



CLINICAL OUTCOME AMONG MODERATE-SEVERE COVID-19 PATIENTS TREATED WITH STANDARD DRUG THERAPY PLUS LMW HEPARIN

Internal Medicine

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ABSTRACT

Introduction The aim of the research is to evaluate the clinical outcome among moderate-severe COVID-19 patients treated with standard drug therapy plus LMW Heparin as compared to those not given LMW Heparin. It has several objectives such as to evaluate the clinical outcome among moderate-severe COVID-19 patients admitted to RUHS-HMS and treated with LMW Heparin along with Standard Treatment Protocol by assessing their in-hospital course of illness, duration of hospital stays, recovery, and mortality. To identify the possible risk factors associated with COVID Patients. **Methods** A retrospective, observational study is undertaken. The study is conducted in the hospital attached to RUHS College of medical sciences, Jaipur, Rajasthan. The study is conducted over a period of eight months. The data which is achieved from the study is analyzed statistically. For this, the usage of SPSS version 17.0 software is done. The test which is used is the standard deviation. The normal distribution of the continuous variables between the groups is analyzed with the help of a t-test the significance level is set up at less than 0.05. **Results** It revealed that the administration of heparin was associated with lower mortality in patients admitted with COVID-19 as in group A patients who received LMW Heparin, mortality was 11% with or without comorbidities whereas in group B it was found 18.68%. The presence of the disease is found to be associated with several other underlying conditions like liver, cardiovascular, kidney disease, and others. **Conclusion** It is concluded that the heparin usage is helpful and effective while treating the infection of COVID-19. Moreover, it is accountable for declining the rate of mortality in the patients. The current study also states that the underlying cardiovascular diseases are responsible for increasing the threat of mortality in patients who are suffering from COVID-19.

KEYWORDS

COVID-19, moderate-severe, LMW Heparin, Coagulopathy, D- dimer, IL-6, Outcomes

INTRODUCTION

The spread of Covid-19 infection was a global problem which led to several problems in the lives of the people in the entire world. It affected the world physically, mentally, economically, and in several other ways. During the initial phase of the development of the disease, the symptoms of the disease were like those of pneumonia. Later, it was identified as Covid-19. The virus which is responsible for causing the disease is SARS-COV2 which stands for severe acute respiratory syndrome coronavirus-2. The disease cases were first reported in Wuhan in China and then spread relatively fast throughout the world. This was then reported as a global pandemic by WHO. Because of this, social isolation was made mandatory in several parts of the world, affecting the world severely. The spread of the disease was extremely quick and it also caused an extreme amount of deaths.

The disease shows a high correlation with mortality as the concentration of the D-dimers increases. Studies indicate that the disease has caused several deaths including around 154,010 deaths in India till January 2021. Thus, this research is being conducted to determine the clinical outcomes in the patients by using anti-coagulants as data indicates the presence of thrombi in the tissues of the infected patients.

The aim of the research is to evaluate the clinical outcome among moderate-severe COVID-19 patients treated with standard drug therapy plus LMW Heparin as compared to those not given LMW Heparin. It has several objectives such as to evaluate the clinical outcome among moderate-severe COVID-19 patients admitted to RUHS-HMS and treated with LMW Heparin along with Standard Treatment Protocol by assessing their in-hospital course of illness, duration of hospital stay, recovery and mortality. To identify the possible risk factors associated with COVID Patients.

The spread of the virus began in December 2019 which imposed a major health problem in the world. The virus is a single-stranded RNA which has a diameter of about 100-150nm. The virus is enveloped and belongs to the family *Coronaviridae*. The virus consists of four proteins which include nucleocapsid, membrane, and spike and

envelop protein (Thachil, et al, 2020).

There are several types of treatment methods which are used for the disease. This includes the usage of antiviral drugs; the usage of steroids and immune-modulator or suppressive drugs; and the usage of anticoagulants. The usage of anticoagulants is done in the form of low molecular weight heparins which prevent the clotting of the blood. The possible pathophysiology of the hypercoagulable state in the infection may include the induction of disseminated intravascular antiphospholipid, then the activation of the complement cascade and then the endothelial dysfunction (Liu, et al, 2020). Some studies mentioned that the excessive complement activation is associated with the COVID-19 infection. This can be indicated by the elevated levels of LDH, bilirubin, D- dimer, decreased level of platelets, renal and cardiac injury, anaemia as well as diffuse thrombotic microangiopathy. Hence, it may indicate that the usage of an intervention which focuses on inhibiting this activation as well as performance anticoagulation could be extremely beneficial for COVID-19 infection (Campbell & Kahwash, 2020).

There are several studies which indicate that occurrence of impaired coagulation in COVID-19 infection takes place. D'Ardes, et al, 2022 mentioned in your study that there is a relationship among the impaired coagulation, liver dysfunction and COVID-19 infection. As per the study, this infection can induce multiple vascular district atherothrombosis. Along with that, it also affects the cerebral, coronary and peripheral vascular beds. Myocardial injury has also been identified and 7% to 17% of the patients who had been hospitalised with the COVID-19 infection. Another study conducted by Qin, et al, 2020 mentioned that the impaired immune and coagulation system might be considered as early risk factors for the patience of COVID-19 infection as it can increase the chances of mortality in the COVID-19 patients. Another study indicates that the increase in the levels of d-dimer in the patients of Covid 19 is a major question regarding the existence of impaired coagulation in them (Jose & Manuel, 2020).

Along with these findings, the usage of heparin has been found to

induce anti-inflammatory activities in the Covid-19 patients. Studies indicate that the usage of heparin for treatment of COVID-19 infection can be beneficial as this is effective in treating the coagulopathy that takes place in this disease. A study conducted to determine the effects of heparin for COVID-19 infection indicated that the heparan sulphate is a component which is responsible for entry and infection of the coronavirus. And this heparan sulphate binds with the spike protein of the virus. Hence the usage of heparin can interact with the spike protein and prevent the infection (Hippensteel, et al, 2020). Randomised trials have also been conducted to determine the effects of heparin in COVID-19 infection. It has also indicated that the usage of heparin can induce significant reduction in the death of the patients who have moderate infection but it has not been found effective for severely ill patients (Sholzberg, et al, 2021). Along with this, several studies also indicate that heparin has the ability to perform anti-inflammation in the COVID-19 patients which is beneficial as well. Studies indicate that the reduction of release of IL-6 takes place in order to perform anti-inflammation (Vitiello & Ferrara, 2021). A decrease in the levels of IL-6 leads to a decrease in the binding of the HS receptors which leads to the activation of the signal receptors and production of paracrine effects. Hence, usage of heparin could be done for the treatment of covid-19 infection as it produces anti-inflammatory as well as anti-viral effects.

MATERIALS AND METHODS

Study Participants

This is a retrospective, observational study. The study was conducted in the hospital attached to RUHS College of medical sciences, Jaipur, Rajasthan. The study was conducted over a period of eight months. In the study, the patients who were diagnosed with COVID-19 and admitted to the hospital were enrolled. The sample size for the study was around 480-720 patients. Then, from this sample size the patients who fulfil the criteria of inclusion selected for the study. The data of the patient was kept confidential and it has not been disclosed in the study.

The data was collected from the medical records of the hospital. For the conduction of the study, the ethical approval was obtained from the institutional ethics committee, RUHS CMS, Jaipur. Then the case files of the patients were analysed for selecting them on the basis of inclusion and exclusion criteria. The recording of the data was done in the format of

- demographic data - Which included the patient's initials, age, gender, address, weight, social habits as and the existing medical conditions;
- hospital admission data - which included the information regarding the admission time, duration of stay, first Covid positive report, diagnosis, symptoms, so we are day, investigations, sampling details and course during stay in hospital;
- treatment data which included name of the drug, its dosage, its frequency;
- adverse event profile which included any adverse drug reactions which were observed in the patient.

After the analysis of the data from the patients, the classification of the patients was done into two categories which were moderate and severe where as per their clinical features. Then the clinical parameters were noted down from the date of admission till the time of discharge or till the time of death of the patient.

Methods

The experimental group in the study received LMW Heparin with Standard Treatment Protocol (Group-A) while the control group received Standard Treatment Protocol of COVID -19 without LMW Heparin (Group-B). Along with this, subgroup analysis was also done by categorising the patients in the subgroup as moderate and severe; with or without come morbidities like hypertension, cardiovascular diseases, diabetes mellitus or something else.

Statistical Analysis

The data which was achieved from the study was analysed statistically. For this, the usage of SPSS version 17.0 software was done. The tests which were used in and a standard deviation. Normal distribution of the continuous variables between the groups were analysed with the help of t-test the significance level was set up at less than 0.05.

RESULTS AND DISCUSSION

The results which had been obtained from the study along with the necessary demographic information is mentioned in this section.

Results of Group-A: (received LMW Heparin with Standard Treatment Protocol)

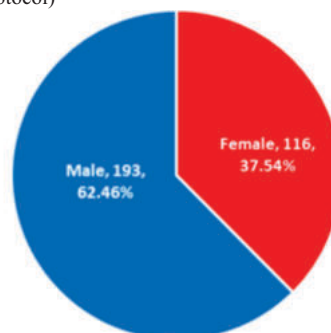


Figure 1- gender distribution in sample.

- This figure shows that in the group A, there were more males in comparison to the females which might indicate a bias in sample selection or more susceptibility of males to COVID-19.
- The clinical features of the patients who have been included in the study is shown in table 1.

Table 1- clinical feature.

Clinical features	Minimum	Maximum	Median	IQR	Mean $\pm$ SD
Systolic blood pressure (SBP) (in mmHg)	100	160	130	120 - 139.5	128.61 $\pm$ 11.77
Diastolic blood pressure (DBP)	58	102	81	78 - 90	82.60 $\pm$ 7.71
Oxygen saturation (SPO2) (in %)	86	100	96	92-97.5	94.67 $\pm$ 3.41
D-Dimer (ng/ml)	514	1990	943	837 - 1086	1004.27 $\pm$ 309.567
HRCT score	9	8	15	13-15	14.39 $\pm$ 1.916

- The figure shows that the mean systolic blood pressure of the group members was near the normal value, i.e., 120. Similarly, the mean diastolic blood pressure of the group members was near the normal value, i.e., 80. Similarly, the mean SPO2 of the group members was near the normal value, i.e., 95% or higher. But, the mean D-dimer value of the group members was not near the normal value, i.e., <500ng.ml. The HRCT score indicates moderate severity of disease.
- Since there were 309 patients in the study who had comorbidities, the effect of the comorbidities has also been analysed. These effects are shown in figure 2.

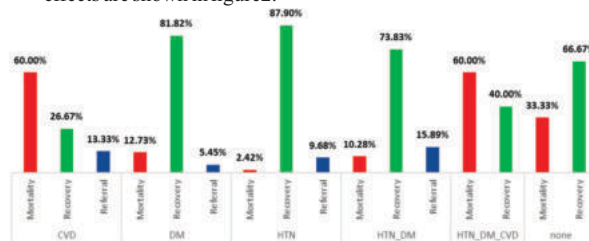


Figure 2- Effects of comorbidities.

- The figure shows that recovery rate was highest in HTN indicating its least influence on mortality. While the highest mortality rate was in CVD and HTN-DM-CVD.

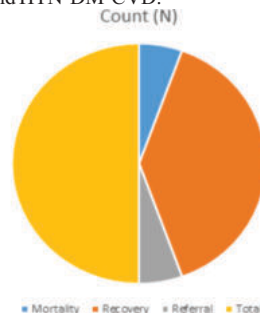


Figure 3- Outcome of Treatment.

- As per the results, the treatment was successful in providing higher rates of recovery in comparison to mortality or referral.

Results of Group-B

(Received Standard Treatment Protocol of COVID -19 without LMW Heparin)

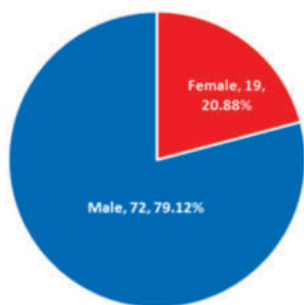


Figure 4-Gender distribution

This figure shows that in the group B, there were more males in comparison to the females which might indicate a bias in sample selection or more susceptibility of males to COVID-19.

Table 2- Clinical feature.

Clinical features	Mini mum	Maxi mum	Median	IQR	Mean $\pm$ SD
Systolic blood pressure (SBP) (in mmHg)	102	154	125	120 – 135	126 $\pm$ 11.64
Diastolic blood pressure (DBP)	58	106	80	76 - 87	80.73 $\pm$ 8.35
Oxygen saturation (SPO2) (in %)	80	106	96	94 – 97	80.73 $\pm$ 8.35
D-Dimer (ng/ml)	234	1849	465	376 – 546	534.43 $\pm$ 305.60
HRCT score	9	18	10	9-12	11.13 $\pm$ 2.813

The figure shows that the mean systolic blood pressure of the group members was near the normal value, i.e., 120. Similarly, the mean diastolic blood pressure of the group members was near the normal value, i.e., 80. But, the mean SPO2 of the group members was not near the normal value, i.e., 95% or higher. But, the mean D-dimer value of the group members was not near the normal value, i.e., <500ng.ml. The HRCT score indicates moderate severity of disease.

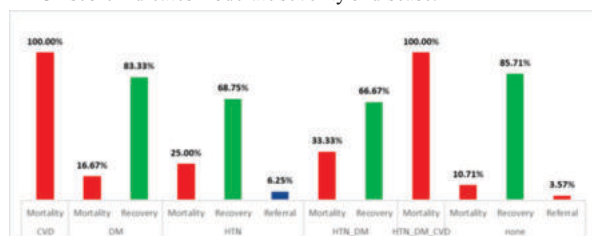


Figure 5- Effect of Comorbidities.

The figure shows that recovery rate was highest in no comorbidities. While the highest mortality rate was in CVD and HTN-DM-CVD.

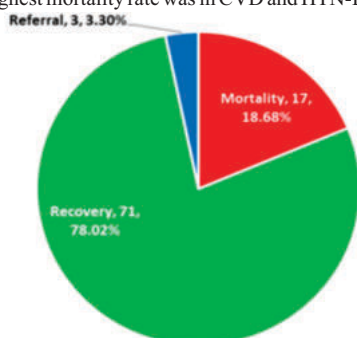


Figure 6- Outcome of Treatment.

As per the figure, the treatment was successful in providing higher rates of recovery in comparison to mortality or referral.

Comparison of two groups

The comparison of the two groups was done with the help of t-test. The comparison of several diameters was done in this study. These parameters are shown in table 3.

Table 3- Comparison of two groups

Parameters	Group A (N =309)	Group B (N = 91)	t-test	p-value
	Mean $\pm$ SD	Mean $\pm$ SD		
Age	63.03 $\pm$ 11.04	44.21 $\pm$ 13.02	-13.697	0.000
Systolic BP	128.61 $\pm$ 11.77	126 $\pm$ 11.64	-1.714	0.087
Diastolic BP	82.60 $\pm$ 7.71	80.73 $\pm$ 8.35	-1.997	0.046
SPO2 (in %)	94.67 $\pm$ 3.41	95.13 $\pm$ 3.33	1.165	0.246
Hospital Stay	6.72 $\pm$ 1.867	6.49 $\pm$ 2.172	-0.982	0.327
D-DIMER	1004.27 $\pm$ 309.57	534.43 $\pm$ 305.60	-12.753	0.000
HRCT Score	14.39 $\pm$ 1.92	11.13 $\pm$ 2.81	-12.673	0.000

The clinical outcomes of the patients, after giving them the treatment and analysing their comorbidities, have been compared and are shown in the table 4 below:

Table 4- Comparison of clinical outcomes

	A			Total	B			Total
	Morta lity	Recov ery	Referr al		Morta lity	Recov ery	Referr al	
CVD	9 (2.91 %)	4 (1.29 %)	2 (0.65 %)	15 (4.85 %)	3 (3.30 %)			3 (3.30 %)
DM	7 (2.27 %)	45 (14.56 %)	3 (0.97 %)	55 (17.80 %)	2 (2.20 %)	10 (10.99 %)		12 (13.19 %)
HTN	3 (0.97 %)	109 (35.28 %)	12 (3.88 %)	124 (40.13 %)	4 (4.40 %)	11 (12.09 %)	1 (1.10 %)	16 (17.58 %)
HTN_D M	11 (3.56 %)	79 (25.57 %)	17 (5.50 %)	107 (34.63 %)	1 (1.10 %)	2 (2.20 %)		3 (3.30 %)
HTN_D M_CVD	3 (0.97 %)	2 (0.65 %)		5 (1.62 %)	1 (1.10 %)			1 (1.10 %)
none	1 (0.32 %)	2 (0.65 %)		3 (0.97 %)	6 (6.59 %)	48 (52.75 %)	2 (2.20 %)	56 (61.54 %)
Total	34 (11.00 %)	241 (77.99 %)	34 (11.00 %)	309 (100.0 %)	17 (18.68 %)	71 (78.02 %)	3 (3.30 %)	91 (100.0 %)

Hence, with this comparison, the results which have been obtained, can be expressed graphically.

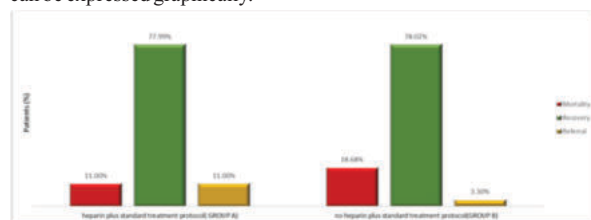


Figure 7- clinical outcomes in both groups

The aim of the study was to evaluate the clinical outcome among moderate-severe COVID-19 patients treated with standard drug therapy plus LMW Heparin as compared to those not given LMW Heparin. COVID-19 has adversely affected the global health. It has caused a large amount of deaths since its emergence. The development of vaccines and treatment interventions has been done continuously since the emergence of the disease. There are several types of treatment interventions which are used for the treatment of this disease which include anti-viral drugs, anticoagulation drugs, immunosuppressant drugs and many more. The development of the disease is associated with a decrease in the immune response of the individual. This can also lead to abnormal inflammatory response which can increase the severity of the condition by increasing the severity of the symptoms (Macera, et al, 2020). Cytokine storm has also been observed in the patients of Covid 19 which can cause infiltration of the lungs. Hence, it is important that the treatment interventions are also focused on the anti-inflammation aspects of the infection. Along with that, it has also been discussed in previous actions about the hyper coagulation which

might take place during the infection. Hence, this study was conducted so that the effects of LMW heparin could be identified in influencing the treatment plan in the patients. The study was focused on determining the correlation between this treatment intervention and the outcomes observed in the hospitalised patients of COVID-19 (Shi, et al, 2020).

In this study, a total of 700 patients of Covid 19 were included. Out of them only 400 were able to fulfil the inclusion and exclusion criteria. These patients were divided into two groups and were given treatment accordingly.

In this study, the mean age of the patients was 63.03 ± 11.04 and 44.21 ± 13.02 years respectively. A similar study conducted in the past has indicated that the older patients have lower levels of lymphocytes which are elevated during viral infections but our decreased during severe acute respiratory syndrome as well as COVID-19 infection. Hence this could be a key indicator in determining the severity of the disease. Along with that, age is a major risk factor of infection (Tang, et al, 2020).

In this study, 66.25% were males and 33.75% of the patients were females which may indicate that males have had more infection. And some other studies conducted in the past also indicate that males have had more severe COVID-19 infection. This might be because of the cultural aspect of women to stay more at home in India which may protect them from getting the infection (Falcone, et al, 2021).

For determining the effectiveness of the treatment plan, there were three variables which were studied. The first variable was the duration of hospital stay which was a median of six days for group A and same for group B. But the P value was 0.327 and was less significant.

The second variable was the clinical features of the patient with me included systolic BP, diastolic BP, SP O₂, d-dimer level and HRCT score. The significant variables which were found in the study were the increased levels of d-dimer in the group which was treated with anticoagulant. These results have also been shown in the studies which have been done previously which show a good clinical prognosis is observed if the levels of D dimer are increased (Li, et al, 2020). But, the HRCT score was higher for group A in comparison to the group B. And studies have indicated that increase level of this score or associated with the severity of the disease (Verma, et al, 2022).

The third variable in the study was the clinical outcome of the patients. In this study, a good clinical outcome was observed in both the groups. But the clinical outcome of the group A it was better than the group B. The mortality rate in group A was much lesser in compare to the group B. Hence, these results might indicate that the usage of heparin could be beneficial in the treatment of COVID-19 infection as well as in decreasing the mortality rates in these patients. Along with this, the subgroup analysis of the patients indicated that the underlying cardiovascular disease might be responsible for increasing the risk of mortality among the COVID-19 patients (Bansal, 2020).

Hence, the results which have been obtained from the study clearly indicate that the usage of heparin for the treatment of COVID-19 infection is efficient and effective as it decreases the mortality rates in the patients who had been admitted to the hospital. The mortality rate was 11% with or without comorbidities in the group A while it was 18.68% in the group B. And similar results have also been obtained in other studies done in the past as well.

There were some limitations in the study. The study was conducted on the basis of data which has already been collected in the hospital in the past. Hence there was no scope for investigating the data in more detail. Along with that it is not clear if the usage of heparin was done on the basis of some selection bias. For instance it might have been used for the patients with specific symptoms or medical history or something else. Along with that, the data which has been collected was recorded at the time of first wave of the pandemic and at that time, there were not sufficient medical resources to treat the infection. Hence the mortality rate might be an indicative of that and not the treatment interventions.

CONCLUSION

From this study, it would be concluded that the usage of heparin is beneficial and effective in treating the COVID-19 infection. Along

with that, it is responsible for decreasing the mortality rate in the patients. The study also indicates that the underlying cardiovascular diseases are responsible for increasing the risk of mortality in the COVID-19 patients.

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