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Original Article

Management of COVID-19 Pneumonia: Experience in a Peripheral Tertiary Level Hospital in Bangladesh

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Abstract:

Background: Since the detection of the first case of the novel SARS-CoV-2 virus in Wuhan, China, on December 31, 2019, the world stepped into an era of the pandemic as declared by WHO on March 11, 2020. With no prior knowledge regarding this new pandemic, the evidence-based practice of medical management was at stake. Experience sharing from different corners of the world played an essential role in building knowledge to save the world.

Methods: The researchers collected data for this retrospective study, from hospital records of the COVID-19 dedicated unit of Sylhet Women's Medical College, Sylhet, Bangladesh, that was formed temporarily in July 2020, in response to the pandemic situation in the country. This article includes data on 3408 admitted COVID-19 patients with moderate to severe symptoms, managed in the isolation unit including its intensive care unit (ICU) up to November 2021.

Results: The mean age of the patients was 57.21±12.58 years and male to female ratio was 1:1.8. Fever (44.4%), cough (38.9), and fatigability (33.3%) were the common symptoms. Diabetes mellitus (67.7%), systemic hypertension (63.7%), asthma (8.65%), chronic obstructive pulmonary disease (21.94%), and, ischemic heart disease (31.2%) were the top co-morbid conditions. Of the study subjects, 68.2% were RT-PCR positive for COVID-19, 67.3% had an abnormal baseline chest X-ray, and 91.1% had a ground glass shadow on a high-resolution CT scan of chest. Average C-reactive protein, D-dimer, and serum ferritin values were 71.68±60.38, 1.16±2.11, and 839±748.57 respectively. Hypoxemia, which was a common problem among them, was managed with oxygen therapy with an appropriate delivery device, with or without supplementation by dexamethasone (78.3%), or methylprednisolone (18.8%). Eighteen (18) patients refused to receive any antiviral therapy, 61 received oral Favipiravir and the rest of them received injectable Remdesevir. Standard care was augmented with Baricitinib in 60 patients. Thirty-six (36) patients in the ICU, with poor response to standard care, were treated with Tocilizumab. Death rates were 9.46% in the non-ICU block, but they were 6-10 times higher in the ICU.

Conclusion: Every medical professional learned from the initial two years of the COVID-19 pandemic. Lessons learnt from experience helped building up the knowledge pool necessary for generating effective protocols for COVID-19 pneumonia management.

Keywords: COVID-19, pandemic, Tocilizumab, Baricitinib, COVID-19 mortality

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Introduction:

It all began with the detection of the first case of SARS CoV-2 or COVID-19 virus in Wuhan, China, on the 31st of December 2019, when the world stepped into an era of a new pandemic, the COVID-19 pandemic, as declared by the World Health Organization (WHO) on the 11th March, 2020.[1,2]

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The pandemic appeared before the global population like a 'panic'. It caused a 'ban' on the globe and there was a massive social, economic, and academic disruption everywhere.[3] The world adopted masks, hand-washing, social distancing, and many such novel behavioral protocols.[4] The cities were locked down, the stores were empty, and the streets were barren but, to the contrary, the Intensive Care Units (ICU) of hospitals were over-whelmed and, the graves of COVID-19 victims kept expanding.[5] With no prior knowledge about how to handle this new virus, the evidence-based practice (EBP) was about to collapse. Social media became the COVID-19 'specialist', continuously prescribing countless non-scientific 'do-and-don't'.[6,7] Under these circumstances, experience sharing from different parts of the world became the main source of knowledge for managing COVID-19 patients.[8] As a very small part of this endeavor, the authors share here from experience some of the facts and findings of managing COVID-19 pneumonia patients in the Sylhet Women's Medical College Hospital (SWMCH), Bangladesh, from July 2020 to November 2021. In Bangladesh, the first case of this novel virus was reported on the 8th of March, 2020.[9] From then on, many COVID-19 dedicated hospitals, both government and non-government, were formed and they functioned effectively to combat the pandemic situation in the country.[10] Sylhet Women's Medical College Hospital, a tertiary-level non-government teaching hospital, lent a promising hand in this service.

Materials and methods:

The researchers collected data for this retrospective, cross sectional study from hospital records of the COVID-19 dedicated unit of Sylhet Women's Medical College, Sylhet, Bangladesh, that was formed temporarily in July 2020, in response to the pandemic situation in the country. Approval from the Institutional Review Board (IRB) was obtained. The majority of the researchers were either directly or indirectly related to COVID-19 management of this unit. This article included data from all the admitted COVID-19 patients of the hospital from the above mentioned period up to November 2021. They were all the suspected or confirmed cases of COVID-19 pneumonia with one or more of the following criterion, for which they got admitted- i) clinical and radiological evidence of pneumonia, ii) respiratory rate >30/min, iii) Oxygen saturation <93%, iv) critical cases- Acute Respiratory Distress Syndrome (ARDS) and/ or, septic shock, v) presence of co-morbid conditions, prothrombotic state and, malignancy. Though triage, diagnosis and management of COVID-19 had been the different capacities of COVID-19 management of the hospital, this article focused only on the inpatient management of the COVID-19 patients in the dedicated unit. Oxygen saturation was initially assessed by pulse oxymetric measurements and in selected cases arterial blood gas analysis was done. The COVID-19 unit was equipped with 4 High Flow Nasal Cannula (HFNC), 4 BiPAP machines and 4 mechanical ventilators. This unit had its own separate Intensive Care Unit (ICU) having 10 beds in it and, 8 more beds in its High Dependency Unit (HDU). The frontline team comprised of internist, cardiologist, and intensivists and, trained nurses. Nearly all patients received a standard therapy comprising of- i) oxygen therapy by appropriate delivery system, ii) systemic corticosteroid, iii) antiviral therapy.

The issues explored in this study were- i) symptoms of patients at presentation and their co-morbidities, ii) diagnostic test positivity rates among patients, iii) management of hypoxemia, iv) specific treatment and add-on therapy v) ICU transfer, vi) area of uncertainty: antibiotic therapy and, vii) outcome: death rates.

Results:

A total of 6,694 patients presented to the triage capacities of the hospital with COVID-19 symptoms. Of them 3,408 patients had moderate to severe symptoms (falling under admission criteria) and, were admitted into the COVID-19 dedicated unit of the hospital from July 2020 to November 2021. The highest number of admission (387) was observed in July 2021 (Figure 1). The admission curves showed two surges of patient flow (wave 1 and wave 2) during the study period. The mean age of patients was 57.21±12.58 years and male to female ratio was 1:1.8.

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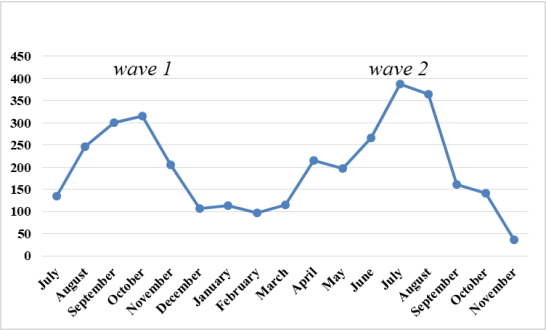
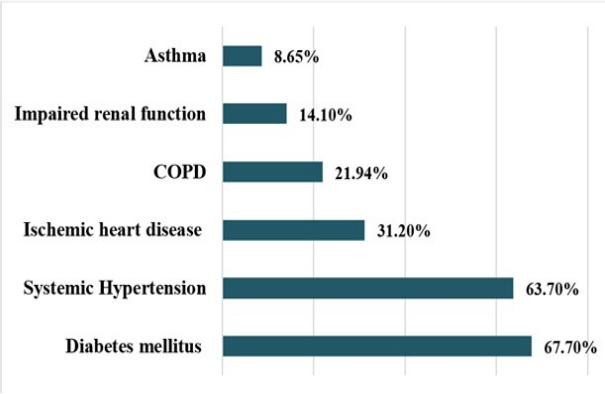
Figure 1: Monthly admission of COVID-19 patients in SWMCH (2020-2021)



Symptoms at presentation and co-morbidities

Fever was the commonest (44.4%) symptom at presentation followed by cough (38.9%) and fatigability (33.3%). Around 75% of RT-PCR (Real-Time Polymerase Chain Reaction) positive and 66% of RT-PCR negative patients had clinical signs of pneumonia. Diabetes mellitus (67.7%), systemic hypertension (63.7%), asthma (8.65%), chronic obstructive pulmonary disease (21.94%), ischemic heart disease (31.2%), and impaired renal function (14.1%) were the top co-morbid conditions among the patients (Figure 2). The presence of comorbidity was related to the severity of the disease, as evidenced by the fact that 80% of the patients with severe disease had one or more comorbidities.

Figure 2: Co-morbid conditions among the COVID-19 pneumonia patients

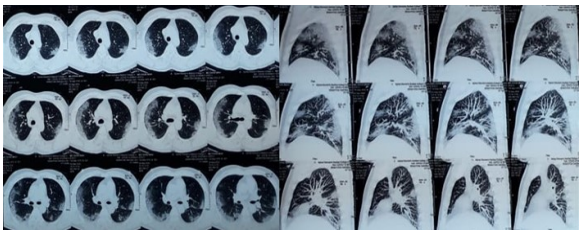


Diagnostic test positivity rates

The diagnosis was made on the basis of suggestive clinical features, RT-PCR test positivity for the COVID-19 virus, and radiological evidence for lung involvement. Of the admitted patients, 68.2% were RT-PCR positive, 67.3% had an abnormal baseline chest X-ray (Figure 3), and 91.1% had a ground glass shadow on a high-resolution computed tomography (HRCT) chest (Figure 4). HRCT chest was done in patients when chest radiograph was inconclusive and in patients who were seriously ill and with comorbidities. About 77.6% of the RT-PCR-positive admitted cases had radiological features of severe pneumonia showing bilateral patchy infiltrates. On the other hand, 68.3% of RT-PCR-negative patients had at least some of the suggestive radiological features.

Figure 3: Common X-ray findings among COVID-19 pneumonia patients

Figure 4: Ground glass opacity on HRCT chest



Other auxiliary tests that were done in all patients were C-reactive protein (CRP), D-dimer and, serum ferritin which helped to assess severity of patients; the average values of these three tests were 71.68±60.38, 2.11±1.16 and, 839±748.57 respectively. Abnormal blood counts were observed in 34% of patients. Thrombocytopenia was present in 21.75% (95% CI: 14.6-28.9 %) of them and it was associated with a more severe form of. Levels of serum procalcitonin were elevated in 20.1% of the severely ill patients with average values of 0.99±0.89 ng/ml.

Management of hypoxemia

Hypoxemia was common. The average oxygen saturation of the patients by pulse oximetry was 74.5% (95% CI: 57-92 %). All the admitted

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patients had some degree of low oxygen saturation (at least <93%) at presentation. The oxygen delivery protocol was adopted according to the prevailing National Guidelines of Bangladesh. Hypoxemia was supplemented by dexamethasone and methylprednisolone in 78.3% and 18.8% of cases respectively. However, 2.9% of them received no steroids and their hypoxemia improved with oxygen therapy alone.

Specific Treatment and add-on therapy

The majority of the admitted patients were managed with standard treatment including an antiviral drug. Anticoagulant was initiated early, within 48 hours of admission but, in selected cases with risk of thromboembolism, e.g. those with raised D-dimer levels. Enoxaparin (0.5-1mg/kg 12 hourly) was administered in these patients during hospital stay and oral Rivaroxaban (10 mg once daily) was prescribed for up to 4 weeks at discharge. Repeat D-dimer test after 5 days of Enoxaparin therapy showed improvement in 63% of patients. Remdesivir was the antiviral given to all patients except 61 who received Favipiravir. Eighteen (18) patients did not receive any form of antiviral therapy due to non-consenting attendants. A number of 60 patients with non-improving hypoxemia after 5 days of standard care, but not requiring ICU or not on NRM (Non-Rebreathing Masks) were given Baricitinib at a dose of 4 mg daily for up to 14 days. Baricitinib showed benefits in terms of home oxygen requirement- only 5.11% of the Baricitinib treatment group had hypoxemia at discharge and required home oxygen therapy for up to 7 days as compared to 50.31% of the control group who required home oxygen for up to 14 days after discharge (Figure 5). Tocilizumab was given to 36 patients in the ICU, with non-improving hypoxemia and raised serum IL-6 levels, on top of the standard care. This drug showed benefits in terms of duration of hospital stay (p-value 0.116), need for mechanical ventilation (p-value 0.023), and survival (p-value 0.001) [Figure 6].

Figure 5: Benefits with Baricitinib add-on therapy: 5.11% of Baricitinib group required home oxygen for 1 week compared to 50.31% of the control group requiring home oxygen for 2 weeks

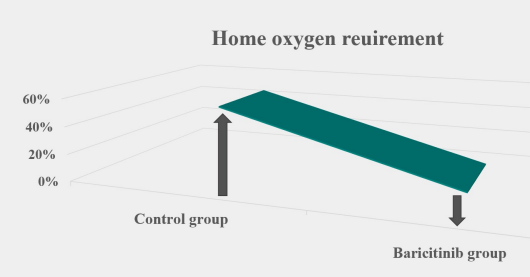
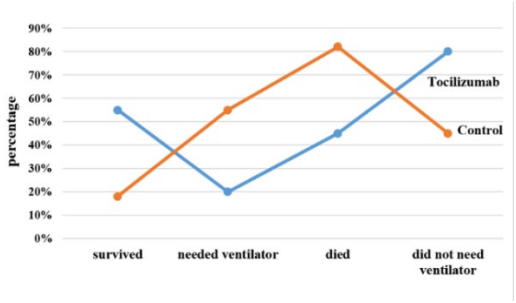


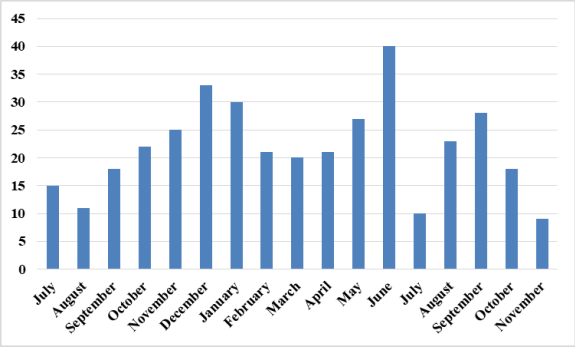
Figure 6: Benefits of Tocilizumab add-on therapy: Tocilizumab showed benefits on 28-day mortality and need for mechanical ventilation



ICU transfer

A total of 371 patients (10.88%) needed transfer to the ICU and 98.4 % of them required ventilator support at one point of management. Patients requiring more than 30L/min oxygen were put on HFNC. However, failure rates of this device were high (57%) among those who survived for some time after shifting. Highest ICU admission was observed in June 2021 (Figure 7). The common indications for ICU transfer were type I and type II respiratory failure, multi-organ failure, and refractory hypoxemia.

Figure 7: Monthly ICU admission



Area of uncertainty: use of antibiotics

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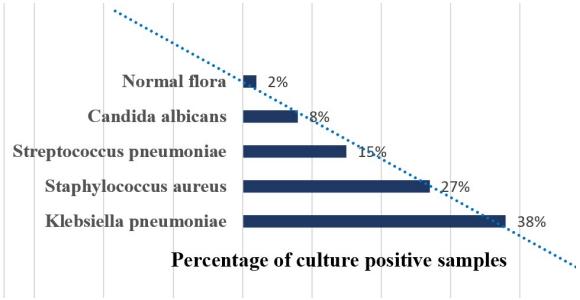
Empiric antibiotic therapy in almost all admitted COVID-19 pneumonia patients had been debated. Retrospective data from records of the microbiology laboratory of the hospital showed, out of 621 sputum samples from RT-PCR-positive COVID-19 pneumonia patients, 124 (19.97%) had yielded growth of microbes. Among the positive sputum specimens, growth was obtained in the following order (Figure 8) - Klebsiella pneumonia (38%), Staphylococcus aureus (27%), and Streptococcus pneumoniae (15%), and, Candida albicans (2%). However, these findings could not demonstrate who among the COVID-19-positive patients were at risk of acquiring a co-infection. But, the results afterwards, made the use of empiric antibiotics justified to some extent.

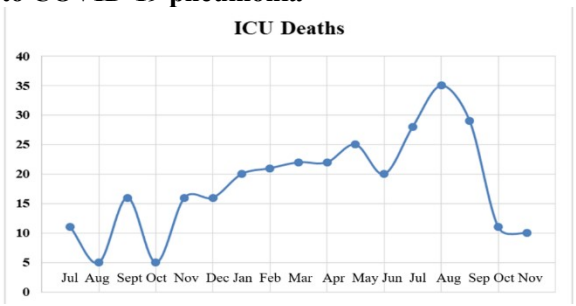
Figure 8: Percentage of different isolates in sputum samples of COVID-19 pneumonia patients



Outcome: death rates

Average death rates in the isolation unit were 9.46%, but in the rates in the ICU were higher than this- ranging from 56.76% to 94.6%. Figure 9 depicts the monthly number of deaths in the ICU. The highest numbers of deaths were observed in the months of July, August, and September 2021. However, the curve showed a decline in October and November of the same year. Premature discharge rates without any advice (discharge on risk bond) gradually declined throughout 2021. Of the 113 admitted patients in January 2021 14 (12.39%) were discharged without advice whereas, this percentage was 4.56% in May 2021 (09 patients out of 197). The death rates were calculated excluding these patients.

Figure 9: Institutional death curves (ICU) due to COVID-19 pneumonia



Discussion:

The outbreak of COVID-19 introduced a new era in the world's history of pandemics.[1,2] In the early days of this new pandemic, effective management protocols meant triage, diagnosis, and treatment. Knowledge and facility constraints were the first obstacles in handling this crisis.[4,7] After making its first appearance in China, the pandemic sequentially spread to more Asian countries like Japan, Korea, and Hong Kong, and then to the USA, Europe, and Australia within January 2020.[11] Bangladesh had duly anticipated its entry which actually happened in March 2020.[12]

This study reports the findings obtained from the experience of managing this pandemic in a non-government tertiary care teaching hospital in Sylhet, Bangladesh. Fever, cough, and fatigue were the common symptoms at the presentation. Overt breathlessness was uncommon which may be attributable to the so-called 'happy hypoxemia' of COVID-19 pneumonia.[13] In a US-based study, Stokes et al found that two-thirds of COVID-19 pneumonia patients had a fever, cough, and breathlessness, one-third had myalgia and one-third had a headache.[14]

Patients with suggestive symptoms in this study were diagnosed on the basis of RT-PCR positivity and/or radiological evidence. Peripheral patchy infiltrate on the chest X-ray and variable degree of ground glass opacities on HRCT scan were common radiological findings in this study, as well as in other studies.[15] Admitted patients with moderate to severe symptoms of COVID-19 pneumonia, with or without serological test positivity, and with or without radiological evidence of pneumonia,

were the study subjects in this study. Blood count abnormalities like leukopenia, thrombocytopenia, and increased neutrophil-to-lymphocyte ratio were almost universal among COVID-19 pneumonia patients.[12] The commonest blood abnormality in this study was thrombocytopenia which was related to the severity of the disease. However, according to other studies, a more precise marker reflecting severity is the platelet-to-lymphocyte ratio which actually reflects the development of 'cytokine storm'.[12,16,17]

Deaths due to COVID-19 pneumonia were mostly due to complications mimicking Adult Respiratory Distress (ARDS). So, the biggest challenge in the inpatient management of COVID-19 patients was the management of hypoxemia in these patients.[18,19,20] This article reports findings of a newly and temporarily formed COVID-19 unit in a peripheral tertiary care teaching hospital in the first two years of the pandemic. In spite of adopting the existing national guideline-based management protocols[20], the overall death rates were around 10% in normal wards. But the ICU death rates were six to ten times higher than this. However, it does not include the deaths of patients at home who were withdrawn from hospital care according to the patient's/guardian's decision. However, we started experiencing a second wave of disease that started in April and peaked in June-July 2021 (Figure 1). This synchronized to the global emergence of the delta variant.[21]Researchers observed a remarkable decline in hospitalization rates and deaths, a few months following the initiation of mass vaccination programs in the country. This was similar to the global trends.[21,22]

Corticosteroids have long been used as an anti-inflammatory drug. Its use during the COVID-19 era was adopted with the projected thinking that it might also help against the immune-mediated lung inflammation caused by this virus.[23] In a summary of 11 studies, it was reported that corticosteroids acted positively in managing COVID-19 pneumonia. It reduced death for two months post-treatment of viral pneumonia and increased the number of ventilator-free days. However, the study could not find conclusive results regarding adverse events or hospital-acquired bacterial infection rates due to its use.[14,24] In the index study, 97.1% of patients received systemic corticosteroids, mostly injectable dexamethasone. No comparative assessment could not be done between steroid and non-steroid recipients. Methylprednisolone was used in (18.8%) of COVID syndromes like Adult Respiratory Distress Syndrome (ARDS) and Cytokine Release Syndrome (CRS). In a study on 86 COVID-19 patients, dexamethasone and methylprednisolone were compared but yielded inconclusive results[14] and a systematic review found similar effects with the two glucocorticoids.[25]

All admitted patients in this study received standard care, (defined as a combination of oxygen therapy, steroids, and antiviral therapy) and the majority of them got injectable Remdesivir, a SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) inhibitor, as an antiviral medication. Though respiratory failure, renal failure, elevated liver enzymes, and gastrointestinal upset have been described as common side effects of this drug[26,27], no major adverse event was reported in this study. The few patients (61), who received Favipiravir, also did not show any hepatic impairment which has been reported in some studies.[28,29] Eighteen (18) patients declined to receive any of the antiviral medications. None of the study patients received hydroxychloroquine, amantadine, or azithromycin. Baricitinib, a Janus kinase (JAK) inhibitor, usually used as an anti-rheumatic drug[30], was used as an add-on treatment of sixty (60) COVID-19 patients with non-improving hypoxemia, and it proved to be beneficial in terms of oxygen requirement post-discharge. CRS in COVID-19 is presumed to be mediated by IL-6, hence, a humanized monoclonal antibody Tocilizumab, with anti-IL-6 properties is found to be beneficial in a systematic review of 63 articles.[31] A small number of patients (36) in the ICU with raised IL-6 levels were prescribed with this drug and, significant benefits were observed with respect to the requirement of ventilator and reduction in hospital stay and improvement in survival. A meta-analysis on the effect of this drug on short-

term mortality found a pooled RR of 1.09 (95% CI 0.80–1.49, I2 = 0%), and on the need for mechanical ventilation, the pooled RR value was 0.71 (95% CI 0.52–0.96, I2 = 0%).[32] Anticoagulation therapy was not routine but given with Enoxaparin in selected patients with raised D-dimer levels and with a risk of thrombosis within 48 hours of admission. Repeat D-dimer test after 5 days of therapy showed improvement in 63% of patients. However, this study could not explore the time-length when the thromboembolism risk is the greatest in the COVID-19 pneumonia patients. In a self-controlled case series and matched cohort study, incidence rate ratios for pulmonary embolism in the first and the second week of COVID-19 infection were 36.17 and 46.40 (95% confidence interval) respectively.[33]

Physicians had to work upon the benefits of the doubt due to the lack of well-defined and scientifically established protocols, especially in the early days of the COVID-19 era. Use of antibiotics in admitted COVID-19 pneumonia patients was a debated issue everywhere.[34] In the COVID-19 isolation unit almost all patients received empiric antibiotics which warrant justification. The most commonly used antibiotics were Ceftriaxone, Imipenem, Meropenem, and Moxifloxacin. This retrospective study found about 20% microbial culture-positive rates among the sputum samples of COVID-19 pneumonia patients. However, it failed to demonstrate reliable risk factors for bacterial or fungal co-infection.

The anticipations of the COVID-19 pandemic in Bangladesh had been very scary. But miraculously enough, the toll of the pandemic on the mass people of this country turned out to be less devastating than the projections.[35] The epidemiological graphs took favorable trails quickly with the implementation of national vaccination schedules in Bangladesh.

Conclusion: Every medical professional learned through trial and error, from the initial two years' experience of the COVID-19 pandemic management. And the cumulative results of their experience contributed a lot to build up the Evidence Based Practice for COVID-19 management.

Disclaimer: The authors of this article declare no conflict of interest

Limitations: It was a retrospective study. It could not explore all research questions regarding management of COVID-19 pneumonia. Records were sometimes incomplete due lack of logistics in the early days of the pandemic. Further prospective well designed studies can yield better results.

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