ORIGINAL RESEARCH PAPER

Anaesthesiology

COMPARISON OF CLINICAL OUTCOMES AND MORTALITY IN COVID 19 PATIENTS ADMITTED DURING THE FIRST VERSUS SECOND WAVE IN THE ICU OF A TERTIARY CARE CENTRE IN NORTH INDIA.

KEY WORDS: COVID 19, ICU, North India.

Loveleen kour* MBBS, MD Anesthesia, senior resident Dept of anesthesia GMC Jammu. *Corresponding Author

Smriti gulati Professor and head, Dept of anesthesia, GMC Jammu.

ABSTRACT

Background- India, like many countries, has experienced two surges of the COVID 19 pandemic. Empirical data shows a difference in the effects of the virus between the two periods. We decided to compare the behaviour of the disease in its two major outbreaks in critically ill patients so as to obtain a better understanding and improve clinical outcomes.
Methods- This was a retrospective study conducted by obtaining patients data from hospital records during the first wave from 1st April 2020 to 30 June 2020 and comparing it to the records in second wave 15 March 2021 to 15 June 2021. Patient demographics, clinical presentation, mechanical ventilation and overall ICU outcomes were compared.
Results- 89 patients admitted during first wave and 100 patients admitted during second wave during the chosen period were selected for the purpose of this study. Second wave predominantly involved the young and middle aged while majority of patients during first wave belonged to older age group with co morbidities. The most frequent signs and symptoms during both waves were fever, cough, pneumonia and tachypnea.
Conclusion- The second wave was characterised by higher infectivity in a comparatively younger age group whereas first wave showed older age groups being primarily infected. However, the case fatality rate during first wave was higher than second wave.

INTRODUCTION-

The COVID 19 pandemic began in Wuhan, China with first case being reported in December 2019. Since then, the disease has ravaged entire countries and even continents bringing the global case count to more than 230 million by September 2021. In India alone, the total case count has reached upto 33 million with more than 450 000 deaths.

Several countries around the globe have experienced a two wave pattern of the disease (1). The second wave in contrast to the first wave showed a sharp rise in newly documented cases, yet there was no observed significant rise in death tolls (2). In countries like Germany and Spain, the peak of the second wave was expected to yield 2–3 million infections along with a mortality count in thousands (3). The death rate was reported to be diminished during the second wave as compared to the first wave in 43 out of 53 countries, accounting for no rise in fatality rate around the globe (1). However, this disease is notorious for potraying different behaviour across different socio demographic populations. Hence, the generalisability of these global findings to our local population stands debatable.

In India the first wave started around mid March with maximum daily cases reported in mid September. It ended by January 2021. A second wave beginning in March 2021 was much more devastating than the first. There was an explosive rise in cases which resulted in overburdening of an already compromised health system. This resulted in shortage of vaccines, hospital beds, oxygen cylinders and other medical supplies in certain parts of the country. This second wave peaked by late April 2021, with India reporting the highest new and active cases in the world. However, official figures stated that inspite of recording more than 250 000 deaths, the case fatality rate (CFR) during second wave was 1.28% which was still lower than CFR of 1.41% recorded during first wave.

Understanding the similarities and differences between the two waves assumes significance because it helps in furthering our understanding of the disease and its causative virus. Population comparisons are difficult because of technological and logistical constraints. However, a more accurate comparison is possible with hospitalised patients in whom the disease has been confirmed by reverse transcriptase polymerase chain reaction (RT PCR) and severe symptoms.

In this study we aimed at comparing the clinical characteristics and outcomes in patients admitted in ICU of our institute with severe COVID 19 during the two waves of COVID 19. We evaluated the demographics, clinical features, laboratory parameters , co morbidities and outcomes in the patients enrolled for the study.

METHODS-

This was a single centered , retrospective study conducted in the department of Anaesthesia and Intensive care in one of the largest tertiary care centres in North India. All patients admitted to the ICU with confirmed COVID 19 (confirmed by RTPCR done on naso/oropharyngeal swab) between 1st April 2020 to 30 June 2020 during first wave and between 15 March 2021 to 15 June 2021 in the second wave were selected for the purpose of this study.

As per government policy, our institute served as a primary admission as well as referral centre from nodal hospitals as per government policy. Patients of all grades of severity were referred to our hospital. The referred patients as well as those presenting for the first time were received in a screening area, evaluated as per guidelines and triaged to isolation ward, high dependency unit (HDU) or intensive care unit (ICU) as per clinical severity. Mild cases were kept in isolation ward, whereas, moderate cases were shifted to HDU.

Severe cases – which were defined as those with

1. respiratory rate > 30/min,
2. blood oxygen saturation< 93% on room air,
3. Pao2/FIO2 < 300 ,
4. those with ARDS, confusion, disorientation, sepsis, septic shock, multiorgan failure – defined as critical cases.

The patients fulfilling any of these criteria were admitted to ICU, where treatment was given as per international and institutional protocols. Oxygen therapy with the clinically appropriate devices and prone positioning in eligible patients were done. For patients requiring mechanical ventilation we adhered to ARDS Network strategy (12) of low tidal volume , low PEEP and high FIO2. The aim was to keep plateau pressures less than 30cm H2O and driving pressure below 15cm H2O. Patients were discharged only after two consecutive negative reports of RTPCR and resolution of clinical symptoms and chest x ray changes.

Data collection-

The following data were retrieved from the hospital records – demographic parameters- (age, sex, body weight) of all patients, medical history including underlying co morbidities, clinical symptoms and signs, laboratory investigations (complete blood count, liver/ kidney function tests, chest X ray, ECG etc), mode of respiratory support (oxygen by facemask, high-flow nasal cannula (HFNC), non-invasive or invasive ventilation) ; MV LOS , ICU LOS among survivors and non survivors and final outcome (in terms of still admitted/discharge/death). Patient outcomes were followed upto 15 July 2020 during first wave and 30 June 2021 during the second wave.

Statistical analysis-

The compiled data was entered in a spreadsheet (Micro Excel) and then exported to the data editor of SPSS Version 20.0 (SPAA Inc., Chicago, Illinois, USA). Student's independent *t*-test was employed for comparing continuous variables. Chi-square test was applied for comparing categorical variables.

RESULTS-

During the first wave, 89 patients were admitted in ICU during first wave from 1st April 2020 to 30 June 2020. Out of these, 52 patients were males and 37 were females. On the other hand, our ICU recorded 100 admissions during second wave between 15 March 2021 to 15 June 2021. Out of these, 62 were males and 38 were females. The median age of patients admitted during first wave was 58 years (IQR= 45-78) whereas the median age of presentation during second wave was 45 years (IQR= 25-61). (Table 1)

Fever, cough, dyspnea and pneumonia were the major presenting signs and symptoms in both the waves. The incidence of dyspnea was higher among non survivors in both the groups. The median duration from first symptom onset to hospital admission was 12 days (IQR=9-15) during first wave whereas it was 9 days (IQR=5-14) during the second wave. (Table 1)

The most common co morbidities were hypertension and diabetes mellitus during both waves. During first wave the incidence of hypertension and diabetes were- 52.9% and 27.4% respectively; while during the second wave their incidence was- 54.55% and 24.2% respectively. However, second wave admissions reported a higher incidence of gastrointestinal symptoms like vomiting and abdominal pain (10%) , coronary artery disease (CAD) (12%), chronic obstructive pulmonary disease (COPD) (14%), chronic kidney disease (CKD) - (11%) and any other significant co morbidity (like chronic liver disease, associated malignancy) - (10%). Majority of deceased patients belonged to the younger age group with a median age of 48 years (IQR= 40-55) during second wave while majority of deaths in first wave belonged to the advanced age group 62 years (IQR=56-78). (Table 1)

Laboratory findings showed lymphocytopenia, neutrophilia and thrombocytopenia were more severe during the second wave. Inflammatory markers like CRP, LDH, D dimer were raised in almost all patients but their elevation was more significant during first wave where lymphocyte and neutrophil counts were not as significantly elevated. (Table 1)

We also evaluated the differences in treatment in both the groups. Patients during second wave showed a higher requirement of invasive and non invasive ventilation. Whereas, during first wave there was a higher incidence of conventional oxygen therapy.The MV LOS (mechanical ventilation length of stay) was longer during the first wave - 18 days (IQR =8-22) than during second wave- 6 days (IQR=3-11). Regarding pharmacological interventions, patients in the first wave received lopinavir, ritonavir and hydroxychloroquine, while those in the second wave received remdesivir and tocilizumab.

Out of 89 patients admitted during first wave, 15 died, out of which 3 were on mechanical ventilation (MV). Hence overall ICU mortality during first wave was 16.85 % and MV related mortality was 33.07%. During second wave, among the total 100 admissions, 12 patients died, out of which 5 were on ventilators. Hence, MV related mortality during the second wave as reported by our study was 41.2% while the overall ICU mortality was 12 %. (Table 2)

Tables- Demographic characteristics, co morbidities and laboratory parameters in survivors and non survivors.

Variables	First wave (n= 89)	Second wave(n=100)	P value
Age(years)	58 (45-78)	45 (25-61)	<0.001
Sex (M/F)	52/37	62/38	0.435
Fever	62%	75%	<0.001
Dyspnea	32%	52%	<0.001
Pneumonia	54%	65%	<0.001
Duration from first symptom to hospital admission (days)	12(9-15)	9(5-14)	<0.001
Co Morbidities			
Hypertension	52.9%	54.5%	0.362
Diabetes mellitus	27.4%	24.2%	0.423
Gastrointestinal symptoms	2.8%	10%	<0.001
Coronary artery disease	6%	12%	<0.001
Chronic kidney disease	7.2%	11%	<0.001
Laboratory investigations			
Peak CRP levels(mg/L)	210	140	<0.001
Peak LDH levels (U/L)	765	577	<0.001
Peak D dimer (mcg/ml)	8.88	3.90	<0.001
Peak Neutrophil count(%)	85	92	<0.001
Lowest Lymphocyte count(%)	10	4	<0.001
Lowest platelet count ($x10^9$/uL)	172	152	<0.001

Student independent t test and chi square test were used for statistical analysis.

Table 2- ICU outcomes in patients with COVID 19 in first and second wave.

Outcomes	First wave	Second wave	P value
Still admitted	40	32	0.321
Discharged	34	56	<0.001
MV associated mortality	33.07%	41.2%	<0.001
Overall ICU mortality	16.85%	12%	<0.001

DISCUSSION-

In this study we compared the characteristics of the first and second wave of COVID 19 in terms of- patient characteristics, clinical features, co morbidities and clinical outcome. While analyzing the demographic data, it comes to light that average age of presentation during second wave in our study was significantly lower than during the first wave. Among gender distribution, males were preferentially affected in both waves.

The average time of presentation to the hospital is lower during the second wave than the first wave.The longer time taken to seek medical attention during first wave could be due to ignorance and fear of social stigma. Also, co morbidities like diabetes mellitus could also impair the perception of dyspnea leading to delay in seeking medical

attention (4).While during the second wave, there was more public awareness due to continued government efforts but because of the explosive rise of cases and overburdening of hospitals and ICUs leading to dearth of beds. All these contributed to delay or death prior to admission in second wave.

While hypertension and diabetes remained the most frequent co morbidities during first wave. The second wave showed a greater incidence of gastrointestinal symptoms. This is an interesting behaviour on the part of the disease and whether it is solely because of viral mutation or has a relation to patient demographics remains a subject of further study and research.

Fever, dry cough, tachypnea (increased respiratory rate) were the main presenting symptoms during the first wave whereas the second wave showed more cases of breathlessness (dyspnea). Decreased oxyhaemoglobin saturation <90% at the time of presentation was also more commonly seen during the second wave. This assumes significance because the unique pathophysiology of this disease leads to "happy hypoxemia". Most of the patients do not complain of dyspnea even in the presence of alarming levels of hypoxemia.

Dyspnea is defined as a sensation of difficult or laboured breathing which occurs when the demand for ventilation is out of proportion to the patient's ability to respond. It is therefore different from tachypnea (rapid breathing) and hyperpnea (increased tidal ventilation). COVID 19 patients usually present with hypoxia (low PO2) and low CO2. Respiratory chemoreceptors are highly sensitive to increased PaCO2 levels whereas hypoxemia plays a minor role in the sensation of breathlessness. Experimental models have shown that dyspnea only occurs when PaO2 drops below 40 mmHg, whereas at PaO2 levels between 65 and 40 mmHg, there is a rise in minute ventilation, increase in the respiratory rate, without dyspnea. Therefore, tachypnea and hyperpnea, not dyspnea, are the clinical signs of impending hypoxemic respiratory failure in COVID 19 patients (5 ,6). Dyspnea in COVID 19 patients, though not routinely present should alert the clinician, as it indicates deterioration and failing lung compliance (7).

In April 2020, Gattinoniet al. (8) published a very interesting paper in Critical Care:"COVID-19 pneumonia: ARDS or not?". In this article, the authors hypothesize the existence of two pathophysiological phenotypes of COVID-19 ARDS: the light phenotype(type L) and the heavy phenotype (type H). The light phenotype has preserved lung compliance (low elastance i.e. high compliance), low ventilation/perfusion ratio (V/Q ratio), low weight and low reclutability. This phenotype is typical of the early phase of disease, but it can be seen in some severe cases as well (9). The type H phenotype has high lung elastance (i.e. low compliance), high right to left shunt, high weight and high reclutability. This phenotype is often seen in the later phase of the disease. The patients with this phenotype are usually more severe and their condition clearly resembles classical ARDS.

Dyspnea in a COVID 19 patient tells the clinicians that lung compliance is falling, and that the patient might be evolving from an L phenotype to a more life threatening H phenotype (10).The higher incidence of dyspnea during the second wave indicates a more rapid progression to H phenotype which in turn co relates with lower oxyhaemoglobin saturations in these patients at the time of presentation.

Coming to laboratory investigations, elevated inflammatory markers like CRP,LDH, procalcitonin co related with increased mortality and need for mechanical ventilation during the first wave whereas in the second wave neutrophil, lymphocyte and platelet counts co related better with in hospital events. Our findings are similar to those of Asghar et al (11) who did a study comparing the severity markers in the two waves of covid 19 in Pakistan. There was also a modification in the treatment protocols followed during the two waves. In this regard, during the second period, patients were treated more frequently with dexamethasone, as suggested by the RECOVERY study (12). Hydroxychl oroquine and loponavir-ritonavir were substituted by remdesivir and tocilizumab, which several studies have reported to be more effective in preventing death andshortening the duration of hospital stays (13,14,15). Hydroxychloroquine was initially recommended during the first wave of COVID, however, its use is controversial. Some studies have shown it to be of some benefit (16) while others have found it to be of no benefit (17). Despite its use during the first wave in our institute, we updated our treatment protocol in accordance with new guidelines from health ministry and did not use during the second wave. Hence could not compare effectiveness of hydroxychloroquine in the two waves.

The overall mortality during the second wave was lower than during first wave. This could be due to better preparedness for emergency response in second wave (because of the experience of first wave). Also during the first wave, patients predominantly belonged to older age with presence of serious co morbidities like diabetes, cancer, chronic obstructive pulmonary disease. This could also be one of the contributing factors for their higher mortality.As highlighted in our study the longer delay in seeking medical help during the first wave also played a role. Our results are similar to Iftimie S et al (18) who compared the two waves in Reus, Spain and reported lower fatality during second wave. However, the higher mechanical ventilation associated mortality during second wave as seen in our study could be due to the more virulent delta strain which caused serious COVID associated ARDS and acute decompensation resulting in decreased pulmonary compliance (H phenotype) and lethal hypoxia resistant to even mechanical ventilation.

CONCLUSION-

The second wave ,although, associated with higher infectivity among the younger population, showed a lower case fatality rate than the first wave. While elevated inflammatory markers co related with increased mortality in the first wave ; neutrophil, lymphocyte and platelet counts co related better with in hospital events during the second wave. No amount of advanced treatment can undermine the importance of COVID appropriate behaviour and thus social distancing and masking should be practiced on all occasions.

REFERENCES-

1. Fan G, Yang Z, Lin Q, et al. Decreased case fatality rate of COVID-19 in the second wave: a study in 53 countries or regions. Transbound Emerg Dis. 2020;00:1–3.
2. Linden M, Dehning J, Mohr SB, et al. The foreshadow of a second wave: an analysis of current COVID-19 fatalities in Germany. arXiv:2010.0585.2020.
3. Castro FD. Modelling of the second (and subsequent) waves of the coronavirus epidemic. Spain and Germany as case studies. MedRxiv. 2020.[Preprint].DOI:10.1101/2020.06.12.20129429
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
5. Vaporidi K, Akoumianaki E, Telias I, Goligher EC,Brochard L, Georgopoulos D. Respiratory drive incritically ill patients pathophysiology and clinical implications. Am J Respir Crit Care Med. 2020;201:20-32.
6. Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. N Engl J Med. 1995;333:1547-53.
7. Oldani S, Ravaglia C, Bensai S, Bertolovic L, Ghirotti C, Puglisi S et al. Pathophysiology of light phenotype SARS-CoV-2 interstitial pneumonia: from histopathological features to clinical presentations. Pulmonology. 2021 Mar 26:S2531-0437(21)00078-7.
8. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care. 2020;24:1-3.
9. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M,Bellani G, et al. Pathophysiology of COVID-19-associatedacute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8:1201-8.
10. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lam-brecht BN. Conceptions of the pathophysiology ofhappy hypoxemia in COVID-19. Respir Res. 2021;22:1-9.
11. Asghar MS,Yasmin F, Ahsan MN, Alvi H, Taweseedet P, Surani S. Comparison of

first and second waves of COVID-19 through severity markers in ICU patients of a developing country. Journal of Community Hospital Internal Medicine Perspectives, 11:5, 576-584.
12. RECOVERY Collaborative Group. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med. 2020; July 17.
13. Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: Recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. Curr Med Chem. 2020; 27: 4536–4541.
14. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020; 396: 1345–1352.
15. Lam S, Lombardi A, Ouanounou A. COVID-19: A review of the proposed pharmacological treatments. Eur J Pharmacol. 2020; 886: 173451.
16. COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. Eur J Intern Med. 2020; 82: 38–47.
17. Ip A, Ahn J, Zhou Y, Goy AH, Hansen E, Pecora AL, et al. Hydroxychloroquine in the treatment of outpatient with mildly symptomatic COVID-19: a multi-center observational study. BMC Infect Dis. 2021; 21: 72.
18. Iftimie S, López-Azcona AF, Vallverdú I, Hernández-Flix S, de Febrer G, Parra S, et al. (2021) First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. PLoS ONE 16(3): e0248029.