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Instant review

# The importance of laboratory medicine in the era of COVID-19 pandemic: a challenge for patients, pediatricians, obstetricians, and clinical pathologists

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## Abstract

The dramatic and rapid widespread of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is causing millions of infected subjects and thousand of deaths worldwide. The current global goal is to mitigate or suppress the burden of COronaVIrus Disease 2019 (COVID-19) and to adopt effective targeted therapies. Laboratory tests include molecular diagnostics and viral antigens recognition for the identification of SARS-CoV-2 in human biological materials, serologic methods for detecting serum antibodies against SARS-CoV-2 and routine blood and urine tests. Many molecular tests, mainly based on real-time polymerase chain reaction (RT-PCR), have been developed after the publication of the SARS-CoV-2 full-length genome sequence; several factors may affect their accuracy, including inadequate sample collection, thermal inactivation, viral load, and cross-reactivity. *In-vitro* diagnostic (IVD) companies have developed serologic methods optimized on high throughput analytical platforms; however very few methods currently detect IgM and the accurate quantitative measurement of antibodies are not still ready. Sensitivity and specificity require robust validation; point of care (POC) lateral flow immunochromatographic assays are far to be highly sensitive and specific and data obtained by these methods should be evaluated with caution. The effectiveness of serologic tests depends on the appropriateness of test request too. Routine biochemical data in adults with COVID-19 reveal alterations of various tests, including lymphopenia, thrombocytopenia, hypoalbuminemia, and serum elevation of several biomarkers, including D-dimer, ferritin, C-reative protein (CRP), cytokines.

Cardiac troponins and N-terminal pro-brain natriuretic peptide (NT-pro BNP) are predictors of adverse outcome and death. Vertical transmission of SARS-CoV-2 has been not yet demonstrated exhaustively. Regrettably, in pregnant women, newborns and children with COVID-19, very limited and confusing data hamper a definitive conclusion on the value of routine laboratory tests. Emerging opportunities arise from the introduction of microbiomics, metabolomics, and pharmacometabolomics for improving patient's care and outcome.

### Keywords

Laboratory medicine, SARS-CoV-2, COVID-19, real-time polymerase chain reaction, serologic tests, routine laboratory tests, pregnant women, children, newborns.

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### Introduction

Between December 2019 and January 2020, a novel betacoronavirus has been detected and isolated in hospitalized patients with pneumonia of unknown cause in Wuhan, China [1]. The virus has spread at an unprecedented rate and the worldwide burden of the disease is still growing. The International Committee on Taxonomy of Viruses named this virus Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2). In late January 2020, the World Health Organization (WHO) declared the COronaVIrus Disease 2019 (COVID-19) as "a global public health emergency of international concern with a very high risk of transmission, requiring a coordinated global response". Since COVID-19 pandemic began, a never seen before impressive number of scientific studies have been published in a very short time, both as papers in peer-reviewed journals, preprints, and preliminary reports [2]. And, currently, the number of papers under revision as well as that of papers ahead of publication continues to rise weekly at an unbelievable rate. Few months of massive scientific research have considerably improved knowledge on viral genetics, host immunological response, molecular basis of virus replication, clinical features, and potential drug targets. Indubitably, results arising from these studies can contribute to achieving the current global goal, namely to mitigate or suppress the burden of COVID-19 within a short time. But no less substantial appears the new challenge for laboratory medicine, the hidden clinical science and discipline that saves lives providing metabolic, immunological, molecular, and microbiological data which are basic for clinical decision making [3, 4]. What is emerging from most studies is the need of novel accurate, reproducible, specific and sensitive diagnostic tests, easy to implement into the routine of clinical laboratories and with an adequate turn around time (TAT) for timely therapeutic interventions. For clinical pathologists and laboratory medicine professionals, these requirements have long since been put into daily practice; notably, laboratory medicine plays a basic role in reducing the length of the path from bench to bedside [4]. This is why, more than ever, laboratory tests should be considered crucial by any public health strategic plan designed to deal with the COVID-19 global emergency. Available and new tests are needful for: the screening of symptomatic and asymptomatic SARS-CoV-2 infections; the early diagnosis of COVID-19; the evaluation of serological immunity within communities; the monitoring of infected pregnant women over gestation and post-partum; the prevention of multiple organ failure; the post-infection serological follow-up. A tentative classification of diagnostic tests for COVID-19 includes: molecular diagnostics carried out by clinical laboratories; point of care (POC) molecular testing and tests based on the viral antigens detection; serologic tests, including POC testing; and biochemical-hematological tests.

### SARS-CoV-2 molecular tests

On 3 February 2020, the full-length genome sequence of SARS-CoV-2 was published [6] and genomic data have been shared by using online platforms (e.g., GISAID, GenBank). Thereafter, diagnostic companies, public health laboratories,

and clinical laboratories worldwide started to develop various reverse-transcription real-time polymerase chain reaction (rRT-PCR)-based methods for SARS-CoV-2 identification in human biological samples [7, 8]. Early, two SARS-CoV-2 molecular assays with high analytic sensitivity and specificity and minimal cross-reactivity with other coronavirus strains have been developed: the first one by the WHO [9] and the second one by the Centers for Disease Control and Prevention (CDC) [10]. These methods differ from each other in targeting genomic regions in the viral genome. The Foundation for Innovative New Diagnostics (FIND), a WHO collaborating center for laboratory strengthening and diagnostic technology evaluation, is conducting an independent evaluation of multiple SARS-CoV-2 assays that are currently in use; this evaluation will become available in the next future. Over 200 submissions were received and 21 methods were selected for the first round of independent evaluation. The latter is based on scoring criteria including the limit of detection (LOD), regulatory status, type of organization, quality management system, and the availability of other products in low- and middle-income countries. On 15 April 2020, data results were available for 5 molecular test kits fulfilling requirements. Several factors may affect SARS-CoV-2 assay inaccuracy [11], such as the lack of universal reference standard, unsatisfactory assay reproducibility (in terms of cycle threshold values), inadequate sample collection (including swabs containing substances potentially inhibiting PCR testing), transportation and pretreatment, thermal inactivation, and changes in viral load over time [12-14]. Besides, SARS-CoV-2 genome mutations in the primer and probe target regions may lead to false-negative results [15]. Nevertheless, rRT-PCR methods with high sensitivity and specificity, and performed by accredited laboratories managing high-complexity testing, remain the gold standard for COVID-19 diagnosis [16, 17]. Albeit saliva, bronchoalveolar lavage (BAL), and endotracheal aspirate display greater sensitivity compared to upper respiratory tract specimens, nasopharyngeal specimens for swab-based molecular testing are widely used for testing asymptomatic people in a healthcare setting, including long-term care facilities. Even oropharyngeal, mid-turbinate and anterior nares samples may be suitable [18]. False negative results are common in serum and urine samples, depending on the severity of the illness; conversely, viral nucleic acid is recognizable in feces, confirming the possible viral transmission by the fecal route [19]. This finding is of extreme relevance in the perinatal age, because of the likelihood of contamination during spontaneous delivery. It is reasonable to argue that the use of different specimen types during different stages minimizes the risk of inconsistent results.

## Point-of-care molecular tests and viral antigen detection assays

POC is strategic for a rapid identification of infected people, especially in emergency (e.g. resource-limited settings, aboard a cruise ship, military troops). Several *in-vitro* diagnostic (IVD) companies have developed rapid diagnostic tests outside laboratory settings either by implementing new cartridge-based assays on pre-existent platforms or by fine-tuning assays based on the detection of viral proteins (antigens). Some platforms have been successfully used in the past, for example to detecting *Mycobacterium tuberculosis* (MBT), Human Immunodeficiency Virus (HIV), Respiratory Syncytial Virus (RSV). With the dramatic global spread of SARS-CoV-2, the US Food and Drug Administration (FDA) started to authorize multiple real-time polymerase chain reaction (RT-PCR) assays; most of them require a robust validation in order to determine their sensitivity and specificity. A couple of platforms received a preliminary evaluation: the first one is a batch-based qualitative assay (90 samples/run every 90 minutes) that detects the SARS-CoV-2-specific ORF1 and part of the E-gene conserved across sarbecoviruses, including SARS-CoV-2. Even the second one, a 45-minute random-access assay, detects the pan sarbecovirus E-gene; in addition, the method detects the N2 region of the N-gene as specific target [20].

Viral antigens can be detected directly from clinical specimens by immunoassays using specific monoclonal antibodies against the nucleocapsid protein of SARS-CoV-2; results are evaluated by the naked eye by way of chromatographic particles, occasionally resulting in ambiguous or non-interpretable clinical information. Theoretically, these immunoassays are reliable, as claimed in a pre-peer reviewed paper [21], ideal for particular communities, such as children and infants, easy to perform, rapid, and convenient; however, they require a high viral count to work effectively [22] and generally they are marked by poor accuracy [23]. As a consequence, positive results must be

confirmed by accredited clinical laboratories with reference molecular tests. Negative results should be evaluated carefully, and the test should be repeated when COVID-19 clinical signs and symptoms are suspected or when the subject has had a possible contact with someone infected by the SARS-CoV-2. With the limited currently available data, WHO decided to discourage the use of antigen-detecting rapid diagnostic tests [24]. Nevertheless, the dissemination of commercially available POC immunoassays for detecting viral antigens is rapidly growing and diagnostic developers seem to promise more reliable POC methods in the near future [25]. It is crucial to highlight that POC does not mean self-testing, self-interpretation, and self-management. Foremost, the quality of diagnostic tests and devices used outside laboratory should be monitored by laboratory professionals; otherwise, test results may be unreliable and arguable, inducing errors in clinical decision making. Second, test results should be interpreted by laboratory medical staff, in order to convert a number or a device report into a clinical information. Third, self-management must be avoided: each result should be evaluated by general practitioners or clinicians for an appropriate intervention.

## Serology testing

The next frontier in SARS-CoV-2 testing is the detection of antibodies produced by anyone who has been infected by the virus, namely serologic tests. Two critical issues affect this diagnostic tests: how to optimize the *in-vitro* production of viral antigens to avoid false-positive and false-negative results; how to interpret results and what they mean. One of the main obstacles in the development of reliable serologic tests is the knowledge of the viral protein target(s) (antigens) against which the human immune system responds by producing antibodies. Theoretically, all viral proteins elicit antibody response; however, the most reactive antigen eliciting antibodies is the spike (S) protein. The spike protein is a large, highly glycosylated type I transmembrane protein assembled into trimers on the virion surface to form the distinctive crown-like appearance (corona); experimental studies showed that the recombinant spike protein can bind with recombinant ACE2 protein [26]. Such serologic tests use protein spike subunit(s) as antigen(s) (e.g. the receptor binding domain, RBD), while others use a mixture of nucleocapsid (N) protein with spike protein. A further critical step encountered by diagnostic developers is to reproduce the right structure of the viral proteins (or polypeptide subunits). Actually, the complex protein structure may be unstable, assuming deformed shapes that can mask the antibody target, hampering either the complete recognition of the antigen (that means false-negative results) or an incomplete recognition of the antigen (that means underestimation of the antibodies titer). The choice of viral protein(s) or their subunits and their stabilization are key factors for producing serologic tests with high specificity, minimizing the odds of cross-reactivity with antigens expressed by other coronaviruses, for example SARS-CoV (that means minimization of false-positive results). Clearly, achieving these goals takes time and this is why only in April 2020 the market started to make available a growing list of serologic tests detecting IgG and IgM antibodies anti-SARS-CoV-2 and based either on chemi-luminescent immunoassays (CLIA), optimized for high-throughput analytical platforms, or enzyme-linked immunosorbent assays (ELISA). However, the road ahead is still long: first, the evaluation of these methods by official agencies (e.g. FDA, WHO), academic researchers and clinical laboratories has just started [27-29] and requires to test hundreds of COVID-19 positive cases and thousands of negative ones [30]. Second, currently only few methods detect IgM antibodies. Third, results are still semi-quantitative, making more difficult test interpretation, especially when the result falls in the so-called “grey zone”, that means doubtful result (equally may be false positive or false negative); in these cases, a second serologic test is mandatory and should be performed by using a different method. Obviously, IVD companies are making great efforts to closing these gaps and investing resources to develop new tests, such as the detection of IgA in saliva and neutralizing antibodies. Before April, various POC lateral flow immunochromatographic assays were commercially available and currently their number is ramping up quickly. These devices, cheap and easy to use, and combining qualitative test for IgG and IgM antibodies, require a couple of drops of blood withdrawn by finger prick and deliver results in few minutes. Results simply consist of a qualitative evaluation, positive or negative, that is black or white, without any further information [31]; more important, their sensitivity and specificity are far below 100% [32]. Last, but not least, their cost is apparently lower than that of

CLIA and ELISA; actually, for large batch testing, lateral flow assays are more expensive and time consuming than high-throughput analytical systems for immunology- and serology-based tests. Despite evident analytical limitations, various studies based epidemiological surveys on lateral flow assays, generating more controversy than clarity, and affecting social and economic policies [33]. It could argue that previous data obtained by lateral flow immunochromatographic assays might be questionable: hypothesis as "individuals who were infected and developed severe COVID-19 display undetectable production of antibodies" as well as "several mild or asymptomatic patients don't develop antibodies" might be deceptive and require robust confirmations by using next generation quantitative serological tests, validated by official agencies and academic bodies. As stated by the American Department of Health and Social Care "an unreliable test is worse than no test" [34]. Test result interpretation needs specific knowledge on possible analytical pitfalls affecting the accuracy of data and on the pathophysiology of the human immune response. Moreover, results should be interpreted on the basis of the question supporting test request: "why, to whom, and when should a serologic test be performed?". The rationale of serologic tests lies on several purposes: to explore the magnitude of asymptomatic individuals in a population; to screen health workers; to better understand how quickly COVID-19 patients start to develop antibodies against the virus; to provide key data for shaping the course of the pandemic; to inform whether and how to reopen schools, given that few cases have been diagnosed among children, but it isn't clear whether that's because they don't get infected or because their infections are generally so mild that they go unnoticed; and to understand how long immunity to the virus lasts, a key issue for any future vaccine [35]. In addition, serologic tests allow the identification of candidate plasma donors to treat critically ill patients [36]. The appropriate request of serologic tests require knowledge on their diagnostic window; a recent exposure to the virus may yield to false negative results. In 173 patients with SARS-CoV-2 infection it was observed that specific IgM antibodies become detectable in about 70% of symptomatic patients after 8-14 days from the viral infection; after 11-24 days, 90% of total antibodies become positive and after 39 days the cumulative seropositive rate reaches 100% [37]. Other researches found seroconversion in 50% of patients by day 7 and 100% by day 14 [38]. Wide use of serology testing is thought to be useful in detecting and determining prevalence of "silent" carriers. Therefore, some authorities have raised the idea of granting "immunity passports" to people who recover from the virus, allowing their return to daily life without restrictions. Clearly, the hope is that the presence of the antibodies is an indication that the person is protected from another infection. However, the "presumed" immunity should be proven and the current limitation of reliable data is causing controversial opinions. In April 2020, Anthony Fauci, the head of the US National Institute of Allergy and Infectious Diseases, claimed "it's a reasonable assumption that this virus is not changing very much. If we get infected now and it comes back next February or March we think this person is going to be protected." Simultaneously, Maria D. Van Kerkhove, an American infectious disease epidemiologist serving as the WHO's technical lead for COVID-19, said "right now, we have no evidence that the use of a serologic test can show that an individual is immune or is protected from reinfection". Very recently, WHO expressed concern about "immune passports", because how much protection the antibodies confer and for how long is still unknown [39]. WHO is also warning that many testing kits to check for SARS-CoV-2 antibodies still need to be properly validated. Further concerns have been expressed on what level of antibodies might be required for a person to be protected from a second SARS-CoV-2 infection; whether a high initial antibody titer will take longer to wane than low levels; and whether the strength of the antibody response could correlate with the severity of infection. All these questions may be addressed in the near future only if three conditions are met: the delivery of strategic plans, tailored for each specific purpose; the delivery of reliable results, which should be a part of the so called big data (individual and collective) managed by innovative tools, for example artificial intelligence (AI) [40]; the governance of data results by clinical laboratories and scientific bodies, for example the harmonization between methods and analytical platforms. Otherwise, any conclusion cannot be definitive, deriving from uncontrolled and fragmented data. Ultimately, the choice of methods cannot rely on kit price solely: the quality must be the driver to selecting those methods with best analytical performances. On the

other hand, if the low-cost of diagnostics and analytical instrumentation corresponds to low quality, global costs arising from low accuracy in test results overcome costs of diagnostic systems with high-quality, as demonstrated elsewhere [41].

## Routine clinical laboratory tests in COVID-19 adult patients

Laboratory-based clinical decision making is basic not only for the direct or indirect detection of SARS-CoV-2 infection: routine urine and blood biochemical, hematologic, and coagulation tests offer information on the severity, the progression and complications of the COVID-19, depicting the effectiveness of therapeutic treatment [42]. Abnormalities in clinical laboratory tests can also indicate the progressive multi-organ failure, often associated with the adverse evolution of the disease. Interestingly, C-reactive protein (CRP), lactic dehydrogenase (LDH), and lymphocyte count have been included in AI-based prediction models for severe prognosis in COVID-19 patients [43]. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has promptly created a task force of laboratory medicine experts from all over the world, led by Prof. Giuseppe Lippi [44]. This group is intended to help clinical pathologists and laboratory medicine professionals to face the COVID-19 emergency by several free available tools, including tentative guidance and consensus documents for harmonizing the use of diagnostic and serological tests for COVID-19; clinical, technical and organizational perspectives of laboratory-based and POC testing in COVID-19 patients; integration of data on COVID-19 laboratory abnormalities from all over the world, and promotion or coordination of new studies; repository of scientific articles on laboratory testing for diagnosing, prognosticating and monitoring COVID-19. Altered test results may help to identify infected patients at the early stage of COVID-19 either not identified by SARS-CoV-2 diagnostic tests (false negative) or never tested for SARS-CoV-2. Despite a considerable heterogeneity among published studies (due to variables such as the number of patients enrolled in the study, patient's classification and age, clinical outcome, preanalytical factors, analytical methods, reference ranges and decision levels), there is a substantial concordance on the most common laboratory features in patients with COVID-19 and on the predictive value of several tests. In most cases, it was registered lymphopenia, associated with a considerable decrease of CD4 and CD8, thrombocytopenia, and hypoalbuminemia, together with high levels of: ferritine, C-reactive protein (CRP); D-dimer; creatine kinase (CK); lactate dehydrogenase (LDH); transaminase; creatinine; and myoglobin [45-50]. As confirmed by an elegant retrospective study, abnormal levels of tests previously mentioned are exacerbated in deceased patients, while other tests, such as cardiac troponins (I and T), N-terminal pro-brain natriuretic peptide (NT-pro BNP), cytokines, and procaltitonin, are predictive of patient's mortality [51]. Cytokines have been found increased in various studies, confirming the frequent presence of the cytokine release syndrome (CRS) in COVID-19 patients [52]; in particular, interleukin-6 (IL-6) has been found significantly increased in most studies, reflecting respiratory failure and acute respiratory distress syndrome (ARDS), and predicting adverse outcome. The risk of severe SARS-CoV-2 infection is around 5-fold higher (Odds Ratio [OR] 4.76; 95% C.I., 2.74-8.29) in patients with increased procalcitonin, suggesting the importance of serial measurements of this biomarker during the course of the disease for predicting the evolution towards severe forms [53]. However, further studies with larger number of patients are required to confirm these data. Due to the lack of cut-off levels standardization and high biological variability, the literature on thrombocytopenia in COVID-19 patients is partially discordant; indeed, few studies reported thrombocytopenia in non-severe COVID-19 patients, while the majority of publications reported the opposite [54]. In definitive, thrombocytopenia discriminates between severe and mild COVID-19, reinforcing the notion that platelets depletion may be an early index of intravascular coagulopathy, which in turn evolves towards disseminated intravascular coagulation and patient's death. This is confirmed by the association between the severity of COVID-19 and D-dimer elevation: a pooled analysis revealed that, in 4 studies involving a total of 553 patients, D-dimer values ranged 2.5-9 folds higher in severe COVID-19 [55]. A simple urine dip stick test may be predictive of COVID-19 severity: in a cohort of 119 COVID-19 patients and 45 healthy adults, glycosuria and proteinuria discriminated critical (n = 10) and severe (n = 42) patients from those with moderate COVID-19 (n = 67); when COVID-19 patients were compared with controls, hematuria and proteinuria were significantly different, while leucocytes were not [56]. Since urinalysis is a

simple, cheap test, easily practicable at home, in newborns and children, and in low-income communities, the utilization of this test might be relevant for an early diagnosis on the progression of the disease before hospital admission.

## Laboratory tests in pregnant women with COVID-19

Pregnant women are vulnerable to viral infections; during pregnancy, cell-mediated immunity favors the protection of the fetus by shifting the predominance of T-helper (Th) from Th1, producing microbicidal and proinflammatory cytokines (e.g., IL-1α, IL-1β, IL-6, IL-12) to Th2, producing anti-inflammatory cytokines (e.g., TGF-β, IL-4, IL-10, IL-13). However, evidences suggest that an early adaptive immune responses in pregnant women with COVID-19 [57] results in milder disease severity compared with adults and non-pregnant women. On the other hand, pregnant women with either pre-existent chronic diseases or complicated pregnancy (e.g., gestational diabetes, preeclampsia) are at increased risk of severe COVID-19. Vertical transmission seems to be unlikely, albeit very few neonates born from COVID-19 infected mothers were found RT-PCR SARS-Cov-2 positive [58-60]. Two different research groups hypothesized vertical transmission in neonates on the basis of their elevated SARS-CoV-2 IgM antibody levels after birth [61, 62]; however, their respective nasopharyngeal swabs were RT-PCR SARS-CoV-2 negative, raising concerns on the reliability of serological tests (in both studies, data on sensitivity and specificity of SARS-CoV-2 IgM antibodies were difficult to verify) and suggesting caution in interpreting the results [63]. Only robust evidences on positive testing in amniotic fluid, umbilical cord blood, and breast milk could support in the future the SARS-CoV-2 vertical transmission. Available data from the literature on routine laboratory tests in COVID-19 pregnant women are limited, often incomplete, heterogeneous, and sometimes minimal or confusing. These limitations, together with the low number of patients enrolled in the studies, make hard an overview on biochemical and hematologic tests in COVID-19 pregnant women; regrettably, such studies and even reviews reported no test result in infected pregnant women [60, 64-68]. A robust study involved 116 pregnant women, 65 of them RT-PCR SARS-CoV-2 positive and 51 with clinically-diagnosed COVID-19 [69]. In the group of 65 laboratory-confirmed pregnant women, 4.6% exhibited lymphocytosis, 58.5% lymphopenia, and 49.2% high levels of CRP; no further laboratory results have been reported for this group. Eight women were admitted in Intensive Care Unit with pneumonia and their laboratory results are better detailed (**Tab. 1**). A very preliminary evaluation suggests similar, but less severe, alterations than those observed in adults admitted in Intensive Care Units. **Tab. 1** summarizes the most frequent laboratory data found in the literature.

**Table 1.** Laboratory test results in pregnant women with COVID-19.

| Test | Chen H. et al. [58] (n = 9) | Yu N. et al. [59] (n = 7) | Chen L. et al. [66] (n = 118) | Dashraath P. et al. [64] (n = 55) [a] | Cao D. et al. [68] (n = 10) [b] | Yan J. et al. [69] (n = 8) [c] |
|---|---|---|---|---|---|---|
| **Leucocytosis** | 11% | 0% | n.r. | 38% | 20% | 62% |
| **Lymphopenia** | 55% | 71% | 44% | 22% | 60% | 75% |
| **Thrombocytopenia** | n.r. | 29% | n.r. | 13% | n.r. | 12% |
| **Hypoalbuminemia** | n.r. | 71% | n.r. | n.r. | n.r. | n.r. |
| **Elevated D-dimer** | n.r. | 100% | n.r. | n.r. | 0% | 50% |
| **Elevated ferritin** | n.r. | 33% | n.r. | n.r. | n.r. | n.r. |
| **Elevated CRP** | 75% | 100% | n.r. | n.r. | 60% | 100% |
| **Elevated procalcitonin** | n.r. | 67% [d] | n.r. | n.r. | n.r. | 87% |
| **Elevated IL-6** | n.r. | 100% [e] | n.r. | n.r. | n.r. | n.r. |
| **Elevated LDH** | n.r. | 100% | n.r. | n.r. | 30% | 50% |
| **Elevated AST** | 33% | 29% | n.r. | n.r. | 0% | 25% |

[a] Cumulative results from 55 pregnant women; [b] after delivery; [c] 8 out of 116 COVID-19 pregnant women admitted in the Intensive Care Unit; [d] measured in 6 women; [e] measured in 4 women.
n.r.: not reported.

### Laboratory tests in newborns and children with COVID-19

Limited epidemiologic and clinical data are available for newborns, children and teenagers with COVID-19. An early epidemiological retrospective analysis of COVID-19 among 2,135 Chinese children (34.1% identified as laboratory-confirmed cases and 65.9% as suspected cases) aged 0-18 years (median age of 7 years, IQR 2-13 years) showed no statistical difference between males and females [70]. A small number of children (4.4%) were asymptomatic and 5.8% exhibited severe COVID-19 clinical signs and symptoms; only a child died. The disease severity was inversely correlated with patient's age, being higher over the first year of life (10.6%) and then progressively decreasing up to 3.0% in teenagers aged 15-18 years. Newborns and infants resulted more vulnerable to COVID-19, even though the overall rate of severe disease in this population was significantly lower than in adults. Beyond anecdotal reports and suggestive hypothesis, such as the co-existing presence of other viruses in the respiratory tract of young children, a lower risk of exposure to the virus in childhood, a more active innate immune response, and reduced ACE2-binding activity in infants and children, no definitive evidence-based conclusion has been published on the less susceptibility of children to the SARS-CoV-2 infection [71, 72]. Cumulative laboratory data in COVID-19 in infants and children are consistent with the low frequency of severe clinical features and thus the number of altered tests and the magnitude of their alterations are less pronounced than in severe adult COVID-19. As previously evidenced for COVID-19 in pregnant women, most published articles on COVID-19 in children have reported few, heterogeneous, confusing, and incomplete laboratory test results; in addition, follow-up data are almost always not reported, partially reported or not mentioned. A systematic review included 18 articles on SARS-CoV-2 infection in children and adolescent, reporting data on diagnosis, clinical symptoms, therapeutic management, prognosis, and radiologic tests [73]. Unfortunately, no routine laboratory data was either reported or commented in the review, as if this type of information were unnecessary. Two retrospective Chinese studies, published by the same group, analyzed all newborns with COVID-19 born between December 8, 2019 and February 6, 2020 and between December 8, 2019 and March 13, 2020, respectively [74, 75]. No routine laboratory data was showed. The lack of information on laboratory tests in pediatric and neonatal populations with COVID-19 is confirmed in a recent paper synthesizing laboratory data from 12 published articles, corresponding to a total of 66 pediatric patients [76]. Reading the table reporting the characteristics of the 12 studies, it is clear that clinical data are rigorously complete in each article, while laboratory data are largely incomplete and probably incomparable between studies in terms of biomarker concentration and reference ranges. For example, serum albumin was reported in 3 studies only, D-dimer in 4, LDH in 5, creatinine in 6 (50%). It is disappointing to note that an article reported only a test, leucocyte count; another study "forgot" to indicate the lymphocyte count within the hematologic profile, and 2 articles reported incomplete hematologic data together with 2 biochemical tests only [76]. CRP, a biomarker basically useful for clinical decision making, was reported by 10 studies and procalcitonin by 8. Leucocyte count was the unique laboratory test result reported by 100% of articles. This means that currently a robust elaboration of laboratory data available from most published studies on COVID-19 in pediatric and neonatal populations is unlikely; moreover, the searching of a biomarker cut-off level discriminating children with severe from those with mild-to-moderate COVID-19 clinical course is hampered by the paucity of results, lack of standardization of sample collection time during the follow-up, heterogeneity in units of measurement, reference intervals, methods, and, ultimately, by the lack of harmonization. Laboratory findings in 10 confirmed COVID-19 children aged 1-12 years evidenced no high-risk factor: no child had lymphopenia, 10% of children had leukocytosis and increased CRP levels, 20% increased AST, and no one presented increased ferritin [77]. Interestingly, in a child treated for 6 days, molecular testing from throat swab samples were repeatedly negative, but nucleic acid test from stool swab performed 15 days after the onset of the disease was positive over 7 days, suggesting that the disappearance of SARS-CoV-2 from the respiratory tract does not exclude the likelihood of viral transmission via oral-fecal contamination. In a study on 19 full-term newborns born from mothers with COVID-19, 10 laboratory-confirmed and 9 clinically-diagnosed, RT-PCR SARS-CoV-2 were negative in all the newborns; no newborn manifested clinical and radiologic evidences of the disease [78]. Thrombocytopenia was observed in 15.7% of newborns, lymphopenia

in 21%, elevated CRP in 10.5%. Authors did not report reference ranges; therefore, on the basis of current literature, it is reasonable to assume that no baby showed leukocytosis and elevated level of ALT and creatinine. The analysis of the literature suggests several reflections: there is the lack of robust data on routine clinical laboratory tests in newborns, infants, and teenagers with COVID-19; most studies ignore laboratory data; longitudinal follow-up are necessary to associate clinical outcomes to changes in biomarker concentration.

## Future perspectives

In the era of COVID-19 pandemic, emerging technologies, knowledge, and bioinformatics offer novel challenges for laboratory medicine: from one hand, individualized patient's care and precision medicine require an holistic approach based on the interplay of "omics" sciences, including genomic, proteomic, metabolomics, and metagenomics. On the other hand, clinical laboratories are characterized by an incessant technological innovation able to improve test quality specifications (i.e., accuracy, reproducibility, linearity, analytical specificity and sensitivity) and laboratory automation. Over the past years, a growing number of clinical chemistry analytical methods have been optimized on mass spectrometry-based platforms, for example therapeutic drug monitoring, steroid hormones, vitamins and many others [79]. Clinical microbiology has been revolutionized by the introduction of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and by nucleic acid-based methods, including metagenome analysis platforms [80, 81]. One of the most intriguing questions emerging during the clinical course of COVID-19 is whether the severity of the disease and adverse outcome are correlated with a migration of gut bacteria to the lung, due to increased permeability of the intestinal mucosa. This bacterial translocation reshapes lung microbiota, worsening inflammation and organ damage, and inducing increased alveolus-capillary hyper-permeability, which in turn increases the microbial immigration [82]. Microbiomics and metabolomics (the study of the metabolic profile in a biological fluid or tissue) could reveal these changes much earlier than clinical signs, improving the patient's care. It is important to highlight that costs associated with omics are overcome by cost savings deriving from a shorter stay of patients in Intensive Care Unit and, more relevant, by saving the patient's life in most cases. Even pharmacometabolomics could represent a fascinating perspective for applying precision medicine in COVID-19 patients. Pharmacometabolomics enables targeted individual therapies on the basis of the metabolic fingerprint, originated by the interplay between genomics, microbiomcs, environment, and the viral infection [83]. Experimental studies start to be published in this field [84]. Collection of big data may accelerate the effective role of pharmacometabolomics, even though data standardization is mandatory. Clearly, laboratory professional should improve and update their expertise, making available interpretative comments and medical counseling for an optimal clinical use of laboratory data.

## Conclusions

The emergency of COVID-2 pandemic has negatively influenced the accuracy of most studies and thus laboratory data currently available are largely incomplete and must be evaluated with caution, especially in pregnant women and in neonatal and pediatric patients. After few months of COVID-19 pandemic, knowledge on molecular, immunological, and pathological mechanisms are still insufficient to formulate exhaustive elucidations on current and future trajectories of the disease and the appropriate therapeutic treatment. An emblematic example is the urgent need to demonstrate whether or not newborns can be infected by SARS-CoV-2 vertical transmission. Analytical pitfalls and inaccuracies affect molecular and serologic tests, especially POC testing, and thus it is hard to depict an accurate map of the global viral spread: perhaps, 100% sensitivity and specificity remain the "holy grail". However, our fate will be favorable if both sensitivity and specificity are not below 99% and this threshold is crucial also for assessing the effectiveness of future vaccines. WHO recommendations and alerts should be better divulged and accepted until they are contradicted by evidence-based findings. Thus, the claim "point of care tests should be used only for research" [30] calls for adopting strategies based on reliable tests performed within clinical and research laboratories. And ultimately, laboratory professionals are called to cooperate with clinicians, researchers, policy makers and public administrators for designing effective strategies of public health. We urgent need to stop the virus spread: this challenge cannot be won without the essential contribution of laboratory medicine.

## Declaration of interest

The Author declares that there is no conflict of interest.

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