A novel severity scoring system to determine need for hospital beds - In preparation of anticipated COVID-19 waves

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Abstract: The COVID-19 scenario has put an extraordinary burden on healthcare systems all over the world including India. This study aimed to develop a novel severity scoring system to assess severity in context to hospital bed occupancy, enabling preparation for the forthcoming infection wave in India. Clinical data for confirmed COVID-19 patients admitted in Central Railway Hospital, Maligaon, Guwahati, India was collected. Severity score was developed based on Differential Leukocyte Count (DLC) and blood oxygen saturation. Thereafter, patients were categorized; duration of hospital stay was analyzed. Cox proportional hazards regression analyses were performed. Kaplan-Meier plots were developed to check efficacy of the scoring system developed. Among the hospitalized patients (N=463), 62.6% were males and 33.26% had co-morbidities. Spearman's correlation revealed duration of hospital stay to significantly associate with blood sugar levels (r=0.106, p<0.05); serum creatinine (r=0.186, p<0.01) and Neutrophil-Lymphocyte Ratio (NLR)(r=0.139, p<0.01). Hemoglobin level and recovery period correlated negatively (r=–0.118, p=0.013). Cox regression analysis revealed that sugar level and Total Leukocyte Count (TLC) (p<0.05) significantly affected patient outcomes. Kalpan-Meier analysis portrayed that the patients marked severe as per the scoring system developed, were mostly older (>60 years), males, diabetic, hypertensive and had higher creatinine levels (Log-rank test p<0.05 for all). The severity scoring system developed can significantly differentiate patients based on age, sex, comorbidities and thus be used to determine necessity of hospital bed occupancy. Admitting only severe cases can help reduce burden on healthcare providers.

Keywords: COVID-19, NLR, Diabetes, Hypertension, Kidney Failure, Hospital Beds.

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I. INTRODUCTION

In the beginning of December 2019, the first case of novel corona virus was reported in Hubei province of Wuhan, which later spread alarmingly through China, putting the world on high alert. Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) causes some people to remain asymptomatic, but few develop severe forms of the disease, ultimately leading to acute respiratory distress syndrome (ARDS), organ dysfunction or even death [1]. Besides having a generally low death rate [2], this virus affects people disproportionately. Infection is seen to be markedly different based on age, sex and presence of co-morbidities.

Compared to the younger generation, the older individuals are more affected [1]. According to sex-disaggregated data, males are at a 1.7 times higher risk of mortality than females [3] and this difference also extends to the physiological systems, including the immune system. People with diabetes and cardiovascular conditions are at a higher risk of infection [4].

India with its massive population of over 1.3 billion, as of September 29, 2021, needs to cater to the healthcare of a huge number of individuals with disproportionately limited resources [5]. The Ministry of Health and Family Welfare (MoHFW), Government of India (GoI), has issued a set of guidelines to tackle the pandemic effectively. The protocols categorize COVID-19 patients into different groups of severity based on respiratory rate and arterial oxygen saturation [6].

Given the vast numbers of people being infected, only symptomatic patients were being admitted to the hospitals, the others were asked to stay in home isolation [7]. Despite this, there was shortage in hospital beds [8]. Data from *Our World In Data* illustrates an availability of 0.53 beds per thousand people in India [9]. Given that the average infection rate far exceeds the hospital bed availability, it is important to come up with a system that can assess the need and duration for hospital bed occupancy.

Significant changes in the hematological profile during the course of the infection have been seen in many patients. Recent reports have highlighted that a section of the COVID-19 positive cases display elevated leucocyte count in peripheral blood [10-11]. This increased WBC count was also related to a higher degree of systemic inflammation response and that was, to some extent, related to the development of critical illness [12]. A fall in the lymphocyte count and an elevated neutrophil count and neutrophil to lymphocyte ratio were also identified as key risk indicators of severe illness in diseased patients [13]. The outcomes of COVID-19 manifest themselves in a number of hematological parameters. The precise appraisal of clinical indicators is thus an important stairway to assist professionals mete out healthcare.

In this study, Differential Leucocyte Count (DLC) along with blood oxygen saturation was explored in COVID-19 positive patients at the Central Railway Hospital, Guwahati, Assam, India. The aim was to develop a severity scoring system which can enable healthcare providers to determine how serious a COVID-19 positive individual is and if he/she essentially needs a hospital bed. The less severe patients as per the scores can stay in home isolation, thereby reducing the load on the healthcare system.

II. Results & Discussion

Basic demographic analysis revealed that older age was associated with higher severity.

All the patients were allotted severity grouping. Table 1 represents the characteristics of different severity groups of COVID-19. The distribution of the age group was as follows: 34.99% were less than 40 years old, 44.71% between 40-60 years and 20.3% were greater than 60 years of age. Group I (mild), group II (moderate) and group III (severe) included 16.63%, 60.7% and 22.67% patients respectively. The mean age increased with increase in severity ($p<0.05$) (Table 1). Of all confirmed cases, 62.6% were males while 37.4% were females.

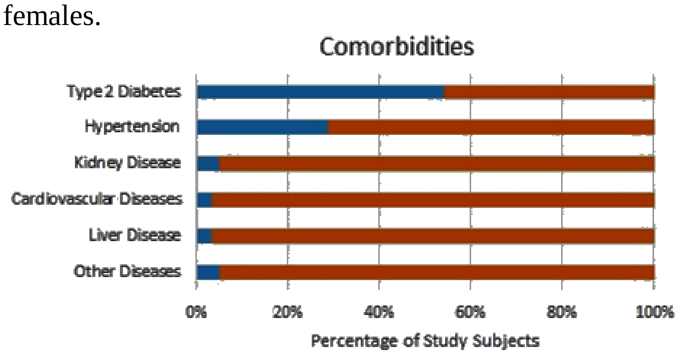

Figure 01: Stacked bar chart presenting co-morbidities in COVID-19 hospitalized patients. (Presence (blue) and absence (red) indicate the occurrence and non-occurrence of co-morbidity).

COVID-19 patients with underlying diseases were more severe than patients without comorbidities

Figure 1 represents the different co-morbidities reported in the study population. Co-morbidity was recorded in 154 patients and 42.2% of them had more than one co-morbidity.

Study of hematological parameters revealed significant differences based on ANOVA between different severity groups

The mean random sugar level significantly differed between the three groups ($p<0.01$) with higher levels in more severe groups (Table 1). Similar were the observations for serum creatinine (Table 1), with elevated levels (>1.2 mg/dL) in 12.09%of the study population. Contrasting observations were made for serum hemoglobin concentrations (Table 1), the mean of which dropped with increase in severity ($p<0.05$).

The mean TLC of the study population increased with increase in severity ($p<0.01$) (Table 1). Differential counts for neutrophil, lymphocyte, monocyte, eosinophil and basophil among the three groups indicated significant statistical difference ($p<0.01$) for each group, except basophil ($p>0.05$). Neutrophils progressively increased among the three groups of severity, whereas the other types of WBCs showed a sharp decline among the severe patients (Table 1).

The mean NLR (Neutrophil-Lymphocyte Ratio) increased progressively in the three groups with increase in severity ($p<0.01$). Similar observations were made for NMR (Neutrophil-Monocyte ratio) and LMR (Lymphocyte-Monocyte Ratio) ($p<0.01$ in both cases) (Table 1).

Important indicators of disease severity predicted by correlational analysis

Spearman's rank correlation test was performed to analyze correlation between the various parameters studied (Figure 2). Correlation analysis revealed a significant positive correlation between length of hospital stay and age ($r=0.211$; $p<0.01$),blood sugar levels ($r=0.106$, $p<0.05$), NLR ($r=0.139$, $p<0.01$) and serum creatinine ($r=0.186$; $p<0.01$) which also correlated to the length of recovery period ($r=0.254$, $p<0.01$); Negative correlation was observed between hemoglobin levels and recovery period ($r=–0.118$, $p<0.05$).

Cox regression analysis for patients' severity outcomes

Since there are multiple risk factors associated with developing a severe form of COVID-19, a multivariate Cox regression analysis was performed with parameters portraying significant correlations- age, blood

Table 1: Characteristics of different severity groups of COVID-19:

		Clinical severity of Covid-19			One-way ANOVA	
	All n = 463	**Mild n = 77**	**Moderate n = 281**	**Severe n = 105**	**F- value**	**Significance p-value**
Age (Mean ± S.D) (years)	46.27 ± 17.56	37.88 ± 15.68	46.68 ± 17.38	51.32 ± 17.31	13.93	< 0.01
Sex (n, %)						
Males	290 (62.6%)	47 (16.20%)	165 (56.9%)	78 (26.9%)		
Females	173 (37.4%)	30 (17.34%)	116 (67.05%)	27 (15.61%)		
TLC (Mean ± S.D) (cells/mm^3)	7030.45 ± 2569.92	5810.39 ± 1676.35	7077.94 ± 2345.22	7798.10 ± 3282.47	14.17	< 0.01
Hemoglobin (Mean ± S.D) (gm/dL)	12.20 ± 1.86	12.76 ± 1.51	12.12 ± 1.89	12.02 ± 1.94	4.18	< 0.05
Neutrophils (Mean ± S.D) (%)	66.31 ± 11.10	55.18 ± 8.63	65.61 ± 9.14	76.33 ± 8.60	126.39	< 0.01
Lymphocytes (Mean ± S.D) (%)	29.19 ± 10.21	37.51 ± 7.98	29.74 ± 9.42	21.62 ± 8.21	71.53	< 0.01
Monocytes (Mean ± S.D) (%)	2.97 ± 1.82	4.96 ± 1.74	3.09 ± 1.48	1.20 ± 0.67	164.01	< 0.01
Eosinophils (Mean ± S.D) (%)	1.45 ± 1.63	2.30 ± 2.28	1.47 ± 1.54	0.80 ± 0.82	20.28	< 0.01
Basophils (Mean ± S.D) (%)	0.08 ± 0.36	0.06 ± 0.37	0.10 ± 0.39	0.04 ± 0.23	1.03	> 0.05
NLR (Mean ± S.D)	3.03 ± 3.02	1.59 ± 0.60	2.69 ± 1.95	5.01 ± 4.91	38.43	< 0.01
NMR (Mean ± S.D)	29.99 ± 20.32	12.25 ± 3.88	25.21 ± 11.89	59.95 ± 18.87	341.47	< 0.01
LMR (Mean ± S.D)	12.92 ± 8.80	8.58 ± 3.61	12.38 ± 8.95	18.29 ± 8.92	30.12	< 0.01
sPO_2 (Mean ± S.D) (%)	95.71 ± 2.53	97.04 ± 1.16	95.86 ± 2.37	94.31 ± 3.01	30.54	<0.01

Table 2: Results of Cox regression analysis of risk factors for COVID-19 positive patients (A) Table specifying model significance (B) Individual significance of model variables used to form the equation.

(A) Omnibus Tests of Model Coefficients[a]

-2 Log Likelihood	Overall (score)			Change from previous step			Change from previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
3703.564	18.856	5	.002	19.951	5	.001	19.951	5	.001

a. Beginning Block Number 1. Method = Enter

(B) Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)
Age	-.008	.003	6.064	1	.014	.992
Sugar Level (mg/dL)	-.001	.001	2.606	1	.106	.999
Creatinine (mg/dL)	-.120	.092	1.700	1	.192	.887
TLC (cells/mm3)	.000	.000	.013	1	.909	1.000
Hb (gm/dL)	.036	.029	1.549	1	.213	1.036

sugar level, serum creatinine, TLC and hemoglobin. The severe cases and mild/moderate cases were used in the status, with non-severe cases being the event. The model was selected on the basis of significant Chi-square value as obtained in the omnibus test for model coefficients (Table 2).

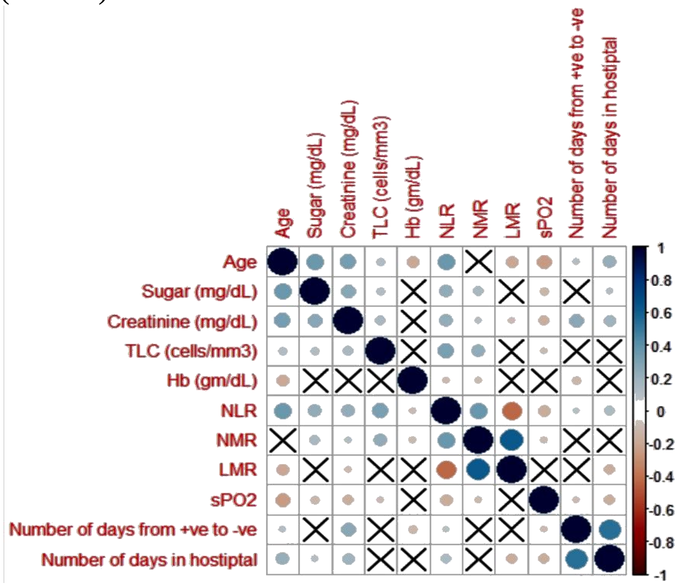

Figure 2: Correlogram showing results of Spearman's correlation test.

Kaplan Meier analyses predict recovery times based on comorbidities

Kaplan-Meier analyses were used to validate the novel severity scoring mechanism developed. As the aim was to identify patients with milder form of the disease who could be exempted from hospital stay, contracting a non-severe form of the disease was considered as an event. Older people (Group 2; >60 years) saw lesser number of events during hospital stay (Figure 3-7; Log-rank test p<0.01 (Table 3)).

Table 3: Log rank (Mantel-Cox) test for Kaplan-Meier plots:

Parameter	Chi-square	df	Sig.
Age based	21.055	1	0.000
Sex based	4.578	1	0.032
Diabetic / Non Diabetic	21.008	1	0.000
Hypertensive / Non hypertensive	21.560	1	0.000
High creatinine / Normal creatinine	19.623	1	0.000

Female patients and non-diabetics of the sample population seemed to be at an advantage with more events (Figure 4 and 5 respectively; Log-rank test $p < 0.05$, $p < 0.01$ respectively; (Table 3)). Patients with hypertension saw lesser event, were seen to have a longer stay at the hospital than other patients (Figure 6; Log-rank test $p < 0.01$ (Table 3)). It was also seen that those patients with higher levels of creatinine (i.e., greater than 1.2 mg/dL) than normal, contracted a more severe form of the disease (Figure 7; Log-rank test p<0.01 (Table 3)).

Since the scoring system could clearly portray differences between subsets of patients based on age, sex, level of blood glucose, creatinine and hypertension, in accordance to previous reports, it can be safely used to determine if the COVID-19 positive individual will essentially need a hospital bed or not once their blood test is done and oxygen saturation checked thus reducing the burden on healthcare system.

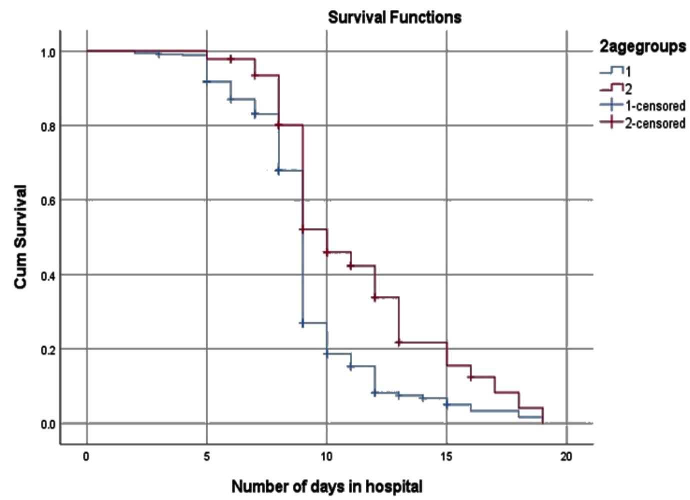

Figure 3: Survival analysis – Comparing duration of hospitalization between people of <= 60 years and > 60 years (1 – <= 60 years, 2 – > 60 years).

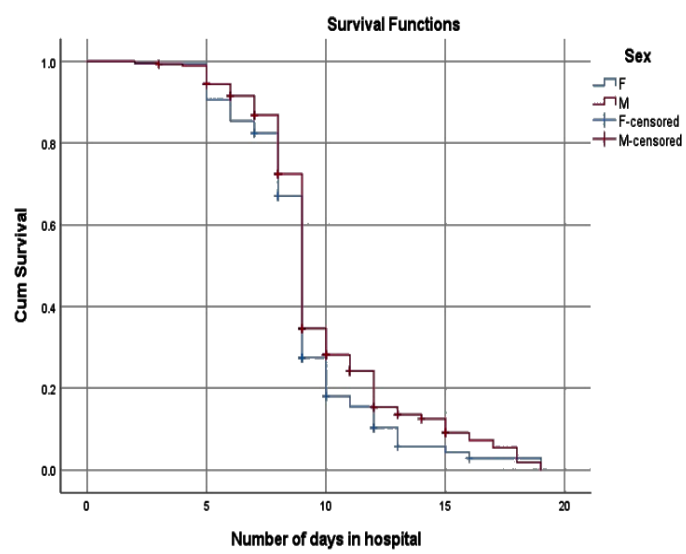

Figure 4: Survival analysis – Comparing duration of hospitalization between male and female patients (M – males, F – females).

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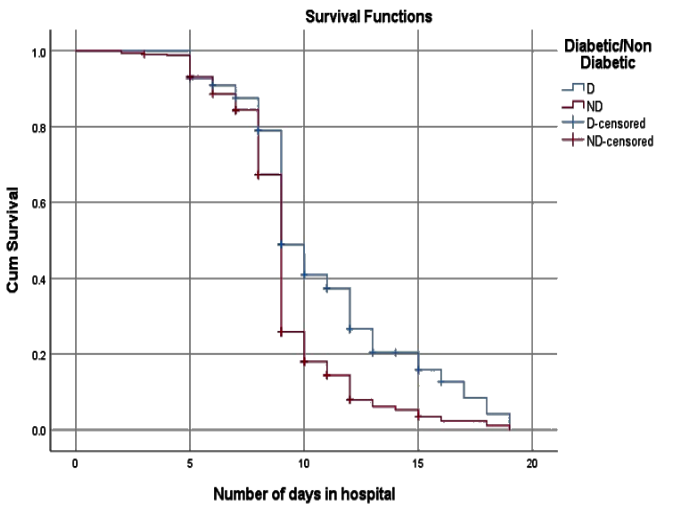

Figure 5: Survival analysis – Comparing duration of hospitalization between diabetics and non diabetics (D – diabetics, ND – non-diabetics).

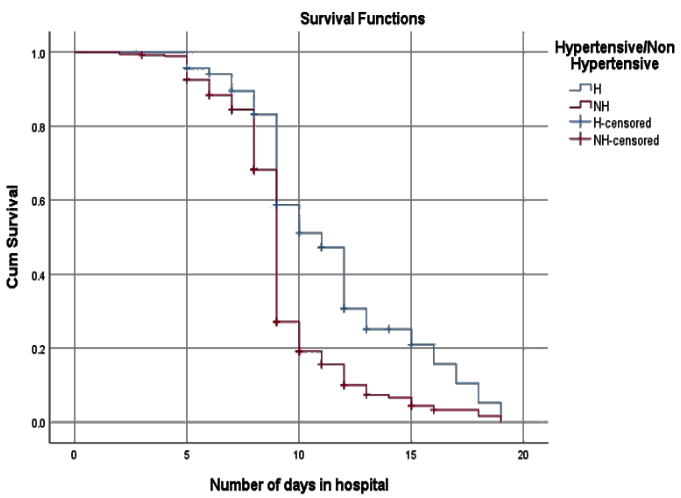

Figure 6: Survival analysis – Comparing duration of hospitalization between hypertensive and non-hypertensive patients (H – hypertensive, NH – non-hypertensive).

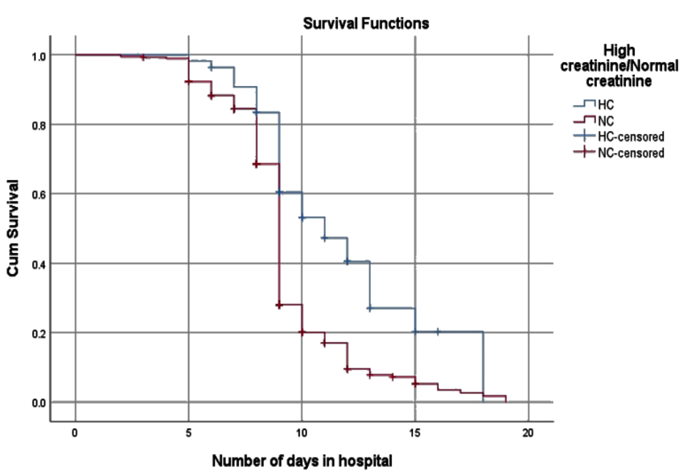

Figure 7: Survival analysis – Comparing duration of hospitalization between patients with normal and high creatinine (NC – normal creatinine, HC – high creatinine). Censored data indicates subjects who have died, dropped out or been referred to a different hospital.

Discussion

The clinical characteristics of COVID-19 positive patients in Assam, India were examined. A novel scoring system developed points for 3 groups of patients with mild, moderate and severe form of the disease. Age was significantly different and higher for patients with severe form of the disease. The occurrence of the infection was 25.2% more in males. These findings were consistent with studies reported from China, USA and Italy [14–16]. Various explanations exist including those that state that women possess stronger immune system due to the presence of an additional X chromosome [17]. Additionally, men are at higher risk of exposure owing to occupational and behavioral differences [17], as well as higher circulating levels of ACE2 [18].

It has been reported that total leucocyte count is high in severely ill COVID-19 positive patients [19]. Simultaneously, Henry et al. has concluded a significant increase in TLC is a strong predictor of poor prognosis [20–22]. Based on these reports, the clinical parameter DLC was exploited in developing a severity scoring system. TLC and DLC (except basophils) were significantly different for the mild, moderate and severe groups based on the novel scoring system generated here. NLR is a widely accepted biomarker that represents immune status and can be considered as a guide for the prognosis of COVID-19 cases [23]. Significant association of NLR with the length of hospital stay ($r=0.117$, $p=0.011$) was observed. In the event of an infection, neutrophils activate the release of extensive amounts of ROS [24], in addition to cytokines and signal proteins like vascular endothelial growth factor (VEGF) [25], which is a significant indicator of severity in case of COVID-19 [26]. Lymphocytes are also a major integrant in viral infections [27], where systemic inflammation significantly reduces cellular immunity, in turn inhibiting CD4+ lymphocytes and up-regulating CD8+ lymphocytes. Thus, inflammation as a result of viral infection, causes an increase in NLR resulting in COVID-19 progression [28]. NLR, NMR and LMR were all significantly different for the mild, moderate and severe groups categorized in this study. Besides, the blood oxygen saturation was also found to differ significantly and observed to decrease from mild to moderate and to severe group. This conforms to previous reports suggesting that COVID-19 is known to decrease the blood oxygen saturation [15,29].

Spearman's correlation analyses exhibited a positive correlation between blood glucose levels and duration of recovery. The same was reflected in Cox regression analyses which re-confirmed the ability of sugar levels to act as relevant variable predicting outcomes in infected patients. Sarvazad et al. postulated that increased blood glucose levels can cause sepsis and systemic inflammation, as these conditions result in elevation of cytokine levels, accompanied by hyperglycemia [29]. Kaplan-Meier plot for diabetics *vs* non-diabetics reveal how patients with diabetes faced more severe form of the disease. A few studies have signaled that hyperglycemia and/or diabetes are significant risk factors influencing mortality and morbidity in community-acquired pneumonia, MERS and SARS [30-31]. Wang et al. also concluded that fasting blood glucose at the time of admission can be considered as a significant prognostic factor to predict COVID-19 patient outcomes [32].

Higher serum creatinine was found to be associated with a longer duration of recovery ($r=0.253$, $p<0.01$) as well as length of stay at the hospital ($r=0.190$, $p<0.01$). Data from RNA sequencing has revealed a greater expression of ACE2 in the kidneys (nearly 100-fold),compared to the lungs [33]. Infection with SARS-CoV-2 may also result in the emergence of tiny clots in the bloodstream, causing blood vessels in the kidney to clog, thus compromising their functionality [34].

Lower levels of hemoglobin ($r = –0.126$, $p<0.01$) as well as SpO_2 ($r=–0.098$, $p<0.05$) were associated with longer duration of recovery. Another study illustrated that 51% patients had hemoglobin below the normal range [10] and highlighted lower levels of hemoglobin in more severe patients [35]. Inflammations caused by infections like COVID-19 are more likely to interfere with erythrocyte / bone marrow metabolism and regulation of iron, resulting in reduction of functioning hemoglobin and thus contributing to hypoxia [36].

Patients with hypertension had a longer duration of hospital stay than non-hypertensive patients. They also had a higher mean NLR compared to the non-hypertensive subset. This poor prognosis might be due to the dysfunction in immune response caused by a fall in lymphocyte count [37]. Chen et al. also portrayed that hypertension could act as a predictor of ARDS in SARS patients [38]. Nevertheless, further research is required to validate the role of hypertension in COVID-19.

The waves of Covid-19 infection at their peak wreaked havoc on the healthcare system causing a huge crisis of hospital beds with high numbers of people getting infected with the virus. The next wave at its peak may also have the same drastic effect and being prepared to face it is of utmost importance. The present scoring system was developed using data from patients already admitted in the hospital as per the Ministry of Health and Family Welfare, Govt. of India guidelines. The patients from “Mild” category as determined by our scoring system can be exempted from hospital stay thus increasing hospital bed availability. In case of further hospital bed availability crisis, the patients with “Moderate” form of the disease may also be exempted from hospital stay focusing only on the “Severe” cases for whom hospital stay is mandatory. This will help reduce the burden on healthcare professionals.

III. Conclusions

The aim of this study was to develop a severity scoring system to assess how essential is a hospital bed for an infected patient. The scoring system was developed using easy to measure hematological parameters and its efficiency was checked by whether or not it could differentiate the severe cases via survival plots. It was observed that the current scoring methodology deeming cases as “Severe” pertained to patients who were older (>60 years), males, diabetic, hypertensive and had higher blood creatinine levels conforming to existing literature. Thus, the novel scoring system was deemed efficient. To summarize, the study evaluated demographic and clinical characteristics of COVID-19 positive patients. A novel scoring system was successfully developed based on arterial oxygen saturation and differential leukocyte count of patients admitted in the hospital in which the patients of “mild” category can be exempted from hospital stay. The results obtained in this study are not in conflict with prior reports; the scoring system developed here can be used by healthcare professionals to determine the need for hospital beds in COVID-19 positive patients.

IV. Materials & methods

Study Area

This retrospective study was performed at Central Railway Hospital (CRH), Maligaon, Guwahati, Assam, which is one of the primary government designated COVID-19 care hospitals in the north-eastern part of India. The study was approved by Institutional Ethical Committee (Human) and approval was taken from the Medical Director, Central Railway Hospital, to obtain the necessary data. All data were taken anonymously and hence no personal information was shared.

Selection criteria, measurements and definition

Reports from the early days of the pandemic demonstrated an association between climate parameters (temperature, relative and specific humidity) and the transmission of SARS-CoV-2 [39-43]. So, case histories of COVID-19 patients admitted from 5th July and 15th November, 2020 were collected. The study included data of 463 patients diagnosed as COVID-19 positive based on guidelines issued by Ministry of Health and Family Welfare, Government of India [44]. An admission at the hospital was defined as a patient being present at the hospital for > 24 hours [45].

Patients and Data Sources

The data was extracted from the hospital's medical records and included patients who were admitted to the hospital during the study period. Case data included the following information: key dates, which included date of diagnosis, date of admission, date of testing negative; date of discharge or death; basic demographic characteristics like age and sex of patients; presence of comorbidities including diabetes, hypertension, liver disease, renal disease, cardiovascular disease and any other diseases; additional information like random sugar level, creatinine, Total Leucocyte Count (TLC), Differential Leucocyte Count (DLC), hemoglobin level and finger oxygen saturation examined during admission. Data provided by the hospital was tabulated into an MS-Excel spreadsheet, for analysis. All medical laboratory tests were performed in the clinical laboratory of the hospital.

Development of severity score

A novel scoring system was designed to classify patients into three categories of clinical severity- mild, moderate and severe based on their arterial oxygen saturation, Neutrophil–Lymphocyte Ratio (NLR), Neutrophil–Monocyte Ratio (NMR) and Lymphocyte–Monocyte Ratio (LMR). The established reference intervals were taken from a study of healthy populations by Sairam et al. [46], as tabulated in Table 4.

Table 4: Assessment parameters for grouping of clinical severity of COVID-19:

Clinical Criteria	Group I	Group II	Group III	Group IV
Arterial oxygen saturation (SPO_2)	> 95% in Room Air	91-95% in Room Air	≤ 90% in Room Air	---
Neutrophil-lymphocyte ratio (NLR)	< 1.6	1.6 – 2.2	2.21 – 4.13	> 4.13
Neutrophil-monocyte ratio (NMR)	< 7.5	7.5 – 20	20.1 – 33.75	> 33.75
Lymphocyte-monocyte ratio (LMR)	< 4.7	4.7 – 9	9.1 – 15.85	> 15.85

Accordingly, patients were assigned scores (Group I-1, Group II-2, Group III-3, Group IV-4) for each of the four parameters and the scores were summated. Therefore, the lowest possible score was 4 and the highest possible score was15. Patients with total score between 4-7 were considered to have contracted very mild form the disease, those scoring 8–11were considered to have mild to moderate form of the disease and patients scoring between 12–15 were considered severe. These severe patients (N=105, as per the scoring system developed) were considered to have highest requirement of hospital beds based on their clinical parameters compared to the other patients (N=358). Figure 8 depicts the workflow of the study.

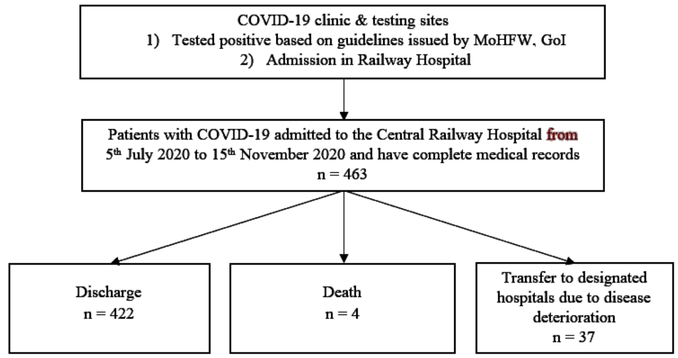

Figure 8: Represents a flowchart of patients being admitted to the Central Railway Hospital, Maligaon, Guwahati, Assam, India.

Statistical analysis

MS-Excel, R (version 4.0.5) and SPSS (version 25, IBM Corporation, New York, USA) were used to conduct all statistical tests. All data was expressed in terms of mean ± SD, median (interquartile range (IQR)) or percentage, as appropriate. Spearman's correlation tests were conducted to calculate correlation between different variables. To deduce the outcome of severity associated with the disease, a Cox proportional hazards regression model was also performed using multiple hematological parameters determining the probability of an event- in this case, contracting a severe form of the disease. Kaplan Meier plots were also developed to visualize efficacy of the scoring system developed. A p-value < 0.05 (two-tailed) was considered to be statistically significant. Categorical data have been expressed in terms of frequency in percentage (%). Quantitative data has been expressed in terms of Mean (±S.D). Significance or p-values has been calculated by performing Chi-square tests (for Cox regression model) and One-way ANOVA (for hematological parameters).

Ethical approvals: Ethical approval was obtained from the Medical Director, Central Railway Hospital, Maligaon, Guwahati, India before accessing the necessary data. No personal information like names and addresses were shared.

Availability of data and material: Data is available from the corresponding author upon request.

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Authors' contribution: RM involved in conceptualization, methodology, investigation, analysis, visualization, interpretation, writing – reviewing of the manuscript; PD involved in data collection, investigation, interpretation, analysis, writing of the original manuscript draft preparation; AM involved in conceptualization, writing – reviewing, investigation and supervision.

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