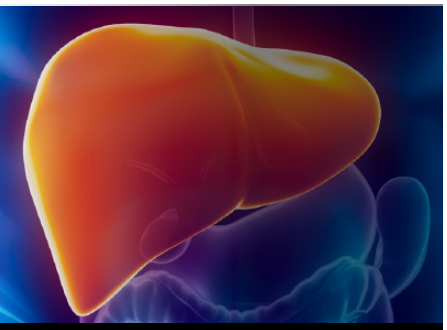
Hepatitis RESEARCH REVIEW™



Making Education Easy

Issue 1 – 2020

In this issue:

Abbreviations used in this issue

CI = confidence interval
DAA = direct-acting antivirals
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
MTCT = mother-to-child transmission
OAT = opioid agonist therapy
OR = odds ratio
PWID = people who inject drugs
RR = relative risk
SVR = sustained virological response

Welcome to this issue of Hepatitis Research Review.

An alarming number of patients with hepatocellular carcinoma in New Zealand are not receiving guideline-recommended surveillance according to the findings of a recent retrospective study. While Australia has made excellent progress on the road to elimination of HCV in people who inject drugs, additional efforts to engage and treat marginalised patients, such as the homeless and incarcerated, are essential to fully achieve their aim. Other topics covered in this issue include simplified monitoring for HCV treatment with glecaprevir/pibrentasvir, caesarean section and non-breastfeeding to reduce HBV transmission, long-term outcomes after fetal exposure to tenofovir disoproxil fumarate, and antiviral therapy for HBV in different trimesters of pregnancy.

We hope you find the papers in this issue useful in your practice and we welcome your comments and feedback.

Kind regards,

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Increasing burden of advanced hepatocellular carcinoma in New Zealand – the need for better surveillance

Authors: Schauer C et al.

Summary: This NZ retrospective study (2003-17) examined all cases of advanced hepatocellular carcinoma (HCC) related to chronic HBV (n = 368) and HCV (n = 278) infection referred to the tertiary HCC service in Auckland, and looked at patient characteristics, surveillance history and outcomes. Of these patients, 75% were not receiving guideline-recommended surveillance. More HBV- than HCV-infected patients were diagnosed with HCC prior to the diagnosis of viral infection (40% vs 28%; $p < 0.01$) and fewer previously diagnosed HBV- than HCV-infected patients were undergoing HCC surveillance (26% vs 42%; $p < 0.01$). Late-diagnosed patients had the worst outcomes; 88% received only palliative care and averaged only 7 months survival time (HBV 5 months vs HCV 8 months; $p = 0.05$).

Comment: This study highlights that advanced HCC is a devastating disease. Few patients are eligible for any treatment by the time they present and as a result median survival is barely more than 6 months. Although approximately 25% of the patients in this cohort developed advanced HCC despite appropriate screening (indicating that screening is far from perfect), for many patients, the development of advanced HCC may have been avoided if readily available interventions had been applied. Almost 40% of those with HBV and 30% of those with HCV had not been diagnosed with viral hepatitis prior to their presentation with HCC and had not received antiviral treatment, which may have reduced their HCC risk. There is good evidence that, in patients with HBV, viral suppression reduces HCC risk, while in the case of HCV, because almost all HCV-related HCC develops in patients with cirrhosis and viral eradication in pre-cirrhotic patients prevents progressions to cirrhosis, successful treatment of pre-cirrhotic patients virtually eliminates risk of HCC. In patients who remain at risk of HCC despite antiviral treatment, screening can have a dramatic effect on outcome, with far better survival for screen-detected HCC than for non-screen-detected HCC. Data from the total NZ HCC cohort showed a median survival of 91.5 months for those patients with screen-detected lesions, but only 43 months for those with non-screen detected HCC. Patients with screen-detected lesions were almost 6-fold more likely to receive curative-intent treatments. Unfortunately, approximately 40% of the patients in this study met criteria for screening but were not being screened at all (a staggering 41.7% of the HCV-HCC patients) or were enrolled in screening but this was being carried out in a suboptimal fashion. We need to do better, both from a public health perspective to ensure more patients have their viral hepatitis diagnosed and treated, and also as individual clinicians to ensure that those patients meeting criteria are identified and indeed screened appropriately. Lives will be saved as a result!

Reference: NZ Med J 2020;133(1515):25-34

Abstract

Reinfection following successful direct-acting antiviral therapy for hepatitis C infection among people who inject drugs

Authors: Cunningham EB et al.

Summary: This pooled analysis of data from two clinical trials (SIMPLIFY and D3FEAT) of people with recent injecting drug use or current opioid agonist therapy (OAT) use examined HCV reinfection during HCV DAA treatment. Among the population at risk for reinfection (n = 177; 73% male; median age 48 years) 73% reported ongoing injecting drug use. Over a total follow-up of 254 person-years (median 1.8 years), 8 confirmed reinfections occurred giving an overall incidence of 3.1/100 person-years (95% CI 1.6-6.3) with an incidence of 17.9/100 person-years (95% CI 5.8-55.6) among those reporting sharing of needles and/or syringes. HCV reinfection was associated with younger age and needle/syringe sharing.

Comment: This review has discussed the treatment of HCV in people who inject drugs (PWID) many times and with good reason. In high-income countries, PWID represent the predominant group in whom new infections arise. A previous study surmised that removing the increased risk for HCV transmission among intravenous drug users in high-income countries would prevent 79% of new infections in those countries. As a result, eliminating the virus from this group will need to be a central plank in any national programme aiming to render their population HCV-free. A major issue in eliminating HCV among PWID is re-infection; however, there has been a paucity of long-term data, particularly in the DAA era, to both quantify the extent of re-infection and determine the risk factors associated with re-infection. It is clearly important to understand these so that action can be taken to mitigate them. This study draws on two multinational studies of HCV treatment in patients with a history of injecting drugs, including in the last month prior to starting treatment in 62%. Both demonstrated that recent drug use was not a barrier to successful treatment with high SVR rates of 91% and 94%. Patients were followed for up to 2 years after treatment and long-term data was available for 177 patients who achieved an SVR and hence were at risk of re-infection. More than 70% injected drugs again following treatment, with at least daily use in 49%. Eight patients were re-infected with HCV and, as one would expect, the risk was much greater in those injecting at least daily as compared to those using less than daily (6.0 vs 1.1 per 100 person-years). Patients on OAT had lower re-infection rates (1.7 vs 6.8 per 100 person-years), presumably reflecting less ongoing injecting drug use. The effect of needle or syringe sharing was even more marked with the rate of re-infection 17.9 per 100 person-years in those that did share and 2.4 per 100 person-years in those that did not. It should be borne in mind that these patients were involved in a clinical trial and the closer follow-up that resulted may have mitigated against re-infection to some extent, and therefore re-infection rates may be higher in 'real-world' populations. However, despite the follow-up, a high proportion continued to inject drugs and it is encouraging that re-infection rates were still relatively low. The study does highlight the positive impact that both OAT and avoidance of sharing drug injecting paraphernalia have on re-infection rates, and indicates that ongoing engagement with these patients to promote harm-reduction measures is essential.

Reference: Clin Infect Dis. 2020;Mar 12 [Epub ahead of print]
Abstract

Progress towards elimination of hepatitis C infection among people who inject drugs in Australia: The ETHOS engage study

Authors: Valerio H et al.

Summary: The Australian observational ETHOS Engage study estimated prevalence of current HCV infection and treatment uptake among 1443 PWID (64% injected in the last month; 74% were receiving OAT). In this cohort, 28% were uninfected, 16% had spontaneous clearance of HCV, 32% had treatment-induced clearance and 24% were currently infected. A current HCV infection was more likely among homeless people (adjusted OR [aOR] 1.47; 95% CI 1.00-2.16), those incarcerated in the previous year (aOR 2.04; 95% CI 1.38-3.02), and those injecting drugs ≥1 per day (aOR 2.26; 95% CI 1.43-2.42). Among previous chronic or current HCV patients, 66% reported receiving HCV treatment. In an adjusted analysis, HCV treatment was lower among females (aOR 0.68; 95% CI 0.48-0.95), the homeless (aOR 0.59; 95% CI 0.38-0.96), and those injecting ≥1 per day (aOR 0.51; 95% CI 0.31-0.89). HCV treatment was more likely in people aged ≥45 years of age (aOR 1.46; 95% CI 1.06-2.01) and people receiving OAT (aOR 2.62; 95% CI 1.52-4.51).

Comment: As mentioned in the previous commentary, treating HCV in PWID is an essential part of any eradication programme. In the era of interferon, there was a reluctance to treat PWID, but there is now data demonstrating that, at least in the setting of clinical trials, DAA treatment achieves high cure rates with relatively modest reinfection rates. But what's happening in the real world? Can broad access to these drugs for PWID result in high cure rates and hence reduced prevalence rates in PWID. Australia has been a world leader with regards to provision of hepatitis C treatment for their population. Since March 2016, HCV DAA treatment for adults has been fully reimbursed regardless of disease stage or ongoing drug or alcohol use and hence is truly unrestricted. This study suggests that this has indeed resulted in high treatment uptake, at least in people attending drug treatment centres and needle/syringe programmes. However, it identifies that even within the PWID population there are groups who are still less likely to receive treatment, including the homeless and incarcerated, and while Australia has made excellent progress on the road to elimination of HCV in PWID, additional efforts to engage and treat these particularly marginalised patients are essential to fully achieve their aim. It is highly likely that the same factors will be in play in NZ and in many areas links have already been established with drug treatment centres, prisons and services providing care to the homeless to promote testing and treatment of HCV, but this study reinforces the importance of these efforts.

Reference: Clin Infect Dis. 2020;May 18 [Epub ahead of print]
Abstract

Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir, a randomised non-inferiority trial

Authors: Dore GJ et al.

Summary: This multicentre, open-label, non-inferiority phase IIIb trial tested a simplified treatment monitoring schedule (baseline, post-treatment week 12; n = 253) versus a standard schedule (baseline, week 4, week 8, post-treatment week 12; n = 127) in patients receiving glecaprevir/pibrentasvir 300/120 mg per day for chronic HCV. SVR at 12 weeks (SVR12) did not reach non-inferiority in an intent-to-treat analysis being achieved by 92% (95% CI 89-95) of simplified schedule recipients versus 95% (95% CI 92-99) of standard schedule recipients (difference -3.2%; 95% CI -8.2 to 1.8); in a per-protocol analysis, SVR12 was achieved by 97% (95% CI 96-99) versus 98% (95% CI 96-100).

Comment: Treatment of HCV with DAAs is as far removed from interferon treatment as one could imagine. While the latter involved frequent clinic visits to gently shepherd patients through up to 12 months of arduous and often fruitless treatment, treatment with DAAs is relatively uncomplicated, of short duration and highly effective. Glecaprevir/pibrentasvir [Maviret™] could be regarded as the pinnacle of DAA therapy, with once-daily dosing and treatment for only 8 weeks in almost all patients. It should therefore lend itself to a 'hands-off' approach to management. This study, compared a simplified monitoring strategy (clinic visits at the start of treatment and at week 12 post-treatment, but otherwise just 2 phone calls during treatment) with 2 clinic visits in addition to the phone calls at week 4 and 8. Active or recent drug users and patients who were considered by the treating clinician to require extra treatment adherence support were excluded from the study. Intention-to-treat analysis showed that the simplified strategy did not meet non-inferiority criteria with a slightly higher SVR rate in the standard group (95% vs 92%), but the simplified strategy should not be dismissed completely. Analyses of the modified intention-to-treat and per-protocol populations, which both excluded the 1 patient who died and the 14 patients (4 in the standard arm and 10 in the simplified arm) who were lost to follow-up, showed SVR rates that were similar (97% simplified, 98% standard in both analyses). This suggests that there may not be too much difference between the two strategies particularly if fine-tuning of selection allowed identification of patients at higher risk of being lost to follow up in whom standard management would be more appropriate. Treatment of non-cirrhotic patients in the community is essential if the levels of treatment required for elimination are to be reached. A simplified treatment strategy could aid this by reducing the workload of already over-stretched general practitioners and potentially could reduce the cost, both in time and money, for patients. It is likely that, in appropriate patients, there is a place for such simplified strategy in the management of HCV.

Reference: J Hepatol. 2020;72(3):431-440
Abstract

Decreased risk of hepatocellular carcinoma recurrence with direct-acting antivirals compared with no treatment for hepatitis C: A meta-analysis

Authors: Lui FH et al.

Summary: This meta-analysis examined the short- and long-term recurrence rates of HCC related to HCV after DAA treatment based on 6 publications (n = 3017). Over follow-up periods of 1.25 to 4 years, there was a >60% lower risk of HCC recurrence in DAA recipients versus controls (OR 0.36; 95% CI 0.27-0.47; p < 0.001; I^2 88%). Sensitivity analyses, excluding studies with the lowest recurrence rates, also suggested that DAA recipients had a 60% lower risk of developing HCC (OR 0.4; 95% CI 0.26-0.61; p < 0.0001; I^2 39%) and a 66% lower risk of developing HCC beyond 1 year (OR 0.34; 95% CI 0.22-0.54; p < 0.00001; I^2 0%).

Comment: In 2016, a Spanish group reported an unexpectedly high incidence of HCC recurrence in patients who had had prior curative treatment but who were subsequently treated with DAAs. Shortly after this, an Italian study raised similar concerns. Since that time, there has been significant interest in the interplay between HCC risk and DAA treatment. There have subsequently been a number of studies refuting the hypothesis that DAA treatment increases the risk of HCC recurrence, but this meta-analysis examines this further, consolidating data from 6 high-quality studies. Five of the studies were retrospective and 1 prospective and between them include over a thousand DAA-treated patients matched to nearly 2000 controls, the latter comprising both treatment-naive and interferon-experienced patients. Follow-up was for up to 4 years. All the studies included patients in whom HCC was treated with the curative-intent treatments of radio-frequency ablation or liver resection while two also included patients treated with trans-arterial chemo-embolisation, not generally regarded as a curative treatment. Not only does the meta-analysis confirm that DAAs do not increase the risk of HCC recurrence, but treatment with these agents significantly reduced HCC recurrence with an overall 64% lower rate of HCC recurrence in DAA-treated patients as compared to controls. The benefit was even more striking when risk of HCC recurrence 2 to 4 years after DAA treatment was considered, in which case HCC recurrence was 80% lower in DAA-treated patients. The reason for discrepancy between the initial studies that caused concern and the subsequent, more reassuring, studies is unclear and the possibility that what were thought to be recurrent tumours could instead have been radiologically undetectable residual tumour has been raised, particularly as the apparent recurrences frequently occurred very early after HCC treatment. Regardless, there is now sufficient evidence that DAA treatment is beneficial in those with prior HCC and should not be withheld.

Reference: Ann Gastroenterol. 2020;33(3):293-298
Abstract

The role of caesarean section and nonbreastfeeding in preventing mother-to-child transmission of hepatitis B Virus in HBsAg- and HBeAg-positive mothers: Results from a prospective cohort study and a meta-analysis

Authors: Pan Y-C et al.

Summary: This Chinese prospective cohort study in 852 mothers and 857 newborns and a meta-analysis of 13 studies examined the effect of caesarean section and non-breastfeeding on mother-to-child transmission (MTCT) in HBV HBsAg- and HBeAg-positive mothers. At 7 months, 41 (4.78%) infants were HBsAg-positive. Multivariate analysis suggested that higher maternal HBV DNA level (>108 IU/mL) was associated with an increased infection risk (RR 3.03; 95% CI 1.41-6.52), but caesarean section and non-breastfeeding did not reduce the risk of infection. In contrast, the meta-analysis suggested that the risk of infection with caesarean section was lower than with vaginal delivery (RR 0.58; 95% CI 0.46-0.74) and the risk in the non-breastfeeding group was also lower (RR 0.74; 95% CI 0.56-0.98).

Comment: Globally, the vast majority of new infections with HBV occur via vertical transmission, from mother to newborn. The risk is very much reduced if the newborn receives both passive and active immunisation, but transmission can still occur at rates of up to 10% if the mother's HBV viral load is very high (>6 log IU/mL) at the time of delivery. This study examines the role of delivery method and breastfeeding in mother-to-child transmission of the virus. It includes both a meta-analysis and a prospective study, the latter recruiting nearly 900 HBeAg-positive mothers and their infants. As one would expect given their HBeAg-positive status, HBV DNA was very high with a mean level of 8.08 log IU/mL. Nearly 5% of the infants were HBsAg positive at 7 months of age, indicating failure of immunoprophylaxis. The study suggested reduced transmission if delivery was by caesarean section (RR 0.61) or if breastfeeding was avoided (0.88), findings reinforced by the meta-analysis. However, the real take-home message from this study is that women with high viral load should receive antiviral therapy in the last trimester of pregnancy! There is a wealth of data demonstrating that treatment with tenofovir in late pregnancy, and during breastfeeding, is both safe and highly effective in preventing mother-to-child transmission and allows the infant to reap the benefits of both vaginal delivery and breastfeeding. Furthermore, now that these drugs are available as generics, cost should not be an issue.

Reference: J Viral Hepat. 2020;May 3 [Epub ahead of print]
Abstract

Long-term growth and bone development in children of HBV-infected mothers with and without fetal exposure to tenofovir disoproxil fumarate

Authors: Wen W-H et al

Summary: This study recruited children from a prospective, multicentre trial of maternal tenofovir disoproxil fumarate (TDF; n = 71) versus control (n = 57) for the prevention of MTCT of HBV in order to assess long-term safety outcomes following fetal exposure to TDF. During a follow-up to the age of 2 to 7 (median 4.1) years, there were no between-group differences in z-scores for weight-for-age, height-for-age, or estimated glomerular filtration rate. After adjustment for age, sex and HBV status, TDF and control recipients did not differ in levels of serum calcium, phosphorus, bone-specific alkaline phosphatase, calcidiol and bone mineral density of lumbar spines or left hip.

Comment: As alluded to in the previous commentary, tenofovir is highly effective at reducing MTCT of HBV in mothers with high viral loads and importantly does not have any adverse effect on pregnancy outcomes. However, questions have been raised as to whether tenofovir may have an adverse effect on fetal/infant growth or bone development or renal function. These concerns stem from the recognition that in a small percentage of adults treated with TDF, long-term use can result in renal impairment and/or bone disease, the latter characterised by reduced bone mineral density that can result in increased fracture risk. Most studies in infants to date have been reassuring, but have focussed on short-term outcomes i.e., the first year of life. This prospective, multicentre non-randomised study from Taiwan included children born to mothers treated with tenofovir from 30-32 weeks' gestation until delivery and followed them for a median of 4 years. They were compared to a control group of children whose mothers were eligible for tenofovir but declined. Follow-up was thorough with data including biochemical markers of renal function and bone metabolism and bone densitometry collected annually. As one would expect, approximately 10% of the children who did not receive TDV were HBsAg positive, compared to only 1.5% of those whose mothers were treated in late pregnancy. Interestingly, the only other baseline difference between the two groups was a significantly lower rate of breastfeeding in the TDV-treated group (43.7% vs 66.7%). In terms of parameters of growth (including height and weight), renal and bone markers and bone density, there was no significant difference between the children exposed to tenofovir and those not exposed. Analysis also did not suggest any effect from neonatal exposure to tenofovir via breast milk. Overall, although the number of participants in this study was relatively small, the absence of any suggestion of a negative impact on growth and development from tenofovir exposure is reassuring and allows us to continue to recommend tenofovir during pregnancy and breastfeeding for mothers at high risk of MTCT.

Reference: J Hepatol. 2020;72(6):1082-1087
Abstract

LUCY MILLS' SELECTION

Real-world effectiveness from the Asia Pacific Rim liver consortium for HBV risk score for the prediction of hepatocellular carcinoma in chronic hepatitis B patients treated with oral antiviral therapy

Authors: Yang H-I et al.

Summary: The purpose of this multinational study was to develop a risk score (Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV; REAL-B) to predict HCC using routine clinical variables in an adult Asian chronic hepatitis B cohort of 8048 patients receiving oral antivirals. REAL-B includes 7 variables (gender, age, alcohol use, diabetes, baseline cirrhosis, platelet count, and alpha fetoprotein), and categorises risk as low risk (0-3), moderate risk (4-7) and high risk (8-13). The area under the receiver operating curve scores for HCC risk were >0.80 at 3, 5 and 10 years, and these were higher than other risk models ($p < 0.001$).

Comment: The development of a reliable score to predict HCC risk could be a game changer for HBV infected patients and their clinicians. HCC survival is poor, since many cancers are only detected when they are already at an incurable stage. A tool that categorises HCC risk would allow us to develop a NZ-wide surveillance strategy to enable better outcomes for our patients. The REAL-B score allows for the identification of HCC risk in Asian patients on antiviral therapy. Six of the 7 variables are easily identified from demographics and laboratory results, with only 1 (alcohol use) requiring additional patient information, making this an easy tool to use. Of note, however, family history of HCC was not included in the study, which may limit its applicability. The REAL-B score could be a useful tool in HCC risk categorisation for the 8-9% of people of Chinese or South East Asian ethnicity with HBV in NZ. However, liver disease due to HBV infection disproportionately affects Māori and Pacific peoples. For this score to be fully applicable to our NZ population it needs to be validated in Māori and Pacific HBV patients, as well as other non-Asian groups. Finally, even patients categorised into the "low-risk" group carry some risk of HCC and therefore may need surveillance. Difficult decisions still need to be made about allocating scarce resources.

Reference: J Infect Dis. 2020;221(3):389-399
Abstract

Independent commentary by Lucy Mills

Lucy Mills is a Gastroenterology Clinical Nurse Specialist at Middlemore Hospital, Counties Manukau Health and Greenlane Medical Specialists. She has worked in liver transplant and gastroenterology since 2007. She has a varied nursing background including intensive care, flight nursing and endoscopy. She enjoys working with patients and whanau to manage their chronic conditions.

Efficacy and safety of antiviral therapy for HBV in different trimesters of pregnancy: Systematic review and network meta-analysis

Authors: Wu Y et al.

Summary: This network meta-analysis was conducted to examine the effectiveness of different antiviral agents for blocking MTCT of HBV based on 3 randomised and 32 non-randomised studies (n = 6738 mothers). The network analysis suggested that any antiviral agent was more effective than placebo, but no agent was significantly more effective than the others, although a trend was observed for telbivudine and tenofovir. Treatment in either the 1st or 2nd trimester was equally effective, but a lower rate of MTCT was observed when therapy was initiated before the 3rd trimester (RR 0.045; 95% CI 0.0053-0.20). Similar effects were observed for suppressing maternal HBV DNA level at delivery and converting serum HBeAg. There were no differences among maternal and fetal safety outcomes if mothers received antiviral agents before 28 weeks.

Comment: This systematic review and meta-analysis examined the efficacy and safety of different initiation timings of specific antiviral therapies in preventing MTCT of HBV. Whilst there was no statistically significant difference between different antiviral therapies in terms of effectiveness, initiating treatment in early or middle pregnancy was better at preventing MTCT. Current NZ guidelines recommend offering antiviral therapy to women with a high viral load during late pregnancy (generally 30-32 weeks) to reduce viral load prior to delivery, and the risk of MTCT. This study would suggest that for mothers at high risk, starting antiviral therapy earlier can allow adequate time to suppress the level of HBV DNA and decrease the risk of viral breakthrough and prophylaxis failure in the infant. Of course all of this is reliant on effective universal HBV screening for all pregnant women, regardless of previous testing or vaccination.

Reference: Hepatol Int. 2020;14(2):180-189
Abstract

The lived experience of chronic hepatitis B: A broader view of its impacts and why we need a cure

Authors: Tu T et al.

Summary: This review examines the broad range of psychosocial impacts of chronic hepatitis B, including fear, anxiety, financial instability, stigma, discrimination and societal rejection, which directly affect patient diagnosis, management and treatment. It also highlights the roles of the research community in accounting for and mitigating these factors.

Comment: With the recent focus on HCV elimination and the importance of removing barriers to treatment including stigma, I have been guilty of neglecting the stigma that patients with HBV experience. This study reviews the literature examining the true impact of HBV on individuals and aims to inform researchers seeking a cure about the context of the lived experience. It is a timely reminder that the impact of HBV is much broader and greater than the physical disease itself. They take a close look at the stigma and discrimination that people experience from their communities and institutions. Of particular interest and concern is stigma and discrimination by healthcare providers. Patients are dependent on us and our colleagues. Lack of accurate and up-to-date knowledge by healthcare workers can impact on patient health outcomes. We are therefore beholden as "experts-in-the-field" to ensure that we not only educate our patients about their condition but our colleagues too.

Reference: Viruses. 2020;12(5):515
Abstract