# mRNA COVID-19 Vaccination Following PD-1/PD-L1 Inhibitor Therapy and Survival in Liver Cancer

**Authors:** Chenyu Sun,[1,2] Li Liu,[3] Yuntao Zou,[4] Yichen Wang,[5,6] Yan Yan,[6] Liu Yang,[7] *Yuting Huang[6]

1. Division of Public Health, Infectious Diseases, and Occupational Medicine, Mayo Clinic, Rochester, Minnesota, USA
2. Mayo Clinic School of Graduate Medical Education, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA
3. The Second People's Hospital of Hefei, China
4. Division of Hospital Medicine, Department of Medicine, University of California San Francisco, USA
5. Mayo Clinic School of Graduate Medical Education, Mayo Clinic College of Medicine and Science, Jacksonville, Florida, USA
6. Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA
7. Department of Transplant, Mayo Clinic, Jacksonville, Florida, USA

*Correspondence to Huang.yuting@mayo.edu

**Disclosure:** Wang has received an award for the development of algorithm in endoscopic image interpretation from the Mayo Clinic, Florida (Department of Medicine Team of Science Award). The other authors have declared no conflicts of interest.

**Keywords:** Hepatocellular carcinoma (HCC), immune checkpoint blockade, mRNA COVID-19 vaccination, overall survival, programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors.

**Citation:** EMJ Hepatol. 2026;14[1]:74-76. https://doi.org/10.33590/emjhepatol/Q11X9311

## BCKGROUND AND AIMS

Immune checkpoint inhibitors (ICI) targeting programmed cell death-1 (PD-1) and programmed death ligand-1 (PD-L1) have transformed the management of advanced hepatocellular carcinoma (HCC), with combination regimens such as atezolizumab plus bevacizumab now established as preferred first-line options.[1] Despite these advances, objective response rates remain variable. This is attributed in part to the uniquely immunosuppressive tumour microenvironment of HCC, characterised by regulatory T cell enrichment, T cell exhaustion, and myeloid-derived suppressor cell infiltration.[2] Identifying strategies to enhance ICI efficacy in this setting remains a clinical priority.

Emerging preclinical and clinical evidence suggests that mRNA COVID-19 vaccination may serve as a potent immune adjuvant when administered in proximity to ICI initiation. Grippin et al.[3] demonstrated that SARSCoV2 mRNA vaccination triggers a strong Type I interferon (IFN) response that activates innate antigenpresenting cells and enables efficient cluster of differentiation (CD)8$^+$ T cell priming against tumour antigens. This occurs through an IFN-dependent process in which dendritic cells acquire and present peptide–major histocompatibility complex Class I complexes, thereby enhancing anti-tumour immunity.[3] Concomitant ICI treatment was required for maximal anti-tumour efficacy, particularly in immunologically cold tumours. In large retrospective clinical cohorts, mRNA vaccination near ICI initiation was associated with significantly improved overall survival (OS) in patients with non-small cell lung cancer and melanoma.[3] A real-world study in advanced non-small cell lung cancer further confirmed that COVID-19 vaccination enhanced anti-PD-(L)1 immunotherapy efficacy, with vaccinated patients demonstrating superior progression-free survival and OS.[4] More broadly, RNA vaccine platforms activate innate and adaptive immune pathways, including pattern recognition receptor signalling and dendritic cell maturation, thereby supporting potent anti-tumour T cell responses.[5] A meta-analysis of 10 observational studies encompassing 4,929 patients corroborated these findings, demonstrating improved progression-free survival (pooled hazard ratio [HR]: 0.66; 95% CI: 0.48–0.90) and OS (pooled HR: 0.51; 95% CI: 0.39–0.66) in ICI-treated patients with cancer who received COVID-19 vaccination.[6] However, whether this survival benefit extends to HCC had not been specifically investigated.

## METHODS

This study evaluated the association between mRNA COVID-19 vaccination and OS among patients with HCC receiving PD-1/PD-L1 inhibitors using the Mayo Clinic Platform (Mayo Clinic, Rochester, Minnesota, USA). A retrospective cohort analysis included patients who received at least one dose of PD-1/PD-L1 inhibitors without liver surgery, stratified by receipt of mRNA COVID-19 vaccine within 6 weeks of immunotherapy initiation. Adjustments were made to include only BMI <30 and exclude patients with diabetes, cardiovascular disease, or heart failure history.

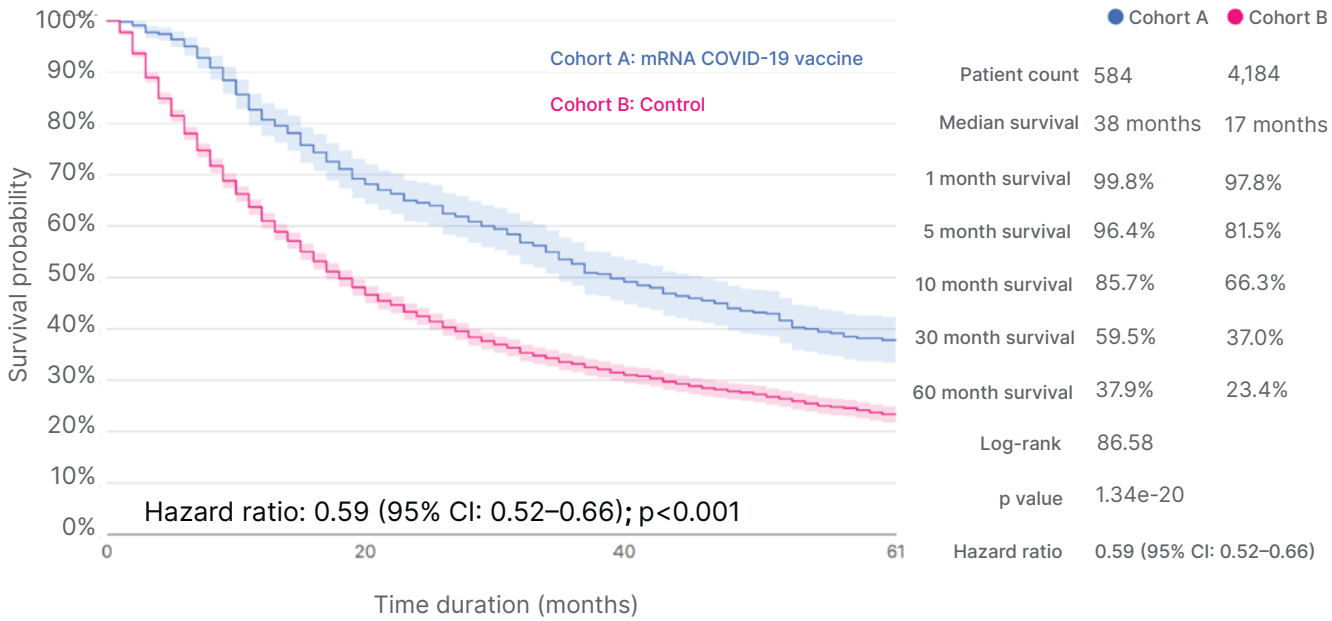
## RESULTS

The study results demonstrate that among 4,768 patients (584 vaccinated; 4,184 controls), baseline demographics were comparable. The vaccination group demonstrated significantly improved 5-year OS compared to controls (37.9% versus 23.4%; HR: 0.59; 95% CI: 0.52–0.66; p<0.001; Figure 1). This benefit remained consistent after covariate adjustment and was observed across both female (35.2% versus 22.1%; HR: 0.63; 95% CI: 0.53–0.76; p<0.001) and male subgroups (38.6% versus 22.8%; HR: 0.55; 95% CI: 0.47–0.64; p<0.001), with sustained benefit through 60 months.[7]

## CONCLUSION

These findings extend prior observations in other malignancies to HCC, supporting the hypothesis that vaccine-induced immune priming may synergise with PD-1/PD-L1 inhibition to overcome the immunosuppressive HCC microenvironment.[3-5] Importantly, COVID-19 vaccination has been shown to be safe in patients who are ICI treated, with no significant increase in immune-related adverse events.[8] Limitations of this study include the retrospective design, potential residual confounding including healthy vaccinee bias, and incomplete follow-up for patients initiating therapy more recently. In conclusion, mRNA COVID-19 vaccination shortly after PD-1/PD-L1 inhibitor initiation

**Figure 1: Kaplan–Meier analysis of survival outcomes stratified by vaccination status.**




Cumulative survival probability over a 60-month follow-up period for patients in the vaccinated group (blue) compared to the control group (red).

may be associated with improved OS in liver cancer, warranting prospective validation and mechanistic investigation.

## References


1. Singal AG et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78(6):1922-65.
2. Chen C et al. Tumor microenvironment-mediated immune evasion in hepatocellular carcinoma. Front Immunol. 2023;14:1133308.
3. Grippin AJ et al. SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade. Nature. 2025;647(8089):488-97.
4. Qian Y et al. COVID-19 vaccination is associated with enhanced efficacy of anti-PD-(L)1 immunotherapy in advanced NSCLC patients: a real-world study. Infect Agent Cancer. 2023;18(1):50.
5. Huang D et al. RNA vaccines for cancer: revolutionizing immunization strategies. Trends Cancer. 2026;12(1):48-67.
6. Xi H et al. COVID-19 vaccination and clinical outcomes of immune checkpoint inhibitors therapy in cancer patients: a meta-analysis of real-world studies. Front Immunol. 2026;17:1807267.
7. Sun Y et al. mRNA COVID-19 vaccination shortly after PD-1/PD-L1 inhibitor is associated with better survival in liver cancer: a Mayo Clinic platform study. Abstract THU-362. EASL Congress, 27-30 May, 2026.
8. Kamboj M et al. Vaccination of adults with cancer: ASCO guideline. J Clin Oncol. 2024;42(14):1699-721.