Clinical characteristics and laboratory biomarkers changes in COVID-19 patients requiring or not intensive or sub-intensive care: a comparative study

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Abstract

Background Identifying risk factors for severe novel-coronavirus disease (COVID-19) is useful to ascertain which patients may benefit from advanced supportive care. The study aims to offer a comparative description of the COVID-19 patients, admitted to a general ward for a non-critical clinical picture, who required or not to be transferred to the intensive (ICU) and/or sub-intensive care (SICU) units.

Methods This observational retrospective study included all COVID-19 patients admitted to the Infectious Diseases Unit. Clinical, laboratory, radiological and treatment data were collected. The primary outcome was a composite of need of transfer to the ICU and/or SICU during the hospitalization. Patients who did not require to be transferred are defined Group 1; patients who were transferred to the ICU and/or SICU are defined Group 2. Demographic and clinical characteristics were compared between the two groups.

Results 303 patients were included. Median age was 62 years. 69 patients (22.8%) met the primary outcome and were defined Group 2. The overall mortality rate was 6.8%. Group 2 were more likely to be men, had a higher mortality (14.5% vs. 3.8%, p<0.01), had more hypertension (72.4% vs. 44%, p<0.01) and diabetes (31.9% vs. 21%, p=0.04) and were more likely to present dry cough (49.3% vs. 25.2%, p<0.01). Overall, chest X-ray at admission showed findings suggestive of pneumonia in 63.2%, and Group 2 were more likely to develop pathological findings during the hospitalization (72.7%vs. 17.2%, p<0,01). At admission, Group 2 presented significantly higher neutrophil count, aspartate-transaminase and C-reactive-protein. At the 3rd measurement, Group 2 presented persistently higher neutrophil count, liver function tests and C-reactive-protein. Group 1 presented a shorter duration from admission to negativization of follow-up swabs (20 vs. 35 days, p<0,01).

Conclusions The presence of comorbidities and the persistent observation of abnormal laboratory findings should be regarded as predisposing factors for clinical worsening.

Introduction

The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing human disease named coronavirus disease (COVID-19) was first reported in China in December 2019 and declared a pandemic by the World Health Organization in March 2020 [1]. The first known cases of local transmission were detected in Italy at the end of February 2020. The northern regions of the country have been so far the most affected by the outbreak [2]. To address the emergency, strict social containment measures have been adopted and health care systems have been reorganized to cope with the enormous increase in the numbers of acutely ill patients [3, 4].

Hospital admission rates for patients with COVID-19 may vary substantially between countries, because of different prevalence in infection and community testing rates and non-homogeneous admission criteria. However, it is estimated that 10 to 20% of adults present clinical conditions requiring hospitalization, and in the majority of the cases this is related due to respiratory distress [5]. The decision about location of care and clinical management depends on various factors, including clinical
presentation, disease severity, need for supportive care, presence of risk factors for severe disease, and conditions at home. While mild to moderate disease in low-risk patients can be managed at home or in primary or secondary level healthcare facilities, severe and critical diseases need tertiary hospitals where high dependency/sub-intensive (SICU) or intensive care units (ICU) are available [6]. The provision of intensive care and the availability of resources may vary substantially between and within countries [7]; therefore the identification of risk factors for severe infection is crucial for clinicians to identify patients who may benefit from aggressive supportive care and for health and government officials to adequately address local outbreaks.

The percentage of patients requiring ICU has ranged from 5–37% [8–13]. The most common reason for intensive care unit admission is hypoxemic respiratory failure leading to mechanical ventilation (MV) or non-invasive ventilation (NIV) [14]. In a large cohort study performed on ICU admitted patients in northern Italy, 88% of the patients required MV and 11% NIV [15]. Patients admitted to intensive care units are reported to be older and predominantly male, and to have more frequently existing comorbidities such as hypertension, heart failure, renal disease and obesity. Lower lymphocyte count, elevated serum troponin, C-reactive protein, D-dimer and white blood cell count are also more commonly seen in patients presenting with severe infections [10, 12–13, 16–17].

We present a clinical and laboratory description of all the patients admitted to the COVID-19 centre of the Division of Infectious Diseases of the Hospital of Padua. We aim to describe the clinical profile and the dynamic changes of laboratory parameters during the course of hospitalization, and to compare the results between patients who required be transferred to ICU and/or SICU and patients who did not.

**Methods**

This is a retrospective study of prospectively collected data of adult patients hospitalized at the COVID-19 centre of the Infectious Diseases Unit (IDU) of the University Hospital of Padua, Veneto region, Italy, between February 22 and May 20, 2020. Inclusion criteria were: a) patients with SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction method; b) being admitted or transferred to the COVID-19 centre of IDU for > 1 day; c) age > 18 years old. Exclusion criterion was being admitted in the ICU or SICU within 12 hours from admission or prior to the permanence in the COVID-19 centre.

Demographic, clinical, laboratory and treatment data were extracted from paper and electronic medical records using a standardised data collection form.

Laboratory confirmation of SARS-CoV-2 infection was obtained by the detection in respiratory specimens (throat-swab) by next-generation sequencing or real-time RT-PCR methods. Follow up swabs were performed every 3 to 5 days. Laboratory tests included: blood count, CD4 T lymphocyte count, activated partial thromboplastin time (APTT), prothrombin time (PT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transferase (GGT), alkaline phosphatase (ALP), total bilirubin,
urea, creatinin, glomerular filtration rate calculation (GFR), C-Reactive Protein (CRP), procalcitonin and D-Dimer.

The laboratory test results considered for the analysis were: the 1° measurement available (at admission), the 3rd measurement since admission, the last measurement (before discharge or death).

Anti SARS-CoV-2 drugs administered during the hospitalization for > 2 days were recorded.

Chest radiographs were done for all patients at admission and repeated according to clinical needs.

Written consent was obtained from patients. Local ethics committees were notified about the study protocol. The study was performed according to the ethical guidelines of the Declaration of Helsinki (7th revision).

**Definitions**

Fever was defined as a body temperature > 37.5 °C.

Patients requiring MV or NIV (defined as assisted ventilation that delivers positive pressure throughout the respiratory cycle with additional phasic increases in airway pressure, without the presence of an endotracheal tube in the trachea [18]) required to be transferred to ICU or SICU. Criteria for the transfer to the ICU were the need for MV or NIV and/or the occurrence of shock or organ failure. Criterion for the transfer in the SICU was the need for NIV.

We defined the primary outcome as a composite endpoint of transfer to the ICU and/or the SICU during the hospitalization. The group of patients who did not require to be transferred are defined Group 1; the patients who were transferred to ICU and/or SICU are defined Group 2.

Criteria for the choice of the therapeutic regimens for COVID-19 followed national guidelines [19] and physicians’ judgements. As a general rule, hospitalized patients with COVID-19 comorbidities, age > 70 years, respiratory symptoms and/or evidence of pneumonia were treated with chloroquine (CQ) (500 mg orally twice daily) or hydroxychloroquine (HCQ) (200 mg orally twice daily). CH and HCQ could be associated with lopinavir/ritonavir (400 mg/100 mg twice daily) or azithromycin (500 mg orally daily); standard duration of therapies was 5–7 days. In addition, tocilizumab and remdesivir were also used. Intravenous high dose glucocorticoids were used only in severe or critical patients. All patients, if not contraindicated, received thromboprophylaxis with daily low-molecular weight heparins.

Chest X rays performed at admission or during the course of hospitalization were considered positive in case of evidence of singular or multiple consolidations and/or interstitial opacities.

A patient was considered negative for SARS-CoV-2 when two throat-swabs, performed in consecutive days, resulted negative.

**Statistical analysis**
Results

A total of 325 adult patients were hospitalised with a confirmed diagnosis of COVID-19 in the study period. 22 patients were excluded because they met the exclusion criterion of being admitted to ICU or SICU within 12 hours since admission or prior to the permanence in the COVID-19 centre. Therefore, a total of 303 were included in the analysis.

The median age was 62 years (IQR 50–74) and 182 (60.1%) were men. 69 patients (22.8%) met the primary composite outcome. Of those, 15 were transferred to the ICU, 36 to the SICU and 18 to both of the units. The median time from hospital admission to the transfer was 5 days (IQR 2-13.5). Overall the mortality rate was 6.8%. All causes of death were due to respiratory failure.

As of June 1, 2020, 4 patients were still hospitalized, and the median duration of hospitalization was 9 days (IQR 6–15).

Table 1 summarizes the main demographics characteristics of the sample and the differences between the two groups of patients: group 2 patients were more likely to be man, had a significantly higher mortality (14.5% vs 3.8%, p < 0.01) and a longer hospitalization (18 vs 7 days, p < 0.01). No differences were found in terms of age.

A total of 183 patients (67.8%) were discharged at home, while 7 (2.6%), 31 (11.5%) and 16 (5.9%) were transferred to a nursing home/community healthcare facility, a secondary level hospital or to a rehabilitation institute respectively. Group 2 patients were less likely to be discharged at home (50.9 vs 71.9%, p < 0.01) and were more often transferred to a secondary level hospital (18.9% vs 9.7%, p = 0.03) or to a rehabilitation institute (15.1% vs 3.7%, p = 0.80) compared to Group 1.
Table 1
Demographic characteristics and outcomes of patients non ICU/SICU (Group 1) and ICU/SICU (Group 2) patients

| Available | All patients | Group 1 | Group 2 | p |
|-----------|--------------|---------|---------|---|
|           | n.303 | n.234, (77.2%) | n.69, (22.8%) | |
| Sex male  | 100% | 182 (60.1%) | 129 (55.1%) | 53 (76.8%) | < 0.01 |
| Age, years | 100% | 62 (50–74) | 60 (47–72) | 68 (56–77) | 0.06 |
| Death     | 100% | 19 (6.8%) | 9 (3.8%) | 10 (14.5%) | < 0.01 |
| Patients still hospitalized (as of June 1, 2020) | 100% | 4 (1.3%) | 1 (0.4%) | 3 (4.3%) | |
| Length of hospitalization, days (as of June 1, 2020) | 100% | 9 (6–15) | 7 (5–12) | 18 (14–24) | < 0.01 |
| Patients discharged | 89.1% | 270 (89.1%) | 217 (92.7%) | 53 (76.8%) | |
| • Discharged at home | 100% | 183 (67.8%) | 156 (71.9%) | 27 (50.9%) | < 0.01 |
| • Transferred to a nursing home, community health facility, hospice | | 7 (2.6%) | 5 (2.3%) | 2 (3.8%) | 0.73 |
| • Transferred to a secondary level hospital | | 31 (11.5%) | 21 (9.7%) | 10 (18.9%) | 0.03 |
| • Transferred to a rehabilitation facility | | 16 (5.9%) | 8 (3.7%) | 8 (15.1%) | 0.80 |

Data presented as median (IQR) or as percentage. In the second column data availability is also shown

ICU: Intensive Care Unit; SICU: Sub-intensive Care Unit.

Table 2 shows the clinical presentation at admission and the coexisting medical conditions. Fever (80.2%), dyspnoea (31.7%) and dry cough (30.7%) were the most common symptoms. A significant difference in the prevalence of dry cough was detected between Group 1 and 2 (25.2 vs 49.3%, p < 0.01).
Table 2
Clinical, radiological characteristics, treatments and follow-up swabs of Group 1 and Group 2 COVID-19 patients. (to be inserted at line n. 209).

| Co-existing medical conditions          | Available All patients n.303 | Group 1 n.234 | Group 2 n.69 | P  |
|----------------------------------------|-----------------------------|---------------|--------------|----|
| Hypertension                           | 153 (50.5%)                 | 103 (44.0%)   | 50 (72.4%)   | < 0.01 |
| Diabetes mellitus                      | 71 (23.4%)                  | 49 (21.0%)    | 22 (31.9%)   | 0.04 |
| (pre-existing and newly diagnosed)     |                             |               |              |     |
| Chronic cardiac disease                | 44 (14.5%)                  | 36 (15.4%)    | 8 (11.6%)    | 0.65 |
| Chronic pulmonary disease              | 26 (8.6%)                   | 19 (8.1%)     | 7 (11.1%)    | 0.67 |
| Chronic gastrointestinal disease       | 26 (8.6%)                   | 24 (10.3%)    | 2 (2.9%)     | 0.16 |
| Active malignancy                      | 26 (8.6%)                   | 21 (9%)       | 5 (7.2%)     | 0.93 |
| Transplant                             | 3 (1.0%)                    | 0 (0%)        | 3 (4.3%)     | 0.02 |
| Urologic disorders                     | 36 (11.9%)                  | 28 (12%)      | 8 (11.6%)    | 0.90 |
| Chronic kidney disease                 | 15 (4.9%)                   | 12 (5.1%)     | 3 (4.3%)     | 0.93 |
| Obesity (BMI > 30)                     | 51 (16.8%)                  | 40 (17.1%)    | 11 (16.0%)   | 0.87 |
| Overweight (BMI > 25)                  | 154 (50.8%)                 | 119 (50.8%)   | 35 (50.7%)   | 0.80 |
| Number of medical conditions           | 100%                        |               |              |     |
| 0                                      | 101 (33.4%)                 | 87 (37.2%)    | 14 (20.3%)   | 0.03 |

Data presented as median (IQR) or as percentage. In the second column data availability is also shown.

ICU: Intensive Care Unit; SICU: Sub-intensive Care Unit; IQR: Interquartile Range; BMI: Body Mass Index; Sat02: Oxygen Saturation; iv: intravenous; NIV: Non-Invasive Ventilation; MV: Mechanical Ventilation.

*Nasal cannula, face-mask. **Two negative throat-swabs obtained in consecutive days.

ADDITIONAL FILE 1
| Available All patients n.303 | Group 1 n.234 | Group 2 n.69 | P    |
|-------------------------------|---------------|--------------|------|
| ≥ 2                           | 96 (31.7%)    | 71 (30.3%)   | 25 (36.2%) | 0.47 |

**Symptoms at admission** 100%

|                   | Available         | Group 1          | Group 2          | P     |
|-------------------|-------------------|------------------|------------------|-------|
| Fever             | 243 (80.2%)       | 187 (79.9%)      | 56 (83.2%)       | 0.73  |
| Dry cough         | 93 (30.7%)        | 59 (25.2%)       | 34 (49.3%)       | < 0.01|
| Productive cough  | 28 (9.2%)         | 24 (10.3%)       | 4 (5.8%)         | 0.54  |
| Sore throat       | 16 (5.3%)         | 10 (4.3%)        | 6 (8.7%)         | 0.21  |
| Dyspnoea          | 96 (31.7%)        | 69 (29.5%)       | 27 (39.1%)       | 0.20  |
| Conjunctivitis    | 3 (1.0%)          | 0                | 3 (4.3%)         | 0.02  |
| Diarrhoea         | 21 (6.9%)         | 17 (7.3%)        | 4 (5.8%)         | 0.81  |
| Myalgia           | 23 (7.6%)         | 16 (6.8%)        | 7 (10.1%)        | 0.55  |
| Arthralgia        | 13 (4.3%)         | 10 (4.3%)        | 3 (4.3%)         | 1     |
| Malaise           | 41 (13.5%)        | 31 (13.2%)       | 10 (14.5%)       | 0.69  |
| Dysgeusia         | 49 (16.2%)        | 40 (17.1%)       | 9 (13.0%)        | 0.52  |
| Skin rash         | 13 (4.3%)         | 12 (5.1%)        | 1 (1.4%)         | 0.33  |
| **Sat02 < 94% in air room at admission** 100% | 134 (44.2%) | 97 (41.4%) | 37 (53.6%) | 0.12 |

Data presented as median (IQR) or as percentage. In the second column data availability is also shown.

ICU: Intensive Care Unit; SICU: Sub-intensive Care Unit; IQR: Interquartile Range; BMI: Body Mass Index; Sat02: Oxygen Saturation; iv: intravenous; NIV: Non-Invasive Ventilation; MV: Mechanical Ventilation.

*Nasal cannula, face-mask. **Two negative throat-swabs obtained in consecutive days.

**ADDITIONAL FILE 1**
| Available | All patients n.303 | Group 1 n.234 | Group 2 n.69 | P     |
|-----------|--------------------|---------------|--------------|-------|
| **Positive chest X-ray at admission** | 92.3% (63.2%) | 177 (60.1%) | 37 (78.7%) | 0.15  |
| **Positivization of chest X-ray during hospitalization** | 24 (23.1%) | 16 (17.2%) | 8 (72.7%) | 0.01  |
| **Anti SARS-CoV-2 treatment** | 100% | | | |
| Chloroquine or Hydroxychloroquine | 183 (60.3%) | 149 (63.7%) | 34 (49.2%) | < 0.01 |
| Lopinavir/ritonavir | 88 (43.3%) | 63 (26.9%) | 25 (36.2%) | 0.01  |
| Remdesivir | 19 (6.8%) | 18 (7.7%) | 1 (1.4%) | 0.01  |
| Tocilizumab | 18 (5.9%) | 12 (5.1%) | 6 (8.7%) | 0.15  |
| Azithromycin | 120 (39.6%) | 99 (42.3%) | 21 (30.4%) | 0.01  |
| **Antibiotic treatment iv** | 100% | | | |
| Low or high flow systems* | 168 (55.4%) | 99 (42.3%) | 69 (100%) | < 0.01 |
| NIV | 61 (20.1%) | 0 | 61 (88.4%) | |
| MV | 30 (9.9%) | 0 | 30 (43.4%) | |
| **Negative follow up swab for Sars-CoV-2**** | 93.7% | 236 (83.1%) | 182 (80.1%) | 0.70  |
| **Days from hospitalization to negativization** | 93.7% | 22 (14–39) | 20 (13.9–32) | 35 (20–57) | < 0.01 |

Data presented as median (IQR) or as percentage. In the second column data availability is also shown.

ICU: Intensive Care Unit; SICU: Sub-intensive Care Unit; IQR: Interquartile Range; BMI: Body Mass Index; Sat02: Oxygen Saturation; iv: intravenous; NIV: Non-Invasive Ventilation; MV: Mechanical Ventilation.

*Nasal cannula, face-mask. **Two negative throat-swabs obtained in consecutive days.
Hypertension (72.4 vs 44%, p < 0.01) and known or newly diagnosed diabetes (31.9 vs 21%, p = 0.04) were more common among patients of Group 2 compared to Group 1. Patients with no comorbidities were less likely to belong to Group 2 (20.3 vs 37.2%, p = 0.03).

Chest X-ray at admission was positive for 63.2% of the patients. No differences were found between the two groups, but Group 2 patients were more likely to develop *de novo* pathological findings at the chest X-ray during the course of hospitalization (72.7% vs 17.2%, p < 0.01).

(Table 2)

Laboratory findings at the 1°, 3rd and last measurements since admission are shown in Table 3 (see additional file 1).

Group 2 patients presented at admission a significantly higher neutrophil count, higher AST and CRP levels. At the 3° measurement since admission, significant differences were found for white blood cell and neutrophil count, liver function tests (AST, ALT, total bilirubin) and C Reactive Protein. At discharge, Group 2 patients were found to have a significantly lower level of haemoglobin. No differences were found in the renal function tests.

Data regarding antiviral drugs use are shown in Table 2. CQ or HCQ, lopinavir/ritonavir and azithromycin were the most common drugs used, prescribed during the course of hospitalization to 60.3%, 43.3% and 39.6% of the patients respectively. Group 2 patients were less likely to receive CQ or HCQ (49.2 vs 63.7%, p < 0.01), azithromycin (30.4 vs 42.3%, p = 0.01) and remdesivir (1.4 vs 7.7%, p = 0.01), and more likely to receive lopinavir/ritonavir (36.2 vs 26.9%, p = 0.01).

Among Group 2 patients, 88.4% required NIV and 43.4% MV.

As of June 1, 2020, 83.1% of patient resulted negative for SARS-CoV-2 at the follow-up swabs. The median duration from hospital admission to negativization (considering the date of the second swab) was 22 day. Patients of Group 1 presented a significant shorter duration compared to Group 2 (20 vs 35 days, p < 0.01) (Table 2).

**Discussion**

In this comparative study, clinical characteristics and laboratory biomarkers of a cohort of 303 patients with a confirmed SARS-CoV-2 infection and primarily hospitalized in the COVID-19 centre of the Infectious Diseases Unit of Padua were analysed. 22.8% of the patients (Group 2) required to be transferred to ICU and/or SICU and overall 19 patients (6.8%) died. Our mortality rate was lower than those reported in recent European and American inpatient cohorts, ranging from 24 to 33% [11–13]. Population and patients’ characteristics, prevalence of community testing and admission criteria can partly explain the differences. In addition, the admission rate to intensive/sub-intensive care observed in our cohort is relatively high when compared with previous studies (rates comprised between 5% and 37% [8–13]) and it can be argued that a more extended aggressive support, especially in the form of timely ventilator
assistance, may guarantee a better management with higher chance of recovery of unstable or borderline patients.

Compared to Group 1, Group 2 patients had a longer hospital stay, were less likely to be discharged at home and required more frequently transferred to a secondary level healthcare facility or to a rehabilitation institute. These results may provide health officials and policymakers a better understanding on interventions needed to properly address also long term consequences of local outbreaks.

Consistently with other studies [8–17], men were more represented than women and were at higher risk for severe disease. It has been reported that the reduced predisposition of females to viral infections could be attributed to the protection given by the X chromosome and sex hormones, which play an important role in the innate and adaptive immunity [20].

The median age was 62 years and the univariate analysis did not show a significant difference between the two groups of patients. This is possibly due to the narrow distribution of the patients in the age class 50–70 years (IQR = 47–74), which mainly reflect our hospital admission criteria.

The presence of underlying medical disorders was associated with a greater risk to be transferred to ICU/SICU. Hypertension and known or newly diagnosed diabetes were significantly more represented in Group 2. The three transplant patients (a lung and two kidney transplants) required to be transferred to the SICU, but they all recovered. These data confirm that more fragile patients have a higher risk for severe disease and often require tertiary care management [21].

As expected, fever was the most common sign at admission in both groups [13, 21]. All the symptoms were equally reported between the two groups, with the exception of dry cough that was more common in Group 2. Dry cough is typical of interstitial pneumonia and it may reflect the progressive severe pulmonary involvement of patients admitted to ICU/SICU.

Overall, 63.2% of patients had pathological findings at the chest x-ray at admission, with no significant differences between the two groups. However, Group 2 patients were more likely to develop a pathological chest X ray during the course of hospitalization. These findings arouse two main observations. First the need of a close monitoring of patients in the early phase of the hospitalization and the suggestion that repeated radiological examinations are useful in identifying patients at risk for complications [22]. Second, the opportunity to consider a computed tomography (CT) chest scan as a first level diagnostic procedure in the context of COVID-19. To date, the best radiological strategy remains undefined. The use of CT-scan for all patients appears be unreasonable in terms of time, costs and radiation exposure [23]. An alternative option could be the combination of chest-X-ray and ultrasound, that has demonstrated a sensitivity of 75% (vs 59% of chest X-ray) in detecting of interstitial lung diseases [24–25].

In terms of laboratory findings, Group 2 patients presented at admission a significantly higher WBC with neutrophilia, higher levels of AST and increased values of CRP. To identify possible early signals of
clinical worsening and considering that the median time from hospital admission to ICU/SICU transfer was of 5 days, we analysed the differences of laboratory findings at the 3rd measurement since admission: the differences between Group 1 and 2 identified at the beginning of the hospitalization were confirmed, with the inclusion of ALT and total bilirubin. However, WBC counts and liver function tests resulted to be only moderately altered in Group 2. The alterations of WBC and liver function tests could be partly explained by concomitant bacterial infections and medications. Nevertheless, the persistent observation of even slightly abnormal WBC count and liver function tests, together with high CRP, should be considered markers of disease severity and should lead physicians to a closer follow-up for the risk of disease progression.

In addition, a significant lower level of lymphocyte T CD4+ count was recorded in Group 2 compared to Group 1. Researches have recently demonstrated that T cell can have a role in contrasting the SARS-CoV-2 infection and the severity of the disease can depend on the strength of T cell responses [26–27]. We could speculate that this partial impaired immune system of Group 2 patients may play a detrimental role in the early phase of the infection, even thought it is still unknown whether T cells can promote the elimination of the virus or even cause a dangerous immune system overreaction [27].

In our cohort, patients transferred to ICU/SICU resulted to be less likely to receive HCQ or CQ and Remdesivir during the course of hospitalization. On the other side, those patients were more often prescribed with Lopinavir/ritonavir, possibly because at the early stage of the outbreak this drug was the only one considered effective, and therefore more used for severe patients. However, no conclusion can be drawn, and the effective role of these drugs used alone or in combination remains uncertain until the results of large controlled randomized studies will be available.

Our study as some limitations: first, the study cohort does not include COVID-19 patients admitted in general wards other than Infectious Diseases; a larger sample may have revealed additional elements not readily apparent in our series. Second, the observational design has the potential for incomplete capture or misclassification of baseline characteristics. Third, the follow up was not long enough to collect complete outcome data from all the patients.

However, the prospective collection of data, the monocentric design and the focus on the characteristics of the patients requiring either sub-intensive or intensive care represents added values.

**Conclusion**

The proper management of COVID-19 patients requires a multilevel diagnostic approach that should be focused on the early recognition of signs of disease severity and progression. The results of our study indicate that not only the presence of comorbidities and of laboratory alterations at admission, but also the persistent observation of slightly abnormal laboratory findings should be regarded with a high index of suspicion for clinical worsening. The availability of tertiary level hospital with adequate provision of sub-intensive and intensive care is a crucial part of the response to the current and possible future outbreaks.
Abbreviations

ALP
Alkaline Phosphatase
ALT
Alanine aminotransferase
APTT
Activated Partial Thromboplastin Time
AST
Aspartate aminotransferase
COVID-19
Coronavirus Diseases 2019
CQ
Chloroquine
CRP
C-Reactive Protein
GFR
Glomerular Filtration Rate
GGT
Gamma-Glutamyl-Transferase
HCQ
Hydroxychloroquine
ICU
Intensive Care Unit
IDU
Infectious Diseases Unit
IQR
Inter-quartile range
MV
Mechanical Ventilation
NIV
Non Invasive Ventilation
PT
Prothrombin Time
RT-PCR
Real Time Polymerase Chain Reaction
SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus 2
SICU
Sub-intensive Care Unit
Declarations

Ethics approval and consent to participate: ethical approval for this study was obtained from the Institutional Review Board of the University of Padua. All participants gave verbal informed consent and all analyses were carried out on anonymised data.

Availability of data and material: the Author confirms that the data supporting the findings of this study are available within the article. More information that supports the findings of this study is available from the corresponding author, AMC, upon reasonable request.

Conflicts of interest/Competing interests: The authors declare that they have no competing interests

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Authors contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Eugenia Di Meco, Alessia Frater, Lolita Sasset, Anna Ferrari, Marco Villano and Federica Gomiero. The first draft of the manuscript was written by Anna Maria Cattelan, Lolita Sasset and Eugenia Di Meco and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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