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Research Article

Humoral and Cellular Immune Response in Kidney Transplant Recipients After COVID-19 Vaccination: A Systematic Review and Meta-Analysis

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Abstract

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between 2021 and mid-2023. With strict literature search and screening processes, it yielded 7 articles from 349 articles of initial literature database. A number of previous studies demonstrated that KTRs or non-KTRs with renal failure markedly reduced vaccine response, whereas adaptive protocols of mRNA COVID-19 vaccination or alternative adjuvant vaccines is now not known yet. A recent study revealed that acute kidney injury and mortality could be caused by SARS-CoV-2 (COVID-19) around 50% and 23% of the infected KTRs.

In conclusion, among the immunocompromised population, including KTRs, DPs, PDs, at least three doses of mRNA-COVID-19 vaccination was recommended to be the preparation of choice. Withdrawal of the immunosuppressants in KTRs and immunocompromised individuals prior COVID-19 vaccination and at least third dose of mRNA-COVID-19 vaccination should be performed.

Keywords: *Cellular; Humoral; Immune; Response; Kidney; Transplant; Hemodialysis; COVID-19; Vaccine; mRNA*

Abbreviations

BAU: Bioequivalent Allergy Unit; BMI: Body-Mass Index; CI: Confidential Interval; CNI: Calcineurin Inhibitor; COVID-19: Coronavirus-2019; DNA: Deoxyribonucleic Acid; DP: Dialysis Patient; eGFR: estimated Glomerular Filtration Rate; HCs: Healthy Controls; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IFNγ: Interferon Gamma; IGRA: Interferon Gamma Assay; IN-KTRs: Infection-Naive Kidney Transplant Recipients; IQR: Interquartile Rank; KTRs: Kidney Transplant Recipients; MMF: Mycophenolate Mofetil; MPA: Mycophenolic Acid; mRNA: messenger Ribonucleic Acid; NPV: Negative Predictive Value; OR: Odds Ratio; p: Probability; PD: Peritoneal Dialysis; PI-KTRs: Previously-Infected Kidney Transplant Recipients; PPV: Positive Predictive Value; RBD: Receptor-Binding Domain; ROC: Receiver Operating Curve; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-type 2; SOTRs: Solid Organ Transplant Recipients; TTV: Torque Teno Virus

Objectives of the Study

The objectives of this study are to identify the better understanding on the immunological responses, both humoral and cellular types between the types of COVID-19 vaccine and number of doses, risk of SARS-CoV-2 (COVID-19) infection and disease and transplantation age among previous hemodialysis or non-hemodialysis patients with kidney transplantation with or without immunosuppressive therapies.

Introduction

With different mRNA COVID-19 vaccination in immunocompromised patients, such as kidney transplant recipients (KTRs), solid organ transplant recipients (SOTRs), etc. binding and neutralizing antibodies measurement clearly revealed lower levels, compared to healthy persons [1-5]. A number of previous studies demonstrated that KTRs or non-KTRs with renal failure markedly reduced vaccine response, whereas adaptive protocols of mRNA COVID-19 vaccination or alternative adjuvant vaccines is now not known yet [6,7]. Whereas protective immunity is further impaired immunosuppressants, thus fully restoring adaptive, cellular immunity and renal function in KTRs cannot occur and increase susceptibility to viral-related malignancies and infections [8-10]. A recent study revealed that acute kidney injury and mortality could be caused by SARS-CoV-2 (COVID-19) around 50% and 23% of the infected KTRs [11]. Among KTRs, severe COVID-19 remained with unchanged high mortality rate of approximately 5% to 10% through conventional vaccine strategies [12]. Due to recent introduction of the modified vaccine strategies, initial recommendation of COVID-19-Vaccine-booster doses was made [2,13-17].

Methods of the Study

Search strategy and inclusion criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between 2021 and mid-2023, following the PRISMA. Our first involved performing searches of article abstract/keywords/title using strings of [(“Kidney Transplantation” or “Kidney Transplant Recipient”, “SARS-CoV-2” or “COVID-19” and “Vaccine” or “Vaccination”, “Humoral Immunity” or “Humoral Immune” or “Humoral Immune Response”, “Immunosuppressants” or “Immunosuppressive Regimens”, “Dialysis”)]. After a first approach of search, published articles focusing on kidney transplantation were retained and the information on immunological response type and COVID-19 vaccination was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from one immunological response type and immunosuppressive regimen variable to bind the population of cases under consideration. Search string for COVID-19-vaccine-type groups include [“Recombinant Subunit Vaccines” or “Protein Subunit Vaccine” or “Virus-like Particle (VLP) Vaccine” or “Nucleic Acid Vaccines” or “DNA-based Vaccines” or “RNA-based Vaccines” or “Viral Vector Vaccines” or “Non-replicating Viral Vector Vaccines” or “Replicating Viral Vector Vaccines” or “Whole Virus Vaccines” or “Inactivated Vaccines” or “Live-attenuated Vaccines”]. The initial literature databases were further manually screened with the following rules: 1) non-kidney-transplanted-recipient-related articles were excluded; 2) articles that did not report a human-humoral-immunological-response or human-immunological-response related to COVID-19 vaccination were not considered, such as commentary articles, or editorial; 3) non-peer reviewed articles were not considered to be of a scholarly trustworthy validity; and 4) duplicated and non-English articles were removed. The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

With strict literature search and screening processes, it yielded 7 articles from 349 articles of initial literature database. Needed article information was extracted from each article by: 1) direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year; 2) place name of the study area; 3) study period; 4) research method used; 5) type of kidney-transplantation-immunological-response variables studied; 6) types of COVID-19 vaccine studied; and 7) the conclusions made about the impacts of related- humoral-immunological-response on kidney-transplanted recipients. An overview of the information required for the present analysis that was captured by those themes was shown in the figure 1.

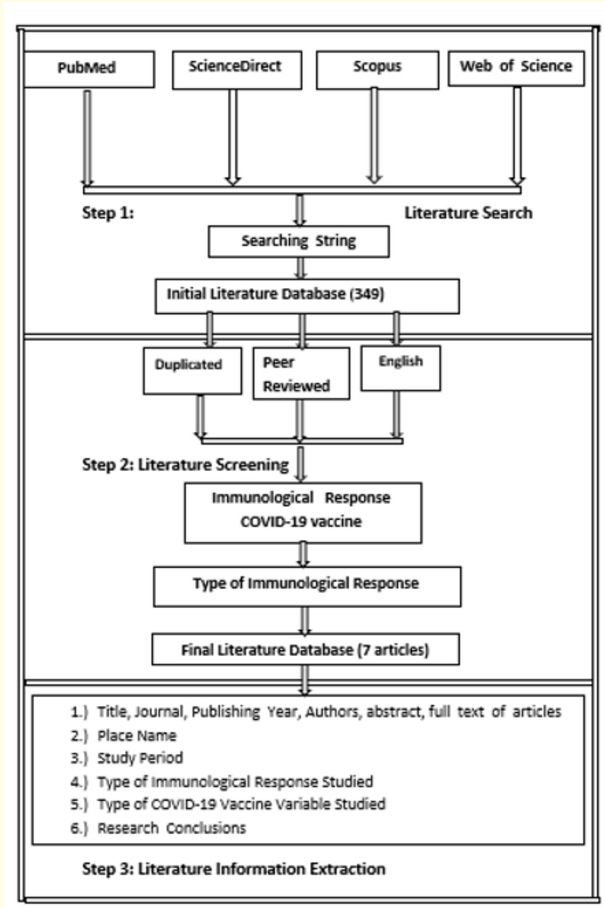

Figure 1: *Literature search and screening flow.*

Results

Year of Publication	Author (s)	Methodology and Study Design	Results	References
2023	Hovd., *et al*.	Prospective cohorts	Humoral vaccine response increased with additional booster doses.	[11]
2023	Mahallawi., *et al*.	Cross-sectional	Serum IgG antibody level seropositivity rate was critically higher than the seronegativity rate in KTRs who received three doses, compared to a single dose or two doses.	[18]

2023	Graninger., *et al*.	Prospective cohorts	Serum IgA and IgG seroconversion rates, neutralizing antibodies, and cellular immune response were lowest in KTRs, after two doses of mRNA-COVID-19 vaccination, compared to DPs. Serum TTV loads were also critically lower in KTRs with cellular and humoral immune responses to mRNA-COVID-19 vaccination, compared to non-responders.	[19]
2022	Benning., *et al*.	Prospective cohorts	35% of KTRs after mRNA-COVID-19 vaccination (at least three doses) revealed anti-spike S1 IgG antibody seroconversion above the predefined cutoff. Serum anti-spike S1 IgG index, % inhibition for serum neutralizing antibodies, and MFI for anti-RBD antibodies before mRNA-COVID-19 vaccination increased from IQRs (medians).	[20]
2022	de Boer., *et al*.	Prospective cohorts	Serum IgG antibody levels were critically higher in EVR-received KTRs, compared to MMF-received KTRs after two doses of mRNA-COVID-19 vaccination. All EVR group (100 % responders) demonstrated higher levels of serum IgG antibodies, compared to the MMF group after the third dose of mRNA-COVID-19 vaccination. Half of MMF group revealed positive T-cell response, whereas EVR group demonstrated 44 %. No association between the presence of serum IgG antibody levels and positive T-cell response ($p = 0.807$)	[21]
2022	Tylicki., *et al*.	Longitudinal observational	PI-KTRs and IN-KTRs demonstrated no differences in the aspects of sex, age, type of immunosuppression, graft vintage, and graft function after the third dose of mRNA-COVID-19 vaccination. 100% of PI-KTRs and 45.78% of IN-KTRs revealed immediately positive serum anti-S antibody response after primary mRNA-COVID-19 vaccination with median titers of 1,219 and 365.3 (117.3 - 915.2) BAU/mL, respectively.	[22]

2021	Rincon-Arevalo., *et al*.	Prospective cohorts	Serum anti-S1 IgA and IgG responses were substantially diminished in KTRs, 68.2% and 70.5%, respectively, compared with DPs and HCs after two mRNA-COVID-19 vaccination. DPs and KTRs demonstrated a typical decrease of absolute B cells with some differences in pre-memory, whereas there was no differences within B-memory-cell compartment after two mRNA-COVID-19 vaccination.	[1]

Table 1: *Demonstrating the cellular and humoral immune response after COVID-19 vaccination in kidney transplant recipients (2021-to mid-2023).*

Discussion

All seven related-published articles (100%) from 349 published articles of the initial databases demonstrated positive humoral immune responses (serum anti-S1 IgA and IgG levels) among the KTRs after booster doses of mRNA-COVID-19 vaccination, particularly the elderly [21] (Table 1) [1,11,18-22], whereas serum TTV loads is an indicator of cellular and humoral immune responses and EVR increased immune responses, compared to MMF [21] after mRNA-COVID-19 vaccination among KTRs [19]. Both dialysis patients and KTRs demonstrated RBD+-B cell (pre-switch-B and naive-B cells) enrichment [1]. Mycophenolic acid (MPA) withdrawal prior mRNA-COVID-19 vaccination in KTRs demonstrated critical rising of serum anti-S1- and anti-S2-IgG levels, including post-booster vaccination, in comparison to those who remained on MPA maintenance treatment [20]. One of the seven related-published positive articles revealed humoral immune responses above 5 BAU/mL at 33 days after the 5th booster dose of mRNA-COVID-19 vaccination [11]. KTR survivors with age above 70 years who received a living-donor organ demonstrated lower-COVID-19-risk-related death, compared to KTRs with an-organ-receiving from deceased donor, in addition to higher risk of COVID-19 infection among female KTRs [11]. Interestingly, a recent study demonstrated that viral-vector, and heterogenous of all homogenous mRNA-COVID-19 vaccines revealed reduction of levels of anti-S1 IgG between the first and third serum samples [18]. No differences between serum anti-S1 IgG levels at one and six-months after mRNA-COVID-19 vaccination in KTRs with one-month-post-mRNA-COVID-19-vaccination-IgG-immune-response seropositivity and different factors through linear regression analysis [18]. Among the immunocompromised population, including KTRs, DPs, PDs, at least three doses of mRNA-COVID-19 vaccination was recommended to be the preparation of choice [20,22].

Conclusion

Withdrawal of the immunosuppressants in KTRs and immunocompromised individuals prior COVID-19 vaccination and at least third dose of mRNA-COVID-19 vaccination should be performed.

Authors Contributions

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn and Professor Dr. Porntep Siriwanarangsun contributed to scientific content and assistance in manuscript writing. All authors read and approved the final version of the manuscript.

Competing Interests

The authors declare that they have no actual or potential competing financial interests.

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