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Designing and Analyzing Studies of COVID-19 and Post Acute Sequelae of SARS-CoV-2 among Immunocompromised individuals

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Despite the large-scale clinical trials of the effectiveness of COVID-19 vaccination in preventing severe disease and post-acute sequelae of SARS-CoV-2 (PASC) in 2020, observational studies of coronavirus disease 2019 (COVID-19) among transplant candidates and recipients remain important. Immunocompromised patients formed a very small proportion of patients included in COVID-19 trials and other analyses of large database analyses. Early data demonstrated increased severity and worse outcomes of COVID-19 in immunocompromised patients along with reduced vaccination responses.[7] Because of limited funding available for COVID-19 research targeting immunocompromised patients, we believe that observational studies regarding COVID-19 within the transplant community will remain relevant.

In two recent papers, Aslam et al.[8] and Sigler et al.[9] investigated the role of vaccination in preventing symptomatic COVID-19 among transplant recipients as well as in preventing PASC among those with prior COVID-19. Below, we summarize the challenges that arise in such research and approaches to addressing them. These studies made use of retrospective cohort designs,[10] in which, a cohort of patients is identified (e.g. by chart review) and retrospective information is collected over a specified time period. Retrospective designs are most useful when the important information is available on a sufficiently large number of patients to provide adequate precision. Analysis of observational studies always requires adjustment for potential confounding factors, such as demographic and clinical factors. One such factor is chronologic time itself—which impacted COVID-19 incidence as well as vaccination patterns. As age impacted time of eligibility for vaccination in 2021, analyses took into consideration this factor as well. Residual confounding may still arise from factors that cannot be easily measured (e.g. tendency to engage in health seeking behaviors). Only randomized studies are guaranteed to guard against unmeasured confounding.

In the case-control study design, which can also be based on retrospective data, cases (e.g. participants with disease history) are matched to controls (with no such history) on potential

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confounding factors.[11] One then estimates the ratio of the odds of exposure in cases and in controls. Prospective study designs can take more time to complete, but allow for more control over study visit times and data to be collected.

A key element of any design is selection of exposure variables (or randomized interventions), outcome variables, and predictors of exposures and outcomes. Study outcomes may be measured as times-to-events (e.g. symptomatic COVID-19), binary outcomes (e.g. presence/absence of PASC diagnosis within 6 weeks of COVID-19 onset), or categorical outcomes (e.g. mild, moderate, or severe COVID-19). Time-to-event analyses usually treat observations from participants who have not developed the endpoint by the end of the study as censored. Comparison is often made between characteristics of participants who develop disease at study time, t, and those of people who were at risk at t but had not yet developed disease (risk set).[12] Final analyses cumulate this effect over the entire follow-up period, using a method like proportional hazards (PH) regression.[12] This method assumes that the ratio of hazard rates (event rates) between two groups is constant over time. This assumption can be evaluated using the methods of Rulli et al.[13] Other model choices do not require it (Cheng et al. 2009).[14]

Baseline for research studies can be the time of start of an intervention (e.g. vaccination) or a specific chronologic time. In the Aslam et al. study, baseline was January 15, 2021—the first date that vaccination was available for any age group. Vaccination was included in regression models as a time-varying exposure; the time at which participants in a given age category entered the risk set (the set to which the person who had an event was compared) was the time at which people in an age category became vaccine eligible.

Often it is of interest to investigate the mechanisms by which effects of interventions arise. For example, Sigler et al. address the question: To what extent was the preventive effect of vaccination on PASC mediated through disease severity? In other words, did vaccination reduce odds of PASC directly, or indirectly by reducing disease severity, which in turn reduced the odds of developing PASC. Figure 1 illustrates the notion that vaccination could have both direct effects and effects mediated through disease severity (Valerie and Vanderwheele[15]). The central idea is that if vaccination and disease severity both reduce PASC, but the observed effect of vaccination on PASC is greatly reduced when the regression model adjusts for disease severity, then it is likely that the former mediates the effect of PASC. As these relationships are subject to confounding, all regression models must take this possibility into account. Figure 1 illustrates the potential confounding effect of gender, which can affect the probabilities of receiving vaccination, of developing severe disease, and of developing PASC.

FUTURE RESEARCH DIRECTIONS

Over time, many transplant recipients will get COVID-19 more than once and receive multiple COVID-19 vaccinations. By extending PH regression to this setting, one can estimate effects of exposures like vaccination or transplantation on the average number of COVID-19 events that have occurred over time, and also adjust for potential confounding factors.

Aslam et al. considered only vaccinations that took place prior to transplantation and only the first COVID-19 event. The time from vaccination to transplantation was variable, and hence so was the time from vaccination to start of immuno-suppression. To model the effect of time of transplantation and the interval from that time to first (and possibly subsequent) vaccination(s) on time-varying risk of COVID-19, we could include in Cox regression models, a time-varying binary indicator of whether or not the participants had received a transplant prior to each time of COVID-19 diagnosis. This relationship could be confounded by factors that are associated both with receiving a transplant and with the COVID-19 outcome. To adjust for confounders at baseline, we can add them as covariates in regression models; but if these factors are themselves time-varying we would need to use causal methods, such as marginal structural models for such adjustment.[16]

We note also that transplantation could potentially modify the effect of vaccination. And the duration of time from vaccination to transplantation might itself impact the extent of this modification. To assess whether transplantation increases the risk of COVID-19, we can include a time-varying indicator of the occurrence of transplantation by any time *t*. If available, we could use the degree of immune suppression both as a main effect on risk of COVID-19 and as a potential modifier of vaccination effect. We note that there is a potential for confounding of the effect of immune suppression on outcome, for example by factors that impact both the decisions to receive vaccination and to receive a transplant, or that impact either of these and the outcome. If confounding factors are time-varying (e,g, heath status) and the exposure is also time varying (e.g. vaccination or immune suppression), structural nested models may be useful.[17] For recurrent event analysis, adjustment for baseline confounding factors by including them in regression models models is straightforward. Adjustment for time-varying confounding in such models is also possible; this is an area of current statistical methods research.[18] As the potential for study of prevention modalities become increasingly rich over time, so will the opportunities for fruitful collaboration between clinical investigators and statisticians.

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Bibliography

1. Latif Farhana MD; Farr Maryjane A. M M C KJ, MD, MSc; Habal Marlena V., MD; Takeda Koji, MD, PhD; Naka Yoshifumi, MD, PhD;, Restaino Susan M S G, MD; Uriel Nir, MD, MSc: : Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019. . JAMA Cardiology 2020.
2. Pereira MR, Mohan S, Cohen DJ, et al. : COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant 2020.
3. Tschopp J, L'Huillier AG, Mombelli M, et al. : First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study. Am J Transplant 2020.
4. Fernandez-Ruiz M, Andres A, Loinaz C, et al. : COVID-19 in solid organ transplant recipients: A single-center case series from Spain. Am J Transplant 2020.
5. Kates OS, Haydel BM, Florman SS, et al. : COVID-19 in solid organ transplant: A multi-center cohort study. Clin Infect Dis 2020.

6. Boyarsky Brian J. W WA, Avery Robin K., Tobian Aaron A. R., Massie Allan B., Segev Dorry L., Garonzik-Wang Jacqueline M.: Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA 2021.

7. Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T: Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One 2013;8:e56974. [PubMed: 23451126]

8. Aslam S, Liu J, Sigler R, et al. Coronavirus disease 2019 vaccination is protective of clinical disease in solid organ transplant recipients. Transpl Infect Dis. 2022; 24:e13788. 10.1111/tid.13788 [PubMed: 34989104]

9. Sigler R, Covarrubias K, Chen B, Barriola R, Torosian K, Ramirez C, Sanchez1 AB, DeGruttola V, Aslam S. Post-acute sequelae of COVID-19 in solid organ transplant recipients. Transpl Infect Dis., to appear.

10. Wang X, Kattan MW. Cohort Studies: Design, Analysis, and Reporting. Chest. 2020 Jul;158(1S):S72–S78. doi: 10.1016/j.chest.2020.03.014. [PubMed: 32658655]

11. Breslow NE (2005). Case-Control Studies. In: Ahrens W, Pigeot I (eds) Handbook of Epidemiology. Springer, Berlin, Heidelberg. 10.1007/978-3-540-26577-1_7

12. Andersen PK Fifty Years with the Cox Proportional Hazards Regression Model. J Indian Inst Sci 102, 1135–1144 (2022). 10.1007/s41745-021-00283-9

13. Rulli E, Ghilotti F, Biagioli E et al. Assessment of proportional hazard assumption in aggregate data: a systematic review on statistical methodology in clinical trials using time-to-event endpoint. Br J Cancer 119, 1456–1463 (2018). 10.1038/s41416-018-0302-8 [PubMed: 30420618]

14. Cheng SC, Wei LJ, & Ying Z (1995). Analysis of Transformation Models with Censored Data. Biometrika, 82(4), 835–845. 10.2307/2337348

15. Valeri L, & VanderWeele TJ (2013). Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychological methods, 18 2, 137–50. [PubMed: 23379553]

16. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000 Sep;11(5):550–60. doi: 10.1097/00001648-200009000-00011. [PubMed: 10955408]

17. Lok JJ. Structural nested models and standard software: a mathematical foundation through partial likelihood. Scandinavian Journal of Statistics. 2007; 34:186–206.

18. Gregorio C, Cappelletto C, Romani S, Stolfo D, Merlo M, Barbati G. Using marginal structural joint models to estimate the effect of a time-varying treatment on recurrent events and survival: An application on arrhythmogenic cardiomyopathy. Biom J. 2022 Dec;64(8):1374–1388. doi: 10.1002/bimj.202100003. Epub 2022 Sep 4. [PubMed: 36058642]

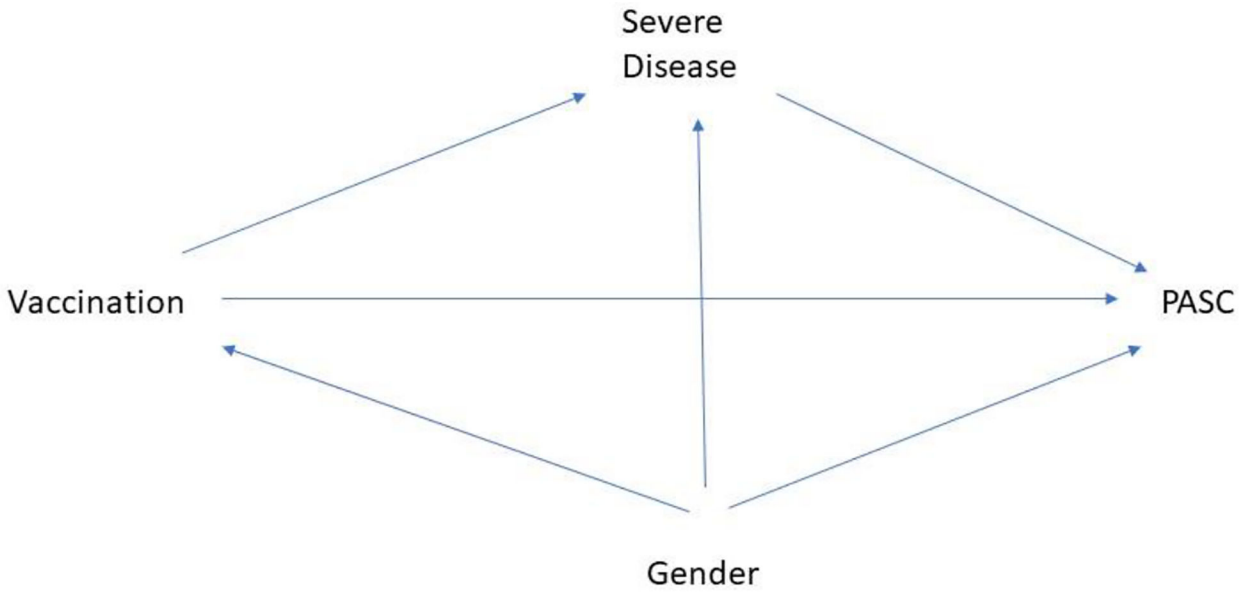

Figure 1.

Mediation analysis allows decomposition of total effects of pre-transplant vaccination on Long Covid into direct and indirect effects (through disease severity). The arrows indicate the direction of effects under study. Gender can confound all of these relationships.