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Evaluation of the EDI enzyme linked immunosorbent assays for the detection of SARS-CoV-2 IgM and IgG antibodies in human plasma

Christian Bundschuh[a], Margot Egger[a], Kurt Wiesinger[a], Christian Gabriel[b,c], Martin Clodi[d], Thomas Mueller[e], Benjamin Dieplinger[a,*]

[a] Department of Laboratory Medicine, Konventhospital Barmherzige Brueder Linz and Ordensklinikum Linz Barmherzige Schwestern, Linz, Austria
[b] Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria
[c] Ludwig Boltzmann Institute for Experimental and Clinical Traumatology Vienna, Vienna, Austria
[d] Department of Internal Medicine, Konventhospital Barmherzige Brueder Linz, Linz, Austria
[e] Department of Clinical Pathology, Hospital of Bolzano, Bolzano, Italy

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ABSTRACT

Background: Besides SARS-CoV-2 RT-PCR testing, serological testing is emerging as additional option in COVID-19 diagnostics. Aim of this study was to evaluate novel immunoassays for detection of SARS-CoV-2 antibodies in human plasma.

Methods: Using EDI™ Novel Coronavirus COVID-19 Enzyme Linked Immunosorbent Assays (ELISAs), we measured SARS-CoV-2 IgM and IgG antibodies in 64 SARS-CoV-2 RT-PCR confirmed COVID-19 patients with serial blood samples (n = 104) collected at different time points from symptom onset. Blood samples from 200 healthy blood donors and 256 intensive care unit (ICU) patients collected before the COVID-19 outbreak were also used.

Results: The positivity rates in the COVID-19 patients were 5.9% for IgM and 2.9% for IgG ≤ 5 days after symptom onset; Between day 5 and day 10 the positivity rates were 37.1% for IgM and 37.1% for IgG and rose to 76.4% for IgM and 82.4% for IgG after > 10–15 days. After 15–22 days the "true" positivity rates were 94.4% for IgM and 100% for IgG. The "false" positivity rates were 0.5% for IgM and 1.0% for IgG in the healthy blood donors, 1.6% for IgM and 1.2% for IgG in ICU patients.

Conclusions: This study shows high "true" vs. low "false" positivity rates for the EDI™ SARS-CoV-2 IgM and IgG ELISAs.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that causes Coronavirus Disease 2019 (COVID-19), has recently emerged to cause a human pandemic. Currently, detection of SARS-CoV-2 with RT- PCR testing from upper or lower respiratory specimens is gold standard method for the confirmation of suspected COVID-19 patients [1–3]. Besides SARS-CoV-2 RT-PCR testing, serological testing is emerging as additional option in COVID-19 diagnostics [4]. Preliminary data show a potential use of specific SARS-CoV-2 antibody tests to aid in the diagnosis of suspected COVID-19 patients [5,6]. Furthermore, there is great interest in antibody testing of healthcare workers to evaluate hospital transmission and in addition antibody tests could ultimately help to see how far the transmission is in the general population [4].

Recently, Epitope Diagnostics Inc. has developed the EDI™ Coronavirus COVID-19 IgM and IgG Enzyme Linked Immunosorbent Assay (ELISA) Kits. To our knowledge there is only very limited peer reviewed published data in the literature on the performance of these novel immunoassays [7]. Before these novel immunoassays can potentially be implemented in clinical routine, they need thorough evaluation in appropriate sized "positive" and "negative" cohorts. Therefore, the aim of this study was to perform an analytical and clinical evaluation of the EDI™ ELISAs for the detection of SARS-CoV-2 IgM and IgG antibodies in human plasma.

* Corresponding author at: Department of Laboratory Medicine, Konventhospital Barmherzige Brueder Linz and Ordensklinikum Linz Barmherzige Schwestern, Seilerstaette 2-4, A-4020 Linz, Austria.
E-mail address: benjamin.dieplinger@bs-lab.at (B. Dieplinger).

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2. Materials and Methods

2.1. Study protocol

This work was performed at the Konventhospital Barmherzige Brueder Linz and Ordensklinikum Linz Barmherzige Schwestern in Linz, Austria. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki,. Using VACUETTE® polyethylene terephthalate glycol blood collection tubes (Greiner Bio-One, Kremsmuenster, Austria) EDTA and lithium-heparin anticoagulated blood were collected and plasma aliquots were frozen at −80 °C until further analysis. Data were statistically analyzed with the MedCalc 13.1.2.0 (MedCalc Software) and SPSS 23.0 (SPSS Inc.).

2.2. SARS-CoV-2 antibody measurements

We measured SARS-CoV-2 IgM and IgG antibodies fully-automated on an Immunomat instrument (Serion Diagnostics) with the EDI™ Novel Coronavirus COVID-19 IgM and IgG enzyme linked immunosorbent assay (ELISA) kits (Epitope Diagnostics Inc.). The EDI™ Novel Coronavirus COVID-19 IgM and IgG ELISA kits are based on the nucleocapsid protein of SARS-CoV-2 (N), are IVD CE-marked, and are approved for the qualitative detection of SARS-CoV-2 IgM and IgG antibodies in human plasma. The measurement of the SARS-CoV-2 IgM and IgG antibodies was performed following the manufactureŕs instruction. The following interpretation rules of the patient results (single run) for the SARS-CoV-2 IgM and IgG assays were used: If the patient sample OD was below the negative cutoff the result was reported negative (-); If the patient sample OD was above the negative cut off but below the positive cutoff the result was reported borderline (+-); If the patients sample OD was above the positive cutoff the patient was reported as positive (+).

2.3. Precision study

To evaluate the precision of the SARS-CoV-2 IgM and IgG assays in our laboratory, we performed a replication study according to the Clinical and Laboratory Standards Institute (CLSI) guideline EP5-A [8]. One negative patient lithium heparin plasma pool and one positive lithium patient heparin plasma pool were aliquoted into 10 1.5 mL plastic tubes for each concentration level and frozen at –80 °C. We analyzed these samples in duplicates in one run per day for 10 days on an Immunomat instrument. Within-run and total analytical imprecision (CV) was calculated with the CLSI single-run precision evaluation test [8].

2.4. Detection limit

The detection limits for the SARS-CoV-2 IgM and IgG assays were determined by assaying a diluted lithium heparin plasma sample of a healthy individual in replicates of 20 and was calculated as 3 SD added to the mean response of the diluted sample. The diluted sample was prepared by mixing a fresh plasma sample in a 1:10 ratio with sample dilution buffer. This prediluted plasma sample was then treated equally with all other patient samples with respect to the assay procedure. The 20 replicates were assayed on the same microwell plate.

2.5. Clinical evaluation of the SARS-CoV-2 IgM and IgG antibody assays

For the clinical evaluation we measured SARS-CoV-2 IgM and IgG antibodies in three different cohorts: First in a “positive cohort” of patients with SARS-CoV-2 RT-PCR confirmed COVID-19 with serial blood samples at different time points from symptom onset. In these confirmed COVID-19 patients SARS-CoV-2 IgM and IgG antibodies were clinically suspected. Second a cohort of healthy blood donors and third a cohort of patients admitted to an intensive care unit (ICU). The healthy blood donors and the ICU patients were recruited prior to the COVID-19 outbreak (December 3rd 2019) and serve as “negative cohorts” were no SARS-CoV-2 IgM and IgG antibodies were clinically suspected.

2.5.1. Study cohort of patients with SARS-CoV-2 RT-PCR confirmed COVID-19

Between 15th of March 2020 and 10th of April 2020 all SARS-CoV-2 RT-PCR (from respiratory specimens) confirmed COVID-19 patients that were treated in one of the two tertiary care hospitals Konventhospital Barmherzige Brueder Linz and Ordensklinikum Linz Barmherzige Schwestern in Linz Austria. Blood samples for clinical routine that were sent to central laboratory were included in the present study. Those left over lithium heparin plasma samples from clinical routine were aliquoted and frozen at −80 °C for further analysis. During the study period a total of 64 SARS-CoV-2 RT-PCR confirmed COVID-19 patients were included. From the 64 patients we have collected a total of 104 serial blood samples at different time points from symptom onset until 10th of April 2020 (i.e. 64 patients had at least one blood draw, 28 patients had two, 9 patients had three and 3 patients had four blood draws). The date of onset of symptoms was retrieved from medical records and was available for all patients.

2.5.2. Study cohort of health blood donors

We used the first 200 consecutive EDTA plasma samples from our previously described cohort of healthy blood donors which were recruited at the Red Cross organization in Linz, Austria from January 31st to February 13th 2008 [9].

2.5.3. Derivation cohort of the Linz intensive care unit (LICU) study

We used the 256 consecutive baseline EDTA plasma samples of patients admitted to the medical intensive care unit of the Konventhospital Barmherzige Brueder Linz, Austria. This cohort of the LICU study was recruited from August 9th 2009 to February 8th 2010 [10].

3. Results

3.1. Analytical assay evaluation – Imprecision and detection limit

The SARS-CoV-2 IgM assay had a within-run CV of 7% and a total CV of 10% at a mean optical density (OD) of 0.103 (negative patient pool), and within-run CV of 4% and a total CV of 10% at a mean OD of 0.297 (positive patient pool). The SARS-CoV-2 IgG assay had a within-run CV of 4% and a total CV of 9% at a mean OD of 0.173 (negative patient pool), and within-run CV of 7% and a total CV of 9% at a mean OD of 0.537 (positive patient pool). The detection limit was an OD of 0.095 for the SARS-CoV-2 IgM and an OD of 0.083 for the SARS-CoV-2 IgG assay.

3.2. Rates of “true” vs. “false” positivity

The final study population consisted of 64 patients (53 males, 11 females) with SARS-CoV-2 RT-PCR confirmed COVID-19 with serial blood samples (n = 104) collected at different time points from symptom onset. The median age was 65 years (range 14–95, IQR 56–87, years). Table 1 shows low “true” positivity rates (i.e. seroconversion rates) for IgM (5.9%) and IgG (2.9%) SARS-CoV-2 antibodies within the first 5 days after symptom onset in patients with COVID-19. Between day 5 and day 10 the “true” positivity rates were 37.1% for IgM and 37.1% for IgG. The “true” positivity rates rose to 76.4% for IgM and 82.4% for IgG after 10–15 days. After 15–22 days the “true” positivity rate was 94.4% for IgM and 100% for IgG SARS-CoV-2 antibodies (Table 1). Of the 64 patients with confirmed COVID-19 two patients (3%) were immune compromised. One patient had an active hemato-onoclogical disease (a diffuse large B-cell lymphoma). This patient did

Table 1
Rates of "true" positivity of SARS-CoV-2 IgM and IgG antibodies in 64 patients with SARS-CoV-2 RT-PCR confirmed COVID-19 with serial blood samples (n = 104) collected at different time points from symptom onset.

Symptom onset	n (%)	IgM	IgG	IgM or IgG
< 5 (days)	34 (100%)	− 30 (88.2%) ± 2 (5.9%) + 2 (5.9%)	− 32 (94.2%) ± 1 (2.9%) + 1 (2.9%)	− 29 (85.3%) ± 2 (5.9%) + 3 (8.8%)
5–10 (days)	35 (100%)	− 19 (54.3%) ± 3 (8.6%) + 13 (37.1%)	− 22 (62.9%) ± 0 (0%) + 13 (37.1%)	− 17 (48.6%) ± 1 (2.8%) + 17 (48.6%)
> 10–15 (days)	17 (100%)	− 3 (17.6%) ± 1 (5.9%) + 13 (76.4%)	− 3 (17.6%) ± 0 (0%) + 14 (82.4%)	− 3 (17.6%) ± 0 (0%) + 14 (82.4%)
> 15–22 (days)	18 (100%)	− 1 (5.6%) ± 0 (0%) + 17 (94.4%)	− 0 (0%) ± 0 (0%) + 18 (100%)	− 0 (0%) ± 0 (0%) + 18 (100%)

- Negative (OD ≤ negative cutoff).
± Borderline (OD > negative cutoff but < positive cutoff).
+ Positive (OD ≥ positive cutoff).

not develop antibodies against SARS-CoV-2 until 13 days after symptom onset and eventually died of COVID 19. The second confirmed COVID-19 patient suffered from immune thrombocytopenia and was treated with immune modulating/suppressing therapies. This patient developed SARS-CoV-2 antibodies on day 13 and fully recovered from COVID-19.

In the cohort of 200 healthy blood donors the "false" positivity rate was 0.5% for IgM and 1% for IgG SARS-CoV-2 antibodies (Table 2). The "false" positivity rate in the cohort of 256 ICU patients was 1.6% for IgM and 1.2% for IgG SARS-CoV-2 antibodies (Table 3).

In the supplementary data we report the quantitative values of OD and the ratio OD/negative control in the cohort of patients with SARS-CoV-2 RT-PCR confirmed COVID-19, in the healthy blood donors as well as in the ICU patients (Supplementary Table 1–3).

4. Discussion

Our evaluation of the EDI™ Novel Coronavirus COVID-19 ELISAs for the qualitative detection of SARS-CoV-2 IgM and IgG antibodies in human plasma confirms that these novel immunoassays meet the quality specification for laboratory medicine. The CVs were ≤ 10%, which is adequate for ELISAs. The detection limits of the SARS-CoV-2 IgM and IgG assays were below the negative control and therefore also appropriate. Furthermore, the clinical evaluation study demonstrated high "true" positivity rates in the SARS-CoV-2 RT-PCR confirmed COVID-19 patients with symptom onset after 15 days with 94.4% for IgM and 100% for IgG SARS-CoV-2 antibodies. Finally, we reported low "false" positivity rates in the healthy blood donors with 0.5% for IgM and 1% for IgG as well as in the ICU patients with 1.6% for IgM and 1.2% for IgG SARS-CoV-2 antibodies.

Prior approaches to serologic detection of infection with emerging coronaviruses including SARS and Middle East Respiratory Syndrome (MERS) have focused on the spike glycoprotein and the nucleocapsid protein, which are considered the immunodominant antigens for these viruses [11]. The EDI™ SARS-CoV-2 IgM and IgG assays are based on the nucleocapsid protein of SARS-CoV-2 (N). In agreement with the proposed SARS-CoV-2 antibody response after symptom onset we found very low seroconversion rates before day 5. Whereas after 15 days we found very high seroconversion rates in our SARS-CoV-2 confirmed COVID-19 patients [5,6,12–14]. In line with our findings, it has recently been reported that serological diagnosis is especially important for patients who may present late, beyond the first 2 weeks of illness onset. At this late stage of disease SARS-CoV-2 RT-PCR might already be negative [15]. It would be tempting to only use SARS-CoV-2 IgG antibody tests to aid in the diagnosis of suspected COVID-19 patients. However, when using IgM in addition to IgG assays, this might allow differentiating an early from a late stage or even past infection. In addition, the combined "false" positivity rates for the EDI™ SARS-CoV-2 IgM and IgG assays we reported in the healthy blood donors (< 2%) and intensive care patients (< 3%) was rather low.

Table 2
Rates of "false" positivity of SARS-CoV-2 IgM and IgG antibodies in 200 healthy blood donors.

n = 200	IgM	IgG	IgM or IgG
200 (100%)	− 199 (99.5%) ± 0 (0%) + 1 (0.5%)	− 198 (99%) ± 0 (0%) + 2 (1%)	− 197 (98.5%) ± 0 (0%) + 3 (1.5%)

- Negative (OD ≤ negative cutoff).
± Borderline (OD > negative cutoff but < positive cutoff).
+ Positive (OD ≥ positive cutoff).

Table 3
Rates of "false" positivity of SARS-CoV-2 IgM and IgG antibodies in 256 patients admitted to an intensive care unit.

n = 256	IgM	IgG	IgM or IgG
256 (100%)	− 248 (96.8%) ± 4 (1.6%) + 4 (1.6%)	− 252 (98.4%)- 244 (95.3%) ± 1 (0.4%) + 3 (1.2%)	− 244 (95.3%)) ± 5 (2%) + 7 (2.7%)

- Negative (OD ≤ negative cutoff).
± Borderline (OD > negative cutoff but < positive cutoff).
+ Positive (OD ≥ positive cutoff).

Of note, with the EDI™ SARS-CoV-2 IgM and IgG immunoassays we only report antibody binding to the recombinant nucleocapsid protein of the SARS-CoV-2 and we did not perform neutralization assays in our SARS-CoV-2 RT-PCR confirmed patients.

Since the EDI™ SARS-CoV-2 IgM and IgG is currently approved as qualitative assay, we did not test the linearity of the assays. However, when interpreting the quantitative data (OD values and the ratios OD/negative control) in Supplementary Table 1, we found a clear antibody response in SARS-CoV-2 antibody positive COVID-19 patients from < 5 days until > 15 days with increasing median OD and the values ratios OD/negative control, demonstrating that the EDI™ SARS-CoV-2 IgM and IgG assays are suitable for serial measurements.

This study is the first thorough evaluation of the EDI™ SARS-CoV-2 IgM and IgG ELISAs and we reported high "true" vs. low "false" positivity rates, indicating the suitability of these novel immunoassays for clinical routine.

CRediT authorship contribution statement

Christian Bundschuh: Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Margot Egger:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Kurt Wiesinger:** Formal analysis, Writing - review & editing. **Christian Gabriel:** Formal analysis, Writing - review & editing. **Martin Clodi:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Thomas Mueller:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Benjamin Dieplinger:** Conceptualization, Resources, Formal analysis, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2020.05.047.

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