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International trends in evaluations of antibody tests and establishment of the reference standard for anti-SARS-CoV-2 antibody

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ABSTRACT— SARS-CoV-2 antigen rapid diagnostic tests (Ag-RDTs) are increasingly being integrated in testing strategies around the world. Studies of the Ag-RDTs have shown variable performance. In this systematic review and meta-analysis, we assessed the clinical accuracy (sensitivity and specificity) of commercially available Ag-RDTs.

KEYWORDS: antibody assay; COVID-19; SARS-CoV-2; serology

1. INTRODUCTION

A new disease, known as coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in the region of Wuhan (China) in December 2019 [1], [2]. The virus spread subsequently all over the world and the WHO officially declared the novel SARS-CoV-2 infection a pandemic. An accurate and prompt detection of SARS-CoV-2 is essential not only for the diagnosis of infected patients, but also for the establishment of infection control measures and prevention of virus spread [3], [4]. Real-time reverse transcription polymerase chain reaction (RT-PCR) using respiratory samples obtained with naso- or oropharyngeal swabs are considered as the reference method for screening and diagnosis of acute SARS-CoV-2 infection [3]. However, the sensitivity of this method may vary depending on time of sampling, the quality and origin of the sample and the viral load [5], [6]. In contrast, serologic testing of anti-SARS-CoV-2 antibodies (IgG, IgM and IgA) can be easily performed by using venous blood samples. SARS-CoV-2 antibody assays are proposed to play an important role in diagnosis of COVID-19 convalescents and in patients with clinical symptoms suggestive for SARS-CoV-2 infection but with negative or not available RT-PCR results [4]. Furthermore, antibody assays may help to understand the epidemiology of SARS-CoV-2 infections, support the selection of convalescent plasma for therapeutic treatments and potentially to evaluate the efficiency of future vaccines [7], [8].

Numerous SARS-CoV-2 antibody assays have been approved including lateral flow tests, enzyme-linked immunosorbent assays (ELISA) and fully-automated electrochemiluminescent (ECLIA) or chemiluminescent immunoassays (CLIA). Due to the increasing numbers of these serological tests, the lack of comparative data in combination with the high demand on serological assays it is essential for laboratory professionals to carefully evaluate SARS-CoV-2 antibody assays. Therefore, the aim of this study was to compare the clinical and analytical performance of three commercially available, fully-automated ELISA-, CLIA- and ECLIA-based SARS-CoV-2 antibody assays. To date, this is the first evaluation of the Siemens SARS-CoV-2 antibody assay.

2. Materials and methods

The study was conducted as part of the diagnostic evaluation of SARS-CoV-2 serologic testing for routine use at the Institute for Clinical Chemistry and Pathobiochemistry at the University Hospital Tübingen

according to the declaration of Helsinki of 1964 and its later amendments in accordance with the local Ethics Committee of the University of Tübingen. Routine blood samples (n=186) of hospitalized COVID-19 patients (n=58) were used for serial antibody measurements. COVID-19 diagnosis was based on detection of SARS-CoV-2-RNA in oro- and/or nasopharyngeal swab by RT-PCR. Median time between positive PCR result and blood sample collection was 19 days (interquartile range: 12–29 days). COVID-19 negative control samples were all obtained before the beginning of the pandemic and comprises intensive care patients (n=88). In addition, potential cross-reactive antibodies (n=35) were investigated using samples from patients with laboratory confirmed acute infections with influenza A virus (n=5), human respiratory syncytial virus (n=1) and common cold coronaviruses (NL63: n=1; HKU-1 + NL63: n=1; NL63 + 229E: n=1). Furthermore, samples with IgM antibodies against human cytomegalovirus (n=5) and varicella zoster virus (n=2), samples from patients with respiratory symptoms not suspicious of COVID-19 disease (n=11), samples containing antibodies (n=6) against chlamydia pneumoniae (IgG, IgA and/or IgM) or candida albicans (IgG and/or IgA) and samples positive for rheumatoid factor (n=2) were included in the study.

3. Discussion

The present study evaluated and compared three SARS-CoV-2 antibody assays by Siemens Healthineers, Roche Diagnostics and Euroimmun which were run on fully-automated platforms. To date, this is the first evaluation of the Siemens SARS-CoV-2 antibody assay. All three assays demonstrated high diagnostic specificity. Only the Euroimmun assay detected three false borderline results. The Siemens assay was found to be slightly more sensitive than the Roche and Euroimmun assays but none of these assays was sufficiently sensitive to safely detect antibodies <14 days after PCR-confirmed SARS-CoV-2 infection. High diagnostic specificity is crucial to reduce the number of false positive results in serological testing. The Roche and Siemens assays demonstrated 100% specificity in samples collected before December 2019 when the virus was not present in Germany and in samples with potential cross-reactive antibodies from acute viral and bacterial or fungal infections. Only in the case of the Euroimmun assay three false borderline results were observed, which were found in two samples with influenza A virus and in one sample with other coronaviruses (HKU-1 and NL63). The specificities of the Roche and Euroimmun assays are similar to those given by the manufacturers and other recent studies [10- 14]. Some reports showed slightly reduced specificities (>96%) for the Euroimmun assay [15], [16]. Specificity of the Roche assay was demonstrated as >98–100% in three other reports [10- 12]. However, specificities between studies are difficult to compare due to different numbers and origins of samples used for the evaluations. Although serological assays exhibit high diagnostic specificity and sensitivity (>99%), the positive predictive value of a single test can be markedly reduced in populations with low prevalence of SARS-CoV-2 [7]. This should be taken into account when evaluating antibody screening studies.

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