Letter to the editor: vaccination against upper respiratory infections is a matter of survival in alcoholic liver disease

We read with great interest the report on SARS-CoV-2 infection in patients with primary biliary cholangitis (PBC) by Ampuero *et al*.[1] An independent association of chronic liver disease with adverse clinical outcome in patients with COVID-19 was previously reported in this journal.[2] However, the impact of SARS-CoV-2 and upper airway infections in general on patients with alcoholic liver disease (ALD) remains widely unknown. Yet, those data would be of high relevance to global public health and vaccination campaigns since alcohol related diseases are endemic. 57% of the population over age 15 has consumed alcohol in the last 12 months, and 2.3 billion people are current drinkers.[3]

With respect to upper airway respiratory infections, patients with chronic liver disease, including those with ALD, are particularly susceptible to infections as the immune system is dysfunctional through several pathological mechanisms including decreased opsonisation, reticuloendothelial dysfunction, neutrophils impairment and abnormal immunoglobulin synthesis.[4 5] Moreover, alcohol abuse, independently from other factors, depresses the immune system by decreasing the lymphocytes and antibodies and the production of cytokines as TNF-alpha, IL-1 and IL-6.[6] Several human and murine studies have reported that patients with chronic alcohol consumption are at higher risk of severe influenza.[7] Thus, respiratory infections such as seasonal flue or SARS-CoV-2 represent a major threat to these patients.

Unfortunately, despite general recommendations for seasonal influenza vaccinations, systematic evaluations of the efficacy of such vaccinations are widely lacking. Even more, the general perception appears, that influenza vaccination is less beneficial in patients with ALD due to a lack of conclusive information (no randomisation, small sample sizes).[8]

In order to determine the benefit of influenza vaccination in (chronic) ALD, we analysed a large cohort of 4667 US patients with ALD for vaccination efficacy between 2000 and 2020. Patient data were obtained through the Observational Health Data Sciences and Informatics (OHDSI) consortium, an open-source, multistakeholder and interdisciplinary collaborative effort.[9] This analysis demonstrated a highly significant benefit of influenza vaccinations, no matter what available strain or year were investigated during the last decade. Vaccinations against seasonal influenza A variants (H1N1 (p=0.000), H3N2 (p=0.000)), influenza B virus (p=0.000), Massachusetts-2–2010-liver variant (p=0.000) and B-Wisconsin-1-2010 (p=0.006) variant all demonstrated a highly significant survival benefit for ALD patients (figure 1). Our data clearly demonstrate the benefit of vaccination against upper airway respiratory (viral) infections, even in a severely ill cohort with 63% of all patients suffering from liver cirrhosis, 32% from ascites and 16% encephalopathy.

A similar trend was observed in an independent Korean cohort of 7339 patients with ALD, which slightly failed statistical significance (p=0.082, figure 2) but showed a clear separation of survival curves. This may be particularly due to a better survival of the non-vaccinated control group. The reasons for that may be manifold: First of all, the Ajou cohort of patients obviously were not as sick as the US cohort as measured by means of symptoms of decompensation. Also, number of patients with mental disorders was clearly lower in South Korean patients, which may well result in a better self-protecting behaviour in order to prevent influenza infections. Finally, generally more people have been wearing masks over the past two decades in Asia.[10]

By reporting these data, we aimed to contribute urgently needed evidence on vaccination against upper airway infections in ALD. We conclude, that vaccination against ongoing or seasonal viral

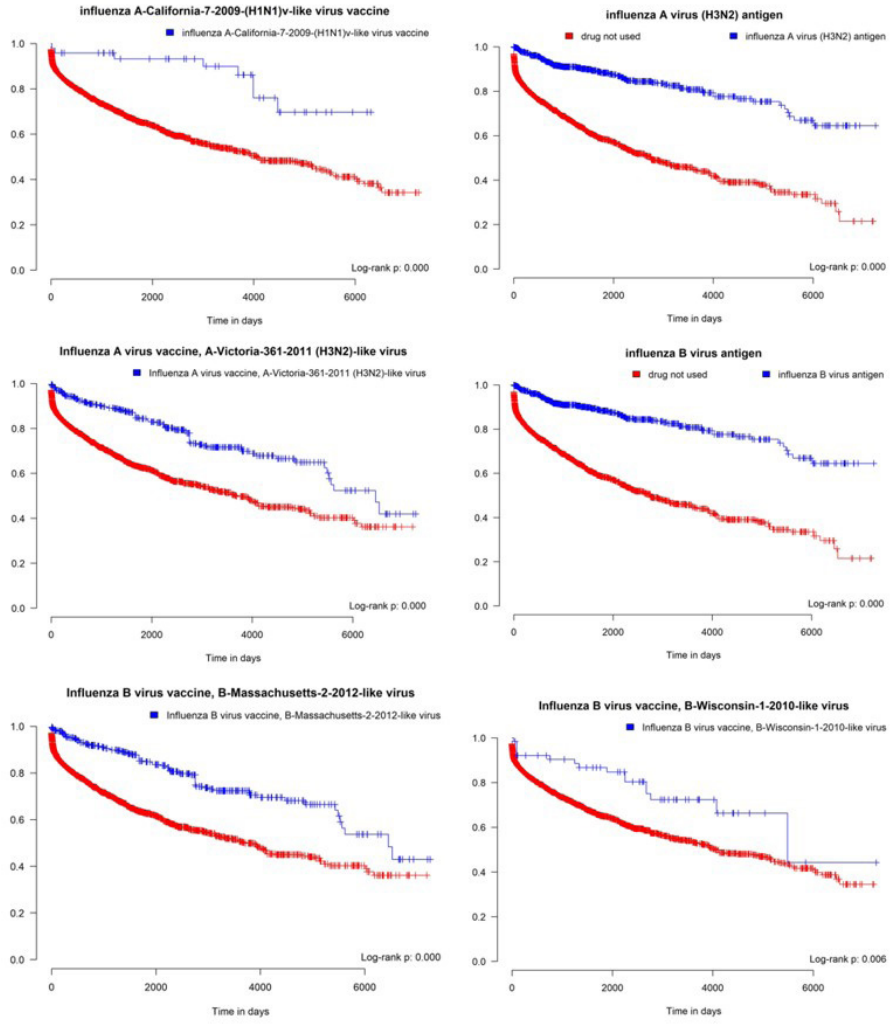

Figure 1 Efficacy of various vaccines against diverse influenza virus strains throughout the past decade in patients with alcoholic liver disease. For all patients who received vaccination against influenza A or B strains in different influenza seasons as recommended by WHO, a significantly longer survival compared with those without vaccination was demonstrated in New York, New York, USA.

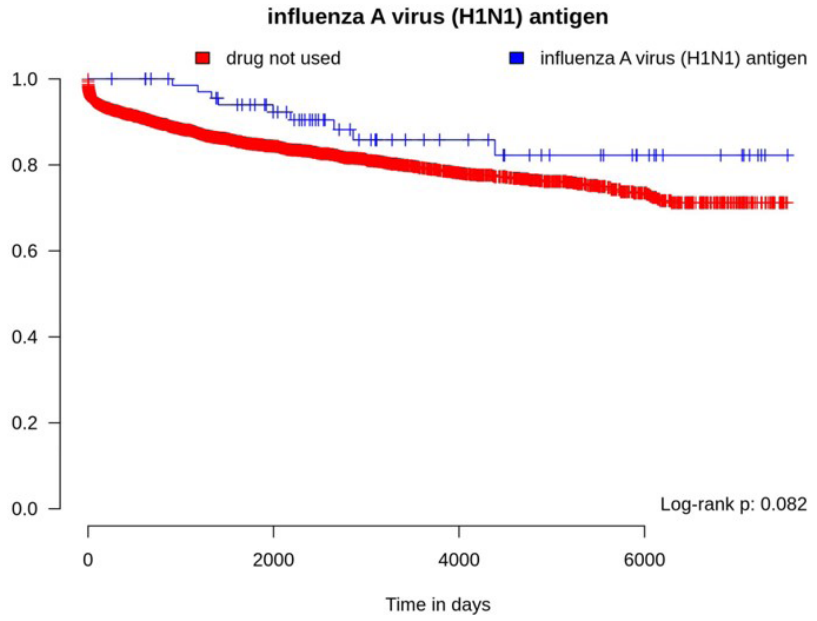

Figure 2 Efficacy of vaccination against the influenza A virus (H1N1) in patients with alcoholic liver disease. Patients who received vaccination had a trends towards longer survival compared with those without vaccination; Ajou University, South Korea (p=0.082).

upper airway infections improved survival of patients with ALD at any investigated time and with respect to any investigated influenza strain in a large USA and similar trend in an Asian cohort. Vaccination must, therefore, be strongly recommended and carried out consistently.

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REFERENCES

1 Ampuero J, Lucena A, Hernández-Guerra M, *et al*. Primary biliary cholangitis and SARS-CoV-2 infection: incidence, susceptibility and outcomes. *Gut* 2021. doi:10.1136/gutjnl-2021-325700. [Epub ahead of print: 07 Dec 2021].
2 Yip TC-F, Lui GC-Y, Wong VW-S, *et al*. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut* 2021;70:733–42.
3 Global status report on alcohol and health 2018. 2018.
4 Stroffolini T, Lombardi A, Ciancio A, *et al*. Low influenza vaccination coverage in subjects with liver cirrhosis. An alert waiting for winter season 2020-2021 during the COVID-19 pandemic. *J Med Virol* 2021;93:2446–52.
5 Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 2014;60:197–209.
6 Nasir M, Vinsard DG, Wakefield D, *et al*. The important role of immunization in alcoholic and non-alcoholic chronic liver disease: a population-based study. *J Dig Dis* 2020;21:583–92.
7 Greenbaum A, Chaves SS, Perez A, *et al*. Heavy alcohol use as a risk factor for severe outcomes among adults hospitalized with laboratory-confirmed influenza, 2005-2012. *Infection* 2014;42:165–70.
8 Szabo G, Petrasek J, Bala S. Innate immunity and alcoholic liver disease. *Dig Dis* 2012;30 Suppl 1:55–60.
9 Hripcsak G, Duke JD, Shah NH, *et al*. Observational health data sciences and informatics (OHDSI): opportunities for observational researchers. *Stud Health Technol Inform* 2015;216:574–8.
10 Chen Y-J, Qin G, Chen J, *et al*. Comparison of Face-Touching behaviors before and during the coronavirus disease 2019 pandemic. *JAMA Netw Open* 2020;3:e2016924.