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Research Article

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Clinical Manifestations, Laboratory Markers and Their Association with Mortality in Patients with Severe Covid-19 Infection in Third Wave of Epidemics in Myanmar

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Abstract

Background

Coronavirus disease 2019 (COVID-19) has been a major threat to health around the world as it causes significant morbidity and mortality. The clinical manifestations range from a common cold to more severe diseases such as pneumonia, severe acute respiratory distress syndrome (ARDS), multi-organ failure, and even death. It is important to identify red flag signs for mortality, helpful for prioritization of treatment especially in poor resource setting. The study aimed to assess association of clinical and laboratory markers and the outcome in patients with severe COVID-19 infection in Myanmar.

Methods

A descriptive study was conducted in COVID-19 treatment centers in Myanmar- Yangon and Nay Pyi Taw, from February 2020 to August 2021. Data were collected by using standardized case report forms and then, a total of 404 confirmed COVID-19 inpatients (>18 years old) were included. The p value and odds ratio with a 95% confidence interval (CI) was used as a measure of association and the independent associated factors for severity of disease were investigated using logistic regression analysis.

Results

Among 404 patients, 258 (63.9%) were discharged; and 146 (36.1%) expired in hospital. Mortality was associated with clinical parameters such as age over 65 years (odds ratio 0.47, 95% CI 0.31– 0.72; p < 0.001), low initial SpO2 less than 85% (95% CI -7.46 – -3.96; p < 0.001), reduced Glasgow Coma Scale score less than '15' (95% CI -0.70 – -0.20; p < 0.001), high Quick Sequential Organ Failure Assessment Score "2 and 3" (qSOFA score) (95% CI 0.08 – 0.91; p = 0.025), high CXR Brixia Score more than '8' (95% CI 3.42 – 4.89; p < 0.001); and, laboratory criteria like total WBC count greater than 12 x 109/L (95% CI 1.81 – 4.33; p < 0.001), CRP greater than 0.5 mg/L (95% CI -61.37 – -23.26; p < 0.001), ferritin greater than 400 ng/mL (95% CI -312.36 – -139.07; p < 0.001), D-dimer greater than 0.5 µg/ml (95% CI -3340.65 – -2945.21; p < 0.001), high serum creatinine greater than 1 mg% (95% CI 0.16 – 0.70; p = 0.002), LDH greater than 225 U/l (95% CI -166.53 – -46.66; p < 0.001), ALT greater than 40 IU/L (95% CI 11.82 – 39.32; p < 0.001) and AST greater than 37 IU/L

(95% CI 21.26 – 55.16; p < 0.001).

Conclusions
Clinical manifestations significantly associated with mortality were low Glasgow Coma Scale score, initial SpO2 less than 85%, qSOFA score '2' and above, and severe chest radiographic involvement (CXR Brixia Score more than '8'). Laboratory markers like neutrophil leukocytosis, high level of inflammatory markers (CRP, ferritin, LDH), high levels of transaminase (ALT and AST), high D-dimer, high creatinine were significantly related with mortality. Awareness, identification of these predictors on admission was essential for early anti-viral therapy and timely anti-inflammatory treatments; hence, better outcome.

Keywords: Covid-19, Predictors, Clinical, Laboratory, Mortality

1. Introduction

A novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected humans in all age groups, of all ethnicities, both males and females while spreading through communities at an alarming rate since December 2019. The clinical manifestations range from a common cold to more severe fatal form- severe pneumonia, severe acute respiratory distress syndrome (ARDS), multi-organ failure, and even death. It is believed that COVID-19, in those with underlying health conditions or comorbidities, has an increasingly rapid and severe progression, often leading to death. Clinical manifestations like low oxygen saturation, falling conscious level, hypotension and severe chest radiographic involvement as well as laboratory parameters like low absolute lymphocyte count, high CRP, high ferritin and high D-dimer were common poor indicators for mortality. Early detection of them was helpful in efficient patient management and possibly minimize the related mortality [1]. This study analyzed the clinical and laboratory parameters, and their association with mortality in patients with severe COVID-19 infection.

2. Methods Study Design and Participants

This descriptive study included 404 adult inpatients (≥ 18 years old) from February 2020 to August 2021. It was carried out at three purposively selected treatment centers, Mingaladon hospital (300-bedded), Phaung Gyi hospital (1500-bedded) and Nay Pyi Taw hospital (1000-bedded), which were designated for confirmed severe COVID-19 patients. Patients from Yangon Region were treated in Dagon hospital, Mingaladon hospital and Phaung Gyi hospital whereas those from Nay Pyi Taw region were hospitalized in Nay Pyi Taw hospital. All treatment centers have ICU facilities and treatment were given by junior physicians, supervised by senior consultant physicians with on line meeting at least daily.

All inpatients with severe SARS-CoV-2 infection confirmed by a positive result on RT-PCR testing of a nasopharyngeal sample and WHO severity score were included in this study. History taking, physical examination, chest radiograph and blood tests (ferritin, LDH, D-dimer and CRP), complete picture, liver enzymes, serum creatinine were done as a routine procedure; all were recorded till discharge. All patients received at least standard treatment according to Myanmar National guideline; remdesivir, glucocorticoids, antibiotics, prophylactic enoxaparin, oxygen, and nutritional support and supportive care. Follow up was done till discharge from hospital or death. The criteria for discharge were clinical improvement of symptoms, absence of fever for at least 48 hours, and nasopharyngeal swab sample negative for SARS-CoV-2 PCR. All medical records were kept confidential. Informed consent was taken from patients or from the patient's legally authorized representative who could provide oral consent with appropriate documentation by the investigator. This study was approved by the hospital research and ethics committee of No.(1) Defence Services General Hospital (1000-Bedded) Mingaladon, Yangon.

3. Data Collection

The clinical outcome was evaluated daily till discharge or death. Both clinical, radiological and laboratory data were collected in standardized proforma and confidentiality was maintained. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator.

4. Operational Definitions

The hospital outcome at the time of discharge from hospital (survival status) was either survivor or non-survivor. The discharge criteria were determined by attending physician.
Timing/duration of symptoms onset to admission (days) was time from first symptom to arrival at hospital. Quick Sequential Organ Failure Assessment Score (qSOFA score) was assessed by systolic pressure less than 100 mmHg, GCS and respiratory rate. Maximum score was 3; and minimum was "0". Low qSOFA score was "0" and "1". High score was "2" and "3". Severity of lung parenchyma involvement in CXR was calculated by Brixia Score as "0 to 18". lungs were divided into six zones on a postero-anterior (PA) or antero-posterior (AP) projection. In the second step, a score (0 to 3) is assigned to each zone based on lung abnormalities as follows: (1) "0" if there was no lung abnormalities; (2) "1" if there was interstitial infiltrates; (3) "2" if there was interstitial and alveolar infiltrates with interstitial predominance; and, (4) "3" if there was interstitial and alveolar infiltrates with alveolar predominance. Finally, the scores of the six lung zones are then added to obtain an overall CXR score ranging from 0 to 18.

Based on WHO severity score, the severity of COVID-19 was classified as mild, moderate, severe disease and critical disease. Mild disease was symptomatic patients without evidence of viral pneumonia in CXR or hypoxia. Moderate disease was confirmed patients with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing), CXR showed pneumonia and SpO2 on air is

≥ 95%. Severe disease was confirmed patient with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) adding one of the following: respiratory rate > 30 breaths per min, severe respiratory distress and SpO2 < 90% on room air. Critical disease was confirmed COVID-19 patient with one or more of the followings: ARDS, sepsis, septic shock and acute thrombosis (pulmonary embolism, acute coronary syndrome, and acute stroke).

Neutrophil leukocytosis was high total WBC count more than 12 x 109 /L with neutrophils dominant (80%). Absolute lymphocyte count was low if it was less than 1.0 x 109 /L. The level of ferritin was defined as elevated when it was higher than 400 ng/mL (30 – 400 ng/mL). The level of LDH was defined as elevated when it was higher than 225 U/L (135 – 225 U/L).The level of D-dimer was defined as elevated when it was higher than 0.5 µg/mL (< 0.5 µg/mL). CRP, an acute-phase reactant reflecting the inflammatory activity, was defined as elevated when it was higher than 0.5 mg/L (< 0.5 mg/L). The level of AST was raised if it was more than 37 IU/L; the level of ALT was raised if it was more than 40 IU/L.

5. Statistical Analysis

Continuous and categorical variables were present as mean (± SD) and number (%), respectively. We used Pearson chi-square test, X2 test and odd ratio with 95% confident interval level to detect association between clinical characteristics, risk factors and outcome among COVID-19 infected patients. To compare the mean clinical characteristics and laboratory markers' differences between survivors and non-survivors, student t-test was used. *P* value of less than 0.05 was considered statistically significant. Data entry was done into Microsoft Excel worksheet and statistical analyses were done using the SPSS software (version 22).

6. Results

A total of 404 inpatients; 150 cases from Mingaladon hospital (300-bedded), 150 cases from Phaung Gyi hospital (1500-bedded) and 104 cases from Nay Pyi Taw hospital (1000-bedded) were included. Nearly two third of patients (258) were survivors; one third (146) did not make it. Table (1) shows baseline clinical characteristics and Table (2) reveals frequency distribution of clinical characteristics in groups. Mean age was 62 years; however, half of the cases were over 65 years. Most of them were male (60.6%). The majority of patients came to hospital at day 7 after symptom onset; nevertheless, the late comers arrived to hospital at day 28. Their mean qSOFA score was 0.74 ± 0.76; and, mean pulse rate was 93.08 ± 15.3 beats per minutes. Most of them had tachycardia and low SpO2 on arrival. Mean respiratory rate was 22.06 ± 3.35 per minutes; and mean initial SaO2 on air was 86.07 ± 9.02 percent. Mean score of chest radiograph Brixia score was 8.18 ± 4.12; the range was 4 to 16. In Table (3), the associations between mean values of clinical characteristics and outcomes among COVID-19 infected patients were illustrated; age over 60 years, high qSOFA score and CXR lesion more than 50% were good predictors for their outcome. Patients over 65 years old (odds ratio 0.47, 95% CI 0.31– 0.72; p < 0.001), quick Sequential Organ Failure Assessment Score qSOFA more than 2 (odds ratio 0.27; 95% CI 0.08 – 0.91; p < 0.025) and lung parenchymal involvement more than 50% (odds ratio 0.39; 95% CI 0.24 – 0.61; p < 0.001) were very prone to death. In Table (4), the comparison of mean differences of clinical characteristics between survival and non-survival groups is demonstrated; SpO2 percent on air (95% CI – 7.46 – -3.96; p < 0.001), conscious level in term of GCS (95% CI -0.71 – -0.20; p < 0.001), qSOFA score (95% CI 0.25 – 0.55; p < 0.001), and chest Xray Brixia score (95% CI 3.42 – 4.89; p < 0.001) were strongly correlated with survival. However, initial temperature (95% CI -0.07 – 0.26; p = 0.245), pulse rate (95% CI -0.16 – 6.05; p = 0.063), systolic blood pressure (95% CI 0.13 – 8.55; p = 0.043), respiratory rate (95% CI 0.63 – 1.97; p < 0.001), and time interval between symptom onset to hospital admission (95% CI 0.27 – 1.69; p = 0.007) did not determine prognosis. The comparison of mean differences of laboratory markers between survival and non-survival groups is illustrated in Table (5).

Total WBC count greater than 12 x 109/L (95% CI 1.81 – 4.33; p < 0.001), absolute neutrophil count (95% CI -5.95 – -8.00; p = 0.01), high CRP greater than 0.5 mg/L (< 0.5 mg/L) (95% CI -61.37 – -23.26; p < 0.001), high ferritin greater than 400 ng/mL (30 – 400 ng/mL) (95% CI -312.36 – -139.07; p < 0.001), high D-dimer greater than 0.5 µg/mL (< 0.5 µg/mL) (95% CI -3340.65 – -2945.21; p < 0.001), high serum creatinine greater than 1.1 mg% (95% CI 0.19 – 0.70; p = 0.002), high LDH greater than 225 U/L (135 – 225 U/L) (95% CI -166.53 – -46.66; p < 0.001), high ALT greater than 40 IU/L. (95% CI 11.82 – 39.32; p < 0.001) and high AST greater than 37 IU/L (95% CI 21.26 – 55.16; p < 0.001) were strong predictors for clinical severity and death. On the other hand, absolute lymphocyte count (95% CI -0.14 – 0.13; p = 0.94), and platelet count (95% CI -7.90 – 48.85; p = 0.15) were not the determinant of mortality. Figure (2) shows changes in inflammatory markers at Day '0', Day '3', Day '7', and Day '14'. Not only the initial Day '0' level but also the remaining Day'3', Day '7' and Day '14' levels of CRP, ferritin and LDH were different between survivors and non-survivors; non-survivors had higher inflammatory markers.

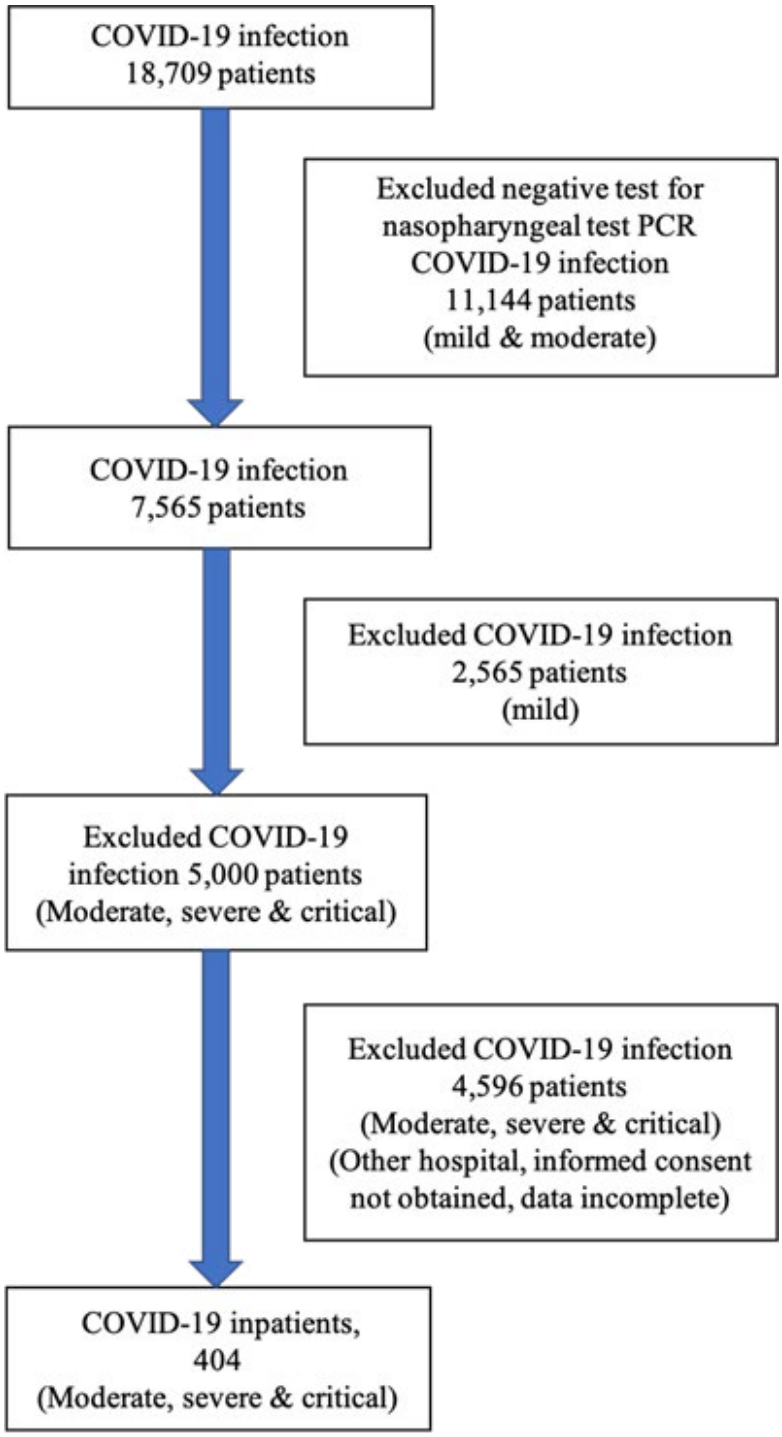

Figure 1: Flow chart

Table 1: Baseline clinical characteristics in patients with severe COVID-19 infection (n = 404)

Baseline Clinical Characteristics (n = 404)	Mean ± SD	Minimum	Maximum
Age (year)	62.95 ± 13.15	21	100
CXR Braxia Score	8.18 ± 4.12	4	16
Symptom Onset to Admission (days)	7.10 ± 3.51	1	26
Initial SpO2 (%)	86.07 ± 9.02	50	99
Initial Temp (ºF)	98.14 ± 0.81	90	102
Inital Pulse rate (/min)	93.08 ± 15.3	56	142
Initial GCS (Glasgow Coma Scale)	14.75 ± 1.26	3	15
Initial Systolic Blood Pressure (mmHg)	126.95 ± 20.76	70	180
Initial Respiratory Rate (/min)	22.06 ± 3.35	16	40
qSOFA Score	0.74 ± 0.76	0	3

Table 2: Frequency distribution of clinical characteristics in patients with severe COVID-19 infection (n = 404)

Clinical Characteristics		No. of Patients	Percent
Age Group	< 65	205	50.7
	≥ 65	199	49.3
Gender	Male	245	60.6
	Female	159	39.4
Outcome	Non-survivor	146	36.1
	Survivor	258	63.9
qSOFA score	Low Score	392	97
	High Score	12	3
Symptoms Onset to admission Group	≤ 7days	251	62.1
	8 - 14days	142	35.1
	>14 days	11	2.7

Table 3: Associations between clinical characteristics and outcomes in patients with severe COVID-19 infection (n = 404)

Clinical Characteristics	Outcome n (%)		*p* value	X^2	OR	95% CI	
	Non-survivor	Survivor					
Age Group							
< 65 years	57 (27.8%)	148 (72.2%)	< 0.001	12.52	0.47	0.31	0.72
≥ 65 years	89 (44.7%)	110 (55.3%)					
Gender							
Male	91 (37.1%)	154(62.9%)	0.60	0.27	1.12	0.73	1.69
Female	55 (34.6%)	104 (65.4%)					
qSOFA score							
low score (0&1)	138 (35.2%)	254 (64.8%)	0.025	4.994	0.27	0.08	0.91
high score (2&3)	8 (66.7%)	4 (33.3%)					
Symptom Onset to Admission							
≤ 7days	81 (32.3%)	170 (67.7%)	0.01	8.99			
8-14days	57 (40.1%)	85 (59.9%)					
>14 days	8 (72.7%)	3 (27.3%)					
p value by Pearson Chi-square							

Table 4: Comparison of clinical characteristics in patients with severe COVID-19 infection between survival and non-survival groups (n = 404)

Baseline Clinical Characteristics	Total patients (Mean ± SD) (n = 404)	Non survivor (Mean ± SD) (n = 146)	Survivor (Mean ± SD) (n = 258)	*p* value	Mean Difference	95% CI	
Initial SaO2 (%)	86.07 ± 9.02	82.42 ± 10.55	88.14 ± 7.26	< 0.001	-5.71	-7.46	-3.96
Initial Temperature (ºF)	98.14 ± 0.81	98.19 ± 0.52	98.11 ± 0.94	0.245	0.10	-0.07	0.26
Initial Pulse Rate (PR/min)	93.08 ± 15.30	94.97 ± 17.32	92.02 ± 13.96	0.063	2.95	-0.16	6.05
Initial GCS score	14.75 ±1.26	14.46 ± 1.88	14.91 ± 0.64	< 0.001	-0.46	-0.71	-0.20
Initial Systolic Blood Pressure (mmHg)	126.95 ± 20.76	129.72 ± 25.23	125.38 ± 17.60	0.043	4.34	0.13	8.55
Initial Respiratory Rate (/min)	22.06 ± 3.35	22.89 ± 3.53	21.59 ± 3.16	< 0.001	1.30	0.63	1.97
qSOFA Score	0.74 ± 0.76	0.99 ± 0.87	0.59 ± 0.66	< 0.001	0.40	0.25	0.55
CXR Brixia Score	8.18 ± 4.12	10.84 ± 2.87	6.68 ± 3.96	< 0.001	4.16	3.42	4.89
Symptom Onset to Admission (days)	7.10 ± 3.51	7.73 ± 4.17	6.75 ± 3.02	0.007	0.98	0.27	1.69
p value by student t-test							

Table 5: Comparison of laboratory parameters on admission in patients with severe COVID-19 infection between survival and non-survival groups (n = 404)

Laboratory Parameters	Total patients (Mean ± SD) (n = 404)	Non-survivor (Mean ± SD) (n=146)	Survivor (Mean ± SD) (n=258)	*p* value	Mean Difference	95% CI	
Total WBC	10.92 ± 5.85	12.71 ± 6.61	9.64 ± 4.86	< 0.001	3.07	1.81	4.33
Absolute Lymphocyte Count	0.95 ± 0.61	0.94 ± 0.68	0.95 ± 0.55	0.94	-0.00	-0.14	0.13
Platelets	178.36 ± 12.72	172.34 ± 133.05	151.87 ± 142.80	0.15	20.47	-7.90	48.85
Neutrophil	15.93 ± 13.95	6.21 ± 11.43	9.57 ± 13.26	0.01	-3.38	-5.95	-8.04
CRP	122.87 ± 97.99	147.59 ± 118.07	105.27 ± 76.39	< 0.001	-42.32	-61.37	-23.26
Ferritin	772.84 ± 473.08	920.64 ± 450.97	694.92 ± 410.59	<0.001	-225.72	-312.36	-139.07
D dimer	1619.26 ± 981.65	3626.16 ± 1563.69	483.23 ± 309.34	< 0.001	-3142.93	-3340.65	-2945.21
Creatinine	1.18 ± 1.34	1.45 ± 1.95	1.03 ± 0.78	0.002	0.43	0.16	0.70
LDH	464.39 ± 295.97	534.34 ± 369.97	427.74 ± 241.54	0.05	-106.60	-166.53	-46.66

ALT	42.91 ± 68.58	59.23 ± 95.56	33.67 ± 44.56	< 0.001	25.57	11.82	39.32
AST	50.06 ± 85.16	74.46 ± 130.50	36.25 ± 35.12	< 0.001	38.21	21.26	55.16
p value by student t-test							

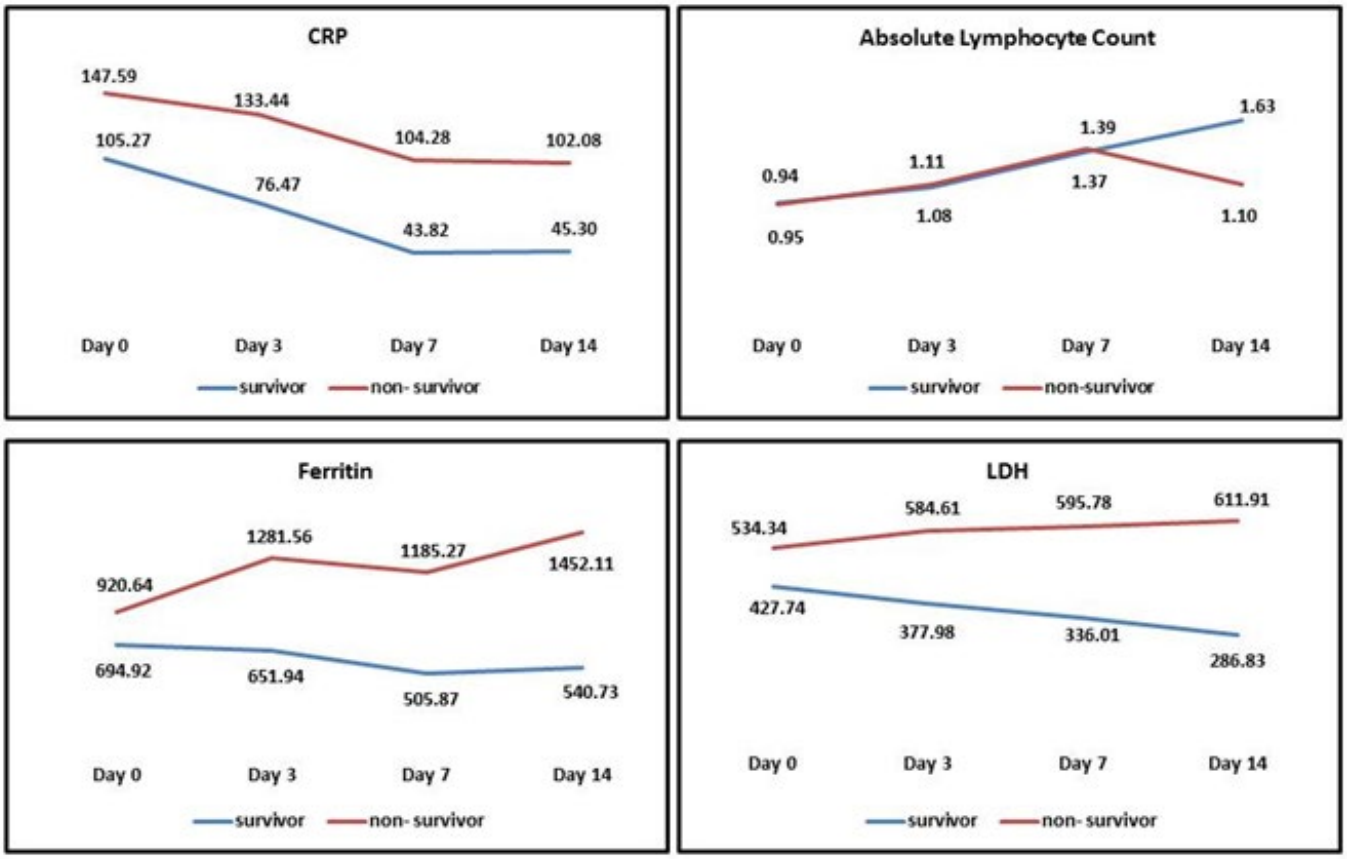

Figure 2: Changes in level of inflammatory markers till Day 14 among survivors and non-survivors

7. Discussion

Coronavirus disease 2019 (COVID-19) has been a major threat to health around the world since end of 2019. It is believed that COVID-19, in those with underlying health conditions or comorbidities, has an increasingly rapid and severe progression, often leading to death. The study aimed to assess clinical and laboratory parameters determining the outcome in patients with severe/critical COVID-19 infections in second and third wave of epidemics in Myanmar. A hospital based prospective study was conducted in COVID-19 treatment centers in Myanmar -Yangon and Nay Pyi Taw, Mingaladon Hospital, Phaung Gyi Hospital and Nay Pyi Taw Hospital from February 2020 to August 2021. Total 404 cases with confirmed severe COVID-19 infection were included; 258 (63.9%) survived and 146 (36.1%) dead.

Patients over 65 years old (OR: 0.47, 95% CI 0.31– 0.72; p < 0.001) were found to be risk factor for severity and mortality; it was mentioned in the previous findings [2-4]. Report from one meta-analysis, patients with age over 50 years were associated with 15.4 folds significantly increased risk of mortality compared to patients with age younger than 50 years [5]. Regarding gender, male sex was not a risk factor for mortality in this study (OR: 1.12, 95% CI 0.73 – 1.69; p = 0.60); nevertheless, male sex was prone to severe COVID-19 infection and death in meta-analysis [5,6]. Mentioned that male sex had higher risk of COVID-19 infection; moreover, they were likely to have severe infection and death.

Several clinical severity score were applied in earlier studies to assess the severity of COVID-19 pneumonia and mortality. CURB-65, NEWS2 and qSOFA underestimate 30-day mortality among patients admitted to the hospital with COVID-19. [7]found that CURB-65 and NEWS2 were slightly better at predicting early mortality. However mentioned that none of the risk scores (CURB65, qSOFA, Lac-CURB65, MuLBSTA, The 4C Mortality Score and NEWS2) identified admission to intensive care or death within 7 days of admission, early severe adverse events (ESAE) [8]. In this study, those having Sequential Organ Failure Assessment SOFA Score more than 2 had significant mortality (OR: 0.27;

95% CI 0.08 – 0.91; p = 0.025); alarming early clinical sign which guided early treatment and prognosis for attending physician. Conscious level in term of GCS (95% CI -0.71 – -0.20; p < 0.001) was a significant predictor for mortality; reduced conscious level was noted in patients with cerebrovascular disease, critical form of COVID-19 infection according to WHO. It was due to obstruction of cerebral artery leading to infarction. This finding again pointed out the underlying etiology and prognosis; thus, it was included in 4C Mortality Score which was used for risk stratification of COVID-19 cases ("Risk Stratification of Patients Admitted to Hospital with Covid-19 Using the ISARIC WHO Clinical Characterisation Protocol: Development and Validation of the 4C Mortality Score," 2020).

Nevertheless, initial temperature (95% CI -0.07 – 0.26; p = 0.245), pulse rate (95% CI -0.16 – 6.05; p = 0.063), systolic blood pressure (95% CI 0.13 – 8.55; p = 0.043), respiratory rate (95% CI 0.63 – 1.97; p < 0.001), and time interval between symptom onset to hospital admission (95% CI 0.27 – 1.69; p = 0.007) did not determine prognosis. However, the combination of clinical parameters, oxygenation, respiratory rate, and laboratory markers might determine the outcome like 4C Mortality Score – number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein (score range 0-21 points) ("Risk Stratification of Patients Admitted to Hospital with Covid-19 Using the ISARIC WHO Clinical Characterisation Protocol: Development and Validation of the 4C Mortality Score," 2020).

The typical chest x-ray findings in patients with COVID-19 is peripheral ground glass opacity affecting the lower lobes; therefore, it can be used in diagnosis and follow up in patients with COVID-19 pneumonia [9]. The Larger the extent of pneumonia, the more severe the disease generally. The earlier findings from China highlighted that severe ground-glass opacity in CT scan of chest were related with severity of COVID-19 pneumonia and mortality [10]. Those having severe chest radiographic lesions were significantly related with mortality [11-13]. The severe the lung involvement, the lower the oxygen saturation and respiratory failure because consolidated pulmonary parenchyma could not perform gas exchange. Those having low SaO2 percent on air less than 85% were significantly associated with death (95% CI – 7.46 – -3.96; p < 0.001); thus, health education on self-monitoring of SaO2 percent at home was extremely important. In this study, high CXR Braxia Score more than '8' had significant mortality (95% CI 3.42 – 4.89; p < 0.001); their respiratory rate was increased and SaO2 on air was reduced. Chest Xray severity criteria by Brixia score (95% CI 3.42 – 4.89; p < 0.001) was very useful for A&E physician; pointing to timely effective treatment, monitoring and prognosis.

Total WBC count greater than 12 x 109/L (95% CI 1.81 – 4.33; p < 0.001) and absolute neutrophil count higher than 8.0 x 109/L (95% CI -5.95 – -8.00; p = 0.01) were good indicators for poor prognosis because of possible secondary bacterial infection - Streptococcus pneumoniae, Hemophilus influenza, Klebsiella species and Staphylococcus aureus. It was very difficult to perform sputum culture during COVID-19 epidemic because of high prevalence of COVID-19 infection among laboratory staffs. The anti-microbial therapy according to guideline, cephalosporin, penicillin and meropenum would not be effective due to growing anti-microbial resistance. "Compared with patients not treated in ICU, patients treated in the ICU were older, reduced T lymphocytes, elevated neutrophils and organ failure" reported by (Cao et al., 2020). Patients with severe COVID-19 were characterized by lymphocytopenia (low CD3+, CD4+, and CD8+T-cell counts), caused by direct viral cytopathic effects, inhibitory effects of cytokines including TNF-α, IL-6, and IL-10, and immune cell redistribution into the lungs and lymphoid organs. Severe COVID-19 infection was characterized by significantly increased levels of pro-inflammatory cytokines and reduced T lymphocytes [14]. Absolute lymphocyte count (95% CI -0.14 – 0.13; p = 0.94), and platelet count (95% CI -7.90 – 48.85; p = 0.15) were not the determinant of mortality in this study; it was contrary to most of the report 'lymphopenia was one of the indicators of severity and low platelet count was a late sign as a result of DIC'. In the study from Indonesia, low platelet count was reported as a marker for grave prognosis however, this study did not prove it [15]. Hyper inflammatory condition and cytokine storm usually takes place in patients at advanced stages of COVID-19 and develops a rapid inflammatory signaling cascade [16].

High CRP greater than 0.5 mg/L (< 0.5 mg/l) (95% CI -61.37 – -23.26; p < 0.001) and high Ferritin greater than 400 ng/mL (30 – 400 ng/mL) (95% CI -312.36 – -139.07; p < 0.001) were excellent indicators for cytokine storm; guiding energetic treatment. In countries with poor resource setting, IL 6 level were non-accessible, CRP was the cheapest laboratory marker for deciding treatment and prognosis ("Risk Stratification of Patients Admitted to Hospital with Covid-19 Using the ISARIC WHO Clinical Characterisation Protocol: Development and Validation of the 4C Mortality Score," 2020). Laboratory parameters to monitor disease progression reported by Gao et al. (20210 were lactate dehydrogenase, procalcitonin, high-sensitivity C-reactive protein, proinflammatory cytokines such as interleukin (IL)-6, IL-1β, Krebs von den Lungen-6 (KL-6), and ferritin [17]. Meta-analyses of multiple studies have shown significant correlations between several laboratory factors and the severity and mortality of COVID-19. These laboratory parameters included the following: (1) changes in blood cell counts, including increased leukocyte and neutrophil counts, neutrophil-to-lymphocyte ratio, and decreased lymphocyte and eosinophil counts; (2) increase in the level of biochemical parameters: lactate dehydrogenase, CRP, procalcitonin, aspartate amino transferase, alanine aminotransferase, and blood urea nitrogen; and (3) changes in coagulation indicators: decreased platelet counts, increased D-dimer, fibrinogen, change in prothrombin time (PT), and activated partial-thromboplastin time (APTT). These changes may be associated with an aggravated disease course of COVID-19.

High D dimer greater than 0.5 µg/ml (< 0.5 µg/ml) (95% CI -3340.65 – -2945.21; p < 0.001) was also excellent marker for inflammation as well as thrombosis, thus it was useful for both therapeutic and prognostic purpose. COVID-19 triggerred coagulation disorders leading to high incidence of thromboembolic events (Lin et al., 2021). High serum creatinine greater than 1.1 mg% (95% CI 0.16 – 0.70; p = 0.002) was a poor prognostic sign as it was caused by pre-renal failure and intrinsic renal failure-acute interstitial nephritis or glomerulonephritis. One PM report revealed SARS-CoV2 virus in glomeruli. Thus, our findings show the prevalence of kidney disease on admission and the development of AKI during hospitalization in patients with COVID-19 is high and is associated with in-hospital mortality. Hence, clinicians should increase their awareness of kidney disease in patients with severe COVID-19 (Y. Cheng et al., 2020). Although high serum creatinine was regarded as a sign of severity of severe COVID-19 infection and death, raised blood urea level generally count the same ("Risk Stratification of Patients Admitted to Hospital with Covid-19 Using the ISARIC WHO Clinical Characterisation Protocol: Development and Validation of the 4C Mortality Score," 2020).

High LDH greater than 225 U/L (135 – 225 U/L) (95% CI – 166.53 – -46.66; p < 0.001) was also good indicator for severity as it reflected underlying inflammation and tissue injury.
High ALT greater than 40 IU/L (95% CI 11.82 – 39.32; p < 0.001) and high AST greater than 37 IU/L (95% CI 21.26 – 55.16; p < 0.001) were strong predictors for clinical severity and death; direct liver damage. Acute liver injury was a sing of poor prognosis [18].

8. Conclusion

Clinical awareness is important to detect those with low Glasgow Coma Scale score, initial SaO2 less than 85%, qSOFA score '2' and above, and severe chest radiographic involvement (CXR Braxia Score more than '8') to get treatment timely to reduce mortality. Laboratory markers like neutrophil leukocytosis, high CRP level, high ferritin level, high LDH level, high transaminase (ALT and AST) level, high D dimer level, high creatinine levels were significantly related with mortality. From therapeutic aspect, they should be in the first lists for hospital during pandemic period in order to reduce morbidity and mortality. The patients their selves and their family members should be aware of these red flag signs. The treating physician should have awareness on importance of clinical data, risk factors and disease biomarkers to get efficient patient management and possibly minimize the related mortality [19-45].

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Declaration of Conflict of Interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

Ethical Approval

This study was approved by Hospital Research and Ethic Committee from Defence Services General Hospital (1000-Bedded) Mingaladon, Myanmar. Informed consent was also taken from each patient.

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