Letter to the Editor

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Laboratory abnormalities in patients with COVID-2019 infection

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To the Editor,

Coronavirus disease 2019 (COVID-19), a form of respiratory and systemic zoonosis caused by a virus belonging to the Coronaviridae family, originated from the town of Wuhan in China, is still spreading around the world, thus assuming the dramatic features of a pandemic emergency [1]. According to the recent statistics of the World Health Organization (WHO), the disease has already involved all continents, with over 80,000 diagnosed cases in 34 different countries, and nearly 2700 deaths until February 26, 2020 [2]. Despite the severity of COVID-19 seems lower than that of the two previous coronavirus diseases, i.e. SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), the long incubation period and the relatively low pathogenicity compared to that of the two previous homologous viruses are contributing to sustain and amplify the outbreak inside and outside China.

Although the clinical characteristic of COVID-19 have been broadly defined [3], an outline of the most representative laboratory abnormalities found in patients with COVID-2019 infection is still lacking to the best of our knowledge. It was previously highlighted that laboratory medicine plays an essential role in the early detection, diagnosis and management of many diseases [4]. COVID-2019 makes no exception to this rule, whereby real-time reverse-transcription polymerase chain reaction (rRT-PCR) enables direct virus identification, whilst detection of anti-COVID-19 antibodies by means of fully-automated immunoassays is the mainstay of serological surveillance [5]. Nevertheless, the role of laboratory diagnostics extends far beyond etiological diagnosis and epidemiologic surveillance, whereby *in vitro* diagnostic tests are commonly used for assessing disease severity, for defining the prognosis, for following-up patients, for guiding treatment and for their therapeutic monitoring [6]. Therefore, the aim of this article is to provide a brief overview on the most frequent laboratory abnormalities encountered in patients with COVID-2019 infection.

An electronic search was performed in Medline (PubMed interface), Scopus and Web of Science, using the keywords "2019 novel coronavirus" or "2019-nCoV"or "COVID-19" without date (i.e. up to February 24, 2020) or language restrictions. The title, abstract and full text (when available) of all articles identified according to these search criteria were scrutinized by the authors, and those describing significant laboratory abnormalities in patients with severe COVID-19 infection were finally selected. The references of identified documents were also crosschecked for detecting additional studies.

Overall, 217 articles could be originally identified using our search criteria, 206 of which were excluded after title, abstract or full text reading, because they did not report specific data on laboratory test results (data now shown, due to space constrains). Therefore, a total number of 11 studies were finally selected, eight of which reported the rate of abnormal laboratory test results, as summarized in Table 1 [7–14]. One additional study, published by Pan et al. and involving 21 patients (71% women; age range, 25–63 years) with non-severe COVID-19 infection, did not clearly describe the rate of patients with laboratories abnormalities, but only reported the most frequent abnormalities, including increased values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) and D-dimer [15].

As regards prognostic laboratory data, which may be even more vital for the timely identification of patients at

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Table 1: Main characteristics of the included studies.

Characteristics	Zhang et al. [7]	Huang et al. [8]	Chen et al. [9]	Xu et al. [10]	Liu et al. [11]	Wang et al. [12]	Chen et al. [13]	Chen et al. [14]
Location	Wuhan, China	Wuhan, China	Wuhan, China	Zhejiang, China	Shenzhen, China	Shenzhen, China	Wuhan, China	Wuhan, China
No. cases	140 (58 severe)	41 (13 severe)	99 (17 severe)	62 (1 severe)	12 (6 severe)	34 children (no severe)	29 cases (14 severe)	9 pregnant
Age	57 years (median)	49 years (median)	56 years (mean)	41 years (median)	54 years (mean)	8 years (median)	56 years (median)	30 years (mean)
Women, %	49%	27%	32%	44%	33%	59%	28%	100%
Setting	Hospitalized patients	Hospitalized patients	Hospitalized patients	Hospitalized patients	Hospitalized patients	Hospitalized patients	Hospitalized patients	Hospitalized patients
Laboratory data								
Leukocytes	↑12%; ↓20%	↑30%; ↓25%	↑24%; ↓9%	↑2%; ↓31%	↑8%	↑15%	↑21%; ↓21%	↑22%
Neutrophils	N/R	N/R	↑38%	N/R	↑17%	↑15%	N/R	N/R
Lymphocytes	↓75%	↓63%	↓35%	↑58%; ↓42%	↓55%	↓3%	↓69%	↓56%
Eosinophils	↓53%	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Platelets	N/R	↓5%	N/R	↓5%	↓8%	N/R	↓17%	N/R
Hemoglobin	N/R	N/R	↓50%	N/R	N/R	N/R	↓41%	N/R
CRP	↑91%	N/R	↑86%	N/R	↑83%	↑3%	↑93%	↑75%
Procalcitonin	↑35%	↑8%	↑6%	↑11%	↑8%	↑3%	↑0%	N/R
ESR	N/R	N/R	↑85%	N/R	N/R	↑15%	N/R	N/R
Albumin	N/R	N/R	↓98%	N/R	↓50%	N/R	↓52%	N/R
ALT	N/R	N/R	↑28%	N/R	↑17%	N/R	↑17%	↑33%
AST	N/R	↑37%	↑35%	↑16%	↑8%	N/R	↑24%	↑33%
Bilirubin	N/R	N/R	↑18%	N/R	↑0%	N/R	↑3%	N/R
Creatinine	N/R	↑10%	↑3%	↑5%	↑17%	N/R	↑7%	N/R
CK	↑7%	↑33%	↑13%	N/R	↑17%	N/R	N/R	N/R
LDH	N/R	↑73%	↑76%	↑27%	↑92%	↑29%	↑69%	N/R
Myoglobin	N/R	N/R	↑15%	N/R	↑17%	N/R	N/R	N/R
Cardiac troponins	N/R	↑12%	N/R	N/R	↑8%	N/R	N/R	N/R
Ferritin	N/R	N/R	↑63%	N/R	N/R	N/R	N/R	N/R
Glucose	N/R	N/R	↑52%	N/R	N/R	N/R	N/R	N/R
D-dimer	↑43%	N/R	↑36%	N/R	N/R	↑9%	N/R	N/R

Laboratory data are reported as percent of patients with abnormalities defined according to the local reference ranges. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; N/R, not (clearly) reported.

higher risk of adverse outcome, an interesting report has been published by Wang et al. who examined the behavior of six laboratory parameters throughout 19 days of hospital admission in 138 patients with COVID-19 infection (33 with severe disease), five of whom died during their hospital stay [16]. Several significant differences were noted between patients who needed admission to the intensive care unit (ICU) and those who did not, especially encompassing higher white blood cell (WBC) count (1.5-fold), higher neutrophil count (1.7-fold), lower lymphocyte count (0.9-fold), as well as higher values of LDH (2.1-fold), alanine aminotransferase (ALT) (1.5-fold), aspartate aminotransferase (AST) (1.8-fold), total bilirubin (1.2-fold), creatinine (1.1-fold), cardiac troponin I (2.2-fold), D-dimer (2.5-fold) and procalcitonin (1.2-fold). As regards this last parameter, the rate of patients with abnormal values admitted to the ICU was over 3-fold higher than that of those who were not (75% vs. 22%; $p < 0.001$). It has also been reported that non-survivors more frequently developed lymphopenia and leukocytosis, along with abnormal values of D-dimer, blood urea nitrogen and creatinine. In the study of Zhang et al. based on 140 COVID-19 patients (58 with severe disease) [7], significantly higher values of D-dimer (2-fold), CRP (1.7-fold) and procalcitonin (2-fold) could be observed in patients with severe disease compared to those with a milder form. In the study published by Huang et al. involving 140 COVID-19 patients (13 with severe disease) [8], significant predictors of ICU admission were leukocytosis (2.0-fold increased in ICU patients), neutrophilia (4.4-fold increased), lymphopenia (0.4-fold, i.e. decreased), prothrombin time (PT; 1.14-fold increased), D-dimer (4.8-fold increased), albumin (0.8-fold, i.e. decreased), ALT (1.8-fold increased), total bilirubin (1.3-fold increased), LDH (1.4-fold increased) and procalcitonin, whose values were increased in 25% of patients who were admitted to the ICU compared with 0% who were not ($p = 0.029$). Similar findings emerged from the article published by Liu et al. who found that disease severity could be predicted by lymphopenia, neutrophilia, low values of albumin, as well as by increased values of LDH and CRP [11]. Finally, Tang et al. followed-up 183 patients with confirmed COVID-19 infection (54% women; mean age, 54 years) during their hospital stay [17], and found that coagulation parameters were more frequently deranged in those who died ($n = 21$) than in those who survived. Specifically, the values of PT, D-dimer and fibrin/fibrinogen degradation products (FDP) were found to be 1.14-, 3.5- and 1.9-fold higher in non-survivors than in survivors, respectively. Overall, 71.4% of patients who died fulfilled the criteria for diagnosing disseminated intravascular coagulation (DIC) compared to only 0.6% of those who survived.

Although some limitations must be acknowledged in our analysis of the current scientific literature (i.e. limited samples size, all COVID-19 cases originating from the same country, operative definitions are still underway, some clinical studies are still ongoing or undergoing publication), the currently available data suggests that many laboratory parameters are deranged in patients with COVID-19 (Table 1), and some of these may also be considered significant predictors of adverse clinical outcomes (Table 2). With the exception of the study of Liu et al. which only included children with mild COVID-19 infection, the most frequent abnormalities were lymphopenia (35–75% of cases), increased values of CRP (75–93% of cases), LDH (27–92% of cases), ESR (up to 85% of cases) and D-dimer (36–43% of cases), as well as low concentrations of serum albumin (50–98% of cases) and hemoglobin (41–50%). Many laboratory abnormalities were instead predictive of adverse outcome, as summarized in Table 2.

A particular mention shall be made for procalcitonin and coagulation tests. The former test does not appear substantially altered in patients with COVID-19 at admission, but the progressive increase of its value seemingly mirrors a worse prognosis. This is not unexpected, whereby serum procalcitonin levels are typically normal in patients with viral infections (or viral sepsis), whilst its gradual increase probably mirrors bacterial superinfection [18], which may then contribute to drive the clinical course towards unfavorable progression. The measurement of other innovative sepsis biomarkers, such as presepsin, for example, would probably help in increasing the accuracy in identification of severe COVID-19 cases, as well as for improving the current approach used for mortality risk prediction [19]. As concerns hemostasis

Table 2: Main laboratory abnormalities in patients with unfavorable progression of coronavirus disease 2019 (COVID-19).

– Increased white blood cell count
– Increased neutrophil count
– Decreased lymphocyte count
– Decreased albumin
– Increased lactate dehydrogenase (LDH)
– Increased alanine aminotransferase (ALT)
– Increased aspartate aminotransferase (AST)
– Increased total bilirubin
– Increased creatinine
– Increased cardiac troponin
– Increased D-dimer
– Increased prothrombin time (PT)
– Increased procalcitonin
– Increased C-reactive protein (CRP)

tests, the evidence that laboratory criteria for diagnosing DIC are present in nearly three-fourths of patients who died underscores the critical role of these tests in this and other clinical settings [20], thus suggesting that their assessment shall be considered a routine part of COVID-19 patient monitoring.

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