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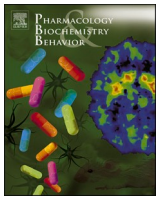

# A spotlight on HCV and SARS-CoV-2 co-infection and brain function

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Co-infection with pathogenic RNA viruses, including hepatitis C virus (HCV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), can affect disease severity and clinical outcomes (Devi et al., 2021). There are limited data on the effects of HCV infection on outcomes in individuals with coronavirus disease 2019 (COVID-19), and no data on outcomes in individuals with long-term symptoms associated with COVID-19 (long COVID syndrome; post-acute sequelae of SARS CoV-2 infection [PASC]). Liver injury has been reported in association with SARS-CoV-2 infection (e.g., Weber et al., 2021), but evidence is lacking regarding the impact of pre-existing HCV infection on COVID-19 outcomes. Cognitive impairment and neuropsychiatric dysfunction are documented sequelae of both HCV (Adinolfi et al., 2015; Hilsabeck et al., 2002; Huckans et al., 2009; Yarlott et al., 2017) and long COVID syndrome (Frontera et al., 2021; Graham et al., 2021), but little is known about the consequences of co-infection on central nervous system (CNS) and related neuropsychiatric outcomes. Since co-infection may alter both treatment and prognosis, attention to the neurological and neuropsychiatric manifestations of HCV and SARS-CoV-2 co-infection is critical in disease surveillance and development of evidence-based strategies that optimize treatment.

Various immune factors (cytokines, chemokines) and cells (endothelial cells, T cells) show dysregulation during co-infection, which enhances disease severity such as liver fibrosis and hepatocyte inflammation (Roe and Hall, 2008; Zignego et al., 2012); the progression of HIV to Acquired Immunodeficiency Syndrome (AIDS) (Chew and Bhattacharya, 2016; Operskalski and Kovacs, 2011); CNS pathology (Jarvis et al., 2013; Okurut et al., 2020); and neuropsychiatric disorders (Abdoli et al., 2020). In general, co-infections can be harmful, insignificant, or helpful for disease outcomes, and this is particularly important to consider given the COVID-19 pandemic. The effects of co-infection depend on the type of interactions between pathogens, which can be positive or negative (McArdle et al., 2018; Li et al., 2021). Positive interactions occur when pathogens act synergistically and lead to worsening of disease symptoms, severity, and outcomes (Kehe et al., 2021). Negative interactions occur when one pathogen hinders the growth of another pathogen through competition, parasitism, or interference (e.g., Hoffman et al., 2006). Negative interactions can result in short-lived protective effects, as has been observed between influenza A virus (IAV) and rhinoviruses (RV). Nickbakhsh et al. (2019) demonstrated that negative interactions, potentially induced by interferon (IFN) (Isaacs and Burke, 1959), contribute to the asynchronous seasonal patterns we observe for IAV and RV. During viral infections, one pathogen may influence the replication and disease severity caused by the other. This is known as viral interference and leads to early clearance of one infection and persistence of the other one (Kumar et al., 2018). In addition to interactions between co-infecting pathogens, host response also plays a key role in determining the outcome of co-infections. The host response depends on multiple factors, including demographic (e.g., age), psychological (e.g., stress), genetic, environmental, and other factors.

Importantly, for HCV and SARS-CoV-2, the degree and nature of their interactions and the underlying mechanisms remain largely unexplored,

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**Fig. 1**
Textbox summarizing the mechanisms that contribute to adverse effects associated with HCV and SARS-CoV-2 co-infection (Ronderos et al., 2021).

- Transmembrane protease serine 2 (TMPRSS2) expression. TMPRSS2 can potentiate SARS-CoV-2 viral entry (Hoffmann et al., 2020).TMPRSS2 is over-expressed in patients with HCV (Esumi et al., 2015), which may lead to exaggerated SARS-CoV-2 infection in these individuals.
- Circulating immune complexes and immune-mediated cellular toxicity. HCV is a systemic diseaseassociated with extrahepatic morbidity, which can occur independently of liver injury (Gill et al., 2016). The induction of circulating immune complexes and immune-mediated cellular toxicitythat also occurs in SARS-CoV-2 may be related to the potentiated effects on the virus inindividuals with HCV.
- Immune response overlap. In chronic HCV infection there are correlations between the productionof pro-inflammatory cytokines, such as IFN-gamma (IFN-γ) and tumor necrosis factor-alpha(TNF-α) and the degree of liver injury and extrahepatic effects (e.g., depressive symptoms) (Rehermann, 2009; Loftis et al., 2008). These pro-inflammatory cytokines are also elevated inSARS-CoV-2 and associated with worse clinical outcomes. For example, a recent study showedthat higher levels of IFN-γ are associated with elevated mortality in patients with COVID-19 (Gadotti et al., 2020). These findings and others suggest that baseline inflammatory status inindividuals with HCV could be related to the higher morbidity in those patients when contractingCOVID-19, as well as the potential for the development of long COVID symptoms.
- Vascular endothelial dysfunction. HCV and SARS-CoV-2 both induce endothelial dysfunction,which causes vascular leakage and immune activation. The integrity of the endothelial functionand immune system is important for a regulated immune response in order to help control viralspread (Perico et al., 2021). Consequently, it is hypothesized that direct endothelial cell infectionin individuals with COVID-19 may be exacerbated by the baseline endothelial dysfunctionreported to occur in individuals with HCV infection.

although the potential for disease modulating effects of HCV infection on COVID-19 outcomes, including long COVID symptoms, is highlighted by evidence discussed in recent reviews (Devi et al., 2021; da Mata et al., 2021). For example, one study suggests that among patients with HCV and hepatocellular carcinoma, those with undetectable HCV infection may be at a lower risk of fatality than those with active HCV infection, when diagnosed with SARS-CoV-2 infection (Guler-Margaritis et al., 2021). In a large, retrospective study of individuals with COVID-19 ($n = 1193$), co-infection with HCV added a cumulative increased risk of mortality to clinical and laboratory predictors of mortality risk, and HCV infection was the only strong predictor of mortality after matching individuals with and without HCV for baseline confounding clinical and laboratory predictors of mortality (Ronderos et al., 2021). It was concluded that the pathological effects of SARS-CoV-2 infection are worsened in individuals with HCV compared to those without HCV, regardless of age, sex, baseline clinical status (e.g., medical comorbidities [respiratory disease, hypertension]), or admission laboratory parameters (i.e., test results typically associated with greater rates of in-hospital mortality). No significant increased risk of contracting COVID-19 has been observed in people with HCV (Kovalic et al., 2020), although this population is at increased risk of developing severe illness from COVID-19, especially if compounded by other risk factors such as older age, hypertension, and obesity (Ronderos et al., 2021; Xie et al., 2020). Research suggests that HCV can exacerbate COVID-19-related disease severity and mortality, but the role of co-infecting pathogens and host response on disease pathogenesis remains unclear.

Co-infection can modulate oxidative stress, immune response, and disease severity. Ronderos et al. (2021) eloquently describe four overlapping mechanisms hypothesized to contribute specifically to the positive interactions and adverse effects associated with HCV and SARS-CoV-2 co-infection. These mechanisms are summarized in Fig. 1.

Neuroinflammation, hypoxia, and psychological burnout (a.k.a., "pandemic fatigue") associated with COVID-19 are contributing to the psychiatric symptoms and in more severe cases, mood disorders and posttraumatic chronic stress disorder (PTSD) affecting an increasing number of people (Cénat et al., 2021; Silva et al., 2022; Mazza et al., 2020; Steardo and Verkhratsky, 2020). Many suggest that the most important sequelae of the long-term and chronic forms of the disease are the psychological and neuropsychiatric effects (Rogers et al., 2020). In a study of 402 adults with a history of COVID-19, psychiatric symptoms were assessed at one-month follow-up after hospital treatment. Thirty-one percent of patients self-rated in the psychopathological range for depression (Mazza et al., 2020). Similarly, a recent study of 478 individuals (adult and pediatric patients) found that four months after hospitalization for COVID-19, 51% reported at least one new symptom that did not exist before COVID-19 infection: 31% fatigue, 21% cognitive symptoms, and 16% new-onset dyspnea (Writing Committee for the COMEBAC Study Group et al., 2021)—symptoms likely resulting directly or indirectly from COVID-19's effects on the brain. There appears to be significant overlap in pathological cell states, particularly within astrocytes and microglia, in the brains of individuals with COVID-19 compared to individuals with depression, schizophrenia, cognitive impairment, and other neuropsychiatric disorders (Tang et al., 2021; Vargas et al., 2020; Yang et al., 2021). However, the effects of co-infection with HCV on the brain are unknown.

Since the introduction of direct acting antiviral (DAA) therapy for HCV, there has been an increase in awareness and treatment rates. Importantly, DAA therapy can improve brain function. A study of 135 patients with HCV who achieved virological response found decreases in the prevalence of cognitive impairment and improvements in health-related quality of life (Ibáñez-Samaniego et al., 2021). It is yet to be determined how co-infection with SARS-CoV-2 and the development of COVID-19 impact the mental and physical health improvements that accompany HCV clearance. Further, the COVID-19 pandemic has placed a number of challenges on hepatitis programs and interventions (screening, diagnosis, and treatment). One study examined the percent change in DAA therapy units dispensed (from March to August 2019 to the same period of time in 2020) across 54 countries and found significant declines in DAA therapy utilization ($p < 0.01$) for a number of countries, including the U.S. (Shakeri et al., 2021). Another study used microsimulation methods to estimate the 10-year impact of COVID-19 disruptions in healthcare delivery on HCV outcomes including identified infections, linkage to care, treatment initiation and completion, cirrhosis, and liver-related death. Compared to the 'no pandemic' scenario, in the scenario in which there was no return to pre-pandemic levels of HCV care delivery, it was estimated that there would be 1060 fewer identified cases, 21 additional cases of cirrhosis, and 16 additional liver-related deaths per 100,000 people. Only 3% of identified cases initiate treatment and < 1% achieve sustained virologic response (Barocas et al., 2021). Thus, a recommitment to the HCV epidemic, which involves additional resources and increased efforts to screen, identify, and treat people with HCV may be needed to overcome the COVID-19-related disruptions.

The clinical consequences of COVID-19 and HCV co-infection require further attention, particularly concerning the impact of co-infection on neurologic and neuropsychiatric function. Research suggests that HCV can affect the progression of COVID-19, including disease severity and mortality (Devi et al., 2021), which may be related to extrahepatic

effects of HCV leading to enhanced ACE-2/TMPRSS mechanisms of SARS-CoV-2 viral entry, baseline cytokine-mediated pro-inflammation, and endothelial dysfunction/impact on BBB. Further study of these extrahepatic effects will aid in identifying the various neurologic and neuropsychiatric symptoms, long-lasting effects, and appropriate methods of treatment to improve viral clearance and mental health outcomes in individuals with HCV and COVID-19.

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