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Comparison of the Elecsys® Anti-SARS-CoV-2 immunoassay with the EDI™ enzyme linked immunosorbent assays for the detection of SARS-CoV-2 antibodies in human plasma

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ABSTRACT

Background: Here, we report on a head-to-head comparison of the fully-automated Elecsys® Anti-SARS-CoV-2 immunoassay with the EDI™ enzyme linked immunosorbent assays (ELISA) for the detection of SARS-CoV-2 antibodies in human plasma.

Methods: SARS-CoV-2 antibodies were measured with the Elecsys® assay and the EDI™ ELISAs (IgM and IgG) 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: In COVID-19 patients, the percentage of positive results rose with time from symptom onset, peaking to positivity rates after 15–22 days of 100% for the Elecsys® assay, of 94% for the EDI™ IgM-ELISA and of 100% for the EDI™ IgG ELISA. In the 104 blood samples, the agreement between positive/negative classifications of the Elecsys® assay and the EDI™ ELISAs (IgM or IgG) was 90%. The false positivity rates in the healthy blood donors and the ICU patients were < 1% for the Elecsys® assay and < 3% for the EDI™ ELISAs.

Conclusions: Our results indicate a high sensitivity and specificity for the Elecsys® assay and an acceptable agreement with the EDI™ 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.

Besides SARS-CoV-2 RT-PCR testing, currently the method of choice for the confirmation of suspected COVID-19 patients, serological testing is emerging as additional option in COVID-19 diagnostics [1–10].

Recently, Roche Diagnostics (Rotkreuz, Switzerland) has launched the IVD CE-marked Elecsys® Anti-SARS-CoV-2 assay for the qualitative detection of SARS-CoV-2 antibodies on the cobas e immunoassay analyzers. The aim of this study was to compare the clinical performance of the Elecsys® Anti-SARS-CoV-2 assay with the EDI™ SARS-CoV-2 IgM and IgG enzyme linked immunosorbent assays (ELISA), which we have recently established in our laboratory.

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.

2.2. Elecsys® Anti-SARS-CoV-2 assay

We measured SARS-CoV-2 antibodies fully-automated on the cobas

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Table 1
True positivity rates of the Elecsys® assay and the EDI™ ELISAs (IgM and IgG) 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 (%)	Elecsys® assay[a] n negative (%) n positive (%)	EDI™ IgM[b] n negative (%) n positive (%)	EDI™ IgG[b] n negative (%) n positive (%)	EDI™ IgM or IgG[b] n negative (%) n positive (%)
<5 (days)	34 (100%)	33 neg. (97.1%) 1 pos. (2.9%)	32 neg. (94.1%) 2 pos. (5.9%)	33 neg. (97.1%) 1 pos. (2.9%)	31 neg. (91.2%) 3 pos. (8.8%)
5–10 (days)	35 (100%)	17 neg. (48.6%) 18 pos. (51.4%)	22 neg. (62.9%) 13 pos. (37.1%)	22 neg. (62.9%) 13 pos. (37.1%)	18 neg. (51.4%) 17 pos. (48.6%)
>10–15 (days)	17 (100%)	4 neg. (23.5%) 13 pos. (76.5%)	4 neg. (23.5%) 13 pos. (76.5%)	3 neg. (17.6%) 14 pos. (82.4%)	3 neg. (17.6%) 14 pos. (82.4%)
>15–22 (days)	18 (100%)	0 neg. (0%) 18 pos. (100%)	1 neg. (5.6%) 17 pos. (94.4%)	0 neg. (0%) 18 pos. (100%)	0 neg. (0%) 18 pos. (100%)

[a]Elecsys® assay: negative (COI < 1.0); positive (COI ≥ 1.0).
[b]EDI™ ELISAs (IgM and IgG): negative (OD < positive cutoff); positive (OD ≥ positive cutoff).

Table 2
Agreement between positive/negative classifications of the Elecsys® assay and the EDI™ ELISAs (IgM or IgG) in 104 serial blood samples collected at different time points from symptom onset from SARS-CoV-2 RT-PCR confirmed COVID-19 patients.

	EDI™ IgM or IgG ELISA[b] negative	EDI™ IgM or IgG ELISA[b] positive
Elecsys® assay[a] negative	48	6
Elecsys® assay[a]positive	4	46

[a] Elecsys® assay: negative (COI < 1.0); positive (COI ≥ 1.0).
[b] EDI™ ELISAs (IgM and IgG): negative (OD < positive cutoff); positive (OD ≥ positive cutoff).

e801 analyzer (Roche Diagnostics) using the novel Elecsys® Anti-SARS-CoV-2 electrochemiluminescence immunoassay (Roche Diagnostics, reagent lot number 49025801) for the qualitative detection of SARS-CoV-2 antibodies in human plasma. The Elecsys® assay uses a modified double-antigen sandwich immunoassay using recombinant nucleocapsid protein (N), which is geared towards the detection of late, mature, high affinity antibodies independent of the subclass. It is a total SARS-CoV-2 antibody assay (IgA, IgM, and IgG) detecting predominantly, but not exclusively, IgG. Measurement of Anti-SARS-CoV-2 was performed following the manufacturer's instructions. Results are reported as numeric values in form of a cutoff index (COI; signal sample/cutoff) as well as in form of a qualitative results non-reactive (COI < 1.0; negative) and reactive (COI ≥ 1.0; positive).

To evaluate the precision of Elecsys® assay in our laboratory, we performed a replication study adopting the Clinical and Laboratory Standards Institute (CLSI) guideline EP5-A [11]. One negative patient plasma pool and one positive patient plasma pool were analyzed in duplicates in two runs per day for 5 days on the same cobas e801 analyzer. Within-run and total analytical imprecision (CV) was calculated with the CLSI double-run precision evaluation test [11]. The Elecsys® assay had a within-run CV of 3% and a total CV of 5% at a mean value of 0.09 COI (negative patient pool), and within-run CV of 3% and a total CV of 7% at a mean value of 7.0 COI (positive patient pool).

The detection limit for the Elecsys® assay was determined by assaying a 1:10 prediluted (with Diluent Multi Assay) negative patient plasma pool in replicates of 20 and was calculated as 3 SD added to the mean response of the diluted sample. The detection limit was 0.09 COI for the Elecsys® assay.

2.3. EDI™ novel coronavirus COVID-19 IgM and IgG ELISAs

We measured SARS-CoV-2 IgM and IgG antibodies with the EDI™ Novel Coronavirus COVID-19 IgM (reagent lot number P630C) and IgG (reagent lot number P621C) enzyme linked immunosorbent assay (ELISA) kits (Epitope Diagnostics Inc., San Diego, CA, USA). The EDI™ IgM and IgG ELISAs are based on recombinant nucleocapsid protein (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 optical density (OD) was below the positive cutoff the result was reported negative; If the patients sample OD was equal or above the positive cutoff the patient was reported as positive. In our laboratory we found an assay imprecision of ≤ 10% for the IgM and IgG ELISAs.

2.4. Clinical comparison of the Elecsys® assay and the EDI™ ELISAs (IgM and IgG)

We used both assays for the detection of anti-SARS-CoV-2 antibodies in 64 SARS-CoV-2 RT-PCR confirmed COVID-19 patients with serial blood samples (n = 104) at different time points from symptom onset (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), and in two

Table 3
False positivity rates of the Elecsys® assay and the EDI™ ELISAs (IgM and IgG) in 200 healthy blood donors and in 256 patients admitted to an intensive care unit (ICU).

	n (%)	Elecsys® assay[a] n negative (%) n positive (%)	EDI™ IgM[b] n negative (%) n positive (%)	EDI™ IgG[b] n negative (%) n positive (%)	EDI™ IgM or IgG[b] n negative (%) n positive (%)
Blood donors	200 (100%)	200 neg. (100%) 0 pos. (0%)	199 neg. (99.5%) 1 pos. (0.5%)	198 neg. (99%) 2 pos. (1%)	197 neg. (98.5%) 3 pos. (1.5%)
ICU patients	256 (100%)	255 neg. (99.6%) 1 pos. (0.4%)	252 neg. (98.4%) 4 pos. (1.6%)	253 neg. (98.8%) 3 pos. (1.2%)	249 neg. (97.3%) 7 pos. (2.7%)

[a]Elecsys® assay: negative (COI < 1.0); positive (COI ≥ 1.0).
[b]EDI™ ELISAs (IgM and IgG): negative (OD < positive cutoff); positive (OD ≥ positive cutoff).

cohorts of 200 healthy blood donors and 256 intensive care unit (ICU) patients, which were recruited prior to the COVID-19 outbreak (December 3rd 2019). For further details on the clinical study see supplementary data.

3. Results

Table 1 shows low true positivity rates of 3% for the Elecsys® assay and of 9% for the EDI™ ELISAs (IgM or IgG) within the first 5 days after symptom onset in the 64 patients with SARS-CoV-2 RT-PCR confirmed COVID-19. In the COVID-19 patients, the percentage of positive results rose with time from symptom onset, peaking to positivity rates after 15–22 days of 100% for the Elecsys® assay, of 94% for the EDI™ IgM-ELISA and of 100% for the EDI™ IgG ELISA (Table 1). In the 104 blood samples, the overall agreement between positive/negative classifications of the Elecsys® assay and the EDI™ ELISAs was 90% for IgM or IgG (Table 2).

The false positivity rates in the healthy blood donors and the ICU patients were < 1% for the Elecsys® assay and < 3% for the EDI™ ELISAs (Table 3).

In the supplementary data, we report the quantitative results of the Elecsys® assay and the EDI™ ELISAs in the cohort of patients with SARS-CoV-2 RT-PCR confirmed COVID-19, in the healthy blood donors as well as in the intensive care patients (Supplementary Table 1–3).

4. Discussion

The clinical evaluation of the Elecsys® assay revealed very high true positivity rates (i.e. seroconversion rates) of 100% after 15–22 days in the confirmed COVID-19 patients. The false positivity rates of the Anti-SARS-CoV-2 assay were < 1% in the healthy blood donors and in the ICU patients.

As stated above in the method section, the Elecsys® assay has been designed at high specificity for detection of mature/late antibodies which are predominantly, but not exclusively, IgG. Overall, we found an acceptable agreement between the Elecsys® assay and the EDI™ ELISAs (IgM or IgG) in the confirmed COVID-19 patients.

Of note, with the Elecsys® assay and the EDI™ ELISAs, we only report antibody binding to the recombinant nucleocapsid protein (N) and we did not perform neutralization assays in our SARS-CoV-2 RT-PCR confirmed patients. At the limit of detection we found surprisingly low CVs. We assume that these low CV's are due to the absence of SARS-CoV-2 antibodies in the negative plasma pool. A limitation of our study might be that the plasma aliquots of the healthy blood donors and the ICU patients have been stored for a prolonged time at −80 °C.

The Elecsys® assay and the EDI™ ELISAs are currently approved as qualitative assays. However, when looking at the quantitative data in Supplementary Table 1, we found a clear antibody response in SARS-CoV-2 antibody positive COVID-19 patients from < 5 days until > 15–22 days after symptom onset, indicating that these assays might be also suitable for serial measurements. In line with our findings, a very recent work on the antibody responses to SARS-CoV-2 in patients with COVID-19 demonstrated a similar approach using measured chemiluminescence values divided by the cutoff for reporting of SARS-CoV-2 antibody quantitative values/titers [8]. They further showed that serial serological testing may be helpful for the diagnosis of suspected COVID-19 patients with negative SARS-CoV-2 RT-PCR results and for the identification of asymptomatic infections in close contacts [8].

In conclusion, our results indicate a high sensitivity and specificity for the Elecsys® assay and an acceptable agreement with the EDI™ ELISAs.

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Honoraria: Benjamin Dieplinger and Thomas Mueller have received speaking fees from Roche Diagnostics.

CRediT authorship contribution statement

Margot Egger: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Christian Bundschuh:** 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, Methodology, 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.2020.05.049.

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