients.
Zgheib, 2010[13]	172	64.3 (mean)	CA	The authors did not observe a correlation between BAC and coronary angiography-detected CHD, even when CHD severity was considered.
Hekimoğlu, 2012[14]	55	> 40	CA	A significant relationship between intramammarian arterial calcifications and CAD was indicated (OR: 10.8, 95% CI: 3.02–38.59).
Ružičić, 2018[15]	102	> 45	CA	In women > 45 years, there was a significant correlation between the severity of CAD as evaluated by the SYNTAX score and BAC as evaluated by the Likert scale.
Pecchi, 2003[16]	74	< 65	MSCT	Positive association with CAC Linear correlation between BAC severity and coronary calcium content
Maas, 2007[17]	499	49–70	MSCT	Positive association with CAC
Matsumura, 2013[18]	202	30–90	MSCT	Positive association with high-risk CAC score (CAC > 400)
Moradi, 2014[19]	150	> 40	CCTA	No significant correlation of presence and severity of BAC with CAC score
Newallo, 2015[20]	195	46–59	CCTA	Positive association with increased probability of coronary calcification, atherosclerosis, and CAD on CCTA
Mostafavi, 2015[21]	100	34–86	CCTA	The presence of BAC on mammography appears to correlate with CAD as determined by CCTA. The inclusion of BAC as a feature in CAD prediction significantly increased classification results.
Chadashvili, 2016[22]	145	56–61	CCTA	Prediction of coronary artery calcium score of > 11 Significant correlation between BAC and cardiac risk factors, namely diabetes and chronic renal disease
Margolies, 2016[23]	292	39–92	MSCT	Strong quantitative association with CAC Equivalent to both the FRS and PCE for the identification of high-risk women and additive when women with established CAD are included.
Yoon, 2018[3]	2,100	> 40	CCTA	Association of the presence and severity of BAC with the risk of subclinical CAD in asymptomatic women Independent and incremental value over conventional risk algorithms
Kelly, 2018[24]	104	50–65	CCTA	BAC diagnosed on 2 yearly screening mammography predicts CAD-RADS ≥ 3 disease in

Table 3. Longitudinal studies that examined the association between BAC and cardiovascular disease

Author, year	Nation	Population	n	Mean age (years)	BAC prevalence	Follow-up (years)	Outcome	HR	95% CI
Kemmeren,1998[34]	Netherlands	General	12,239	57.5	9.1%	16.8	All-cause mortality	1.29	1.06–1.58
							Cardiovascular mortality	1.29	1.01–1.66
							CHD mortality	1.44	1.02–2.05
							Cerebrovascular mortality	0.88	0.49–1.61
							Other cardiovascular mortality	1.38	0.89–2.16
Iribarren, 2004[35]	United States	General	12,761	56	3.0%	24.8	CHD	1.32	1.08–1.60
							Ischemic stroke	1.41	1.11–1.78
							Heart failure	1.52	1.18–1.98
Schnatz, 2011[36]	United States	General	1,454	56.3	16.3%	5	CHD	3.54 (OR)	2.28–5.50
Abou-Hassan, 2015[37]	United States	End stage renal disease	202	58.3	58.4%	4.1	Coronary artery disease	1.06 (OR)	0.48–2.38
							PAD	4.56 (OR)	1.20–17.3
Hendriks, 2015[38]	Netherlands	General	1,540	57	8.6%	13.2	CHD	1.44	1.02–2.01
							Stroke	1.39	0.92–2.08
							PAD	1.37	0.74–2.52
							Composite of CHD, stroke, PAD	1.39	1.00–1.93

BAC: breast arterial calcification, CHD: coronary heart disease, CI: confidence interval, HR: hazard ratio, n: number of patients, OR: odds ratio, PAD: peripheral arterial disease.

microorganisms

MDPI

Editorial

Special Issue: "Updates on HBV Infection"

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Hepatitis B virus (HBV) infection remains a global public health issue: a number of barriers still hamper the control of the HBV epidemic and in finding a cure for HBV [1,2]. The WHO (World Health Organization) estimates that 2 billion individuals (1 person out of 3) have serological evidence of past or present infection and that 257 million people currently live with chronic HBV infection, which is associated with increased liver disease and liver cancer risk [3]. Around 60% of the world's population lives in areas where HBV infection is highly endemic, including China (total population, 1.3 billion), Indonesia (222 million), Nigeria (132 million), and much of the rest of Asia and Africa. In addition to these high levels of exposure in certain regions around the world, genetic variability within the HBV genome and factors related to its mode of replication in its human host can impact one's risk of liver disease.

HBV belongs to the family Hepadnaviridae: it is an enveloped virus with a nucleocapsid or core that partially encases double-stranded DNA with only 3200 bases, the viral polymerase, and some host-derived proteins. This virus has a very unique replication cycle, which includes a replicative RNA intermediate molecule, which is why the viral polymerase is a reverse transcriptase for genome replication [4]. Several steps in the replication cycle have been exploited as potential targets for the design of antiviral strategies. Among them, the HBV capsid is a particular element that exhibits many of the features that are essential for trafficking to the nucleus, genome replication, and subsequent morphogenesis [5]. Some of these features are still under investigation [6]. Despite the existence of several interesting targets in the HBV replication cycle, antiviral therapy against HBV is still under development [7].

In addition, HBV can also have a latent mode of infection, called occult infection, where classical serological markers of active infection are absent [8]. Highly sensitive molecular tests are needed to detect these clinical presentations [9].

HBV is mostly a hepatotropic virus but may also infect the cells of the lymphatic system [10–12]. It is known that HBV entry into hepatocytes occurs through the binding of the HBV preS1 surface protein to its specific receptor, the bile acid transporter, sodium taurocholate co-transporting polypeptide (NTCP). Despite the fact that the mechanism of HBV entry into lymphatic cells remains unknown, the pre-S1-encoded surface protein is thought to be implicated. Extrahepatic HBV infection has been studied in chronic HBV, and it has been shown that HBV genomes are present in different PBMC subsets from chroni-

check for updates

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and several subgenotypes or subtypes [15] with distinctive distribution patterns and potential clinical associations. The classification is based on the percentage of nucleotide divergence between two HBV sequences. The current global consensus is based on a nucleotide divergence of >7.5% for the definition of distinct genotypes and of 4–7.5% for subgenotypes [16,17]. In Asia, genotypes B and C are known to be more frequently transmitted because mothers generally exhibit a highly replicative and HBeAg-positive infection. In contrast, in Africa, genotype E transmission is almost solely horizontal since the HBeAg seroconversion of the mother occurs at a young age. In low and intermediate endemic countries, transmissions are less exclusive, and exposure routes vary depending on various factors, such as drug usage to healthcare facilities or unprotected sex. Genotypes A–D are the best characterized types, with genotype A being the most frequent in North America, Europe, Southeast Africa, and India. Despite being closer at the genomic level, HBV subgenotypes exhibit very distinct geographical distributions and clinical impacts and deserve further studies [18,19]. With between 4% and 7.5% intergroup nucleotide divergence across the complete genome and good bootstrap support, genotypes A–J can be further organized into almost 40 subgenotypes.

The natural history of chronic hepatitis B virus (HBV) infection and disease is complex and highly variable. Chronic hepatitis B (CHB) and nonalcoholic fatty liver disease are increasingly observed together in clinical practice, and the development of nonalcoholic steatohepatitis (NASH) represents another leading cause of liver-related morbidity and mortality [20–23]. There is a growing understanding of how viral, host, and environmental factors influence disease progression, which could ultimately improve the management of chronic hepatitis B. In this Special Issue, we try to explore the natural history of chronic hepatitis B and emphasize the factors influencing the course of liver disease.

Finally, as described before, the management of hepatitis B disease is quite a complex matter, and it could benefit from the know-how that has already been accumulated by addressing HIV [24].

JOURNAL OF VIRAL HEPATITIS
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ORIGINAL ARTICLE

Global incidence and mortality of hepatitis B and hepatitis C acute infections, cirrhosis and hepatocellular carcinoma from 2010 to 2019

Nicolette Veracruz, Robert G. Gish, Ramsey Cheung, Amit S. Chitnis, Robert J. Wong

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Guarantor of the Article: Dr. Robert Wong had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) contribute to significant healthcare burden globally. We aim to provide an updated and comprehensive analysis of global trends in the incidence and mortality of HBV and HCV related acute infections, cirrhosis and hepatocellular carcinoma (HCC). Estimates of annual cause-specific disease incidence and mortality for HBV and HCV were analysed using the 2010–2019 Global Burden of Diseases, Injuries and Risk Factors Study database. Three distinct disease states were evaluated: acute infections, cirrhosis and HCC. Age-standardized disease incidence and mortality were presented per 100,000 population and stratified by age, sex, year and 21 world regions. From 2010 to 2019, overall incidence of acute HBV declined by 19.3% (95% CI 4.1–32.0, $p < .05$) and HBV cirrhosis declined by 15.0% (95% CI 9.8–20.7, $p < .05$). Incidence of HCV cirrhosis increased by 5.6% (95% CI 0.3–10.2, $p < .05$) and HCV HCC remained stable. Incidence of acute HCV declined until 2015, after which it began increasing. From 2010 to 2019, overall mortality for HBV cirrhosis and HCV cirrhosis declined, whereas mortality for acute infections and HCC remained stable. Major differences in HBV and HCV incidence and mortality trends were observed when stratified by world regions. In conclusion, while our analyses of global trends in HBV and HCV incidence and mortality demonstrate encouraging trends, disparities in disease epidemiology were observed across world regions. These observations will identify regions and populations where greater focus and resources are needed to continue progressing towards viral hepatitis elimination.

Imaging and Clinical Features of COVID-19 Breakthrough Infections: A Multicenter Study

Manuscript Type: Original Research

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* J.E.L. and M.H. contributed equally to this work.

Background: Since vaccines against coronavirus disease 2019 (COVID-19) became available, rare breakthrough infections have been reported despite their high efficacies.

Purpose: To evaluate the clinical and imaging characteristics of COVID-19 breakthrough infections and compare them with those of unvaccinated COVID-19 patients.

Materials and Methods: In this retrospective multicenter cohort study, we analyzed data from three centers of patients (aged ≥ 18 years) registered in an open data repository for COVID-19 between June and August 2021. Hospitalized patients with baseline chest radiograph were divided into three groups according to their vaccination status. Differences between clinical and imaging features were analyzed using Pearson`s chi-square test, Fisher`s exact test, and analysis of variance (ANOVA). Univariable and multivariable logistic regression analyses were used to evaluate associations between clinical factors, including vaccination status, and clinical outcomes.

Results: Of the 761 hospitalized patients with COVID-19, the mean age was 47 years, 385 (51%) were women; Forty seven patients (6.2%) were fully vaccinated (breakthrough infection), 127 were partially vaccinated (17%), and 587 (77%) were unvaccinated. 412 (54%) of the patients underwent chest CT scans during hospitalization. Of patients with CT, the proportions of CT scans without pneumonia was 22% (71/326) of unvaccinated patients, 30% (19/64) of partially vaccinated patients, and 59% (13/22) of fully vaccinated patients (P <.001). Fully vaccinated status was associated with a lower risk of requiring supplemental oxygen than unvaccinated patients (odds ratio [OR], 95% confidence interval [CI]; 0.24, 0.09-0.64, p=.005) as well as lower risk of intensive care unit (ICU) admission (OR, 95% CI; 0.08, 0.09-0.78, p=.02.)

Conclusion: Patients with COVID-19 breakthrough infections had a significantly higher proportion of CT scans without pneumonia compared to unvaccinated patients. Vaccinated patients with breakthrough infections had lower likelihood of requiring supplemental oxygen or ICU admission.

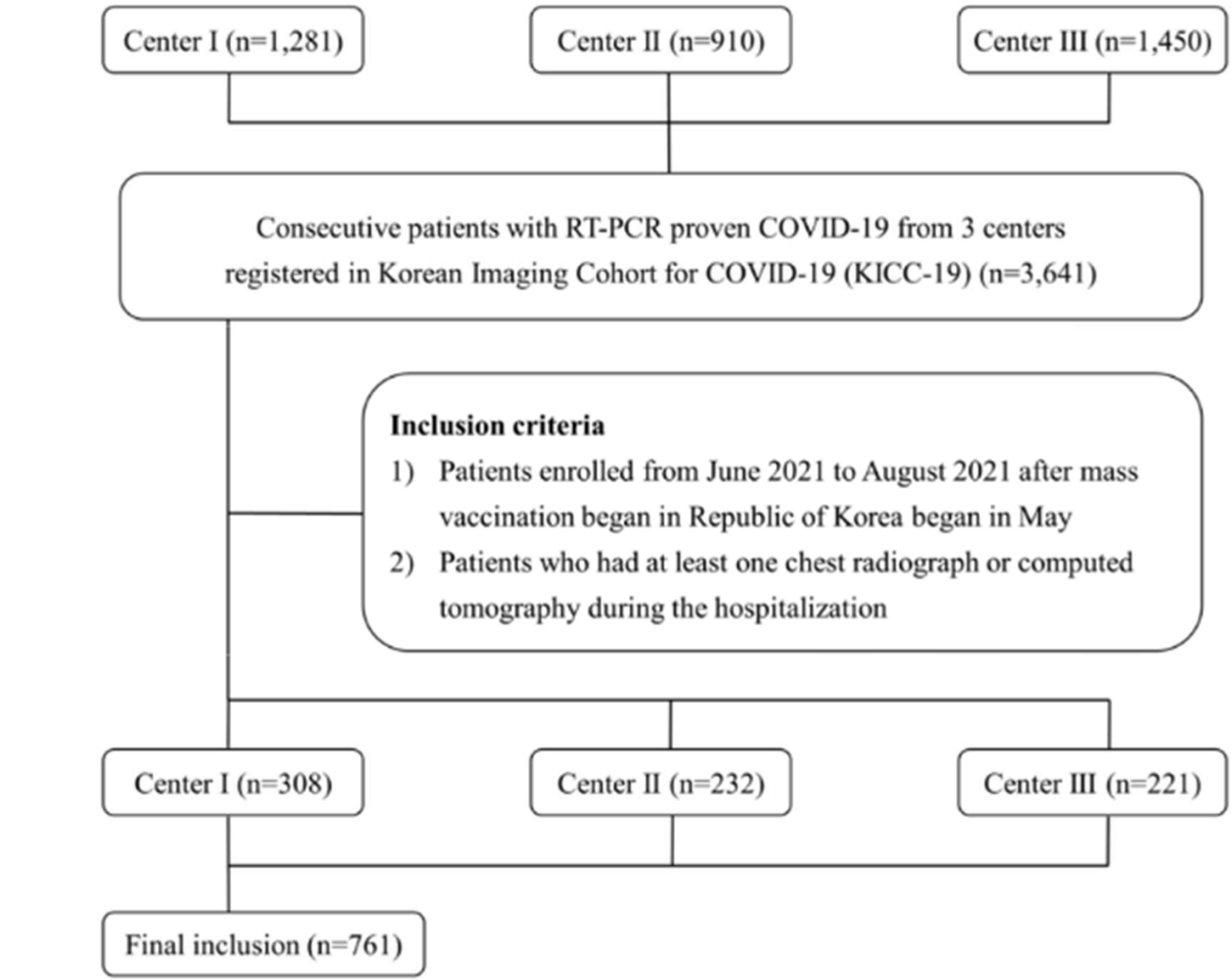
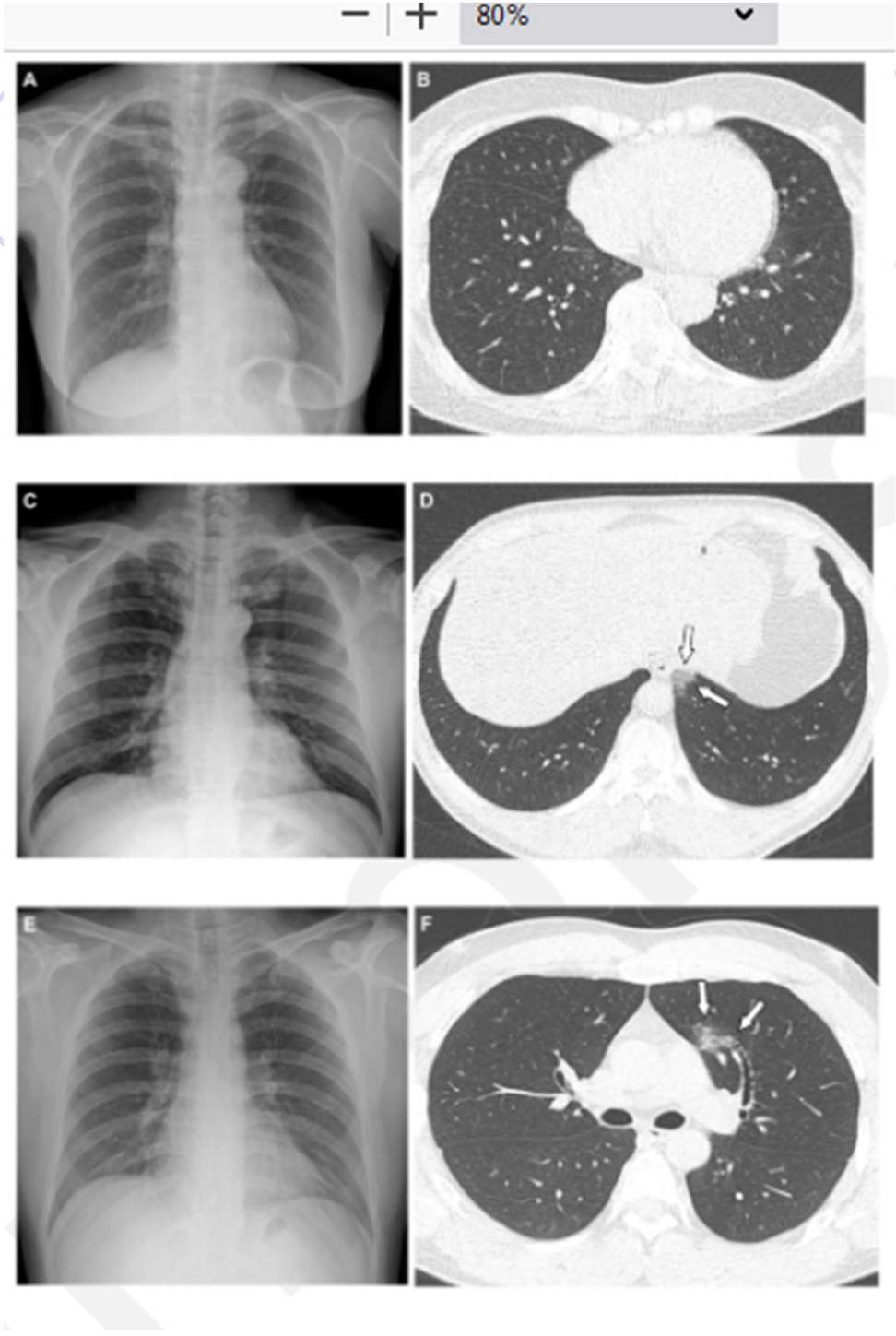


Figure 1. Study flow diagram.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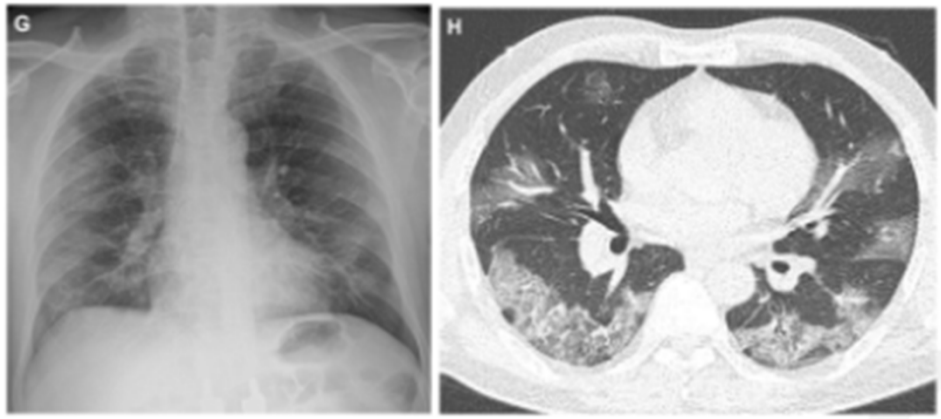

Figure 2. Representative cases showing pneumonia extents and patterns on chest radiographs (CXRs) and computed tomography (CT) images. **(A, B)** A 65-year-old female with breakthrough infection 2 months after a second dose of the BNT162b2 vaccine (fully vaccinated). The patient had a history of hypertension. (A) CXR obtained at admission showing no abnormal opacification in both lung zones. The CXR extent of pneumonia was scored as 0 (no evidence of pneumonia). (B) Axial chest CT image at the lower lobe level (obtained on the same day) showing negatively for pneumonia; CT extent of pneumonia was scored as 0 (no evidence of pneumonia). **(C, D)** A 48-year-old male with 1 month after a first dose of the ChAdOx1 nCoV-19 vaccine (partially vaccinated). The patient had no history of comorbidity. (C) CXR obtained at admission showing no abnormal opacification in both lung zones. The CXR extent of pneumonia was scored as 0 (no evidence of pneumonia). (D) Axial chest CT image obtained on the same day showing unilateral ground-glass opacity with a non-rounded morphology in the left lower lobe (arrows). CT extent of pneumonia was scored as 1 (1-25% involvement) and this case was classified as indeterminate appearance of COVID-19 according to the RSNA chest CT classification system. **(E, F)** A 36-year-old male with no history of vaccination for COVID-19. The patient had no history of comorbidity. (E) CXR obtained at admission showing no abnormal

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PUBLISHED DECEMBER 9, 2021

IN-PHARMACY VACCINES

New FDA-Approved Hepatitis B Vaccine Expected in Early 2022

A new hepatitis B vaccine is expected to be available in the United States early next year. The product, PreHevbrio [Hepatitis B Vaccine (Recombinant)] for the prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults was recently approved by the FDA.

PreHevbrio contains the S, pre-S2, and pre-S1 HBV surface antigens, and is the only approved 3-antigen HBV vaccine for adults in the U.S., according to VBI Vaccines, Inc., a biopharmaceutical company driven by immunology in the pursuit of powerful prevention and treatment of disease.

"As we work to implement the ACIP's new universal hepatitis B vaccine recommendation for all adults ages 19-59, as voted on in November, we benefit from having more tools, including this newly approved 3-antigen hepatitis B vaccine," Chari Cohen, DrPH, MPH, senior vice president of the Hepatitis B Foundation, said in a VBI **press release**. "Having more vaccine options will help us effectively expand vaccine uptake, ensure more people are protected

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REVIEW

Therapeutic vaccination for treatment of chronic hepatitis B

Tamsin Cargill [1,2] | Eleanor Barnes [1,2,3]

Summary

Chronic hepatitis B infection remains a serious global health threat, contributing to a large number of deaths through liver cirrhosis and hepatocellular carcinoma. Current treatment does not eradicate disease, and therefore new treatments are urgently needed. In acute hepatitis B virus (HBV) a strong immune response is necessary to clear the virus, but in chronic infection the immune response is weakened and dysfunctional. Therapeutic vaccination describes the process of inoculating individuals with a non-infective form of viral antigen with the aim of inducing or boosting existing HBV-specific immune responses, resulting in sustained control of HBV infection. In this review we outline the rationale for therapeutic vaccination in chronic HBV infection, discuss previous and ongoing trials of novel HBV therapeutic vaccine candidates and outline strategies to improve vaccine efficacy going forward.

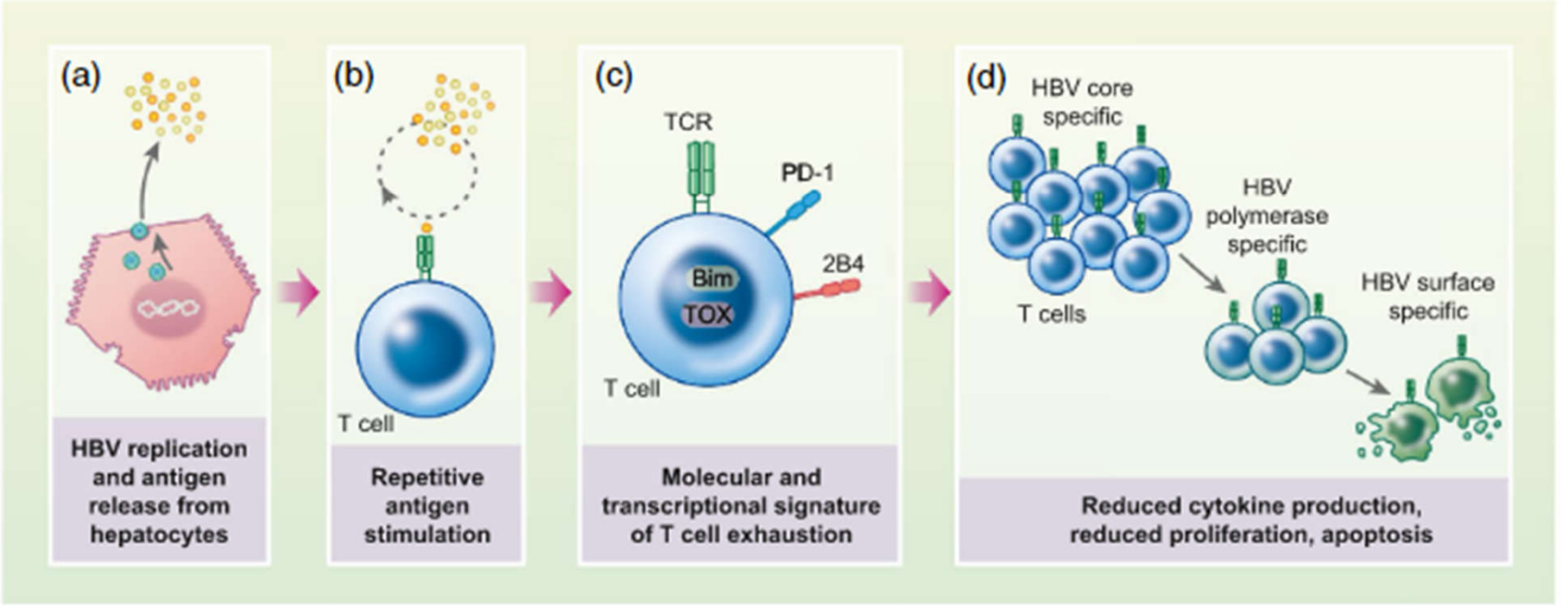

FIGURE 1 CD8 T cells are dysfunctional in chronic hepatitis B virus (HBV) infection. HBV undergoes replication in infected hepatocytes, which release HBV antigens including virions and secreted proteins. HBV-specific T cells are repetitively stimulated by HBV antigen through their T cell receptor (TCR), which leads to the development of a molecular and transcriptional programme of T cell exhaustion, characterized by surface expression of check-point inhibitors such as programmed cell death 1 (PD)-1 and CD244 (2B4), mitochondrial dysfunction and transcription of *TOX* and *Bim*. As a result, HBV-specific T cells become dysfunctional in cytokine secretion and proliferation, eventually undergoing apoptosis. HBV surface-specific T cells are affected more severely than polymerase and core-specific T cells. Figure created with BioRender

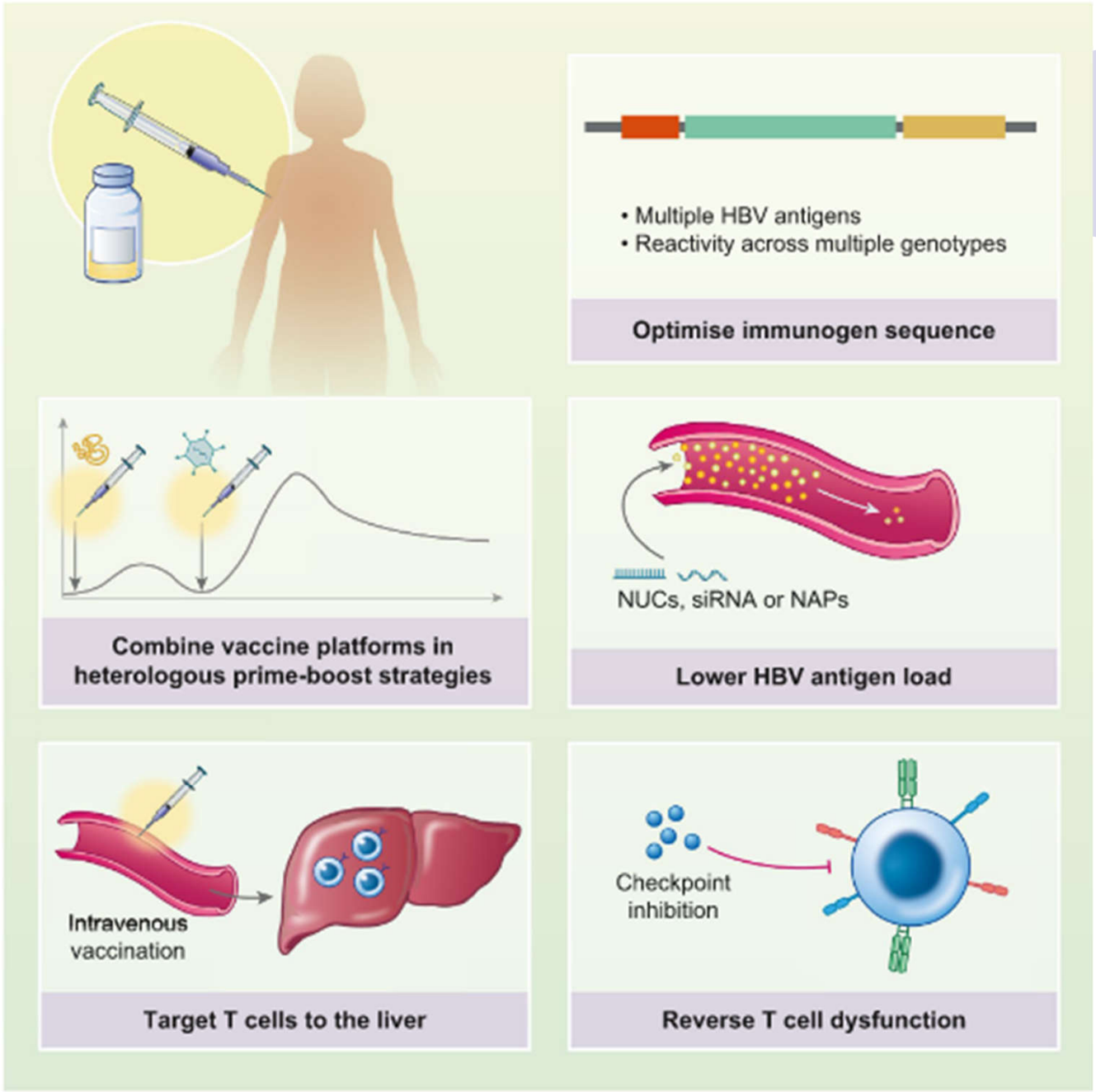

FIGURE 2 Strategies to improve therapeutic vaccination for chronic hepatitis B virus (HBV) infection. Strategies include (i) vaccinatin individuals with lower HBV antigen loads or reducing antigenic load prior to vaccination with nucleos(t)ide therapy (NUCs), small inhibitor

CONCLUSIONS

T cells are key to effective resolution of acute HBV infection. In chronic infection the T cell response is dysfunctional; however, a subset of individuals can go on to develop long-term immunological control of the virus, signalled by loss of HBsAg. Therapeutic vaccination aims to restore the HBV-specific immune response and has demonstrated efficacy in inducing functional cure in animal models of chronic HBV. Despite disappointing results in human clinical trials thus far, therapeutic vaccination remains a promising immunotherapeutic strategy. Optimizing T cell responses by selecting maximally immunogenic vaccine vectors, vaccination routes and immunoprotective epitopes, together with agents that reduce HBV T cell dysfunction such as immune check-point inhibitors, have real potential to overcome the barriers to immunological control imposed by chronic infection.