Reference laboratories

Referenzinstitut für Bioanalytik - RfB

Proficiency testing

The Reference Institute for Bioanalytics (RfB) has run a number of COVID-19 related proficiency tests.

The basis of the first regular survey was a pilot survey in April 2020. Within only 10 days the RfB organized together with the University Hospital Mannheim the pilot survey among 15 selected participants from Germany. Each participant received eight liquid serum samples from Covid-19 patients or patients with other respiratory infections. The patient samples had to be determined for presence of IgG, IgA and IgM antibodies against SARS-CoV-2. The results of all participants were compared with the patient's case history and the result of the virus neutralization test carried out at the Institute for Microbiology of the Bundeswehr in Munich. Due to the lack of a reference system the virus neutralization test was integrated into the study and is used to determine whether a patient sample contains antibodies that prevent cell infection by SARS-CoV-2 *in vitro*.

Seven test systems from different companies were represented in this pilot survey. The results show good specificity and sensitivity in the measurement of IgG and IgA antibodies. Minor problems were observed for the weak-positive sample regarding the sensitivity of some test systems. A significant lack of sensitivity could be seen for the determination of specific IgM antibodies in all test systems.

Since the pilot study confirmed the structure of the EQA scheme, the first regular survey started in May 2020. 180 laboratories, mainly from Europe, were registered as participants. Each laboratory received four samples of patients for the investigation of IgG and IgM. Evaluation of this survey revealed a good specificity for specific IgG testing in all test systems. The sensitivity was limited with serious differences between the different test kits. As in the pilot survey, this was particularly evident in the case of weakly positive samples. For anti-SARS-CoV-2 IgM testing no sensitivity could be determined because no positive samples were sent. However, the specificity testing remained below expectations. For this reason, and because testing for specific IgA antibodies is of greater clinical interest, the determination of IgM antibodies will be excluded from future surveys and the parameter IgA antibodies will be added.

Further surveys are planned for the third and fourth quarter of 2020. Information about the organization of the surveys as well as all results of the past surveys and the following surveys are freely available and published on the RfB website (www.rfb.bio).

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Promoting laboratory result harmonization in COVID-19 avoids confusion and permits unambiguous interpretation of study conclusions

In collaboration with the Clinical Pathology Unit of the 'Luigi Sacco' academic hospital, one of the two Italian reference centres for infectious diseases, CIRME has recently supervised studies on hospitalized COVID-19 patients in order to evaluate the role of laboratory tests as clinical predictors of disease severity. The evaluation of biomarkers was carried out in relation to two major clinical outcomes: death during hospitalization and admission to an intensive care unit (ICU). The focus was on identifying which markers had the best predictive power and, subsequently, on defining interpretative criteria (i.e. cut-off values) that may aid clinicians in evaluating COVID-19 severity. Optimum biomarker cut-offs were specifically selected to have a high rule-in ability in detecting patients at risk of in-hospital death and a high rule-out ability in identifying patients at very low risk of ICU admission (4, 5). At the multivariate analysis, high concentrations of lactate dehydrogenase (LDH) and low concentrations of albumin in serum were significantly associated with higher odds of death, while only low LDH activities remained associated with lower odds of ICU admission. The best cut-offs for death prediction were >731 U/L for LDH and ≤18 g/L for serum albumin, while an LDH activity <425 U/L was associated with a negative likelihood ratio of 0.10 for intensive treatment.

One of the major strengths of the published results was represented by the use of methodologies for which analytical selectivity and standardization had been verified and validated, enabling the universal application of results obtained in our clinical studies and permitting their unambiguous interpretation, providing that institutions implementing them also use standardized assays. Particularly, serum albumin was measured with an immunoturbidimetric assay, which is fully specific for the protein measurement, made traceable to the ERM-DA470k/IFCC reference material, and LDH was measured with a system of which the optimal alignment to the IFCC reference measurement procedure was recently validated (6)

(*Note that both the ERM-DA470k/IFCC reference material and the immunoturbidimetric method (ID no. C1RMP_P4) for serum albumin, and the IFCC reference procedure for LDH (ID no. NRMeth 66) are listed in the JCTLM database*).

These data provide a good example to show that the implementation of assay standardization is an absolute priority for optimizing healthcare, with the example given for COVID-19 patients. Only the use of assays providing standardized results allows the application of common decision limits, as those defined in our COVID-19 studies, worldwide and the comparability of clinical studies performed in different institutions.