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New Insights Into SARS-CoV-2-specific Antibody Levels in Kidney Transplantation Recipients After Three Vaccination Doses

Over the past four years, the world has experienced an unprecedented pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Accordingly, the development and production of vaccination platforms has accelerated. Since November 2021, the Omicron variant of concern has become dominant, and additional vaccine doses are recommended, especially for immunocompromised patients, such as transplant recipients [1]. However, the effectiveness of the third vaccine dose against Omicron is unclear, as the variant can partially evade immunity [2]. While enhanced immune responses have been reported in the transplant population after receiving the third vaccine dose, vaccination induces significantly lower seroconversion rates in immunocompromised individuals [3]. Consequently, immune monitoring is crucial in this immunologically high-risk population.

During the early stages of the pandemic, studies suggested an association between humoral immune markers, such as SARS-CoV-2-specific binding and neutralizing antibodies, and symptomatic infections and disease severity [4-10]. However, studies examining the correlation between antibody levels and clinical courses have produced inconsistent results [11-13], complicating the utilization of SARS-CoV-2-specific antibody titers in aiding medical decision-making.

In kidney transplant recipients (KTRs), studies on the correlation between anti-spike antibody levels after the third vaccination dose and outcomes of SARS-CoV-2 breakthrough infections are limited and have shown variable results [11, 12, 14-17]. Kemlin, *et al*. [11] and Lammert, *et al*. [12] did not find a significant association between post-third vaccination anti-SARS-CoV-2 antibody levels and breakthrough infections. Conversely, Alejo, *et al*. [14], in a US multicenter observational cohort study of 666 solid organ transplant recipients (including 351 KTRs) who had received three or more vaccinations, found that lower anti-receptor-binding domain antibody levels of 0.8–250 IU/mL were associated with an increased risk of breakthrough infection during the Omicron surge. Bertrand, *et al*. [15] found that anti-spike antibody levels <264 BAU/mL (WHO standard) were associated with increased risks of breakthrough infection, hospitalization, and death. Similarly, an Italian prospective cohort study involving 614 solid organ transplant recipients demonstrated that antibody levels <408.5 UI/mL were associated with breakthrough infections [16].

In this issue of Annals of Laboratory Medicine, Han, *et al*. [18] conducted a prospective study in 287 kidney transplant recipients to assess the association between antibody levels and breakthrough infections during the Omicron surge. The Abbott SARS-CoV-2 IgG II Quant test (Abbott, Chicago, IL, USA) was performed within three weeks before and four weeks after the third vaccination. The incidence of symptomatic breakthrough infection and hospitalization from two weeks to four months post-third vaccination was recorded. The authors focused on SARS-CoV-2-specific IgG antibody titers and compared their levels

among three distinct clinical manifestations: no breakthrough infection (N=222), breakthrough infection with mild symptoms (N=52), and breakthrough infection requiring hospitalization (N=12). Based on their findings, the researchers suggested specific cut-off titers, enabling the prediction of symptomatic breakthrough infections (<400 AU/mL, hazard ratio [HR]=3.46, P<0.001) and hospitalization (<200 AU/mL, HR=36.4, P=0.007).

This study is significant as the authors established clear cut-off values for predicting clinical outcomes. However, their statistical analyses indicated that the relationship between antibody titers and breakthrough infections is not linear; instead, it appears to be characterized by a distinct threshold. Antibody levels associated with an increased risk of breakthrough infection have displayed variations across studies [9-17]. The authors proposed several factors that could account for this variability, including disparities in test kits (including the use of non-standardized antibody units), varying levels of patient immunosuppression resulting from diverse drug regimens among hospitals, variations in exposure and viral loads from different sources, differences in healthcare facilities, and variances in the prevalence of Omicron infection within the community.

It is essential to validate the proposed threshold values among a wider spectrum of patients using diverse commercially available assays in future studies. Nonetheless, this study holds significant relevance for clinicians encountering immunocompromised patients, as it offers valuable insights that can assist in development of strategies to combat SARS-CoV-2 infection.

AUTHOR CONTRIBUTIONS

Kang H and Oh EJ contributed to manuscript writing and approved the submission of the final manuscript.

CONFLICTS OF INTEREST

None declared.

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