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Characterization of a Pan-Immunoglobulin Assay Quantifying Antibodies Directed against the Receptor Binding Domain of the SARS-CoV-2 S1-Subunit of the Spike Protein: A Population-Based Study

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Pan-immunoglobulin assays can simultaneously detect IgG, IgM and IgA directed against the receptor binding domain (RBD) of the S1 subunit of the spike protein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 S1-RBD Ig). In this work, we aim to evaluate a quantitative SARS-CoV-2 S1-RBD Ig electrochemiluminescence immunoassay (ECLIA) regarding analytical, diagnostic, operational and clinical characteristics. Our work takes the form of a population-based study in the principality of Liechtenstein, including 125 cases with clinically well-described and laboratory confirmed SARS-CoV-2 infection and 1159 individuals without evidence of coronavirus disease 2019 (COVID-19). SARS-CoV-2 cases were tested for antibodies in sera taken with a median of 48 days (interquartile range, IQR, 43-52) and 139 days (IQR, 129-144) after symptom onset. Sera were also tested with other assays targeting antibodies against non-RBD-S1 and -S1/S2 epitopes. Sensitivity was 97.6% (95% confidence interval, CI, 93.2-99.1), whereas specificity was 99.8% (95% CI, 99.4-99.9). Antibody levels linearly decreased from hospitalized patients to symptomatic outpatients and SARS-CoV-2 infection without symptoms (< 0.001). Among cases with SARS-CoV-2 infection, smokers had lower antibody levels than non-smokers (= 0.04), and patients with fever had higher antibody levels than patients without fever (= 0.001). Pan-SARS-CoV-2 S1-RBD Ig in SARS-CoV-2 infection cases significantly increased from first to second follow-up (< 0.001). A substantial proportion of individuals without evidence of past SARS-CoV-2 infection displayed non-S1-RBD antibody reactivities (248/1159, i.e., 21.4%, 95% CI, 19.1-23.4). In conclusion, a quantitative SARS-CoV-2 S1-RBD Ig assay offers favorable and sustained assay characteristics allowing the determination of quantitative associations between clinical characteristics (e.g., disease severity, smoking or fever) and antibody levels. The assay could also help to identify individuals with

antibodies of non-S1-RBD specificity with potential clinical cross-reactivity to SARS-CoV-2.

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