JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Laboratory test alterations in patients with COVID-19 and non COVID-19 interstitial pneumonia: a preliminary report

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Abstract

Introduction: Coronavirus disease 19 (COVID-19) is the greatest pandemic in modern history. Laboratory test alterations have been described in COVID-19 patients, but differences with other pneumonias have been poorly investigated to date, especially in Caucasian populations. The aim of this study was to investigate differences and prognostic potential of routine blood tests in a series of Italian patients with COVID-19 and non-COVID-19 interstitial pneumonia.

Methodology: Clinical data and routine laboratory tests of a consecutive series of 30 COVID-19 patients and 30 age and sex matched patients with non COVID-19 interstitial pneumonia have been retrospectively collected. Differences in laboratory tests between patients with COVID-19 and non COVID-19 pneumonias have been investigated, as well as differences between COVID-19 survivors and non survivors.

Results: COVID-19 patients had lower white blood cells, monocytes, neutrophils, and higher platelet counts. In addition, COVID-19 patients showed higher mean platelet volume, lower C reactive protein concentrations, and higher De Ritis ratio. Combined blood cell indexes of systemic inflammation were significantly lower in COVID-19 patients. In further analysis of the COVID-19 group, the neutrophil count, neutrophil to lymphocyte ratio (NLR), derived NLR, systemic inflammation response index and De Ritis ratio, were significantly higher in non survivors than in survivors, while the number of platelets was significantly lower in non survivors.

Conclusions: Our study showed several alterations in blood cell populations and indexes in patients with COVID-19 pneumonia in comparison with patients with non COVID-19 pneumonia. Some of these indexes showed promising prognostic abilities. Further studies are necessary to confirm these results.

Key words: pneumonia; coronavirus; COVID-19; SARS-Cov 2; laboratory; blood tests.

J Infect Dev Ctries 2020; 14(7):685-690. doi:10.3855/jidc.12879

(Received 23 April 2020 – Accepted 01 July 2020)

Introduction

Coronavirus disease 19 (COVID-19) is a recently described infectious disease caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV 2) [1]. Other coronaviruses have been responsible for at least two epidemics over the last two decades [2,3], but COVID-19, initially described in Wuhan, China, in late 2019, represents a particularly aggressive form, affecting more than two and a half million individuals and causing more than 150,000 deaths worldwide to date (i.e. April 20, 2020) [4].

SARS-CoV 2 infection is asymptomatic or mild, resembling the common cold, in most cases [5]. However, in more severe cases, it may clinically manifest as interstitial pneumonia, with fever, cough, dyspnoea, and bilateral infiltrates on chest imaging [6]. This might progress to acute respiratory distress syndrome (ARDS), multiple-organ failure, and death, likely as a consequence of an excessive activation of the immune system that leads to a cytokine storm [7,8]. There is increasing evidence of significant differences in clinical, pathological, and radiological patterns between COVID-19 and non-COVID viral interstitial pneumonias. For example, specific imaging differences on chest computed tomography (CT) scans have been described [9,10]. However, less is known about possible differences in basic laboratory tests, particularly in non-Asian COVID-19 populations, that have been associated with inflammation and specific organ damage in other infectious and non-infectious disease states [11,12]. We sought to address this issue by investigating differences and prognostic potential of

such tests in a series of Italian patients with COVID-19 and non-COVID-19 interstitial pneumonia.

Methodology

Patients and clinical data

A consecutive series of 30 COVID-19 patients referred to the Unit of Respiratory Diseases of the University of Sassari between 15 March and 18 April 2020 was included into the study. COVID-19 was confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) in all cases. In addition, 30 age- and sex-matched patients with non COVID-19 interstitial pneumonia, admitted in the same, unit were retrospectively enrolled as controls. The demographic, clinical and laboratory data of each patient were retrieved from clinical records and registered in a dedicated electronic database. The Charlson comorbidity index, the PaO_2/FiO_2 (P/F) ratio, the treatments received (no support, oxygen, non-invasive respiratory support, invasive respiratory support) and the final outcome (death or survival during the period under investigation), were used to stratify the severity of both COVID-19 and interstitial pneumonia.

Laboratory tests

Fasting blood samples were collected with standard venepuncture on the day of admission and analysed in a certified laboratory. The following parameters were assessed: white blood cell count (WBC), monocytes, lymphocytes, neutrophils, platelets, mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV), C-reactive protein (CRP), albumin, CRP/albumin ratio, alanine aminotransferase (ALT), aspartate aminotransferase (AST), the De Ritis Ratio (AST/ALT), and lactate dehydrogenase (LDH). We also assessed combined blood cell indexes of systemic inflammation, such as the neutrophil to lymphocyte ratio (NLR), derived NLR (dNLR: neutrophils / white blood cells – neutrophils), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), Systemic Inflammation Response Index (SIRI: neutrophils x monocytes / lymphocytes), and the Aggregate Index of Systemic Inflammation (AISI: neutrophils x monocytes x platelets / lymphocytes). The study was conducted in accordance with the declaration of Helsinki, and was approved by the ethics committee of the University Hospital (AOU) of Cagliari (PG/2020/10915).

Statistical analysis

Results are expressed as mean values (mean ± SD) or median values (median and interquartile range, IQR). The Kolmogorov-Smirnov test was used to assess normal vs. non-normal distribution. Statistical differences between groups were evaluated using unpaired Student's t-test or Mann–Whitney rank sum test, as appropriate. Differences between categorical variables were assessed by the chi-squared test. Statistical analyses were performed using MedCalc for Windows, version 15.4 64 bit (MedCalc Software, Ostend, Belgium).

Results

Table 1 describes the demographic and clinical characteristics of COVID-19 and non-COVID-19 pneumonia patients. There were no significant between group differences in BMI, P/F ratio, intensity of care, Charlson Comorbidity Index, and prevalence of

Table 1. Demographic and clinical characteristics of the non-COVID and COVID-19 pneumonia patients enrolled in the study.

	Non-COVID Pneumonia (n = 30)	COVID-19 Pneumonia (n = 30)	p-value
Age, years	71 (59-90)	72 (65-68)	0.66
Gender (F/M)	10/20	14/16	0.30
Smoking status (no/yes)	6/24	20/10	**0.0003**
BMI, Kg/m^2	27.0 (24.9-28.5)	27 (24.1-29.4)	0.945
P/F Ratio	272±71	281±90	0.67
Intensity of care (no, OT, RSni, RSi)	9/13/5/3	2/17/6/5	0.13
Charlson Comorbidity Index	4 (2-5)	5 (3-8)	0.13
Cardiovascular disease, (no/yes)	9/21	12/18	0.42
Respiratory disease, (no/yes)	22/8	23/7	0.77
Kidney disease, (no/yes)	29/1	26/4	0.16
Diabetes, (no/yes)	21/9	24/6	0.38
Cancer, (no/yes)	27/3	24/6	0.28
Autoimmunity, (no/yes)	23/7	28/2	0.07
Death during follow-up, (no/yes)	29/1	21/9	**0.006**

BMI: body mass index; COVID-19: coronavirus disease 2019; F: female; M: male; OT: oxygen therapy; P/F: PaO_2/FiO_2; RSi: invasive respiratory support; RSni: non-invasive respiratory support; Statistical significance at 0.05.

diabetes, cancer, cardiovascular, kidney, respiratory or autoimmune diseases. However, COVID-19 patients were more often smokers (66% *vs*. 20%, p = 0.0003) and more likely to die during the follow-up (30% vs. 3%, p = 0.006).

Haematological and biochemical parameters in both groups are summarized in Table 2. COVID-19 patients had lower number of WBCs (median: 6.7 × 10^9 L; IQR: 4.8-11.0 × 10^9 L *vs* 12.1 × 10^9 L; IQR: 8.9-15.2 × 10^9 L, p = 0.002), monocytes (median: 0.3 × 10^9L; IQR: 0.1-0.4 × 10^9L *vs* 0.6 × 10^9L; IQR: 0.5-0.8 × 10^9L, p = 0.0003), neutrophils (median: 5.5 × 10^9 L; IQR: 3.3-9.4 × 10^9 L *vs* 10.5 × 10^9 L; IQR: 5.9-13.7 × 10^9 L, p = 0.004), and higher platelet number (median: 291 × 10^6 L; IQR: 161-261 × 10^6 L *vs* 257 × 10^6 L; IQR: 201-301 × 10^6 L, p = 0.013). In addition, COVID-19 patients showed higher MPV values (median: 8.40 fL; IQR: 8.10-8.98 fL *vs* 8.15 fL; IQR: 7.70-8.50 fL, p = 0.017), lower CRP concentrations (median: 8.1 mg/dL; IQR: 2.3-18.5 mg/dL *vs* 16.9 mg/dL; IQR: 7.5-24.1 mg/dL, p = 0.037), and higher De Ritis ratios (mean: 1.50 ± 0.66 *vs* 1.11 ± 0.46, p = 0.01). Both SIRI (median; 1.8; IQR: 0.8-5.3 *vs* 6.0; IQR 2.8-11.0, p = 0.003) and AISI (median: 434; IQR: 139-1134 *vs* 1306; IQR: 849-3214, p = 0.0007) were significantly lower in COVID-19 patients. By contrast, there were no significant between-group differences in NLR, dNLR, PLR and LMR.

During the 34 days of the study, nine (30%) patients among those with COVID-19 died. In comparisons between the latters and survivors in the COVID-19 group (Table 3), the neutrophil count (median: 3.70 × 10^9 L; IQR: 3.10-7.18 × 10^9 L *vs* median: 10.05 × 10^9 L; IQR: 6.30-16.65 × 10^9 L, p = 0.034), NLR (median: 3.7; IQR: 2.4-11.5 *vs* median: 12.2; IQR: 7.5-25.9, p = 0.011), dNLR (median: 2.6; IQR: 1.9-5.0 *vs* median: 6.8; IQR: 4.1-12.6, p = 0.008), SIRI (median: 1.3; IQR: 0.8-2.7 *vs* median: 5.5; IQR: 2.2-7.6, p = 0.024) and De Ritis ratio (mean: 1.27 ± 0.44 *vs* mean: 2.00 ± 0.79, p = 0.003), were significantly higher in non survivors when compared to survivors. By contrast, the number of platelets was significantly lower in non survivors (median: 210 × 10^6L; IQR: 180-307 × 10^6 L *vs* median: 161 × 10^6 L; IQR: 133-178 × 10^6 L, p = 0.030). No significant differences were observed in the remaining parameters.

Discussion

COVID-19 is the most lethal pandemic of modern history. As the disease outbreak was initially reported in late 2019 in Wuhan, China [13], most research to date has been conducted in Chinese patients, including a

Table 2. Laboratory findings of the patients with non-COVID and COVID-19 pneumonia enrolled in the study.

	Non-COVID Pneumonia ***n = 30***	**COVID-19 Pneumonia** ***n = 30***	**p-value**
Hb, (g/dL)	12.7 ± 1.9	12.8 ± 1.8	0.76
WBC, (×10^9 L)	12.1 (8.9-15.2)	6.7 (4.8-11.0)	**0.002**
Monocytes, (×10^9 L)	0.6 (0.5-0.8)	0.3 (0.1-0.4)	**0.0003**
Lymphocytes, (×10^9 L)	1.1 (0.5-1.7)	1.0 (0.6-1.1)	0.36
Neutrophils, (×10^9 L)	10.5 (5.9-13.7)	5.5 (3.3-9.4)	**0.004**
Platelets, (×10^6 L)	257 (201-301)	291 (161-261)	**0.013**
MCV, (fL)	84.5 ± 12.7	83.9 ± 8.3	0.82
RDW, (%)	15.4 (13.9-17.4)	16 (15.0-16.6)	0.33
MPV, (fL)	8.15 (7.70-8.50)	8.40 (8.10-8.98)	**0.017**
CRP, (mg/dL)	16.9 (7.5-24.1)	8.1 (2.3-18.5)	**0.037**
Albumin, (g/dL)	3.40 (3.10-3.80)	3.35 (3.00-3.85)	0.64
CRP/Albumin ratio	5.2 ± 4.1	3.9 ± 3.2	0.27
ALT, (IU/L)	20 (16-32)	18 (12.30)	0.27
AST, (IU/L)	23.5 (17-35)	25.0 (16.5-41.8)	0.64
De Ritis Ratio, (AST/ALT)	1.11 ± 0.46	1.50 ± 0.66	**0.01**
LDH, (IU/L)	282 (220-336)	272 (204-339)	0.63
NLR	9.1 (4.6-21.2)	6.5 (2.8-12.3)	0.12
dNLR	4.8 (3.2-9.0)	3.2 (2.2-6.7)	0.21
PLR	251 (132-440)	212 (131-341)	0.47
LMR	2.17 ± 1.69	2.95 ± 1.44	**0.06**
SIRI	6.0 (2.8-11.0)	1.8 (0.8-5.3)	**0.003**
AISI	1306 (849-3214)	434 (139-1134)	**0.0007**

AISI: aggregate index of systemic inflammation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; COVID-19: coronavirus disease 2019 dNLR: derived NLR; Hb: haemoglobin; LDH: lactate dehydrogenase; LMR: lymphocyte to monocyte ratio; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio PCR: C reactive protein; PLR: platelet to lymphocyte ratio; RDW: red cell distribution width; SIRI: systemic inflammation response index; WBC: white blood cells. Statistical significance at 0.05.

relatively small number of studies reporting on laboratory test alterations. In a recent review by Lippi and Plebani, the main alterations observed in COVID-19 patients included higher WBC and neutrophil counts, LDH, ALT, AST, bilirubin, and CRP, and lower lymphocyte count and serum albumin concentrations [14]. However, little information is currently available on possible differences in these parameters between COVID-19 pneumonia and other interstitial pneumonias.

Zhao *et al*. analysed the demographic, clinical, and radiological features of 19 patients with COVID-19 pneumonia and 15 patients with other types of pneumonia in Hubei, China [11]. There were no significant differences in WBC, lymphocytes, and CRP. By contrast, AST, ALT and LDH were significantly higher in COVID-19 patients. Chen *et al*. retrospectively compared 78 COVID-19 patients with 26 SARS-CoV 2-negative patients (control patients) [12]. The authors reported significantly lower WBC and neutrophil counts in patients with COVID-19 pneumonia, but no differences in AST, ALT, LDH and CRP when compared to SARS-CoV 2-negative patients. Our series provide significant additional information, particularly regarding the significant between-group differences in monocytes, platelets, and CRP, and the relationship between laboratory parameters surviving status. In particular, non survivors exhibited significant neutrophilia and, as a consequence, higher NLR and dNLR. The latter indexes have been shown to be good predictors of disease severity and prognosis in several chronic and neoplastic diseases [15-19]. In a recent study investigating dysregulations in blood cell populations in 452 Chinese patients with COVID-19, in accordance with our findings, both neutrophil count and NLR were associated with higher severity of the disease [20]. Our additional findings, lower platelet count in non survivors, are also in line with the results of a recent meta-analysis, which showed that thrombocytopenia is common in severe COVID-19 patients and in other patients suffering critical illness [21]. In this context, low platelet count suggests the presence of significant organ dysfunction and development of intravascular coagulopathy, with or without overt disseminated intravascular coagulation (DIC) [22]. The presence of low platelet counts might have attenuated possible differences in the AISI, which includes the platelet count in its calculation, between survivors and non survivors, in contrast to what reported in other clinical

Table 3. Laboratory findings of the patients with COVID-19 pneumonia included in the study after sorting in survivors and non-survivors.

	COVID-19 Pneumonia Survivors ***n = 21***	**COVID-19 Pneumonia Non-survivors** ***n = 9***	**p-value**
Hb, (g/dL)	12.8 ± 1.6	12.8 ± 2.4	0.99
WBC, ($\times 10^9$ L)	5.7 (4.6-10.5)	11.6 (7.8-18.2)	0.051
Monocytes, ($\times 10^9$ L)	0.31 (0.30-0.40)	0.30 (0.24-0.60)	0.76
Lymphocytes, ($\times 10^9$ L)	1.00 (0.55-1.88)	0.60 (0.55-0.88)	0.10
Neutrophils, ($\times 10^9$ L)	3.70 (3.10-7.18)	10.05 (6.30-16.65)	**0.034**
Platelets, ($\times 10^6$ L)	210 (180-307)	161 (133-178)	**0.030**
MCV, (fL)	84.9 ± 7.9	81.3 ± 9.6	0.31
RDW, (%)	15.6 (14.8-16.5)	16.3 (15.8-17.8)	0.09
MPV, (fL)	8.30 (8.08-8.83)	8.60 (8.25-10.30)	0.30
CRP, (mg/dL)	5.62 (2.15-16.95)	11.9 (4.17-21.18)	0.39
Albumin, (g/dL)	3.45 (3.20-3.90)	3.00 (2.90-3.70)	0.41
CRP/Albumin ratio	3.26 ± 3.40	5.36 ± 2.50	0.19
ALT, (IU/L)	17.0 (12.0-28.5)	19.0 (11.5- 31.5)	0.91
AST, (IU/L)	26.0 (15.0-39.0)	23.0 (21.8-57.8)	0.37
De Ritis Ratio, (AST/ALT)	1.27 ± 0.44	2.00 ± 0.79	**0.003**
LDH, (IU/L)	258 (177-312)	289 (260-404)	0.63
NLR	3.7 (2.4-11.5)	12.2 (7.5-25.9)	**0.011**
dNLR	2.6 (1.9-5.0)	6.8 (4.1-12.6)	**0.008**
PLR	191 (124-462)	227 (138-287)	0.66
LMR	3.24 ± 1.44	2.19 ± 1.17	0.08
SIRI	1.3 (0.8-2.7)	5.5 (2.2-7.6)	**0.024**
AISI	288 (126-926)	871 (289-1298)	0.24

AISI: aggregate index of systemic inflammation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; COVID-19: coronavirus disease 2019; dNLR: derived NLR; Hb: haemoglobin; LDH: lactate dehydrogenase; LMR: lymphocyte to monocyte ratio; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio; CRP: C reactive protein; PLR: platelet to lymphocyte ratio; RDW: red cell distribution width; SIRI: systemic inflammation response index; WBC: white blood cells. Statistical significance at 0.05.

conditions [23]. Finally, the De Ritis ratio was significantly higher in non survivors despite the lack of significant between-group differences in AST and ALT concentrations, in line with the results of a recent meta-analysis [24]. Alterations in liver function biomarkers have been widely reported in COVID-19 patients [12, 25-27], and have been also found to be related with the severity of the disease [28-30].

Our study has some limitations, including the retrospective design and the relatively small sample size, largely dictated by the relatively low local incidence of COVID-19 cases (north-west of Sardinia) when compared to other Italian regions. Furthermore, albeit cases with COVID-19 and non-COVID-19 pneumonia were matched for age and gender, there were significant differences in smoking status. On the other hand, to the best of our knowledge this preliminary study is the first to report laboratory test comparisons in Caucasian patients with COVID-19 and non-COVID-19 pneumonia. Other studies, prospectively designed and including larger number of cases are warranted to confirm our preliminary findings.

In conclusion, patients with COVID-19 disease had lower lymphocytes, neutrophils, monocytes and CRP, but higher platelets, De Ritis Ratios and combined blood cell count indexes of systemic inflammation when compared to patients with non-COVID-19 interstitial pneumonia. Neutrophilia, lower platelet count, and altered De Ritis and NLR ratios were significantly higher in non survivors than in survivors. Further prospective studies are warranted to assess the capacity of laboratory parameters to assist with the diagnosis and the capacity to predict treatment response and clinical outcome in patients with COVID-19 interstitial pneumonia.

Funding

This work has been supported by Fondazione di Sardegna Prat. 2016.0917.

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Conflict of interests: No conflict of interests is declared.