14-Day Outcome of Treatment Protocol Given to Patients with COVID-19 Admitted in FIC/HDU Karachi

Muhammad Yahya a*, Saima Ghaus b#, Kiran Saleem c†, Baakh Nusrat c†, Samreena Ishrat c† and Maira Masaud c†

a HDU-FIC Expo Centre Karachi, Jinnah Postgraduate Medical Centre, Medicell Institute of Diabetes, Endocrinology & Metabolism, Pakistan.
b HDU-FIC Expo Centre Karachi, OMI Hospital, Medicell Institute of Diabetes, Endocrinology, & Metabolism, Pakistan.
c HDU-FIC Expo Centre Karachi, Pakistan.

Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/JPRI/2022/v34i39A36236

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/87273

Received 11 April 2022
Accepted 22 May 2022
Published 27 May 2022

ABSTRACT

Aims: To observe outcomes in patients admitted to the High Dependency Unit (HDU) at the Field Isolation Centre Karachi after 14 days of COVID-19 treatment protocol.

Patients and methods: This cross-sectional study was conducted at HDU/FIC Karachi at Expo Centre. The duration of the study was from 1st December 2020 to 10th March 2021. All patients diagnosed as cases of COVID-19, of both genders with age ranging from 18 to 91 years were included.

Methodology: All patients were treated according to the protocols set as under:
Anti-viral drug Remdesivir was given in all patients aged less than 75 years, with moderate to severe disease (based on clinical classification released by National Health Commission of China).
Dexamethasone 6mg IV once daily was initiated in all oxygen dependent patients and increased to twice daily if Ferritin levels were greater than 1000ug/L. As a supportive treatment, patients with moderate or severe disease were given Injection Enoxaparin in prophylactic dose and in therapeutic

* Consultant Physician and Fellow Endocrinology,
# Consultant Physician & Endocrinologist,
† Woman Medical Officer,
*Corresponding author: E-mail: dr.muhmamyahya@yahoo.com;
The first case of COVID-19 infection (caused by SARS-CoV-2 virus) was reported in Wuhan, China in December 2019 [1]. Within no time it spread all over the world; and was declared as global pandemic on March 11 2020 by World Health Organization (WHO) [2]. Like other countries Pakistan also faced a huge number of cases of COVID-19, with the first case being reported in Karachi on 26th February 2020 [3]. The spread of this viral disease was so sudden and rapid that the majority of countries and their institutions were not ready to manage such a huge flow of patients and there was no pre-decided treatment protocol. Numerous preventative strategies and non-pharmaceutical interventions were employed to mitigate the spread of disease including careful infection control, isolation of patients, and social distancing. Despite great efforts, the numbers kept rising. Medical therapy involving corticosteroid and antivirals were encouraged as part of critical management schemes. Despite the strategic implementation of these measures, the mortality from COVID-19 kept increasing at a profoundly alarming rate. As new findings emerge, there was an urgent need for up-to-date management guidelines.

Many trials of various medications as a possible treatment were initiated in different countries. Most importantly, World Health Organization (WHO) conducted the Solidarity clinical trial for COVID-19 treatment, as world’s largest randomized controlled trial enrolling 11,330 patients in 405 hospitals across 30 countries. This trial was performed to see the role of Remdesivir, Hydroxychloroquine, Lopinavir and Interferon-B1a. The main outcomes were mortality and need for assisted ventilation, which were not reduced by any of the four under trial drugs [4].

Due to unavailability of any definite cure and no specific treatment guidelines present, different institutions came up with their own treatment protocols comprising various under trial drugs, which were given to patients according to the disease severity and co-morbidities [5,6]. Similarly at HDU/FIC Karachi, we devised a standard treatment protocol with the aim to provide as much benefit to patients as possible but with no added harm. Aim of the current study was to measure the 14-day outcome of treatment
protocol given to patients with COVID-19, who were admitted in HDU/FIC Karachi during the 2nd wave of this pandemic.

2. PATIENTS AND METHODS

2.1 Design, Setting and Population of the Study

This retrospective observational study was conducted at the Field Isolation Centre/High Dependency Unit Karachi @ Expo Centre which was a field hospital being managed by the joint efforts of Sindh Government and Pakistan Army. The duration of the study was from 1st December 2020 to 10th March 2021. All patients of both genders with age ranging from 18 to 91 years with diagnosis of COVID-19 who got admitted at FIC/HDU Karachi during the study time were included in this study. Before admission the diagnosis of COVID-19 was established by taking a nasopharyngeal swab and reverse-transcription polymerase chain reaction (RT-PCR) was performed on the specimen. COVID-19 was diagnosed by detection of the virus on those samples.

All patients were given a treatment according to the protocol set as under:

- Anti-viral drug Remdesivir with the dose of 200mg on day of admission and 100mg once daily for four days was given in patients of age ≤75 years, with moderate, severe or critically severe disease (based on clinical classification released by National Health Commission of China) (Table-1) [7].
- Dexamethasone 6mg IV OD was given in all oxygen dependent patients. Dose of dexamethasone was increased to twice daily in those with Ferritin levels of > 1000 mcg/L.
- Patients requiring oxygen at the time of admission and those with elevated D-Dimer levels were given subcutaneous anticoagulant Inj. Enoxaparin at a prophylactic (40mg once daily) or therapeutic dose (1mg/Kg body weight, twice daily) respectively.
- Along with this, superadded bacterial infections were treated with broad-spectrum antibiotics and adjusted as per culture and sensitivity.
- Patients were also given H-2 receptor blocker Famotidine (40mg once daily), and anti-hyperlipidemic drug Fenofibrate (200mg once daily) based on initial supportive literature [8,9].
- In patients with known liver diseases or with deranged ALT levels ≥ 5 times upper limits of normal, the same plan of management were executed excluding Fenofibrate and Remdesivir.
- Medications were adjustd according to creatinine clearance as needed.

Quarantine period was for minimum of 14 days (as per the initial recommendations by government). Patients were discharged after two consecutive negative PCR test results on 12th and 14th day of admission respectively.

2.2 Data Collection

All data regarding the medications given, oxygen demand at the time of admission, disease severity, co-morbid conditions and the outcome on 14th day of admission was collected through the online HMIS database and from patient files on pre-approved Performa. Patients' confidentiality was ensured.

2.3 Statistical Analysis

Collected data was analyzed using SPSS version 27.0. Qualitative variables were presented in frequency and percentage while mean and standard deviation was calculated for quantitative variable. Mean comparison was done by one-way ANOVA and dependent t-test as appropriate. Association of outcomes with qualitative variables was checked by using fisher exact/chi-square test as appropriate. P-value<0.05 were considered as significant.

3. RESULTS

A total of 183 patients were included in the study. There were 66.7% male and 33.3% female patients with a mean age 59.01±14.83 years. Majority (72.1%) of patients were of more than 50 years of age. Among 183 patients, 2.2% were smokers, 51.9% were hypertensive and 41% were diabetic while 5.5% had chronic obstructive pulmonary disease (COPD) and ischemic heart disease, and 3.8% were found with asthma. We found 84.7% with shortness of breath, 67.8% of patients with fever, 57.9% with cough, 57.9% with fever, 17.5% with myalgia, 14.8% with fatigue, 4.9% with diarrhea, 2.7% with nausea and 1.6% with vomiting (Fig. 1).
expired. Detailed descriptive statistics are presented in Table-2.

Out of 183 patients, 147 patients needed oxygen at the time of admission, which was reduced to 45 patients after 2 weeks, while 26 patients need NIV at admission, reduced to 21 patients on NIV after 2 weeks, as presented in Fig. 2. We found significant mean difference of age (p=0.000) while significant association of outcome was found with remdesivir given (p=0.039), cough (p=0.025), intubation after 2 weeks (p=0.006), Oxygen need at admission (p=0.000), Oxygen need after 2 weeks (p=0.000), NIV Need at admission (p=0.000) and NIV Need after 2 weeks (p=0.000). Detailed results are presented in Table-3.

4. DISCUSSION

Overall the mortality in this study (35%) was significantly high, probably because the bulk of the sample size comprised of elderly patients (>50 years), with ≥ 2 comorbid conditions and with moderate to severe disease at the time of admission. In this study, the age of patients ranged from 18 to 91 year with the mean age of 59 years, which equates with the various other studies carried out on patients with COVID-19, and all of them including this study show that middle age and older patients are commonly infected and have a greater need for hospitalization as compared to the younger population [10,12,13]. The majority of our patients were males (66.7%) perhaps due to the fact that males have more chances of exposure to the infection due to spending more time out of home and with increased person-to-person interactions as compared to females, in our society. Similar finding was also noted in other studies conducted in Pakistan and China [10,11]. In a study from Indonesia [14], and the systemic literature review and meta-analysis by Ortolan et al [15], male gender was associated with higher mortality in COVID-19 patients, hypothesizing it to be due to the increased expression of ACE2 in males as compared to females [16], differences in immunological reactions and the lack of protective effect of estrogen signaling [17]. But interestingly the mortality was found to be notably higher in female patients (41%) as compared to males (32%) in this study, probably because at the time of admission 85.2% females presented with moderate and severe disease as compared to 77.9% males.

Majority (72.7%) of the patients admitted had comorbidity conditions; with more than 50% having ≥ 2 comorbidities, Hypertension, Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, Ischemic Heart Disease and Asthma were the leading contributors, followed by renal, hepatic and oncologic conditions. Presence of comorbidity, especially Hypertension and Diabetes Mellitus pose a poor clinical outcome

![Fig. 1. Symptoms in patients at admission](image-url)
Table 1. Clinical classification of COVID-19 (by the National Health Commission of China)

| Classification          | Mild Clinical Manifestations | Moderate                                      | Severe                                          | Critically Severe |
|-------------------------|-----------------------------|-----------------------------------------------|------------------------------------------------|-------------------|
| Mild                    | No finding on imaging       | Fever, Respiratory symptoms, Findings on X-Ray or CT Scan | Any of the following: 1. Respiratory Distress (Respiratory Rate ≥ 30/min) 2. Oxygen saturation ≤ 93% at rest 3. Arterial partial pressure of oxygen (PaO2) / Fraction of inspiration oxygen (FiO2) ≤ 300 mmHg (0.133 kPa) | Any of the following: 1. Respiratory failure needs mechanical ventilation; 2. Shock; 3. Combined with other organ failure, patients need ICU monitoring and treatment |

Table 2. Descriptive statistics of study population (n=183)

| Variable                          | n(%)
|-----------------------------------|----------------|
| Gender                            | 183(100)      |
| Male                              | 122(66.7)     |
| Female                            | 61(33.3)      |
| Age (years)                       | 59.01±14.83   |
| Mean±SD                           |               |
| Groups                            |               |
| ≤35 years                         | 11(6)         |
| 36-50 years                       | 40(21.9)      |
| >50 years                         | 132(72.1)     |
| Comorbid                          |               |
| Smokers                           |               |
| Yes                               | 4(2.2)        |
| No                                | 179(97.8)     |
| Diabetes                          |               |
| Yes                               | 75(41)        |
| No                                | 108(59)       |
| Hypertension                      |               |
| Yes                               | 95(51.9)      |
| No                                | 88(48.1)      |
| Asthma                            |               |
| Yes                               | 7(3.8)        |
| No                                | 176(96.2)     |
| Chronic Obstructive Pulmonary Disease |           |
| Yes                               | 10(5.5)       |
| No                                | 173(94.5)     |
| Ischemic Heart Disease            |               |
| Yes                               | 10(5.5)       |
| No                                | 173(94.5)     |
| Outcome                           |               |
| Discharged                        | 107 (58.5)    |
| Discharged on Request (DOR)       | 5 (2.7)       |
| Expired                           | 64 (35)       |
| Referred                          | 7 (3.8)       |

SD: Standard Deviation

Leng, Z., Zhu, R., Hou, W., Feng, Y., Yang, Y., Han, Q., et al. (2020) Transplantation of ACE2-Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging and Disease, 11, 216-228. https://doi.org/10.14336/AD.2020.0228
as the mortality in those with any comorbid condition was seen to be almost three folds higher than those without, which is in conformation with almost similar finding of a nationwide analysis conducted in China [18].

Mortality in those who received Remdesivir was slightly lesser than those who didn’t (33.7% vs 36.6%), despite the fact that Remdesivir was given only to those patients who had presented with moderate to severe disease, the factor which in itself pose poor prognosis as compared to those with mild disease; indicating effectiveness of Remdesivir in reducing overall mortality, specially in moderate to severe disease, as demonstrated by other studies like that of Garcia-Vidal et al. [19]

![Fig. 2. Oxygen demand of patient at admission and after 2 weeks](image)

| Table 3. Association of Outcome with risk factors |
|-----------------------------------------------|
| **Outcome**                                   | **Discharged** | **Discharged on Request** | **Expired** | **Referred** | **P-Value** |
| Gender                                        |               |                            |             |             |             |
| Male                                          | 75(70.1)      | 3(60)                      | 39(60.9)    | 5(71.4)     | 0.624       |
| Female                                        | 32(29.9)      | 2(40)                      | 25(39.1)    | 2(28.6)     |             |
| Age Group                                     |               |                            |             |             |             |
| ≤35 years                                     | 9(8.4)        | 0(0)                       | 1(1.6)      | 1(14.3)     | 0.069       |
| 36-50 years                                   | 28(26.2)      | 2(40)                      | 9(14.1)     | 1(14.3)     |             |
| >50 years                                     | 70(65.4)      | 3(60)                      | 54(84.4)    | 5(71.4)     |             |
| HBA1c                                         |               |                            |             |             |             |
| <5.7%                                         | 27(25.2)      | 0(0)                       | 10(15.6)    | 0(0)        | 0.018*      |
| 5.7-6.4%                                      | 23(21.5)      | 4(80)                      | 11(17.2)    | 2(28.6)     |             |
| 6.5-8%                                        | 41(38.3)      | 1(20)                      | 34(53.1)    | 1(14.3)     |             |
| 8.1-9.5%                                      | 9(8.4)        | 0(0)                       | 5(7.8)      | 1(14.3)     |             |
| >9.5%                                         | 7(6.5)        | 0(0)                       | 4(6.3)      | 3(42.9)     |             |
| Remdesivir given                              |               |                            |             |             |             |
| Yes                                           | 68(63.6)      | 1(20)                      | 41(64.1)    | 7(100)      | 0.039*      |
| No                                            | 39(36.4)      | 4(80)                      | 23(35.9)    | 0(0)        |             |
| Smokers                                       |               |                            |             |             |             |
| Yes                                           | 3(2.8)        | 0(0)                       | 1(1.6)      | 0(0)        | 1.000       |
| No                                            | 104(97.2)     | 5(100)                     | 63(98.4)    | 7(100)      |             |
| Diabetes                                      |               |                            |             |             |             |
| Yes                                           | 46(43)        | 2(40)                      | 24(37.5)    | 3(42.9)     | 0.928       |
| No                                            | 61(57)        | 3(60)                      | 40(62.5)    | 4(57.1)     |             |
|                      | Discharged | Discharged on Request | Expired | Referred | P-Value |
|----------------------|------------|-----------------------|---------|----------|---------|
| **Outcome**          |            |                       |         |          |         |
|                      |            |                       |         |          |         |
| Hypertension         |            |                       |         |          |         |
| Yes                  | 59(55.1)   | 1(20)                 | 29(45.3)| 6(85.7)  | 0.079   |
| No                   | 48(44.9)   | 4(80)                 | 35(54.7)| 1(14.3)  |         |
| **Asthma**           |            |                       |         |          |         |
| Yes                  | 3(2.8)     | 0(0)                  | 4(6.3)  | 0(0)     | 0.646   |
| No                   | 104(97.2)  | 5(100)                | 60(93.8)| 7(100)   |         |
| **COPD**             |            |                       |         |          |         |
| Yes                  | 6(5.6)     | 0(0)                  | 4(6.3)  | 0(0)     | 1.000   |
| No                   | 101(94.4)  | 5(100)                | 60(93.8)| 7(100)   |         |
| **Ischemic Heart**   |            |                       |         |          |         |
| Disease              |            |                       |         |          |         |
| Yes                  | 6(5.6)     | 0(0)                  | 4(6.3)  | 0(0)     | 1.000   |
| No                   | 101(94.4)  | 5(100)                | 60(93.8)| 7(100)   |         |
| **Fever**            |            |                       |         |          |         |
| Yes                  | 70(65.4)   | 2(40)                 | 46(71.9)| 6(85.7)  | 0.330   |
| No                   | 37(34.6)   | 3(60)                 | 18(28.1)| 1(14.3)  |         |
| **Shortness of**     |            |                       |         |          |         |
| **Breath**           |            |                       |         |          |         |
| Yes                  | 92(86)     | 4(80)                 | 53(82.8)| 6(85.7)  | 0.861   |
| No                   | 15(14)     | 1(20)                 | 11(17.2)| 1(14.3)  |         |
| **Cough**            |            |                       |         |          |         |
| Yes                  | 70(65.4)   | 1(20)                 | 33(51.6)| 2(28.6)  | 0.025*  |
| No                   | 37(34.6)   | 4(80)                 | 31(48.4)| 5(71.4)  |         |
| **Fatigue**          |            |                       |         |          |         |
| Yes                  | 16(15)     | 1(20)                 | 8(12.5) | 2(28.6)  | 0.481   |
| No                   | 91(85)     | 4(80)                 | 56(87.5)| 5(71.4)  |         |
| **Myalgia**          |            |                       |         |          |         |
| Yes                  | 24(22.4)   | 0(0)                  | 7(10.9) | 1(14.3)  | 0.192   |
| No                   | 83(77.6)   | 5(100)                | 57(89.1)| 6(85.7)  |         |
| **Nausea**           |            |                       |         |          |         |
| Yes                  | 5(4.7)     | 0(0)                  | 0(0)    | 0(0)     | 0.403   |
| No                   | 102(95.3)  | 5(100)                | 64(100) | 7(100)   |         |
| **Vomiting**         |            |                       |         |          |         |
| Yes                  | 3(2.8)     | 0(0)                  | 0(0)    | 0(0)     | 0.424   |
| No                   | 104(97.2)  | 5(100)                | 64(100) | 7(100)   |         |
| **Diarrhea**         |            |                       |         |          |         |
| Yes                  | 8(7.5)     | 0(0)                  | 1(1.6)  | 0(0)     | 0.352   |
| No                   | 99(92.5)   | 5(100)                | 63(98.4)| 7(100)   |         |
| **Intubation at**    |            |                       |         |          |         |
| **Admission**        |            |                       |         |          |         |
| Yes                  | 0(0)       | 0(0)                  | 1(1.6)  | 0(0)     | 0.415   |
| No                   | 107(100)   | 5(100)                | 63(98.4)| 7(100)   |         |
| **Intubation after** |            |                       |         |          |         |
| **2 weeks**          |            |                       |         |          |         |
| Yes                  | 0(0)       | 0(0)                  | 26(40.6)| 0(0)     | 0.000*  |
| No                   | 107(100)   | 5(100)                | 33(51.6)| 7(100)   |         |
| **Expired**          |            |                       |         |          |         |
| Yes                  | 0(0)       | 0(0)                  | 5(7.8)  | 0(0)     |         |
| No                   | 107(100)   | 5(100)                | 63(98.4)| 7(100)   |         |
| **Oxygen need at**   |            |                       |         |          |         |
| **admission**        |            |                       |         |          |         |
| Yes                  | 80(74.8)   | 1(20)                 | 59(92.2)| 7(100)   | 0.000*  |
| No                   | 27(25.2)   | 4(80)                 | 5(7.8)  | 0(0)     |         |
| **Oxygen need after**|            |                       |         |          |         |
| **2 weeks**          |            |                       |         |          |         |
| Yes                  | 10(9.3)    | 0(0)                  | 29(45.3)| 6(85.7)  | 0.000*  |
| No                   | 97(90.7)   | 5(100)                | 7(10.9) | 1(14.3)  |         |
| Outcome | Discharged | Discharged on Request | Expired | Referred |
|---------|------------|-----------------------|---------|----------|
| Expired | 0(0)       | 0(0)                  | 28(43.8)| 0(0)     |
| NIV Need at admission | | | |
| Yes | 5(4.7) | 0(0) | 17(26.6) | 4(57.1) | 0.000* |
| No | 102(95.3) | 5(100) | 36(56.3) | 3(42.9) | |
| Expired | 0(0) | 0(0) | 11(17.2) | 0(0) | |
| NIV Need after 2 weeks | | | |
| Yes | 1(0.9) | 0(0) | 14(21.9) | 6(85.7) | 0.000* |
| No | 106(99.1) | 5(100) | 11(17.2) | 1(14.3) | |
| Expired | 0(0) | 0(0) | 39(60.9) | 0(0) | |

Chi-square/fisher exact test was applied. 
P<0.05 considered as significant. 
*Significant at 0.05 level.

5. CONCLUSION

In summary, our study revealed various characteristics of COVID-19 patients, especially age of patients, supplemental oxygen requirement and comorbid conditions, to be associated with the outcome at day 14 of admission. Remdesivir was found to decrease mortality especially in patients with moderate to severe disease.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19), Situation Report 80.

Available: https://www.who.int/docs/default-source/coronaviruse/situationreports/20200409-sitrep-80-covid-19.pdf?sfvrsn=1b685d64_6. Published April 9, 2020.

2. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. Accessed March 16, 2020.

3. Shahid BYA. Two coronavirus cases confirmed in Pakistan. 2020;1–5. Available: https://www.pakistantoday.com.pk/2020/02/26/sindh-health-two-coronavirus-cases-confirmed-in-pakistan-confirms-first-coronavirus-case-in-karachi/.

4. Solidarity clinical trial for CoViD-19 treatments. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.

5. Surbhi Sharma, Soumen Basu, Nagaraj P. Shetti, Tejraj M. Aminabhavi, Current treatment protocol for COVID-19 in India, Sensors International. 2020;1:100013, ISSN 2666-3511, Available: https://doi.org/10.1016/j.sintl.2020.100013.

6. Nicola M, O’Neill N, Sohrabi C, Khan M, Agha M, Agha R. Evidence based management guideline for the COVID-19 pandemic - Review article. Int J Surg.
Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2-Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging and Disease. 2020;11:216-228. Available: https://doi.org/10.1016/j.aging.2020.04.001

Freedberg et al. Famotidine use is associated with improved clinical outcome in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. J Gastroenterology. 2020;159:1129-131.

Buschard K, Fenofibrate increases the amount of sulfatide which seems beneficial against covid-19. Epub 2020 Jul 21, Med Hypothesis. 2020;143:110127.

Asghar MS, Haider Kazmi SJ, Ahmed Khan N, et al. Clinical Profiles, Characteristics, and Outcomes of the First 100 Admitted COVID-19 Patients in Pakistan: A Single-Center Retrospective Study in a Tertiary Care Hospital of Karachi [published correction appears in Cureus. 2020 Aug 6;12(8):c34]. Cureus. 2020;12(6):e8712. Published 2020 Jun 20. DOI:10.7759/cureus.8712

Liu K, Fang YY, Deng Y, et al.: Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei province. Chin Med J (Engl). 2020;133:1025–1031. DOI:10.1097/CMD.0000000000000744.

Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei province. Liu K, Fang YY, Deng Y, et al. Chin Med J (Engl). 2020;133:1025–1031.

Comorbidities and mortality in COVID-19 patients, Gaceta Sanitaria. 2021;35, Supplement 2:S530-S532, ISSN 0213-9111, Available: https://doi.org/10.1016/j.gaceta.2021.10.085.

Ortolan A, Lorenzin M, Felicetti M, et al. Does gender influence clinical expression and disease outcomes in COVID-19?. A systematic review and meta-analysis, Int J Infect Dis. 2020;99 496-504.

Zhao Y, Zhao Z, Wang Y, et al. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2, Am J Respir Crit Care Med. 2020;202:756-759.

Channappanavar R, Fett C, Mack M, et al. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection, J Immunol. 2017;198:4046-4053.

Wei-jie Guan, Wen-hua Liang, et al. European Respiratory Journal. 2020;55(5) 2000547; DOI: 10.1183/13993003.00547-2020.

Garcia-Vidal C et al. Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19. J Antimicrob Chemother. 2021; [e-pub].