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Letter to the Editor

LETTER TO THE EDITOR

Neutralizing response against SARS-CoV-2 Omicron BA.5 and XBB.1.5 in hemodialysis patients

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To the Editor,

Booster vaccinations with coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine elicit a robust humoral immune response against SARS-CoV-2 in hemodialysis (HD) patients [1]. In response to the spread of the Omicron variant, adapted bivalent mRNA vaccines targeting the original strain and Omicron BA.1 or BA.4/5 have been developed and are currently recommended as a booster vaccination. However, the emergence of the SARS-CoV-2 XBB lineage, which is characterized by a strong immune resistance and a high transmissibility, urges for a systematic analysis regarding the efficacy of immunization strategies in patient groups facing a high risk for severe COVID-19, such as HD patients [2, 3]. To this aim, IgG anti-receptor binding domain (RBD) of the spike protein (SARS-CoV-2 IgG II Quant by Abbott) and live-virus neutralizing activity against BA.5 and XBB.1.5 (strains isolated from nasal swabs and expanded in VeroE6 cell culture; whole genome analysis performed by Illumina sequencing [4]) were tested in a cohort of 144 HD patients, with different immunization schemes (Fig. 1; Table S1, see online supplementary material). A serum neutralizing titer of 1:250 was defined as sufficient neutralization activity [5]. Serum samples were collected in November 2022. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Cologne, Germany (EK 21–1398).

For all patients, median anti-RBD IgG titer was 6892 BAU/ml (IQR: 8971). There was no difference in median anti-RBD IgG titers between patients with either one dose of bivalent BA.1 or BA.4/5 booster (Mann-Whitney test; $P = 0.371$ and $P = 0.22$). In the group of patients without Omicron immunization (vaccination or infection), median anti-RBD IgG was significantly lower compared to all other groups ($P < 0.001$), even after adjusting for baseline parameters ($P < 0.001$ and $P = 0.019$) (Fig. 1A; Table S2, see online supplementary material).

Median neutralizing activity titers were significant lower against XBB.1.5 than BA.5 (XBB.1.5 1:50, BA.5 1:250, $P < 0.001$)

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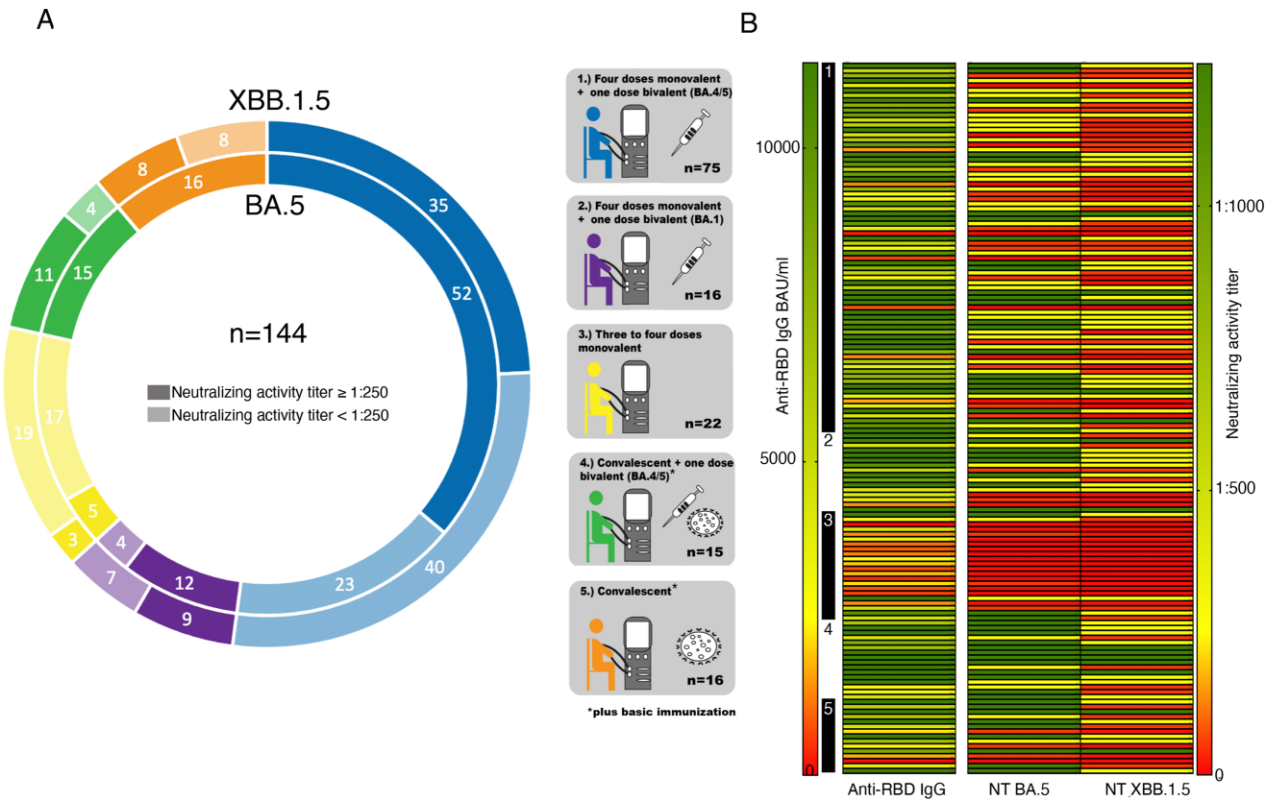

Figure 1: Serum neutralizing activity against SARS-CoV-2 Omicron BA.5 and XBB.1.5 in hemodialysis patients (HD) with different immunization schemes. (**A**) Pie chart of patients with neutralizing activity ≥ 1:250 or < 1:250 and different immunization schemes (inner circle BA.5, outer circle XBB.1.5, transparent bar: neutralizing activity titers <1:250, solid bars: neutralizing activity ≥1:250, numbers in bars: number of patients). Group 1: patients after four doses of monovalent mRNA vaccination (Moderna or BioNTech) and one dose of bivalent BA.4/5 adapted mRNA vaccination; Group 2: patients after four doses of monovalent mRNA vaccination (Moderna or BioNTech) and one dose of bivalent BA.1-adapted vaccination; Group 3: patients after three or four doses of monovalent mRNA vaccination (Moderna or BioNTech); Group 4: patients after three doses of monovalent mRNA vaccination (Moderna or BioNTech), Omicron breakthrough infection and additional mRNA booster vaccination with bivalent BA.4/5 vaccine; Group 5: patients after Omicron breakthrough infection and three or four doses of monovalent mRNA vaccination (Moderna or BioNTech); (**B**) Heat map of anti-RBD (receptor binding domain) titers and neutralizing activity against Omicron BA.5 and XBB.1.5. Each line represents one patient. For anti-RBD IgG titers color ranged from red = 0 to yellow = 1250 and green >12 500 BAU/ml. For neutralizing activity titers color ranged from red = 0, to yellow ≥1:250, to green ≥1:2500. Numbers in black and white boxes to the right represent the different immunization schemes, as reported above. NT, neutralization assay.

(Fig. 1B). In addition, reaching a sufficient neutralizing activity titer of ≥1:250 was significantly more frequent against BA.5 than XBB.1.5 ($P < 0.001$) (Fig. 1A).

A linear regression model for the influence of baseline characteristics, immunizations schemes, and anti-RBD IgG to neutralizing activity titers was performed. After adjusting for baseline characteristics, no immunization scheme was significantly associated to higher neutralizing activity against BA.5 and XBB.1.5. In contrast, anti-RBD IgG was significantly associated to higher neutralizing activity titers against BA.5 and XBB.1.5 ($P < 0.001$) (Tables S3 and S4, see online supplementary material).

The efficacy of immunization against SARS-CoV-2 has been questioned since the emergence of the Omicron variant and its sublineages due to their capacity to evade neutralizing antibodies induced by COVID-19 vaccines [6, 7]. Studies comparing the immune response of healthy individuals induced by original monovalent vaccines to bivalent BA.4/5 booster vaccines revealed no significant difference in terms of neutralization as well as T-cell reactivity against BA.4 and BA.5 between the two groups [6]. However, Omicron sublineages evidenced a marked capacity to evade immune response [7]. In particular, the dominant XBB.1.5 is considered one of the most efficient SARS-CoV-2 strain in terms of transmissibility and immune resistance [8]. Recent data showed that the neutralizing response against XBB.1.5 induced by the bivalent vaccine is strongly reduced in both healthy and different groups of vulnerable patients [9–11].

In the present analysis, the administration of a fifth booster with the bivalent mRNA BA.1 or BA.4/5 vaccine showed induction of a robust neutralization effect against BA.5 in a high proportion of HD patients. Antibody levels and neutralization titers induced by Omicron breakthrough infections and/or bivalent mRNA booster vaccination were comparable, indicating that the humoral response to BA.5 is similar in patients with a history of Omicron natural infection or adapted booster vaccination. On the contrary, neutralizing activity against the subvariant XBB.1.5 was considerably reduced in all patients, regardless of immunization scheme.

Thus, the spread of Omicron subvariants, such as XBB.1.5, evidence the need for further updated vaccines to protect vulnerable groups, as HD patients, from severe COVID-19.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

F.K. is listed as inventor on patent application on SARS-CoV-2 neutralizing antibodies filed by the University of Cologne. The other authors have no conflicts of interest to declare.

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