

COVID-19 vaccination around immune checkpoint inhibitor start and survival in a nationwide cohort of patients with cancer

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

My primary concern is that the pre-ICI analyses do not appear to include direct adjustment for performance status (e.g., ECOG score, home oxygen use, palliative care involvement, hospital or emergency department utilization, opioid use), detailed cancer stage, PD-L1 status, or other clinical and lifestyle factors known to influence both vaccination uptake and prognosis. These variables are also key determinants of cancer outcomes.

Without adjustment for these potentially high-impact prognostic factors, the early survival differences observed may, at least in part, reflect residual confounding related to baseline health status rather than a direct effect of vaccination. In addition, the use of a single negative-control outcome may not fully account for confounding associated with functional status or tumor biology.

Reviewer #2

(Remarks to the Author)

Thanks for this important study where you analyze 95,015 adults initiating ICI in France between Dec 2020-March 2023 as part of the SNDS to examine whether COVID-19 vaccination given before or after ICI is associated with mortality. Your primary findings is that there is a time-dependent modest lower all cause mortality that was short-lived and attenuated by 12-24 months.

Your findings are not new but the similar early mortality reductions across non-mRNA COVID-19 vaccines, Pneumococcal vaccines and other non-COVID-vaccines are novel but limited by sample size.

The strengths of your analysis include the use of a population administrative database with central recording of COVID-19 vaccination

Weaknesses include lack of capture of many important confounding factors that may influence clinical outcome such as performance status (ECOG), symptoms severity, tumor burden, frailty

There is also the potential for time-varying confounding as the probability of vaccination may be significantly impacted by disease progression, ICI toxicity and any sort of decline after ICI initiation

Although the conclusions are reasonable it is not possible to overcome the fact the early benefit suggests against a biological or immune effect which would not be so short-lived however the short-lived nature is much more in keeping with their being a health or performance bias that favors those who were vaccinated. The calendar-time confounding that could explain the earlier and not later benefit may be somewhat overcome by stratifying narrower time windows

A central concern is that patients who receive vaccination after starting ICI therapy are systematically different from those who do not, in ways that are directly related to survival. To be vaccinated during treatment, patients must remain alive, clinically stable, and sufficiently functional to continue engaging with the healthcare system. Patients who experience rapid disease progression, early treatment toxicity, or declining performance status are far less likely to be vaccinated and are also at much higher risk of early death. As a result, the vaccinated group is enriched for patients with better underlying prognosis, independent of any effect of vaccination. This selection is inherent to the clinical context and cannot be fully addressed by analytic adjustment alone.

Relatedly, vaccination during the post-ICI period is closely tied to ongoing healthcare engagement. Receipt of vaccination reflects continued outpatient contact, adherence to care, and access to preventive services, all of which are themselves associated with improved outcomes in advanced cancer. The analysis does not adequately distinguish between the effects of vaccination itself and the broader pattern of sustained healthcare utilization that vaccination represents. As such, vaccination may function primarily as a marker of patient robustness and engagement rather than as an active modifier of cancer biology or treatment response.

The use of overall survival as the primary endpoint during the COVID-19 pandemic further complicates interpretation. COVID-19 vaccination plausibly reduces mortality directly by preventing infection and severe disease, particularly in vulnerable cancer populations. The observed survival differences are modest and occur early after ICI initiation, a pattern that is compatible with reduced infectious or complication-related mortality rather than durable improvement in cancer control. Without clearer separation of cancer-specific outcomes from pandemic-related mortality, it is difficult to attribute the survival association to enhanced ICI efficacy.

The biological interpretation is also limited by the absence of disease-specific or treatment-response endpoints. Outcomes such as progression-free survival, duration of response, early treatment discontinuation, or hyperprogression would be more informative for assessing whether vaccination meaningfully interacts with antitumor immunity. In their absence, mechanistic speculation about immune synergy remains largely unsupported.

Finally, the lack of specificity in the findings weakens causal interpretation. Similar survival associations are observed with multiple types of vaccination, suggesting that the signal is not unique to COVID-19 mRNA vaccines. This pattern is more consistent with vaccination serving as a proxy for preserved functional status and continued care engagement than with a vaccine-specific immune effect.

In summary although your study provides valuable reassurance regarding COVID-19 vaccine safety the data do not convincingly support the conclusion that vaccination improves cancer outcomes or enhances ICI efficacy and require a more cautious framing.

Reviewer #3

(Remarks to the Author)

The authors aim to investigate the association of COVID-19 vaccination around immune checkpoint inhibitor (ICI) start and survival in cancer patients. A nationwide cohort of cancer patients initiating ICI in France was used in this manuscript, comprising of 95,015 patients. The primary endpoint is all-cause mortality.

Vaccination was assigned based on initiation within ± 100 days of ICI initiation and the authors have separated this investigation into vaccination administered in the pre-ICI period and post-ICI period. This makes the analysis more directed and aids interpretation of the results. IPTW was used for the pre-ICI vaccination analysis, while target trial emulation was performed using cloning-censoring-weighting (CCW) approach with IPCW for the post-ICI vaccination analysis and hazard ratios were estimated using the weighted Cox regression method. For this emulated trial, time zero was defined as time of start of ICI initiation and all-cause mortality was measured from time zero to death from any cause. Immortal time bias was handled appropriately using the CCW model. The causal contrast of interest is per-protocol effect in the target trial and hence the observational analogue of per-protocol effect in the emulated trial. This is appropriate based on the assignment of vaccination status that could be made using this data. The authors reported key diagnostics on covariate balance before and after the weighting using standardized mean differences to appropriately address for confounding.

The authors included a thoughtful set of secondary and sensitivity analyses, stratified by cancer types, including COVID-19 deaths as competing risk, association of overall death with other types of vaccination, alternative exposure window of 50 days (grace period) and a negative control outcome analysis using acute cholecystitis.

This manuscript presents a careful and well-written target trial emulation evaluating the association between COVID-19 mRNA vaccination and overall mortality among patients initiating ICI. The statistical methods are generally appropriate and consistent with current best practices in causal inference. And the authors acknowledged the need for future prospective randomised and mechanistic studies to confirm causality. Overall, the manuscript demonstrates a high level of methodological rigor and statistical transparency and only minor points require clarification.

Comments

1. Firstly, it will be good to provide a full description of the target randomized trial, which should include the basic components of the trial design (i.e. is it a parallel two-arm trial, is it a superiority trial, etc.) and data censoring criteria and the estimand (clear primary endpoint measure, which is usually used in sample size calculation in a RCT). These are not included in eTable 4.
2. Abstract. To strengthen the presentation, the authors should consider stating results of the pre-ICI and post-ICI analysis separately instead of grouping them together, especially when the hazard ratios differ. Stating that HRs are ~ 0.7 - 0.8 over 1-6 months is misleading as the HR is reported as 0.93 at 6 months for the pre-ICI analysis. The duration of follow-up should also be mentioned in the abstract.
3. It will be good to provide details on the loss to follow up of patients and discuss whether loss to follow up is independent of the vaccination status.

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The authors have substantially revised the manuscript in response to the reviewers' concerns. Overall, the response letter appropriately acknowledges the main limitations of the study, particularly residual confounding, lack of direct ECOG performance status, incomplete tumor burden and PD-L1 information, and the possibility that vaccination may partly reflect preserved functional status and continued healthcare engagement rather than a vaccine-specific biological effect.

The revised analyses broadly address the key editorial and reviewer requests. The authors expanded adjustment for confounding using multiple SNDS-based proxies for frailty, performance status, disease burden, healthcare utilization, and health-seeking behavior. They also added cancer-specific mortality, non-COVID-19 mortality, rwPFS analyses, and additional negative-control outcomes. Importantly, they have tempered the interpretation of the findings and now frame the results more cautiously, emphasizing that the observed early survival associations do not establish improved antitumor efficacy or a causal vaccine effect.

Before submission, I would still recommend minor editorial refinement to improve clarity and tone, reduce repetition, correct language issues, and avoid overly confirmatory wording. However, the overall scientific positioning is now much more balanced and aligned with the reviewers' concerns.

Reviewer #2

(Remarks to the Author)

Thanks for making substantial improvement in the manuscript. The important alignment here is the acknowledgement that similar early patterns with non-mRNA COVID-19 pneumococcal and other non-COVID adult vaccinations which argue against an mRNA vaccine specific biological effect is particularly important to the interpretation of the data and conclusions.

Major comments:

1. The quantification of residual confounding by performance status (using ECOG proxies) still needs to be addressed. The use of ECOG proxies and collapsing this into binary indicators has the potential to misclassify many patients. I would comment on what you would expect to see ($\text{ECOG} \geq 2$) in a real world metastatic cancer population starting ICI (would this not be expected to be much higher than 19%). Can you perform an E-value analysis for each of the reported hazard ratios to quantify how strong unmeasured confounding would need to be to explain away the association. Can you model distributions of unmeasured ECOG and tumor burden in the vaccinated vs unvaccinated groups? Both of these would provide further clarity as to whether the residual confounding is small enough to preserve the association of large enough to explain it.
2. The cloning censoring weighting/inverse probability of censoring weighting analysis does not completely address the time-varying confounding. I would still be concerned that clinical deterioration (i.e. between billing events) such as a patient progressing rapidly in the weeks following ICI may not live long enough to be vaccinated or generate a billing signal before dying. Please also comment on use of early ICI discontinuation which could be due to toxicity or lack of response/progression. It appears this was not treated as a time-varying covariate in the IPCW model. Other variables such as cancer-specific markers of progression/response including new imaging change in chemotherapy which are not captured in SNDS but could affect both new vaccine update and mortality. Can you add additional sensitivity analyses to help address this by: 1) restricting post-ICI analysis to patients remaining on ICI through day 100 without early discontinuation 2) Perform survival analyses to address time-dependent exposure and covariates at day 30, 60 and 90 with appropriate adjustment 3) Consider continuation of ICI as a time-varying covariate.
3. The post-ICI effect larger than the pre-ICI effect feels internally consistent with a true vaccine-biological-immunological mechanism. Does this not support residual section. This would seem to warrant a more detailed discussion.
4. Thanks for adding additional negative control outcomes and acknowledging the limitations however I would argue that these are not sufficiently distinct to performance status to act as falsification tests. Can you include both true positive and negative controls? e.g. positive control (COVID-19 in weeks after pre-ICI vaccination), negative controls: routine office procedures, dental appointments etc.
5. The fact that survival associations are not exclusive to mRNA COVID-19 vaccines seems to be a major point of this paper and this should affect the order and priority of how conclusions are framed.
6. I am concerned that the real-world progression free survival endpoint does not provide independent confirmation of the survival finding. You should consider cleaning up discontinuation causes where possible. Such as excluding planned stops, identification of toxicity associated discontinuations as well as presenting time to ICI discontinuation and time to death as separate outcomes. Finally the readership should be clear that rwPFS is not a measure of anti-tumor efficacy.
7. Bias in Cancer-specific mortality reporting. Can you report the absolute number of cancer deaths contributing to each analysis (not only hazard ratios) to make the statistical power for the cancer specific endpoints more transparent.
8. Although the SNDS may have minimal intended loss to follow-up there are still ways that this will occur and this should be references in more detail. Perhaps a statement to indicate that loss to follow-up for all-cause mortality is expected to be low but cannot be assumed to be zero.
9. Overall that a subgroup analysis showing a larger post-ICI effect amongst patients not previously vaccinated indicates priming. Patients who received first COVID-19 mRNA vaccine after ICI initiation later in 2021 were those who had potentially delayed vaccination.

10. Provide more transparency as to how patients who die during the grace period are handled. It appears these patients are censored at death however it is unclear whether these deaths contribute to the no vaccination arm event count or whether the PICW weights correctly handle the dependency between death (which clearly precludes future vaccination) and the censored event (failure to vaccinate by day 100)

Additional comments:

1. Missing data is stated as being not applicable in methods but SNDS records can have missing values for patients with missing residential data, income status and region. Can you specify missingness and how it might impact the study?
2. Provide justification for using Fine-Gray models for pre-ICI period and Cox models otherwise for competing risk specification.
3. In methods specify the number of bootstrap replicates and whether bootstrap was performed on weighted or unweighted sample with stratified resampling by exposure
4. In results it is confusing whether 27,395 or 27,463 is the analysis sample
5. Residual confusion in discussion should be residual confounding.
6. Additional copy editing for other typos (i.e. address)

Reviewer #3

(Remarks to the Author)

I thank the authors for their careful revision of the manuscript. My previous comments have been satisfactorily addressed. The inclusion of additional analyses with appropriate adjustment for confounders using proxy variables available in SNDS, as well as the expansion of secondary endpoints and incorporation of additional negative control outcomes, have strengthened the study and improved its overall rigor. I have no further comments.

Version 2:

Reviewer comments:

Reviewer #2

(Remarks to the Author)

Thanks for your responsive revisions. I still have a small number of substantive points and several minor ones.

Major comments

1. The E-values undercut the headline associations more than the current wording conveys. Given that the healthy-vaccinee/care-engagement effect you invoke is almost certainly stronger than this, the honest reading is that the 6-month and later associations are statistically present but causally uninterpretable and this should be declared upfront.
2. Please distinguish "non-specific immune effect" from "healthy-vaccinee/confounding." The manuscript at times uses "non-specific effects" to mean two very different things: (a) genuine non-antigen-specific biology such as trained innate immunity or bystander immune stimulation, which would be a real effect, and (b) healthy vaccinee selection and care engagement, which is confounding. Both produce the cross-vaccine concordance you observe, so the data cannot separate them, but they carry opposite implications for the Grippin hypothesis (one partially supports a biological, if non-mRNA-specific, effect; the other negates it). I would make this distinction explicit and acknowledge that your design cannot adjudicate between them.
3. Residual imbalance in the post-ICI analysis deserves more weight. You note that after weighting, calendar year of ICI initiation and prior non-COVID vaccination remained imbalanced (SMD >0.1; Supplementary Figure 3). Calendar time is a particularly worrying residual confounder here, because it jointly drives vaccine availability/uptake and evolving ICI practice and outcomes, and because the preICI unvaccinated comparator becomes an increasingly atypical group in 2022–2023. Please discuss the direction and plausible impact of this residual imbalance rather than only listing it, and consider a sensitivity analysis additionally finely stratified or with a tighter calendar-time restriction.
4. The negative controls are still not well matched to the confounding of concern. As raised previously, cataract surgery, dental visits, cholecystitis, PE, and femoral neck fracture are only weakly tied to the performance status/tumor trajectory gradient that drives cancer mortality, so their null results provide limited falsification of the specific confounding pathway. Indeed, the slightly elevated HRs for elective procedures (cataract 1.03, dentist 1.03) could be read as a faint healthy-vaccinee signal rather than reassurance. I would temper the reassurance drawn from these controls and acknowledge that an ideal negative control an outcome strongly linked to performance status but not to vaccination is simply not available in the SNDS.
5. Single-dose predominance and absence of dose-response argue against a biological mechanism and should be stated as such. Most "vaccinated" patients received a single dose (median 1 [1–1]) within the window. A genuine immune-priming effect would be expected to show some dose-response. If feasible, a dose-stratified analysis would strengthen the non-specificity argument; if not feasible, please note explicitly that the lack of a tested dose-response is itself evidence against an antigen-specific priming effect and a limitation of the window-based exposure definition.
6. You interpret the null association for documented preICI COVID-19 infection as evidence against infection-driven immune stimulation. However, infection carries competing harms (treatment disruption, severe illness), so a null could reflect cancellation of a harmful infection effect against any beneficial immune stimulation effect rather than the absence of immune stimulation. Please add this caveat.
7. Title and abstract framing. Given the Grippin context and the current climate, the neutral title and the abstract's lead with protective HRs invite the "vaccination improves ICI outcomes" misreading that the body of the paper carefully repudiates. I would surface the non-specificity/null-for-specificity message earlier, ideally signaling in the title or first abstract sentence that the early associations are not specific to mRNA vaccines and are consistent with healthy vaccinee effects.

Minor comments:

The negative and positive control outcomes seem to use a single constant hazard ratio over time, while the main outcomes allow the effect to vary with time, so please either explain this or model them the same way. The absolute survival differences are small (about 1 to 1.5% preICI and 2.6 to 3.4% post-ICI), and recommend that you keep this central in the abstract, where the hazard ratios currently dominate. What about adjustment for the many time points, subgroups, and outcomes tested? A sentence reinforcing that analyses are exploratory would help. For the post-ICI subgroup, please say clearly in the main text that "preICI unvaccinated" is not the same as vaccine-naïve and is tangled up with when people happened to get vaccinated. For rwPFS, note that ICI discontinuation itself may differ between vaccinated and unvaccinated patients and could bias the result. The performance-status proxy discussion is good but repetitive, and could be more concise. Be clear which analyses were run in SAS versus R, briefly justify the different bootstrap replicate counts (1000 vs 500)

A few typos also remain ("residual confounding's" - line 166) and make sure the 27,463 vs 27,395 reconciliation reads consistently across Table 1, the flow chart, and the Figure 2 footnote.

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Response to Reviewers are in blue

Dear Professor Salem,

Your Article, "COVID-19 vaccination around immune checkpoint inhibitor start and survival in a nationwide cohort of cancer patients" has now been seen by 3 referees. You will see from their comments below that while they find your work of interest, some important points are raised. We are interested in the possibility of publishing your study in Nature Medicine, but would like to consider your response to these concerns in the form of a revised manuscript before we make a final decision on publication. In a revised manuscript, we consider of importance to perform additional confounder analyses so that conclusions can be more robust, for example with regards to performance status, cancer stage and health-seeking behavior as pointed out by referees. The inclusion of cancer-specific outcomes in the analysis would provide additional insight. We therefore invite you to revise your manuscript taking into account all reviewer and editor comments. Please highlight all changes in the manuscript text file. We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

Response: Thank you for the opportunity to revise our manuscript and for the constructive and thoughtful comments from the editors and reviewers. We have carefully revised the manuscript accordingly. In particular, we substantially strengthened confounder adjustment by incorporating additional proxies for performance status, frailty, advanced disease burden, and health-seeking behavior; added cancer-specific death and real-world progression free survival analyses; expanded the negative-control outcome analyses; clarified the target trial emulation and censoring assumptions; and revised the framing of the findings to be more cautious regarding causality and biological interpretation. All changes have been highlighted in the revised manuscript (in blue, bold). Altogether, all these new analyses confirmed the analysis already observed in the first iteration already submitted of this work (see **Figures 3- 5**).

Added to Introduction: *"Here, using the French national health data system (Système National des Données de Santé, SNDS),^{14,15} we applied causal inference methods for observational data to the nationwide cohort of all adults initiating ICI therapy between the introduction of COVID-19 vaccines in France and the end of the period during which vaccination was exhaustively recorded in the SNDS. We examined whether receiving COVID-19 vaccination—particularly mRNA vaccination—within a 100 days prespecified windows before or after ICI initiation was associated with all-cause mortality, **while adjusting for multiple prognostic covariates**, using inverse probability weighting (IPTW) and a cloning–censoring–weighting (CCW) approach, respectively, to account for time-dependent vaccination and immortal time bias.¹⁰ **We additionally evaluated cancer-specific and non–COVID-19 mortality.***

Complementary analyses assessed consistency across major cancer sites, stratified by vaccine platform (mRNA vs non-mRNA), considered documented COVID-19 infection and non-COVID adult vaccinations as control exposures, and used negative-control outcomes to explore residual confounding.”

We strongly encourage researchers to follow the ‘Sex and Gender Equity in Research – SAGER – guidelines’ and to include sex and gender considerations for studies involving humans, vertebrate animals and cell lines where relevant to the topic of study (an overview can be found [here](#)). Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. When preparing your revised manuscript, please be aware of our guidance on Sex and Gender reporting). Please note that: 1. If the research findings apply to only one sex or gender, that must be indicated in the title and/or abstract. 2a. For studies involving vertebrates animal and cell lines- The Reporting Summary should include whether sex was considered in the study design. 2b. For studies involving human research participants- The Reporting Summary should include whether sex and/or gender was considered in the study design and whether sex and/or gender of participants was determined based on self-report or assigned (and methodology used). 3. Data should be reported disaggregated for sex and gender where this information has been collected and consent has been obtained for reporting and sharing individual-level data; disaggregated numbers for individual experiments must be provided in the source data as appropriate whereas overall numbers may be provided in the Nature Portfolio Reporting Summary. Information on the 3 points above should be included in the revised manuscript and detailed in the cover letter. In addition, please note that if sex- and gender-based analyses have been performed a priori, results should be reported regardless of positive or negative outcome. We discourage conducting post hoc sex- and gender-based analysis if the study design is insufficient (for example, low sample size) to enable meaningful conclusions. If no sex- and gender-based analyses have been performed, please indicate the reasons for the lack of these analyses in the Reporting Summary.

Response: We have revised the manuscript and reporting materials in accordance with the SAGER guidelines where applicable. In particular, we use the term sex (not gender), as the SNDS records biological sex, and we report the sex distribution of the study population accordingly. Because this was not a sex-specific study, the findings apply to both women and men. We will also ensure that the Reporting Summary clearly state whether sex was considered in the study design, how this variable was captured in the database, and that no dedicated sex-stratified analyses were planned a priori.

Reviewer #1 (Remarks to the Author):

My primary concern is that the pre-ICI analyses do not appear to include direct adjustment for performance status (e.g., ECOG score, home oxygen use, palliative care involvement, hospital or emergency department utilization, opioid use), detailed cancer stage, PD-L1 status, or other clinical and lifestyle factors known to influence both vaccination uptake and prognosis. These variables are also key determinants of cancer outcomes. Without adjustment for these potentially high-impact prognostic factors, the early survival differences observed may, at least in part, reflect residual confounding related to baseline health status rather than a direct effect of vaccination.

Response: Thank you for this important comment. We agree that direct measures such as ECOG performance status, detailed cancer stage, PD-L1 expression, and lifestyle factors were not fully captured by the previous iteration of our work. To mitigate these limitations, we have now adjusted on more prognostic variables following your recommendation, by use of proxies available in SNDS and used in previous studies in the field of cancer using the SNDS data, including several proxies of poor ECOG performance status and advanced disease burden. These comprised in/outpatient ICI initiation, malnutrition, home oxygen use, palliative care stay, emergency department visits, intensive care unit admission, rehabilitation/long-term care stay, at-home hospitalization, home nursing care, repeated ambulance transports, opioid and corticosteroid use, prior cancer treatments (including major surgery, chemotherapy and radiotherapy), metastatic status, and multiple comorbidities, as well as markers of healthcare use and health-seeking behavior.

Added to Methods: *“Baseline covariates included in the models are displayed in Table-1. They included age (categories), sex, low-income status, [deprivation index \(socioeconomic deprivation score\)](#)²⁵ and [region of residence](#). Cancer-related variables included the primary tumor site (categorized as lung/respiratory, melanoma, head and neck, urovesical, kidney, liver, gastro-intestinal, mesothelioma/pleural and other), a proxy for metastatic disease (presence of metastasis codes), the type of ICI regimen (anti-PD1, anti-PDL1, or anti-PD1+anti-CTLA4), [cancer radiotherapy, chemotherapy or major cancer surgeries in the last 3 years and inpatient \(versus outpatient\) initiation of ICI as a proxy of a poorer performance status.](#)²⁶ Centers where ICI was initiated were classified according to patient volume as high-volume (top 10% of centers), intermediate-volume (10–40%), and low-volume (bottom 60%).²⁶ Cancer-related frailty variables were assessed during the 6 months before ICI initiation and updated during the 100 days after initiation. These included malnutrition; at least 2 ambulance transports on separate days; at least 1 emergency department visit; at least 1 intensive care unit admission; at least 1 hospitalization in a rehabilitation or long-term care facility; at least 1 at-home hospitalization; at least 1 home nursing care visit; use of home oxygen therapy; and at least 1 palliative care stay. Baseline treatments before ICI and time-updated treatments during the 100 days after initiation included antiangiogenic agents, opioids, antibiotics, antiepileptics, bisphosphonates, anti-RANKL (receptor activator of nuclear factor kappa-B ligand) agents, proton pump inhibitors, and corticosteroids (defined as at least 7 mg/day prednisone). We also included the number of general practitioner consultations in the previous 6 months as additional proxy for health-seeking behavior and receipt of any non-COVID vaccination within 1 year before ICI initiation as proxy for vaccination-related behavior.”*

In addition, the use of a single negative-control outcome may not fully account for confounding associated with functional status or tumor biology.

Response: Thank you for this relevant comment. To strengthen this assessment, we expanded the analysis to include three negative-control outcomes with different physiological mechanisms—acute cholecystitis, pulmonary embolism, and femoral neck fracture—and none showed a significant association with pre-ICI mRNA COVID-19 vaccination in the weighted analysis. We will clarify, however, that while these additional negative controls provide further reassurance against major residual bias, they cannot definitively exclude residual confounding.

Added to Results: *“We also assessed the potential impact of residual confounding using negative control outcomes, i.e. evaluating whether the occurrence of acute cholecystitis, [pulmonary embolism](#), and [femoral neck fracture](#) differed between individuals who were COVID-19 mRNA vaccinated in the pre-ICI period and those who were not; no significant difference was detected (Figure-4).”*

Added to Limitations: *“[The absence of association between COVID19 vaccination and negative-control outcomes provided some reassurance against major residual bias, but they cannot definitively rule out unmeasured confounding.](#)”*

Reviewer #2 (Remarks to the Author):

Thanks for this important study where you analyze 95,015 adults initiating ICI in France between Dec 2020-March2023 as part of the SNDS to examine whether COVID-19 vaccination given before or after ICI is associated with mortality. Your primary findings is that there is a time-dependent modest lower all cause mortality that was short-lived and attenuated by 12-24 months. Your findings are not new but the similar early mortality reductions across non-mRNA COVID-19 vaccines, Pneumococcal vaccines an other non-COVID-vaccines are novel but limited by sample size. The strengths of your analysis include the use of a population adminisitrative database with central recording of COVID-19 vaccination. Weaknesses include lack of capture of many important confounding factors that may influence clinical outcome such as performance status (ECOG), symptoms severity, tumor burden, frailty.

Response: We agree that residual confounding, particularly related to performance status, frailty, symptom burden, and tumor burden, are weaknesses of this observational study. In the revised manuscript, we therefore substantially strengthened confounder adjustment by incorporating an extended number of prognostic variables, using proxies available in the SNDS, including proxies for poor ECOG performance status, frailty, advanced disease burden, and healthcare engagement. These included inpatient ICI initiation, metastatic status, malnutrition, home oxygen use, palliative care, emergency department visits, intensive care unit admission, rehabilitation or long-term care, at-home hospitalization, home nursing care, repeated ambulance transport, opioid and corticosteroid use, prior cancer treatments, comorbidities, GP consultations, and prior non-COVID vaccination. We agree that these variables cannot fully replace direct clinical measures such as ECOG, PD-L1 expression, or detailed tumor burden, and we have clarified this limitation and further tempered the interpretation of the observed early survival differences accordingly.

Added to Methods: *“Baseline covariates included in the models are displayed in Table-1. They included age (categories), sex, low-income status, [deprivation index \(socioeconomic deprivation score\)](#)²⁵ and [region of residence](#). Cancer-related variables included the primary tumor site (categorized as lung/respiratory, melanoma, head and neck, urovesical, kidney, liver, gastro-intestinal, mesothelioma/pleural and other), a proxy for metastatic disease (presence of metastasis codes), the type of ICI regimen (anti-PD1, anti-PDL1, or anti-PD1+anti-CTLA4), [cancer radiotherapy, chemotherapy or major cancer surgeries in the last 3 years and inpatient \(versus outpatient\) initiation of ICI as a proxy of a poorer performance status](#).²⁶ Centers where ICI was initiated were classified according to patient volume as high-volume (top 10% of centers), intermediate-volume (10–40%), and low-volume (bottom 60%).²⁶ Cancer-related frailty variables were assessed during the 6 months before ICI initiation and updated during the 100 days after initiation. These included [malnutrition; at least 2 ambulance transports on separate days; at least 1 emergency department visit; at least 1 intensive care unit admission; at least 1 hospitalization in a rehabilitation or long-term care facility; at least 1 at-home hospitalization; at least 1 home nursing care visit; use of home oxygen therapy; and at least 1 palliative care stay](#). Baseline treatments before ICI and time-updated treatments during the 100 days after initiation included [antiangiogenic agents, opioids, antibiotics, antiepileptics, bisphosphonates, anti-RANKL \(receptor activator of nuclear factor kappa-B](#)*

ligand) agents, proton pump inhibitors, and corticosteroids (defined as at least 7 mg/day prednisone). We also included the number of general practitioner consultations in the previous 6 months as additional proxy for health-seeking behavior and receipt of any non-COVID vaccination within 1 year before ICI initiation as proxy for vaccination-related behavior.”

Added to Limitations: *“First, as in any observational study, residual confounding cannot be fully excluded. Although we adjusted for a broad range of sociodemographic, oncologic, comorbidity, frailty, and healthcare-use variables, the SNDS does not capture some key clinical factors such as direct measures of performance status, PD-L1 expression, detailed tumor burden, and certain lifestyle characteristics.”*

There is also the potential for time-varying confounding as the probability of vaccination may be significantly impacted by disease progression, ICI toxicity and any sort of decline after ICI initiation. Although the conclusions are reasonable it is not possible to overcome the fact the early benefit suggests against a biological or immune effect which would not be so short-lived however the short-lived nature is much more in keeping with their being a health or performance bias that favors those who were vaccinated. The calendar-time confounding that could explain the earlier and not later benefit may be somewhat overcome by stratifying narrower time windows. A central concern is that patients who receive vaccination after starting ICI therapy are systematically different from those who do not, in ways that are directly related to survival. To be vaccinated during treatment, patients must remain alive, clinically stable, and sufficiently functional to continue engaging with the healthcare system. Patients who experience rapid disease progression, early treatment toxicity, or declining performance status are far less likely to be vaccinated and are also at much higher risk of early death. As a result, the vaccinated group is enriched for patients with better underlying prognosis, independent of any effect of vaccination. This selection is inherent to the clinical context and cannot be fully addressed by analytic adjustment alone.

Response: We agree that, in the post-ICI setting, vaccination may depend on evolving clinical status, including early progression, toxicity, functional decline, and continued contact with care. To address this, we used a cloning–censoring–weighting target-trial emulation with time-varying censoring adjustment, and included additional baseline and time-updated proxies for frailty, performance status, and healthcare use available in the SNDS (described above). We also explored narrower post-ICI exposure windows, with broadly similar results. In addition, the post-ICI estimates were close to those observed in the pre-ICI analysis, arguing against an explanation based solely on factors arising after ICI initiation. However, these approaches cannot fully remove residual time-varying confounding, and we have therefore revised the manuscript to adopt a more cautious interpretation. Overall, the short-lived association, together with similar patterns seen with non-mRNA COVID-19 vaccines and other adult vaccines, does not support a specific or

durable enhancement of ICI efficacy and is also compatible with residual differences in prognosis and healthcare engagement between groups.

Added to Limitations: *“In addition, vaccination in the post-ICI period may partly reflect preserved functional status, continued healthcare engagement ; thus, patients with rapidly progressive disease may have been less likely to be vaccinated after ICI initiation despite the cloning–censoring–weighting approach and inverse probability weighting.”*

Added to Conclusion: *“In a large, nationwide cohort of patients with cancer initiating ICI therapy, peri-ICI COVID-19 vaccination was associated with a modest early survival advantage. The association persisted when restricting to non–COVID-19 deaths and similar early patterns were observed for cancer-specific outcomes, although these findings do not establish a direct effect on antitumor efficacy. Similar early patterns were also observed for non-mRNA COVID-19 vaccines and for other adult vaccinations, arguing that the observed association may not be specific to mRNA COVID-19 vaccination and may partly reflect non-specific correlates of vaccination and/or residual confounding.”*

Relatedly, vaccination during the post-ICI period is closely tied to ongoing healthcare engagement. Receipt of vaccination reflects continued outpatient contact, adherence to care, and access to preventive services, all of which are themselves associated with improved outcomes in advanced cancer. The analysis does not adequately distinguish between the effects of vaccination itself and the broader pattern of sustained healthcare utilization that vaccination represents. As such, vaccination may function primarily as a marker of patient robustness and engagement rather than as an active modifier of cancer biology or treatment response.

Response: We agree that post-ICI vaccination may partly capture continued healthcare engagement, including outpatient follow-up, access to preventive care, and preserved functional status, all of which may themselves be associated with prognosis. To address this, we incorporated multiple additional proxies of healthcare utilization, health-seeking behavior, frailty, and clinical status available in the SNDS, including general practitioner consultations and prior non-COVID-19 vaccination. However, these data cannot fully disentangle vaccination itself from the broader pattern of ongoing care engagement, and residual confounding is likely to remain despite the cloning–censoring–weighting approach and inverse probability weighting. We therefore revised the manuscript to make this point explicit and to frame the post-ICI findings more cautiously. Ultimately, only a randomized study could fully distinguish a vaccine-specific effect from differences in patient robustness, care engagement, and clinical trajectory.

Added to Limitation: *“In addition, vaccination in the post-ICI period may partly reflect preserved functional status, continued healthcare engagement ; thus, patients with rapidly progressive disease may have been less likely to be vaccinated after ICI initiation despite the cloning–censoring–weighting approach and inverse probability weighting.”*

The use of overall survival as the primary endpoint during the COVID-19 pandemic further complicates interpretation. COVID-19 vaccination plausibly reduces mortality directly by preventing infection and severe disease, particularly in vulnerable cancer populations. The observed survival differences are modest and occur early after ICI initiation, a pattern that is compatible with reduced infectious or complication-related mortality rather than durable improvement in cancer control. Without clearer separation of cancer-specific outcomes from pandemic-related mortality, it is difficult to attribute the survival association to enhanced ICI efficacy. The biological interpretation is also limited by the absence of disease-specific or treatment-response endpoints. Outcomes such as progression-free survival, duration of response, early treatment discontinuation, or hyperprogression would be more informative for assessing whether vaccination meaningfully interacts with antitumor immunity. In their absence, mechanistic speculation about immune synergy remains largely unsupported.

Response: We agree that overall survival during the pandemic was influenced by COVID related death, particularly in vulnerable cancer patients and that overall mortality complicates interpretation as it is not cancer specific. To address this, we added analyses of non-COVID-19 mortality and cancer-specific mortality, which showed similar early time-dependent patterns, as well as rwPFS analyses, which were directionally consistent with the mortality results. At the same time, we agree that these findings do not fully demonstrate enhanced ICI efficacy nor a direct biological interaction between vaccination and antitumor immunity. We have therefore revised the manuscript to substantially temper the mechanistic interpretation and to frame the results primarily as reassuring regarding the absence of harm, while emphasizing that residual confounding and non-specific effects remain plausible explanations.

Added to Results: *“Similar early associations were observed for cancer-specific mortality and rwPFS (real-world progression free survival, defined from ICI discontinuation or death),¹⁶ with no longer significant association thereafter, consistently with the overall survival results (Figure-3C, D).”*

“Similar early time-dependent associations were observed for cancer-specific mortality and rwPFS, with disappearance of significant association over time, consistently with all-cause mortality results (Figure-5C, D), suggesting that the observed association was not driven solely by COVID-19–related mortality”.

Added to Discussion: *“However, in our study the associations between peri-ICI vaccination and survival were similar when analyses were restricted to non-COVID-19 mortality, and early association was also observed for cancer-specific mortality. Together, these findings suggest that prevention of fatal COVID-19 alone is unlikely to fully explain the observed associations.”*

Added to Limitations: *“Third, interpretation of secondary endpoints requires caution. Cause-of-death information was only available through 2023, resulting in shorter follow-up for cause-*

specific analyses than for all-cause mortality. Moreover, cancer-specific mortality derived from administrative data should not be interpreted as direct evidence of improved antitumor efficacy, given the possibility of misclassification.”

Added to Conclusions: *“The association persisted when restricting to non–COVID-19 deaths and similar early patterns were observed for cancer-specific outcomes, although these findings do not establish a direct effect on antitumor efficacy. Similar early patterns were also observed for non-mRNA COVID-19 vaccines and for other adult vaccinations, arguing that the observed association may not be specific to mRNA COVID-19 vaccination and may partly reflect non-specific correlates of vaccination and/or residual confounding.”*

Finally, the lack of specificity in the findings weakens causal interpretation. Similar survival associations are observed with multiple types of vaccination, suggesting that the signal is not unique to COVID-19 mRNA vaccines. This pattern is more consistent with vaccination serving as a proxy for preserved functional status and continued care engagement than with a vaccine-specific immune effect. In summary although your study provides valuable reassurance regarding COVID-19 vaccine safety the data do not convincingly support the conclusion that vaccination improves cancer outcomes or enhances ICI efficacy and require a more cautious framing.

Response: We agree that the lack of specificity across vaccine types weakens any strong causal or vaccine-specific interpretation. We have therefore revised the manuscript to avoid interpreting these findings as evidence that COVID-19 vaccination improves cancer outcomes or enhances ICI efficacy. Instead, we now frame the results more cautiously as reassuring regarding the absence of harm, while acknowledging that the observed associations may reflect non-specific correlates of vaccination and/or residual confounding. At the same time, we cannot fully exclude the possibility of a non-specific immune effect shared across vaccine types, although our data do not allow this hypothesis to be distinguished from more parsimonious explanations related to prognosis, healthcare engagement, and selection mechanisms.

In the Conclusion: *“The association persisted when restricting to non–COVID-19 deaths and similar early patterns were observed for cancer-specific outcomes, although these findings do not establish a direct effect on antitumor efficacy. Similar early patterns were also observed for non-mRNA COVID-19 vaccines and for other adult vaccinations, arguing that the observed association may not be specific to mRNA COVID-19 vaccination and may partly reflect non-specific correlates of vaccination and/or residual confounding.”*

Reviewer #3:

The authors aim to investigate the association of COVID-19 vaccination around immune checkpoint inhibitor (ICI) start and survival in cancer patients. A

nationwide cohort of cancer patients initiating ICI in France was used in this manuscript, comprising of 95,015 patients. The primary endpoint is all-cause mortality. Vaccination was assigned based on initiation within ± 100 days of ICI initiation and the authors have separated this investigation into vaccination administered in the pre-ICI period and post-ICI period. This makes the analysis more directed and aids interpretation of the results. IPTW was used for the pre-ICI vaccination analysis, while target trial emulation was performed using cloning-censoring-weighting (CCW) approach with IPCW for the post-ICI vaccination analysis and hazard ratios were estimated using the weighted Cox regression method. For this emulated trial, time zero was defined as time of start of ICI initiation and all-cause mortality was measured from time zero to death from any cause. Immortal time bias was handled appropriately using the CCW model. The causal contrast of interest is per-protocol effect in the target trial and hence the observational analogue of per-protocol effect in the emulated trial. This is appropriate based on the assignment of vaccination status that could be made using this data. The authors reported key diagnostics on covariate balance before and after the weighting using standardized mean differences to appropriately address for confounding. The authors included a thoughtful set of secondary and sensitivity analyses, stratified by cancer types, including COVID19 deaths as competing risk, association of overall death with other types of vaccination, alternative exposure window of 50 days (grace period) and a negative control outcome analysis using acute cholecystitis. This manuscript presents a careful and well-written target trial emulation evaluating the association between COVID-19 mRNA vaccination and overall mortality among patients initiating ICI. The statistical methods are generally appropriate and consistent with current best practices in causal inference. And the authors acknowledged the need for future prospective randomised and mechanistic studies to confirm causality. Overall, the manuscript demonstrates a high level of methodological rigor and statistical transparency and only minor points require clarification.

Response: Thank you for this careful and positive assessment. We appreciate your recognition of the methodological rigor of our nationwide target trial emulation, including the separation of pre-ICI and post-ICI vaccination analyses, the use of IPTW and CCW/IPCW approaches, the handling of immortal time bias, and the breadth of secondary and sensitivity analyses. We are also grateful for your acknowledgment of the statistical transparency and the cautious interpretation of causality. We have addressed the minor points requiring clarification below.

1. Firstly, it will be good to provide a full description of the target randomized trial, which should include the basic components of the trial design (i.e. is it a parallel two-arm trial, is it a superiority trial, etc.) and data censoring criteria and the

estimand (clear primary endpoint measure, which is usually used in sample size calculation in a RCT). These are not included in eTable 4.

Response: We revised the eTable 4 to provide a more explicit description of the target trial framework. Specifically, we clarified that the emulated trial corresponds to an open label multicenter parallel two-arm superiority design comparing vaccination versus no vaccination within 100 days following ICI initiation. We additionally defined the target and emulated estimands, as well as the censoring mechanisms, including administrative censoring and informative censoring due to deviations from assigned strategies, that was handled with IPCW.

2. Abstract. To strengthen the presentation, the authors should consider stating results of the pre-ICI and post-ICI analysis separately instead of grouping them together, especially when the hazard ratios differ. Stating that HRs are ~0.7-0.8 over 1-6 months is misleading as the HR is reported as 0.93 at 6 months for the pre-ICI analysis. The duration of follow-up should also be mentioned in the abstract.

Response: We thank the reviewer for this helpful suggestion and agree that the previous abstract wording was too compressed and could be misleading by grouping pre-ICI and post-ICI analyses together despite different time-specific estimates.

Added to Abstract: *“Pre-ICI mRNA vaccination was associated with lower early all-cause mortality (HR 0.90^(95%CI:0.87-0.94) at 1–3 months; 0.96 (0.93-1.00) at 6 months), and no significant association after 12 months. Post-ICI mRNA vaccination showed a similar early association (HR 0.84(0.80-0.88) at 3 months; 0.86 (0.79-0.94) at 6 months), also no significant association after 12 months. Estimates for non–COVID-19 and cancer-specific mortality were similar to those of overall survival.”*

3. It will be good to provide details on the loss to follow up of patients and discuss whether loss to follow up is independent of the vaccination status.

Response: Thank you for this important point. In our study, loss to follow-up was expected to be very limited because the SNDS national claims database covers the entire territory of France and constitutes the sole social security system for individuals residing in France; consequently, individuals covered by the system—and thus included in this database—do not switch from one social security system to another (which would result in them being lost to follow-up). Since this database is intended for reimbursement and reused for research purposes, the individuals included in the study do not choose to opt out of it; their data are recorded prospectively and comprehensively to ensure reimbursement for their care.

Added to Methods: *“In the SNDS, true loss to follow-up is expected to be minimal because the SNDS national claims database covers the entire territory of France and constitutes the sole social security system for individuals residing in France, and the recording of their data is made for reimbursement purpose.”*

Response to Reviewers are in blue in the resubmitted manuscript

Your Article, "COVID-19 vaccination around immune checkpoint inhibitor start and survival in a nationwide cohort of cancer patients" has now been seen by 3 referees. You will see from their comments below that while some referees are satisfied with the revision, some important points are raised. We are interested in the possibility of publishing your study in Nature Medicine, but would like to consider your response to these concerns in the form of a revised manuscript before we make a final decision on publication.

In a revised manuscript, we consider of importance to provide additional sensitivity analyses and providing true positive and negative controls as per referee 2's comments.

We therefore invite you to revise your manuscript taking into account all reviewer and editor comments. We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

Response: We thank the reviewers and editors for their constructive feedback. In response to these comments, we added a positive-control outcome, COVID-19-related hospitalization, and two additional negative-control outcomes, dentist visit and cataract surgery. These analyses assess whether the design recovers an expected vaccine-associated protective effect on COVID-19-related hospitalization, while also testing for non-specific associations with outcomes not expected to be causally affected by COVID-19 vaccination. The results are now reported in **Figure 4** and discussed in the revised manuscript.

We also performed additional post-ICI sensitivity analyses to address concerns regarding time-varying confounding, early clinical deterioration, and early ICI discontinuation during the 100-day grace period. Specifically, we evaluated post-ICI mRNA COVID-19 vaccination among patients who were alive and still receiving ICI at day 100, and repeated the emulated target-trial analysis under strategies requiring continuous ICI treatment through day 100, with censoring at early ICI discontinuation in addition to censoring at deviation from the assigned vaccination strategy. These results were broadly consistent with the main post-ICI analysis and are now reported in **Supplementary Figure 8**, and in the revised manuscript.

1. If the research findings apply to only one sex or gender, that must be indicated in the title and/or abstract.

Response: The study included both women and men, and the research findings are not intended to apply to only one sex or gender. Therefore, no sex- or gender-specific indication is required in the title or abstract.

2a. For studies involving vertebrates animal and cell lines- The Reporting Summary should include whether sex was considered in the study design.

Response: Not applicable. This study did not involve vertebrate animals or cell lines.

2b. For studies involving human research participants- The Reporting Summary should include whether sex and/or gender was considered in the study design and whether sex and/or gender of participants was determined based on self-report or assigned (and methodology used).

Response: Sex was considered in the study design and included as a baseline covariate in the adjusted analyses. Sex information was obtained from the SNDS administrative records, where it is recorded as part of routinely collected health insurance data; it was not self-reported for the purpose of this study. Gender identity was not available in the SNDS and therefore could not be analyzed separately.

3. Data should be reported disaggregated for sex and gender where this information has been collected and consent has been obtained for reporting and sharing individual-level data; disaggregated numbers for individual experiments must be provided in the source data as appropriate whereas overall numbers may be provided in the Nature Portfolio Reporting Summary.

Information on the 3 points above should be included in the revised manuscript and detailed in the cover letter. In addition, please note that if sex- and gender-based analyses have been performed a priori, results should be reported regardless of positive or negative outcome. We discourage conducting post hoc sex- and gender-based analysis if the study design is insufficient (for example, low sample size) to enable meaningful conclusions. If no sex- and gender-based analyses have been performed, please indicate the reasons for the lack of these analyses in the Reporting Summary.

Response: Sex was collected in the SNDS and is reported in the baseline characteristics, including disaggregation by study group. Sex was also included as an adjustment covariate in the main analyses. No a priori sex-specific effect analyses were planned, and we did not perform post hoc sex-stratified analyses because the study was not designed to support meaningful sex-specific causal conclusions.

Reviewers' Comments:

Reviewer #1 (Remarks to the Author):

The authors have substantially revised the manuscript in response to the reviewers' concerns. Overall, the response letter appropriately acknowledges the main limitations of the study, particularly residual confounding, lack of direct ECOG performance status, incomplete tumor burden and PD-L1 information, and the possibility that vaccination may partly reflect preserved functional status and continued healthcare engagement rather than a vaccine-specific biological effect.

The revised analyses broadly address the key editorial and reviewer requests. The authors expanded adjustment for confounding using multiple SNDS-based proxies for frailty, performance status, disease burden, healthcare utilization, and health-seeking behavior. They also added cancer-specific mortality, non-COVID-19 mortality, rwPFS analyses, and additional negative-control outcomes. Importantly, they have tempered the interpretation of the findings and now frame the results more cautiously, emphasizing that the observed early survival associations do not establish improved antitumor efficacy or a causal vaccine effect.

Before submission, I would still recommend minor editorial refinement to improve clarity and tone, reduce repetition, correct language issues, and avoid overly confirmatory wording. However, the overall scientific positioning is now much more balanced and aligned with the reviewers' concerns.

Response: We thank the reviewer for this positive assessment and constructive recommendation. We have further revised the manuscript to improve clarity, tone and readability, reduce repetition, correct language issues, and avoid wording that could be interpreted as overly confirmatory. In particular, we further softened causal language throughout the Abstract, Discussion and Clinical implications sections. We also corrected wording related to residual confounding and streamlined repeated statements regarding the non-specificity of the observed associations.

Reviewer #2 (Remarks to the Author):

Thanks for making substantial improvement in the manuscript. The important alignment here is the acknowledgement that similar early patterns with non-mRNA COVID-19 pneumococcal and other non-COVID adult vaccinations which argue against an mRNA vaccine specific biological effect is particularly important to the interpretation of the data and conclusions.

Response: We thank Reviewer #2 for the careful reassessment and for highlighting what we agree is now a central interpretive point of the study: the early survival associations observed after peri-ICI mRNA COVID-19 vaccination were not specific to mRNA COVID-19 vaccines, but were also observed, with similar timing, after non-mRNA COVID-19 vaccination, pneumococcal vaccination, and other adult vaccinations. We agree that this finding argues against a strictly mRNA vaccine-specific biological effect and has been placed at the center of the interpretation.

Added to Discussion: *"The modest and transient survival differences observed in this study should be interpreted cautiously, because similar early patterns observed with non-mRNA COVID-19 vaccination, pneumococcal vaccination, and other non-COVID adult vaccinations argue against an mRNA vaccine-specific biological effect."*

Major comments:

1. The quantification of residual confounding by performance status (using ECOG proxies) still needs to be addressed. The use of ECOG proxies and collapsing this into binary indicators has the potential to misclassify many patients.

1.1 I would comment on what you would expect to see (ECOG ≥ 2) in a real world metastatic cancer population starting ICI (would this not be expected to be much higher than 19%).

Response: Indeed, the binary SNDS-derived proxy cannot directly capture Eastern Cooperative Oncology Group performance status (ECOG PS) and may misclassify patients. We have clarified this in the Discussion. In our cohort, this proxy identified 19.3% of patients overall, 23.9% of patients with metastatic cancer, and 25.6% of patients with lung/respiratory cancers. These values should not be interpreted as the true prevalence of ECOG PS ≥ 2 , but rather as the prevalence of claims-detectable poor functional status. They are nevertheless broadly consistent with real-world ICI-treated populations, in which approximately one-quarter to one-third of patients may have poor performance status (ECOG PS ≥ 2) or trial-ineligibility criteria related to ECOG PS ≥ 2 or organ dysfunction. Importantly, ECOG PS ≥ 2 is a strong adverse prognostic factor and may influence both trial eligibility and treatment selection in routine practice, supporting the plausibility that patients with ECOG PS 3–4 represent only a limited proportion of patients initiating ICI.

Added to Limitations: *"The SNDS-derived poor-performance-status proxy should not be interpreted as a direct measure of Eastern Cooperative Oncology Group (ECOG) PS. Its prevalence was 19.3% overall, 23.9% in metastatic cancers, and 25.6% in lung/respiratory cancers, broadly consistent with estimates from real-world ICI-treated populations in which approximately one-quarter to one-third of patients may have ECOG PS ≥ 2 or related trial-ineligibility criteria. However, because ECOG PS ≥ 2 influences treatment selection in routine practice, patients with ECOG PS 3–4 are expected to represent only a limited proportion of patients who actually initiate ICI.¹⁹⁻²¹ »*

References Added:

- Parikh, R.B., et al. Uptake and Survival Outcomes Following Immune Checkpoint Inhibitor Therapy Among Trial-Ineligible Patients With Advanced Solid Cancers. *JAMA Oncology* **7**, 1843 (2021).
- Meyers, D.E., et al. Impact of Performance Status on Survival Outcomes and Health Care Utilization in Patients With Advanced NSCLC Treated With Immune Checkpoint Inhibitors. *JTO Clinical and Research Reports* **4**, 100482 (2023).
- Kapoor, A., et al. Immune checkpoint inhibitors in patients with solid tumors and poor performance status. *Medicine* **100**, e25115 (2021).

1.2 1.2 Can you perform an E-value analysis for each of the reported hazard ratios to quantify how strong unmeasured confounding would need to be to explain away the association.

Response: We have now calculated E-values for the hazard ratios (HR) reported of the effect of mRNA vaccination in the pre-ICI and post-ICI analysis on overall death, with confidence limits closest to the null, to quantify sensitivity to residual unmeasured confounding. For protective associations, HR were inverted before applying the standard E-value formula.

Added to Methods: *"We calculated E-values for the hazard-ratios (HR) quantifying the association between mRNA COVID-19 vaccination and mortality, and the 95% confidence limits closest to the null to quantify sensitivity to residual unmeasured confounding. For protective associations, HR were inverted before applying the standard E-value formula. Lower E-values indicate that weaker unmeasured confounding could fully explain the observed association."*

Added to Results:

"E-values [confidence limit closest to the null] were modest for these associations: 1.36 [1.26] at 1 and 3 months, 1.20 [1.00] at 6-months, supporting cautious interpretation given the possibility of residual unmeasured confounding."

"E-values were modest for these associations: 1.51 [1.41], and 1.46 [1.26] at 3-months, and 6-months, respectively."

"E-values were modest for these associations: 1.56 [1.46], 1.58 [1.39], and 1.44 [1.26] for the corresponding point estimates, respectively."

1.3 Can you model distributions of unmeasured ECOG and tumor burden in the vaccinated vs unvaccinated groups? Both of these would provide further clarity as to whether the residual confounding is small enough to preserve the association of large enough to explain it.

Response: We agree that differences in true ECOG PS and tumor burden between vaccinated and unvaccinated patients could clarify the extent of residual confounding. However, these variables are not directly measured in the SNDS. Modeling their distributions would therefore require unverifiable assumptions about both their prevalence and their joint associations with vaccination and mortality, which could be misleading. Instead, we added E-value analyses (see response to 1.2, just above) to quantify the strength of residual unmeasured confounding needed to fully explain the observed associations, and further emphasized in the Discussion that unmeasured ECOG PS, tumor burden, disease trajectory and clinician-assessed prognosis may still explain part or all of the modest early survival associations observed.

Added to discussion:

"The SNDS-derived poor-performance-status proxy should not be interpreted as a direct measure of Eastern Cooperative Oncology Group performance status (ECOG PS). Its prevalence was 19.3% overall, 23.9% in metastatic cancers, and 25.6% in lung/respiratory cancers, broadly consistent with estimates from real-world ICI-treated populations in which approximately one-quarter to one-third of patients may have ECOG PS ≥ 2 or related trial-ineligibility criteria."¹⁹⁻²¹

"Although adjustment on a large number of potential confounders, control exposures, and control outcomes reduce some concerns, these approaches cannot exclude residual confounding, in particular by evolution of performance status, tumor burden, disease trajectory, or clinician-assessed prognosis."⁹

2. The cloning censory weighting/inverse probability of censoring weighting analysis does not completely address the time-varying confounding. I would still be concerned that clinical deterioration (i.e. between billing events) such as a patient progressing rapidly in the weeks following ICI may not live long enough to be vaccinated or generate a billing signal before dying. Please also comment on use of early ICI discontinuation which could be due to toxicity or lack of response/progression. It appears this was not treated as a time-varying covariate in the IPCW model. Other variables such as cancer-specific markers of progression/response including new imaging change in chemotherapy which are not captured in SNDS but could affect both new vaccine update and mortality. Can you add additional sensitivity analyses to help address this by: 1) restricting post-

ICI analysis to patients remaining on ICI through day 100 without early discontinuation 2) Perform survival analyses to address time-dependent exposure and covariates at day 30, 60 and 90 with appropriate adjustment 3) Consider continuation of ICI as a time-varying covariate.

Response: We acknowledge that we couldn't fully account for some of the time-varying confounding factors in the post-ICI analysis, in particular, rapid clinical deterioration, early progression, treatment changes, or radiographic progression that may occur between reimbursed care events and may influence both vaccination uptake and mortality. These processes are incompletely captured in the SNDS and could therefore contribute to residual time-varying confounding. We have therefore clarified this point in the Discussion.

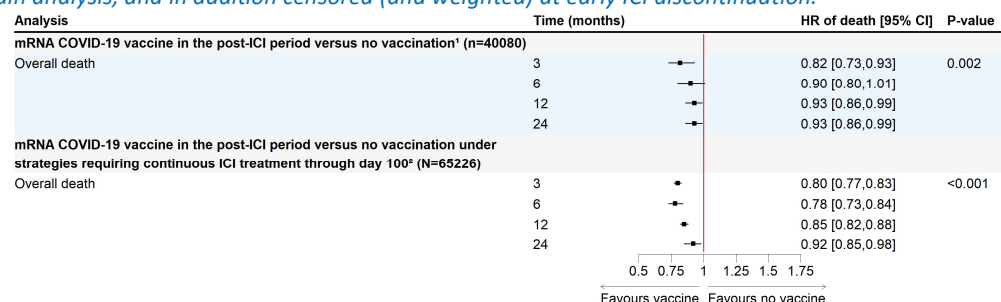
To address this concern, we performed two additional post-ICI sensitivity analyses. First, as suggested, we restricted the analysis to patients who had received no COVID-19 vaccine in the pre-ICI period and who were alive and still receiving ICI 100 days after ICI initiation; in this analysis, the index date was set at ICI initiation + 100 days. Because this analysis includes a selected population not identifiable at ICI initiation (alive and on ICI 100 days after ICI initiation), we interpret it cautiously and consider it only as a sensitivity analysis.

Second, as suggested, we performed an additional sensitivity analysis within the cloning-censoring-weighting target-trial emulation analysis, censoring (and weighting) at early ICI discontinuation. In this analysis, the strategies were modified to require both adherence to the assigned vaccination strategy and continuous ICI treatment through day 100. Accordingly, clones were censored at early ICI discontinuation during the first 100 days, in addition to censoring at deviation from the assigned vaccination strategy, and inverse probability censoring weights were recalculated to account for this additional censoring mechanism.

The results of these two sensitivity analyses were broadly consistent with the main post-ICI analysis and are now reported in Supplementary Figure 8.

Added to methods: *"Post-ICI sensitivity analyses accounted in addition for early ICI discontinuation, as a proxy of rapid clinical deterioration, early progression, treatment changes, or radiographic progression. First, among individuals with no COVID-19 vaccination in the pre-ICI period who were alive and still receiving ICI 100 days after initiation, we compared receipt of at least one dose of COVID-19 mRNA vaccine within the first 100 days after ICI initiation with no COVID-19 vaccination during the same period, using ICI initiation + 100 days as index date. Second, we performed an additional sensitivity analysis within the CCW target-trial emulation analysis, censoring (and weighting) at early ICI discontinuation also. In this latter analysis, the strategies required both adherence to the assigned vaccination strategy and continuous ICI treatment through day 100. Accordingly, clones were censored at early ICI discontinuation during the first 100 days, in addition to censoring at deviation from the assigned vaccination strategy, and inverse probability censoring weights were recalculated to account for this additional censoring mechanism."*

Added to Supplementary Data: *"Supplementary Figure-8. Association between post-ICI mRNA COVID-19 vaccination (vs. no) and overall survival. The first analysis was performed among patients who were alive and still receiving ICI 100 days after initiation, and compared receipt of at least one dose of COVID-19 mRNA vaccine within the first 100 days after ICI initiation with no COVID-19 vaccination during the same period (index date= ICI initiation+100 days). The second analysis used the cloning-censoring-weighting approach as described in the post ICI main analysis, and in addition censored (and weighted) at early ICI discontinuation."*



Added to Results: *“Post-hoc sensitivity analyses accounting for early ICI discontinuation showed results broadly consistent with the main post-ICI analysis (Supplementary Figure-8).”*

3. The post-ICI effect larger than the pre-ICI effect feels internally consistent with a true vaccine-biological-immunological mechanism. Does this not support residual section. This would seem to warrant a more detailed discussion.

Response: We agree that the larger early association observed in the post-ICI analysis could be viewed as compatible with a vaccine-ICI biological interaction. We have now discussed this more explicitly. However, we believe this pattern should not be overinterpreted as evidence of a true immunological priming effect, because the post-ICI setting is also the most vulnerable to healthy-vaccinee and care-engagement bias: patients must remain alive, clinically stable, and connected to care long enough to receive vaccination during the grace period. In addition, broadly similar early survival patterns were observed with non-mRNA COVID-19 vaccines and other adult vaccines, arguing against a strictly mRNA-specific biological mechanism. We therefore revised the Discussion to state that a biologic interaction remains possible, but that residual time-varying confounding and non-specific correlates of vaccination remain plausible explanations.

Added to discussion: *“A biologic interaction between vaccination-related immune activation and ICI remains possible, and the larger early association observed for post-ICI vaccination is compatible with this hypothesis. However, this pattern is also compatible with stronger healthy-vaccinee and care-engagement bias during the post-ICI grace period, and the broadly similar associations observed with non-mRNA COVID-19 vaccines, pneumococcal vaccination, and other adult vaccines prevent attributing the survival pattern to an mRNA-specific mechanism.”*

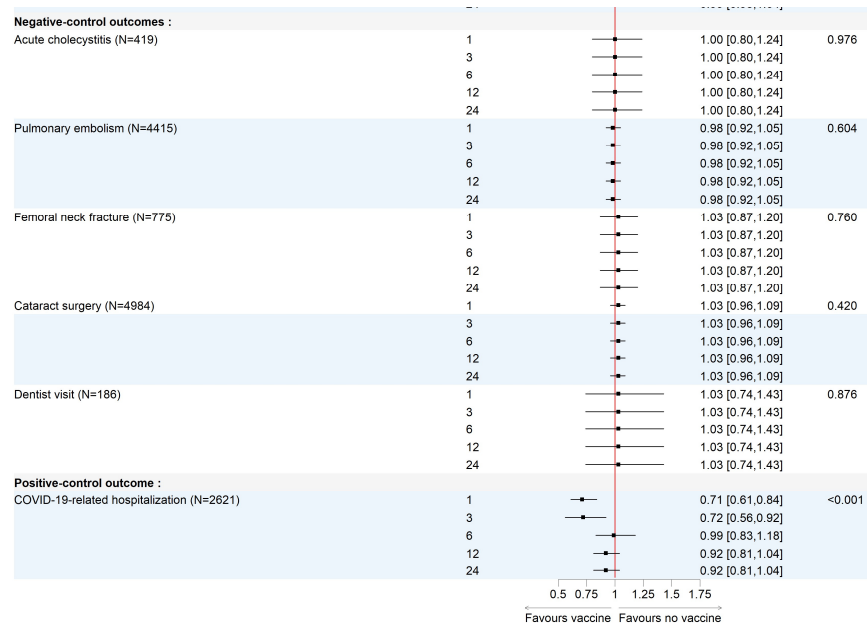
4. Thanks for adding additional negative control outcomes and acknowledging the limitations however I would argue that these are not sufficiently distinct to performance status to act as falsification tests. Can you include both true positive and negative controls? e.g. positive control (COVID-19 in weeks after pre-ICI vaccination), negative controls: routine office procedures, dental appointments etc.

Response: We added a positive-control outcome — COVID-19-related hospitalization — and two negative-control outcomes distinct to performance status as suggested — dentist visit and cataract surgery. These results are now reported in **Figure-4** and discussed in the revised manuscript.

Added to methods: *“We also tested alternative exposure windows of 50 days, negative-control outcome analysis using acute cholecystitis, pulmonary embolism, femoral neck fracture, [dentist visit and cataract surgery](#) to investigate residual confounding [and positive-control outcome using COVID-19-related hospitalization](#).”*

Added to results : *“We also assessed potential residual confounding’s using negative-control outcomes, i.e. evaluating whether the occurrence of acute cholecystitis, pulmonary embolism, femoral neck fracture, [dentist visit and cataract surgery](#) differed between individuals who were COVID-19 mRNA vaccinated in the pre-ICI period and those who were not; no significant difference was detected (Figure-4). [In contrast, the positive-control outcome analysis \(COVID-19-related hospitalization\) showed a time-dependent protective effect of COVID-19 mRNA vaccine.](#)”*

Added to Figure-4: *“**Figure 4. Secondary and sensitivity analyses, including negative-control [and positive-control outcomes](#): associations of pre-ICI exposures with overall mortality.** Exposures were assessed in the 100 days before ICI initiation (50-day window where indicated): COVID-19 vaccination (mRNA, non-mRNA), pneumococcal vaccination, any non-COVID-19 vaccination, and documented COVID-19 infection. Vaccine analyses compare vaccinated vs not vaccinated in the same window; infection analyses (restricted to unvaccinated patients) compare documented infection vs none. The 50-day mRNA analysis was restricted to ICI starts from 28 Dec 2020 to 11 May 2023. Sample sizes are before weighting.”*



5. The fact that survival associations are not exclusive to mRNA COVID-19 vaccines seems to be a major point of this paper and this should affect the order and priority of how conclusions are framed.

Response: We agree. We have reframed the Abstract, Discussion, Clinical implications and Conclusion to give greater priority to the lack of specificity of the association to mRNA COVID-19 vaccination. Accordingly, the conclusion now emphasizes that the findings are reassuring regarding peri-ICI vaccination, but do not establish that mRNA COVID-19 vaccination enhances ICI efficacy.

In Abstract: *“Similar early patterns with non-mRNA COVID-19 and other adult vaccines were identified and suggest non-specific effects or healthy vaccinee effect rather than a specific mRNA COVID-19 vaccine effect.”*

In Discussion: *“The modest and transient survival differences observed in this study should be interpreted cautiously, because similar early patterns observed with non-mRNA COVID-19 vaccination, pneumococcal vaccination, and other non-COVID adult vaccinations argue against an mRNA vaccine-specific biological effect. These findings do not establish that vaccination improves ICI efficacy, but they can at best be viewed as hypothesis-generating for prospective mechanistic or randomized studies.”*

6. I am concerned that the real-world progression free survival endpoint does not provide independent confirmation of the survival finding. You should consider cleaning up discontinuation causes where possible. Such as excluding planned stops, identification of toxicity associated discontinuations as well as presenting time to ICI discontinuation and time to death as separate outcomes. Finally the readership should be clear that rwPFS is not a measure of anti-tumor efficacy.

Response: We have revised the text to avoid presenting rwPFS as independent confirmation of improved antitumor efficacy. In the SNDS, treatment discontinuation cannot be reliably attributed to progression, toxicity, planned treatment completion, hospitalization, death, or care-pathway changes; therefore, further “cleaning” of discontinuation causes would require assumptions that may introduce misclassification. We now explicitly define rwPFS as time to ICI discontinuation or death and interpret it only as a supportive real-world endpoint, not as a direct measure of tumor response or ICI efficacy. We also clarified in the Discussion and Clinical implications that cancer-specific mortality and rwPFS findings do not establish improved antitumor efficacy.

Added in Discussion: *“In addition, rwPFS was based on ICI discontinuation or death and should not be interpreted as a direct measure of antitumor efficacy, because SNDS does not reliably distinguish progression-related discontinuation from toxicity, planned treatment stop, hospitalization, death, or changes in care pathway.”*

7. Bias in Cancer-specific mortality reporting. Can you report the absolute number of cancer deaths contributing to each analysis (not only hazard ratios) to make the statistical power for the cancer specific endpoints more transparent.

Response: Done. These numbers have now been added to the legend of figures 3 and 5.

Added to Figure-3 and Figure-5:

***“Figure 3. Association of pre-ICI mRNA COVID-19 vaccination (≥ 1 dose within 100 days before ICI initiation) versus no COVID-19 vaccination with survival.** Weighted survival curves are shown for overall **death** (A) non-COVID-19 death accounting for COVID-19 death as a competing event (B), and for cancer death accounting for non-cancer death as a competing event (C); numbers at risk displayed beneath the curves in panels A-C correspond to weighted patient counts. Panel (D) presents the forest plot of the primary and secondary analyses, with the number of included patients before weighting shown for each analysis. **A total of 58,723 deaths, 48,580 non-COVID-19 deaths and 42,285 cancer deaths were observed during follow-up.** **rwPFS** stands for real-world progression free survival.”*

***“Figure 5. Association of post-ICI mRNA COVID-19 vaccination (≥ 1 dose within 100 days after ICI initiation) versus no COVID-19 vaccination with survival.** Weighted survival curves are shown for overall **death** (A), non-COVID-19 death treating COVID-19 death as a competing event (B), and for cancer death accounting for non-cancer death as a competing event (C). Panel (D) shows hazard ratios (HRs) with 95% confidence intervals from the primary and secondary (cancer-site) analyses of post-ICI mRNA COVID-19 vaccination. Under the CCW approach, each eligible patient is cloned at baseline into both strategies; numbers at risk therefore start at $n=65,226$ in each arm. **A total of 40,723 deaths, 33,373 non-COVID-19 deaths and 29,058 cancer deaths were observed during follow-up.** **rwPFS** stands for real-world progression free survival.”*

8. Although the SNDS may have minimal intended loss to follow-up there are still ways that this will occur and this should be references in more detail. Perhaps a statement to indicate that loss to follow-up for all-cause mortality is expected to be low but cannot be assumed to be zero.

Response: We have revised the Methods to avoid implying that loss to follow-up is impossible. Because the SNDS covers nearly all residents in France and death dates are centrally recorded, loss to follow-up for all-cause mortality is expected to be very low. However, it cannot be assumed to be zero, for example in cases of emigration or administrative linkage issues. We now state this explicitly.

Added to Methods: *“In the SNDS, loss to follow-up for all-cause mortality is expected to be very low because the national claims database covers nearly all individuals residing in France, serves as the basis for healthcare reimbursement, and records dates of death through linkage to the national death register. However, loss to follow-up cannot be assumed to be zero, for example in cases of emigration or administrative linkage failure.”*

9. Overcall that a subgroup analysis showing a larger post-ICI effect amongst patients not previously vaccinated indicates priming. Patients who received first COVID-19 mRNA vaccine after ICI initiation later in 2021 were those who had potentially delayed vaccination.

Response: We have revised the wording throughout to avoid implying that the subgroup analysis demonstrates immune priming. The subgroup analysis was intended only to describe whether the post-ICI association differed according to absence of vaccination in the 100 days before ICI initiation, not to identify patients who had never been vaccinated or to prove a first-dose priming effect. We now interpret this finding cautiously. We replaced “to explore the potential benefit of an additional post-ICI vaccine dose” with *“to describe whether the post-ICI association differed according to vaccination status in the 100 days before ICI initiation.”*

10. Provide more transparency as to how patients who die during the grace period are handled. It appears these patients are censored at death however it is unclear whether these deaths contribute to the no vaccination arm event count or whether the PICW weights correctly handle the dependency between death (which clearly precludes future vaccination) and the censored event (failure to vaccinate by day 100)

Response: We have clarified this in the Methods. In the post-ICI CCW analysis, follow-up began at ICI initiation for both cloned strategies. Death was the outcome, thus patients dying during the 100-day grace period were not censored but accounted as events. More precisely, patients who died before vaccination and before day 100 contributed as events to both strategy arm(s) (i.e. arms in which they remained compatible with, up to death), and those who died after being vaccinated with the first 100 days contributed only to the vaccination-within-100-days arm.

Added to Methods: *“Deaths occurring during the 100-day grace period were counted as events in the strategy arms they were compatible with, up to death, i.e. in both arms if death occur without being vaccinated before, and in the vaccination arm only if they die after being vaccinated.”*

Additional comments:

1. Missing data is stated as being not applicable in methods but SNDS records can have missing values for patients with missing residential data, income status and region. Can you specify missingness and how it might impact the study?

Response: We agree that sociodemographic and geographic variables in claims databases may have missing data. In our cohort, missing data were present in three variables at a very low percentage: volume of inclusion in the centre (0.3%), deprivation index (1.9%) and region of residence (0.03%). Because these variables were used as adjustment covariates rather than primary exposure or outcome variables, and the proportion of missingness was very low, we used simple imputation methods (median for ordinal variables and mode for categorical variables) to preserve the full study population. Given the very small proportion of missing data, these imputations are unlikely to have materially affected the study results.

Supporting reference: Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials—a practical guide with flowcharts. *BMC medical research methodology*, 17(1), 162.

Added to Methods: *“Missing values were imputed using the median for ordinal variables and the mode for categorical variables.”*

Added to Table-1: *“Missing data were limited to volume of inclusion in the center (0.3%), deprivation index (1.9%), and region of residence (0.03%). Missing values were imputed using the median for ordinal variables and the mode for categorical variables.”*

2. Provide justification for using Fine-Gray models for pre-ICI period and Cox models otherwise for competing risk specification.

Response: We clarified the competing-risk approach. Cause-specific Cox models were used as the primary analysis because our aim was to estimate the direct effect of vaccination on the event of interest, not mediated by competing events. Fine-Gray models were added as a sensitivity analysis only in the simpler pre-ICI IPTW setting, where vaccination was fixed at baseline. They were not used in the post-ICI CCW analysis because the analysis uses a time-dependent exposure and covariates integration, which is not compatible with Fine and Gray models. References added below accordingly.

Added to methods: *“Cause-specific Cox models were used throughout as the primary competing-risk approach because our aim was to estimate the direct effect of vaccination on the event of interest, not mediated by competing events. Fine-Gray models were applied as sensitivity analyses only in the pre-ICI IPTW setting, where exposure was fixed at baseline, and not in the post-ICI CCW analysis because this latter analysis uses a time-dependent exposure and covariates integration, which is not compatible with Fine and Gray models.”³⁰*

References Added:

- Austin, P.C., Lee, D.S. & Fine, J.P. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* **133**, 601-609 (2016).

3. In methods specify the number of bootstrap replicates and whether bootstrap was performed on weighted or unweighted sample with stratified resampling by exposure

Response: We have now added this information in the Methods section.

Added to Methods: *“We reported effect estimates primarily as hazard ratios with 95% confidence intervals (95%CI) and complemented with absolute differences in survival probabilities at 1 (for the pre-ICI analyses only), 3, 6, 12 and 24 months and 95%CI derived using bootstrap resampling on the weighted sample (1000 and 500 replicates for the pre-ICI and post-ICI analyses, respectively).”*

4. In results it is confusing whether 27,395 or 27,463 is the analysis sample

Response: The number 27,463 corresponds to all patients with ≥ 1 mRNA COVID-19 vaccine dose within 100 days before ICI initiation in the descriptive table, including 68 patients who also received a non-mRNA COVID-19 vaccine.

Now in Legend of Figure-2: *“Patients receiving both mRNA and non-mRNA COVID-19 vaccines were included in the mRNA COVID-19 vaccine group for descriptive purposes only (n=68 within 100 days before ICI start and n=25 within 100 days after ICI start). For the primary pre-ICI analysis, patients with mixed mRNA/non-mRNA schedules or only non-mRNA vaccination within the pre-ICI window were excluded, resulting in an mRNA-only analysis sample of 27,395 patients rather than the 27,463 patients shown in the descriptive table.”*

5. Residual confusion in discussion should be residual confounding.

Response: Done

6. Additional copy editing for other typos (i.e. address)

Response: Done

Reviewer #3 (Remarks to the Author):

I thank the authors for their careful revision of the manuscript. My previous comments have been satisfactorily addressed. The inclusion of additional analyses with appropriate adjustment for confounders using proxy variables available in SNDS, as well as the expansion of secondary endpoints and incorporation of additional negative control outcomes, have strengthened the study and improved its overall rigor. I have no further comments.

Response: We thank Reviewer #3 for the positive assessment of the revised manuscript. We are pleased that the additional confounder-adjusted analyses, expanded secondary endpoints, and added negative control outcomes addressed the reviewer's prior concerns and strengthened the rigor of the study. We appreciate the reviewer's careful evaluation and constructive feedback.

Revisions are in blue in the manuscript

Major comments

1. The E-values undercut the headline associations more than the current wording conveys. Given that the healthy-vaccinee/care-engagement effect you invoke is almost certainly stronger than this, the honest reading is that the 6-month and later associations are statistically present but causally uninterpretable and this should be declared upfront.

Response: We have revised the Discussion to make the causal limitation explicit.

Added to Discussion: *"E-values were modest, indicating that relatively weak unmeasured confounding could explain these associations; therefore, the 6-month and later associations should be considered statistically detectable but causally uninterpretable, particularly given their vulnerability to healthy-vaccinee and care-engagement confounding."*

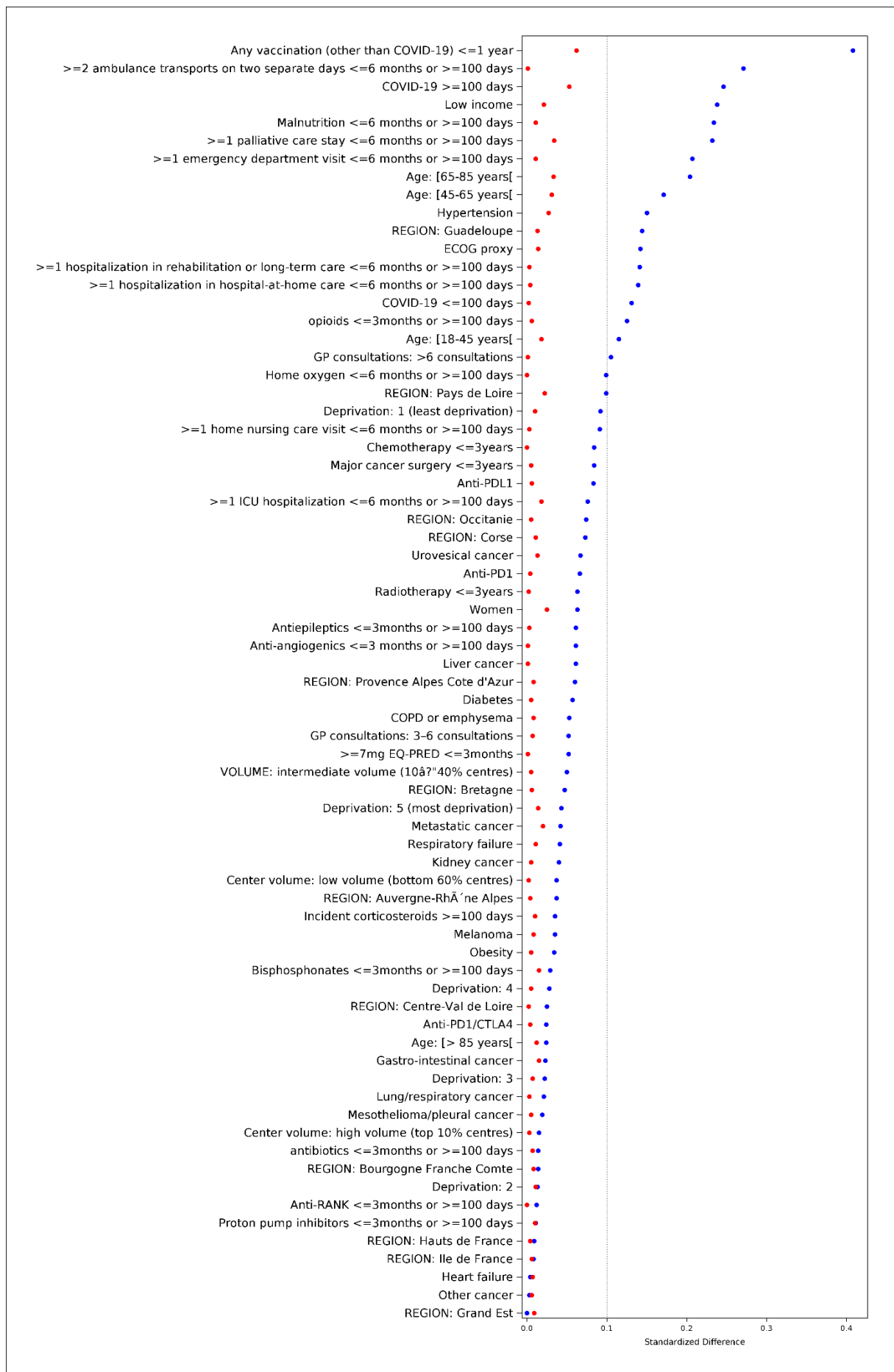
2. Please distinguish "non-specific immune effect" from "healthy-vaccinee/confounding." The manuscript at times uses "non-specific effects" to mean two very different things: (a) genuine non-antigen-specific biology such as trained innate immunity or bystander immune stimulation, which would be a real effect, and (b) healthy vaccinee selection and care engagement, which is confounding. Both produce the cross-vaccine concordance you observe, so the data cannot separate them, but they carry opposite implications for the Grippin hypothesis (one partially supports a biological, if non-mRNA-specific, effect; the other negates it). I would make this distinction explicit and acknowledge that your design cannot adjudicate between them.

Response: We clarified this distinction in the Discussion. We now separate genuine non-antigen-specific immune biology from healthy-vaccinee/care-engagement confounding and state that our design cannot distinguish them.

Added to Discussion: *"These concordant cross-vaccine patterns may reflect either genuine non-antigen-specific immune effects, such as bystander non-specific immune stimulation, or non-causal correlates of vaccine uptake, including healthy-vaccinee selection and care engagement. These explanations have opposite implications for the Grippin et al. hypothesis,⁸ and our observational design cannot adjudicate between them."*

3. Residual imbalance in the post-ICI analysis deserves more weight. You note that after weighting, calendar year of ICI initiation and prior non-COVID vaccination remained imbalanced (SMD >0.1; Supplementary Figure 3). Calendar time is a particularly worrying residual confounder here, because it jointly drives vaccine availability/uptake and evolving ICI practice and outcomes, and because the preICI unvaccinated comparator becomes an increasingly atypical group in 2022–2023. Please discuss the direction and plausible impact of this residual imbalance rather than only listing it, and consider a sensitivity analysis additionally finely stratified or with a tighter calendar-time restriction.

Response: We have expanded the Limitations to discuss the potential impact of residual calendar-time imbalance. We also clarified that the 2020–2021 restricted post-ICI analysis (Supplementary Figure 7) provides a tighter calendar-time sensitivity analysis; in this restricted analysis, all covariates were well balanced after weighting and results showed a similar early pattern to the main analysis. For reviewer assessment, we now provide the corresponding balance plot, showing all standardized differences below 0.10 after weighting (see below).



Added to Limitations: *“Residual imbalance in calendar year and prior non-COVID-19 vaccination persisted after weighting in the post-ICI analysis. Calendar time may have biased estimates through changes in vaccine uptake, COVID-19 epidemiology, ICI practice, and outcomes, although the direction of bias is difficult to predict. This concern was partly addressed by the 2020–2021 restricted analysis, in which all variables were well balanced after weighting and results showed a similar early pattern (Supplementary Figure-7).”*

4. The negative controls are still not well matched to the confounding of concern. As raised previously, cataract surgery, dental visits, cholecystitis, PE, and femoral neck fracture are only weakly tied to the performance status/tumor trajectory gradient that drives cancer mortality, so their null results provide limited falsification of the specific confounding pathway. Indeed, the slightly elevated HRs for elective procedures (cataract 1.03, dentist 1.03) could be read as a faint healthy-vaccinee signal rather than reassurance. I would temper the reassurance drawn from these controls and acknowledge that an ideal negative control an outcome strongly linked to performance status but not to vaccination is simply not available in the SNDS.

Response: We tempered the interpretation of the negative-control analyses. We now state that their null results do not rule out the specific performance-status/tumor-trajectory confounding pathway.

Added to Limitations: *“The absence of association with negative-control outcomes provides only limited reassurance, because these outcomes may not fully capture the PS and tumor-trajectory gradients most relevant to cancer mortality. An ideal negative-control outcome strongly linked to these gradients, but unrelated to vaccination, was not available in the SNDS.”*

5. Single-dose predominance and absence of dose-response argue against a biological mechanism and should be stated as such. Most "vaccinated" patients received a single dose (median 1 [1–1]) within the window. A genuine immune-priming effect would be expected to show some dose-response. If feasible, a dose-stratified analysis would strengthen the non-specificity argument; if not feasible, please note explicitly that the lack of a tested dose-response is itself evidence against an antigen-specific priming effect and a limitation of the window-based exposure definition.

Response: We did not perform dose-stratified analyses because most vaccinated patients received a single dose within the peri-ICI window. We therefore tempered the biological interpretation and we now further expanded this as a limitation.

Added to Limitations: *“Second, our exposure definitions relied on prespecified 100-day peri-ICI windows to further investigate Grippin’s findings,⁸ and most vaccinated patients received only one dose within these windows. This limited our ability to assess dose-response, dose sequence, or precise timing, thereby limiting interpretation in terms of antigen-specific immune priming.”*

6. You interpret the null association for documented preICI COVID-19 infection as evidence against infection-driven immune stimulation. However, infection carries competing harms (treatment disruption, severe illness), so a null could reflect cancellation of a harmful infection effect against any beneficial immune stimulation effect rather than the absence of immune stimulation. Please add this caveat.

Response: We added this caveat and softened the interpretation of the COVID-19 infection analysis.

Added to Discussion: *“Notably, we did not observe a comparable survival beneficial association in analyses with documented COVID-19 infection as exposure in the same pre-ICI window, which makes a purely infection-driven stimulation explanation less likely. However, this null finding should be interpreted cautiously, because potential immune stimulation from infection could have been offset by competing harms, including severe illness, treatment disruption, or COVID-19–related mortality.”*

7. Title and abstract framing. Given the Grippin context and the current climate, the neutral title and the abstract's lead with protective HRs invite the "vaccination improves ICI outcomes" misreading that the body of the paper carefully repudiates. I would surface the non-specificity/null-for-specificity message earlier, ideally signaling in the title or first abstract sentence that the early associations are not specific to mRNA vaccines and are consistent with healthy vaccinee effects.

Response: We have revised the abstract framing to reduce the risk of interpreting the findings as evidence that vaccination improves ICI outcomes. We have also changed the title, following the editors recommendations.

Modified in Abstract : *"Similar early patterns with non-mRNA COVID-19 and other adult vaccines suggest modest, transient associations or healthy vaccinee effects, rather than a specific mRNA COVID-19 vaccine effect."*

Minor comments:

1. The negative and positive control outcomes seem to use a single constant hazard ratio over time, while the main outcomes allow the effect to vary with time, so please either explain this or model them the same way.

Response: For all the survival models used, we checked the proportional hazard assumption by scaled Schoenfeld residuals. For the negative and positive control outcomes, this assumption was met ; thus we reported a single constant HR overtime. We clarified that time-varying HRs were reported only if the proportional hazard assumption was not met.

Added to Methods : *"Proportional hazards assumptions were assessed by scaled Schoenfeld residuals. When this assumption was not met, we modeled time-varying effects by splitting the follow-up into intervals in which the proportional hazards assumption was verified and held, and by including interactions between exposure and time such as t or log(t), when appropriate, to obtain time-varying hazard ratios at clinically relevant time points. Otherwise, we reported a single HR, considering the effect was not time-dependent."*

2. The absolute survival differences are small (about 1 to 1.5% preICI and 2.6 to 3.4% post-ICI), and recommend that you keep this central in the abstract, where the hazard ratios currently dominate.

Response: Because of the abstract word-count limit, we cannot add the full set of absolute survival differences, but we revised the concluding sentence to explicitly characterize the observed associations as modest and transient (see above).

3. What about adjustment for the many time points, subgroups, and outcomes tested? A sentence reinforcing that analyses are exploratory would help.

Response: Done

Added to Methods: *"Two-sided $P < 0.05$ were considered statistically significant; no adjustment for multiple testing was done as secondary, subgroup, and sensitivity analyses were considered exploratory."*

4. For the post-ICI subgroup, please say clearly in the main text that "preICI unvaccinated" is not the same as vaccine-naive and is tangled up with when people happened to get vaccinated.

Response: Done

Added to Methods: *"In this analysis, "pre-ICI unvaccinated" refers only to the absence of COVID-19 vaccination during the 100-day pre-ICI window, not to vaccine-naïve status."*

5. For rwPFS, note that ICI discontinuation itself may differ between vaccinated and unvaccinated patients and could bias the result.

Response: We clarified in the Limitations that rwPFS may be biased because ICI discontinuation itself may differ by vaccination status.

Added to Limitations: *"Moreover, ICI discontinuation itself may differ by vaccination status and could therefore bias rwPFS estimates."*

6. The performance-status proxy discussion is good but repetitive, and could be more concise.

Response: We agree and have shortened the performance-status proxy discussion in the Limitations.

7. Be clear which analyses were run in SAS versus R, briefly justify the different bootstrap replicate counts (1000 vs 500)

Response: We clarified which analyses were performed in SAS versus R. The post-ICI bootstrap was initially limited to 500 replicates because of computational constraints; we have now rerun it with 1,000 replicates, with similar results, and report 1,000 replicates throughout.

Added in Methods:

"We reported effect estimates primarily as hazard ratios with 95% confidence intervals (^{95%}CI) and complemented with absolute differences in survival probabilities at 1 (for the pre-ICI analyses only), 3, 6, 12 and 24 months and ^{95%}CI derived using bootstrap resampling on the weighted sample (1000 replicates for both the pre-ICI and post-ICI analyses)."

"Data management, including cohort construction, was performed using SAS Enterprise Guide version 4.3. All statistical analyses, including weighting, survival models, bootstrap estimation of absolute survival differences, and figure generation, were performed using R version 4.2.1."

8. A few typos also remain ("residual confounding's" - line 166) and make sure the 27,463 vs 27,395 reconciliation reads consistently across Table 1, the flow chart, and the Figure 2 footnote.

Response: Done