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Clinical Characteristics and Initial Laboratory Results associated with Severe COVID-19 Pneumonia in Hospitalized Patients

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Abstract

Background: Severe COVID-19 pneumonia needed early appropriate management to decrease morbidity and mortality. The aim of this study was to identify clinical features and initial laboratory results associated with severe COVID-19 pneumonia among hospitalized COVID-19 patients.

Methods: A cross sectional study was conducted between January 2021 and December 2021 at Srinagarind Hospital, Khon Kaen University, and a tertiary care center in Northeastern Thailand.

Results: 401 hospitalized patients (124 severe and 277 non-severe pneumonia) were diagnosed with COVID-19 pneumonia. Patients with dyspnea (aOR 2.0, 95% CI 1.0 to 4.1), RR >24/min (aOR 2.9, 95% CI 1.2 to 7.4), SpO_2 <96% at room air (aOR 1.9, 95% CI 1.0 to 3.7), chronic kidney disease ≥stage 3 (aOR 3.7, 95% CI 1.3 to 10.7), absolute lymphocyte count (ALC) (aOR 1.0, 95% CI 1.0 to 1.0), neutrophil/lymphocyte (N/L) ratio (aOR 1.1, 95% CI 1.0 to 1.3), C-reactive protein (CRP) (aOR 1.0, 95% CI 1.0 to 1.0), and CRP/L ratio (aOR 1.0, 95% CI 1.0 to 1.0) were statistically significant to have severe COVID-19 pneumonia. The

highest accuracy of initial laboratory results related to severe COVID-19 pneumonia on admission was the CRP/L ratio (AUC = 0.817, 95% CI 0.772-0.862), followed by CRP (AUC = 0.783, 95% CI 0.735-0.832), N/L (AUC = 0.781, 95% CI, 0.731-0.831), and ALC (AUC = 0.755, 95% CI 0.706-0.804). The optimal cutoff value of the CRP/L ratio related to severe COVID-19 pneumonia was >10 with a sensitivity of 83.1% and specificity of 64.3% (95% CI, 58.3-69.9), CRP >12 mg/L with a sensitivity of 79.0% and specificity of 60.3%, N/L ratio >2.4 with a sensitivity of 81.4% and specificity of 58.1%, and ALC was <1.2 x 10^9 cells/L with a sensitivity of 63.7% and specificity of 71.5%.

Conclusions: Patients with dyspnea, RR >24/min, SpO_2 <96% at room air, chronic kidney disease ≥stage 3, absolute lymphocyte count <1.2 x 10^9 cells/L, CRP >12 mg/L, N/L ratio >2.4 and CRP/L ratio >10 on admission were associated with severe COVID-19 pneumonia.

Keywords: Severe COVID-19 pneumonia, COVID-19, CRP/L ratio, CRP, N/L ratio, Absolute lymphocyte count

Introduction

The coronavirus disease 2019 (COVID-19) is the recent pandemic infectious disease spread worldwide since the end of 2019. WHO globally reported the situation in 2021 that there have been more than 260 million confirmed cases and more than 5.2 million deaths [1]. In Thailand at the same time, there were 2.1 million confirmed cases and 20,944 deaths [1]. The severity of COVID-19 infection varied from asymptomatic to severe symptoms and death [2]. Usually severe symptoms included severe COVID-19 pneumonia [2]. Systematic review and meta-analysis in severe disease found that severe COVID-19 pneumonia increased intensive care unit (ICU) admission (10.9%), acute respiratory distress syndrome (ARDS) (18.4%), and death (4.3%) [3].

Thailand has been critically affected by the COVID-19 infection and is considered to be among the top countries in handing the outbreak [4]. The first COVID-19 wave in Thailand occurred during March–May 2020, followed by the second wave between December 2020 and February 2021, and the third wave in April 2021, and the fourth wave beginning in June 2021 [5]. Between January and March 2021, Alpha variant was more common identification than Delta variant. However, between April and June 2021, Delta variant overtook the Alpha variant as the dominant strain [6]. After mid-2021, Delta variant was the single identified COVID-19 variant in Thailand until the end of 2021, Omicron variant had been beginning reported [6]. Due to the extensive transmission of the Delta variant in 2021, the number of cases and deaths rose exponentially, alongside an increasing of hospitalizations and intubated patients [7].

The incidence of pneumonia in hospitalized COVID-19 patients reported in Thailand was 39%; hospitalized cases 16.6% needed ICU admission, 3.1% developed ARDS, and 2.1% died [8]. Early detection of clinical severity before organ dysfunction and appropriate management decreased morbidity and mortality [2]. A previous study in China reported that the rate of ICU admission in COVID-19 pneumonia patients was related to increasing age, comorbidities, and dyspnea [9].

Due to a limitation of medical resources in Thailand, the purpose of this study was to identify the initial clinical features and initial laboratory results to triage severe COVID-19 pneumonia for intensive monitoring and treatment. The cutoff values of initial laboratory results observed in cases of COVID-19 severe pneumonia were also determined.

Materials and Methods

Study participants and data collection

During the study period (January 2021 and December 2021), 1346 COVID-19 patients were admitted at Srinagarind Hospital, a tertiary care center in Northeastern Thailand.

Nasopharyngeal swabs, throat swabs, tracheal swabs or bronchoalveolar lavage fluids from all hospitalized COVID-19 patients were submitted to real-time reverse transcription polymerase chain reaction (RT-PCR) detection of SARS-CoV-2 RNA regarding to the Center of Disease Control (CDC) guideline [10]. Adult (age ≥ 18 years) COVID-19 patients with pneumonia detected by chest radiographs showing new infiltrations were included in the study. Patients who did not have initial laboratory results within 24 hours after admission were excluded.

Patients were categorized as non-severe COVID-19 pneumonia and severe COVID-19 pneumonia according to WHO guidelines [11]. Patients with non-severe COVID-19 pneumonia did not require oxygen or ventilatory support and pulse oxygen saturation (SpO_2) at room air ≥ 94%. Patients with severe COVID-19 pneumonia had SpO_2 at room air < 94% or needed oxygen therapy to maintain SpO_2 ≥ 94% or were on a high flow nasal canula (HFNC) or on noninvasive ventilation (NIV) or on a mechanical ventilator. Sample size calculation was determined to be 339 cases of COVID-19 pneumonia with 95% confidence level (Zα=1.96) and a margin of error 4% [12]. This study was approved by the Human Research Ethics Committee, Khon Kaen University (approval number HE651001).

Demographic data including age, sex, body weight and body mass index (BMI) were obtained from medical records. The patient's medical histories including chief complaint, history of present illness, date of onset of symptoms (DOI), and underlying comorbidities were reviewed. Initial body temperature (BT), blood pressure (BP), respiratory rate (RR), and percentage of SpO_2 at room air were recorded. Chest radiography at initial admission and during the hospital courses were reviewed by a radiologist and the results were obtained from the radiology report. Initial blood tests within the first 24 hours of admission were obtained including complete blood count (CBC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte (N/L) ratio, C-reactive protein (CRP), CRP-to-lymphocyte (CRP/L) ratio, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DB), albumin (Alb), blood urea nitrogen (BUN), creatinine (Cr) and estimated glomerular filtration rate (eGFR). Daily monitored SpO_2 and hospital course of needed oxygen therapy to maintain SpO_2 ≥ 94% or on high flow nasal canula (HFNC) or on noninvasive ventilation (NIV) or on mechanical ventilator were monitored to classify infection as severe or non-severe COVID-19 pneumonia. All complications during hospitalization and treatment outcomes were also recorded.

Statistical analysis

Means, standard deviations (SD), medians and interquartile ranges (IQR) were calculated for continuous data; numbers and percentages were used to describe categorical data. The Fisher's exact test, Pearson's χ2 test, unpaired t-tests, and the Mann-Whitney *U* test were used to analyze differences between groups depending on the data. Logistic regression analysis was used to determine factors associated with severe COVID-19 pneumonia. Variables with a p-value < 0.05 on univariate analysis were included in the multiple logistic regression model. The Pearson correlation was used to control for collinearity between independent variables. Crude and adjusted odd ratios (ORs) and 95% confidence intervals (CI) were reported. The diagnostic accuracy of the initial laboratory tests for severe COVID-19 pneumonia was assessed by an area under the receiver operating characteristic curve (AUC). Sensitivity, specificity, positive predictive and negative predictive values were determined from the selected probability cut-off. All statistical analyses were performed using SPSS version 28.0 (IBM SPSS Statistics Subscription Trial). A p-value <0.05 was considered statistically significant.

Results

Four hundred and one cases of adults aged 18 years or over had chest radiography that showing new infiltrates and were diagnosed with COVID-19 pneumonia. Of these, 124 cases (30.9%) were severe pneumonia, and 277 cases were non-severe pneumonia. The overall median age of 401 COVID-19 pneumonia patients was 44.8 (IQR 31.0-56.0) years, 18.4% (n=74) aged > 60 years. Forty seven percent (n=190) of them were male. Only three percent (n=13) were pregnant women. The median body mass index (BMI) was 24.5 (IQR 22.3-27.5) kg/m^2, 14.7% (n=59) BMI ≥ 30 kg/m^2. One hundred and seventy-one (42.6%) patients had comorbidities; the two most common comorbidities were diabetes mellitus (20.4%) and hypertension (20.4%), followed by chronic kidney disease (CKD) (11.2%), dyslipidemia (5%), ischemic

stroke (2%), chronic liver disease (1.2%), asthma (1%), chronic obstructive pulmonary disease (COPD) (0.7%), ischemic heart disease (0.7%), human immunodeficiency virus (HIV) (0.7%), and connective tissue disease (0.5%). Severe COVID-19 pneumonia patients had a statistically significant older age, greater weight, and more comorbidities (especially CKD, diabetes mellitus and hypertension) than non-severe COVID-19 pneumonia patients as shown in Table 1.

The median DOI of patients with COVID-19 pneumonia was 4 (IQR 3-7) days. One hundred and forty-six patients (36.4%) presented with DOI > 5 days. The most common presenting symptom was fever (74.8%), followed by dry cough (39.4%), sore throat (28.2%), dyspnea (23.9%), myalgia (19.2%), runny nose (17.7%), productive cough (16.7%), anosmia (10.5%), headache (8.0%), diarrhea (4.7%), taste dysfunction (1.7%), nausea and/or vomiting (1.0%), and rash (0.2%). Only ten percent had an initial body temperature (BT) increase at admission > 38°C with mean arterial pressure (MAP) 97.1 (SD 12.7) mmHg. The median respiratory rate (RR) was 20 (IQR 20-22) breaths/min, and 13.7% RR was more 24 breaths/min. The median SpO_2 on admission was 97 (IQR 95-98) %, and 35.4% SpO_2 was less than 96%. Patients with severe COVID-19 pneumonia had more DOI than the non-severe group as shown in Table 2. The symptoms that differed significantly found in severe COVID-19 pneumonia were fever, dyspnea, and anosmia. The statistically significant runny nose symptom was found in non-severe COVID-19 pneumonia. The initial vital signs in severe COVID-19 pneumonia patients had statistically significant higher RR and lower SpO_2 (Table 2). Thirty-two percent of severe COVID-19 pneumonia patients had RR > 24/min, while five percent of non-severe COVID-19 pneumonia patients had RR > 24/min. Sixty-seven percent of severe COVID-19 pneumonia patients had SpO_2 < 96%, while twenty percent of non- se-

Table1: Demographic and clinical characteristics of 401 COVID-19 pneumonia patients on admission.

Characteristic	Severe COVID-19 pneumonia (n = 124)	Non-severe COVID-19 pneumonia (n = 277)	P-value
Median age in years (IQR)	50.5 (39.0, 61.0)	42.0 (30.0, 53.0)	< 0.001*
Age >60 years, n (%)	35 (28.2)	39 (14.1)	< 0.001*
Male sex, n (%)	65 (52.4)	125 (45.1)	0.176
Median weight in kg (IQR)	67.5 (60, 80)	64 (57, 73)	0.004*
BMI ≥30 kg/m^2, n (%)	26 (21.0)	33 (11.9)	0.018*
With any comorbidities, n (%)	73 (58.1)	98 (35.4)	< 0.001*
Comorbidities n (%)			
Diabetes	36 (29.0)	46 (16.6)	0.004*
Hypertension	34 (27.4)	48 (17.3)	0.021*
Chronic kidney disease	27 (21.8)	18 (6.5)	< 0.001*
Dyslipidemia	5 (4.0)	15 (5.4)	0.557
Ischemic stroke	4 (3.2)	4 (1.4)	0.259
Ischemic heart disease	2 (1.6)	1 (0.4)	0.227
COPD	2 (1.6)	1 (0.4)	0.227
Asthma	1 (0.8)	3 (1.1)	1.0
Chronic liver disease	1 (0.8)	4 (1.4)	1.0
Connective tissue disease	0 (0)	2 (0.7)	1.0
HIV	1 (0.8)	2 (0.7)	1.0

**P-value<0.05, IQR: Interquartile Range, BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, HIV: Human Immunodeficiency Virus.*

Table 2: Initial symptoms and vital signs of COVID-19 pneumonia patients on admission.

Symptoms and signs	Severe COVID-19 pneumonia (n = 124)	Non-severe COVID-19 pneumonia (n = 277)	P-value
Median DOI in day (IQR)	6 (3, 10)	4 (2, 6)	< 0.001*
DOI > 5 days, n (%)	64 (51.6)	82 (29.6)	< 0.001*
Symptoms, n (%)			
Fever	102 (82.3)	198 (71.5)	0.022*
Runny nose	9 (7.3)	62 (22.4)	< 0.001*
Sore throat	33 (26.6)	80 (28.9)	0.641
Dry cough	54 (43.5)	104 (37.5)	0.256
Productive cough	19 (15.3)	48 (17.3)	0.619
Anosmia	6 (4.8)	36 (13.0)	0.014*
Dyspnea	59 (47.6)	37 (13.4)	< 0.001*
Myalgia	25 (20.2)	52 (18.8)	0.744
Headache	11 (8.9)	21 (7.6)	0.660
Diarrhea	6 (4.8)	13 (4.7)	0.949
Nausea vomiting	2 (1.6)	2 (0.7)	0.591
Taste dysfunction	2 (1.6)	5 (1.8)	0.892
Initial vital signs			
Median BT, (IQR), °C	37.0 (36.5, 37.6)	36.8 (36.4, 37.3)	0.012*
BT >38 °C, n (%)	17 (13.7)	24 (8.7)	0.123
Mean MAP (SD), mmHg	96.8 (13.2)	97.2 (12.5)	0.890
Median RR, (IQR), /min	20 (20, 24)	20 (18, 20)	< 0.001*
RR >24/min, n (%)	40 (32.3)	15 (5.4)	< 0.001*
Median oxygen saturation (IQR) %	94 (90, 97)	98 (97, 99)	< 0.001*
SpO_2 (room air) <96%, n (%)	84 (67.7)	58 (20.9)	< 0.001*

**P-value<0.05, DOI: Date of Onset, BT: Body Temperature, IQR: Interquartile Range, SD; Standard Deviation, SpO_2: Pulse Oxygen Saturation.*

vere COVID-19 pneumonia patients had SpO_2 < 96% at initial admission.

The initial blood tests within 24 hours of admission in COVID-19 pneumonia were obtained. The results were reported as the following: median white blood cell count 5.88 (IQR 4.52-7.52) x 10^9/L, absolute lymphocyte count (ALC) 1.35 (IQR 0.93-1.86) x 10^9/L, neutrophil-to-lymphocyte (N/L) ratio 2.56 (IQR 1.55, 4.78), C-reactive protein (CRP) 13 (IQR 4.28-46.60) mg/L, CRP-to-lymphocyte (CRP/L) ratio 10.10 (IQR 2.62-43.38), alanine aminotransferase (ALT) 27.0 (IQR 15.0-44.0) U/L, aspartate aminotransferase (AST) 30.0 (IQR 22.0-47.0), total bilirubin (TB) 0.40 mg/dL, direct bilirubin (DB) 0.20 (IQR 0.10-0.20) mg/L, and albumin (Alb) 4.3 (IQR 3.9-4.6) mg/dL. Patients with severe COVID-19 pneumonia had statistically significant lower absolute lymphocyte count (ALC), higher N/L ratio, higher CRP, and higher CRP/L ratio than non-severe COVID-19 pneumonia patients (Table 3). Eight percent of COVID-19 pneumonia patients had initial chest radiography considered normal; but progressed later after admission. Ninety-two percent had an initial chest radiograph considered abnormal, bilateral ground glass opacity (GGO) (56.6%), unilateral GGO (33.2%), unilateral consolidation (1.5%), and bilateral consolidation (0.7%). In severe COVID-19 pneumonia initial chest radiographic this finding showed bilateral GGO more than non-severe COVID-19 pneumonia. On the other hand, non-severe COVID-19 pneumonia initial chest radiographic findings showed unilateral GGO more than in severe COVID-19 pneumonia (Table 3).

On multivariate analysis, factors significantly associated with severe COVID-19 pneumonia were: patients with underlying CKD stage ≥3 (Adjusted OR: 3.73; 95% CI: 1.30-10.70), symptoms of dyspnea (Adjusted OR: 2.05; 95% CI: 1.02-4.12), initial RR >24/

Table 3: Initial laboratory results of COVID-19 pneumonia patients on admission.

Laboratory	Severe COVID-19 pneumonia (n = 124)	Non-severe COVID-19 pneumonia (n = 277)	P-value
WBC, median (IQR), x10^9 /L	6.74 (5.02, 9.17)	5.71 (4.46, 7.01)	< 0.001*
Absolute lymphocyte count, (IQR) x10^9 /L	0.99 (0.69, 1.35)	1.54 (1.14, 2.05)	< 0.001*
Neutrophil/Lymphocyte (N/L) ratio, (IQR)	5.15 (2.73, 10.07)	2.20 (1.36, 3.23)	< 0.001*
C-reactive protein (CRP), median, mg/L	49.26 (16.05, 81.50)	8.50 (2.94, 24.54)	< 0.001*
CRP/Lymphocyte ratio, (IQR)	52.27 (17.25, 105.99)	4.75 (1.71, 18.49)	< 0.001*
ALT, median (IQR), U/L	34.5 (20.0, 58.0)	24.0 (14.0, 40.0)	0.010*
AST, median (IQR), U/L	41.0 (29.0, 60.5)	27.0 (20.0, 40.0)	< 0.001*
TB, median (IQR), mg/dL	0.40 (0.40, 0.60)	0.35 (0.20, 0.50)	0.012*
DB, median (IQR), mg/dL	0.20 (0.10, 0.30)	0.20 (0.10, 0.20)	0.004*
Alb, median (IQR), g/dL	3.9 (3.5, 4.3)	4.5 (4.1, 4.7)	0.010*
Initial chest radiography			
Normal, n (%)	10 (8.1)	22 (7.9)	0.967
Unilateral GGO infiltration, n (%)	11 (8.9)	122 (44)	< 0.01*
Unilateral consolidation, n (%)	4 (3.2)	2 (0.7)	0.076
Bilateral GGO infiltration, n (%)	96 (77.4)	131 (47.3)	< 0.01*
Bilateral consolidation, n (%)	3 (2.4)	0 (0)	0.029*

**P-value<0.05, IQR: interquartile range, WBC: White Blood Cell Count, Hct: Hematocrit, ALT: Alanine Transaminase, AST: Aspartate Transaminase, TB: Total Bilirubin, DB: Direct Bilirubin, Alb: albumin, GGO: Ground Glass Opacity.*

Table 4: Univariate and multivariate analysis of factors associated with severe COVID-19 pneumonia.

Studied factors	Crude OR (95%CI)	Adjusted OR (95%CI)	P-value*
Age > 60 years	2.40 (1.43-4.03)	1.29 (0.50-3.34)	0.61
BMI ≥30 kg/m^2	1.96 (1.12-3.45)	1.71 (0.69-4.28)	0.25
With any comorbidities	2.61 (1.69-4.04)	2.12 (0.89-5.05)	0.09
Diabetes mellitus	2.05 (1.24-3.39)	0.62 (0.26-1.47)	0.28
Hypertension	1.80 (1.09-2.98)	0.56 (0.23-1.35)	0.20
CKD stage ≥3	4.00 (2.11-7.60)	3.73 (1.30-10.70)	0.014*
DOI > 5 days	2.54 (1.64-3.92)	1.15 (0.61-2.16)	0.67
Dyspnea	5.89 (3.59-9.65)	2.05 (1.02-4.12)	0.044*
RR >24/min	8.32 (4.38-15.81)	2.98 (1.20-7.42)	0.019*
SpO_2 (room air) <96%	7.93 (4.93-12.75)	1.93 (1.01- 3.68)	0.047*
Absolute lymphocyte count	0.998 (0.998-0.999)	0.999 (0.998-1.00)	0.001*
N/L ratio	1.30 (1.20-1.40)	1.15 (1.03-1.27)	0.012*
CRP	1.02 (1.02-1.03)	1.02 (1.01-1.03)	0.004*
CRP/L ratio	1.02 (1.02-1.03)	1.007 (1.001-1.014)	0.007*
AST	1.01 (1.00-1.02)	1.00 (0.98-1.01)	0.688
ALT	1.01 (1.00-1.01)	1.00 (0.99-1.02)	0.284
TB	1.97 (1.11-3.52)	0.26 (0.04-1.58)	0.145
DB	9.63 (2.38-39.07)	15.66 (0.55-448.17)	0.108
Alb	0.14 (0.08-0.23)	0.57 (0.32-1.01)	0.055
Bilateral GGO	3.82 (2.36-6.19)	1.36 (0.67-2.70)	0.375

**P-value of 95%CI of adjusted OR, BMI: Body Mass Index, CKD: Chronic Kidney Disease, DOI: Date of Onset, RR: Respiratory Rate, SpO_2: Pulse Oxygen Saturation, N/L: Neutrophil/Lymphocyte, CRP: C-Reactive Protein, CRP/L: C-Reactive Protein/Lymphocyte, AST: Aspartate Transaminase, TB: Total Bilirubin, DB: Direct Bilirubin, Alb: albumin, GGO: Ground Glass Opacity.*

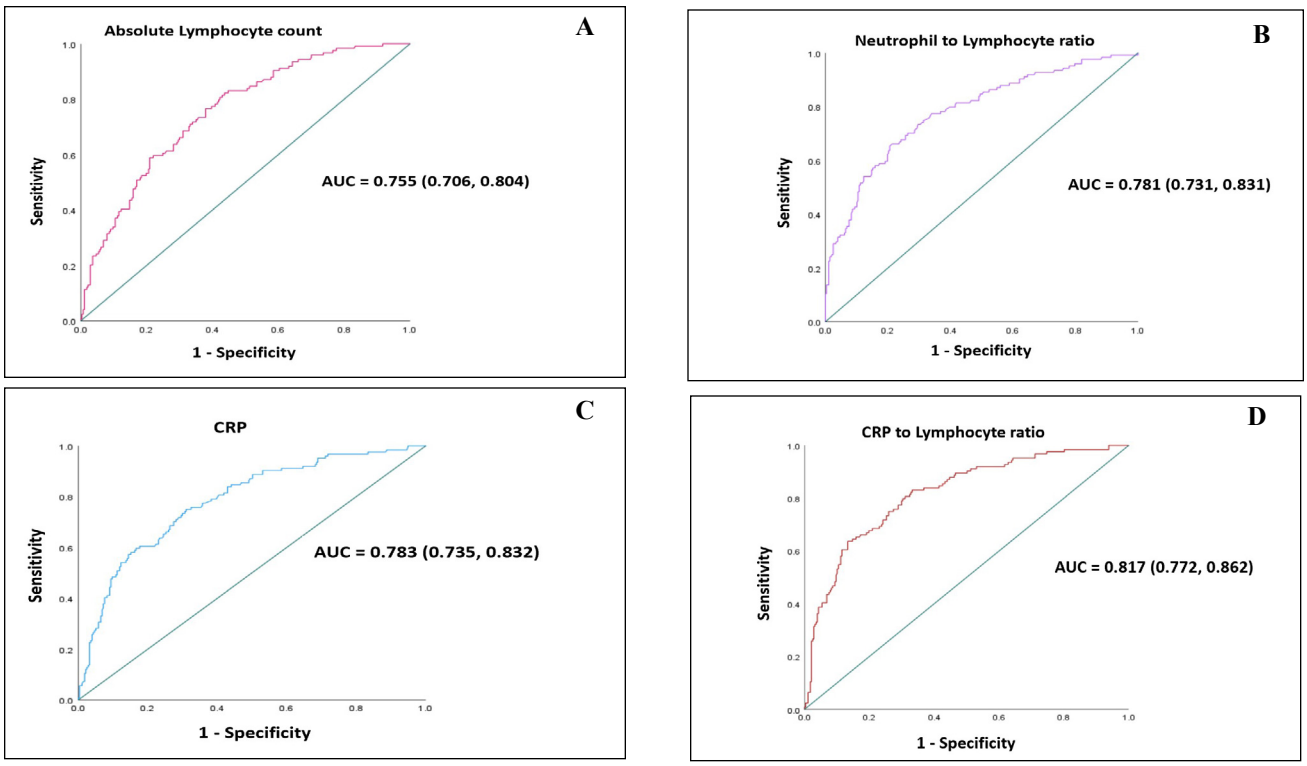

Figure 1: ROC Curve of absolute lymphocyte count, N/L, CRP, CRP/L for diagnosis of severe COVID-19 pneumonia.

min (Adjusted OR: 2.98; 95% CI: 1.20-7.42), initial SpO_2 < 96% (Adjusted OR: 1.93; 95% CI: 1.01-3.68), absolute lymphocyte count (ALC) (Adjusted OR: 0.999; 95% CI: 0.998-1.00), N/L ratio (Adjusted OR: 1.15; 95% CI: 1.03-1.27), CRP (Adjusted OR: 1.02; 95% CI: 1.01-1.03), and CRP/L ratio (Adjusted OR: 1.007; 95% CI: 1.001-1.014) (Table 4).

The diagnostic accuracy of the initial laboratory tests related with severe COVID-19 pneumonia was assessed by an area under the receiver operating characteristic curve (AUC) as shown in Figure 1. The AUC of ALC was 0.755 (95% CI, 0.706-0.804), N/L ratio 0.781 (95% CI, 0.731-0.831), CRP 0.783 (95% CI, 0.735-0.832), and CRP/L ratio 0.817 (95% CI, 0.772-0.862).

The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were determined from the selected probability cut-off (Table 5). The optimal cutoff value of absolute lymphocyte count related with severe COVID-19 pneumonia was <1.2 x 10^9 cells/L, sensitivity 63.7% (95% CI, 54.6-72.2), specificity 71.5% (95% CI, 65.8-76.7), PPV 50.0% (95% CI, 44.3-55.7), and NPV 81.5% (95% CI 77.5-84.9). N/L ratio was >2.4, sensitivity 81.4% (95% CI, 73.5-87.9), specificity 58.1% (95% CI, 52.1-64.0), PPV 46.5% (95% CI, 42.5-50.6), and NPV 87.5% (95% CI 82.7-91.1). CRP was >12 mg/L, sensitivity 79.0% (95% CI, 70.8-85.8), specificity 60.3% (95% CI, 54.3-66.1), PPV 47.1% (95% CI, 42.3-51.4), and NPV 86.5% (95% CI, 81.8-90.2). CRP/L ratio was >10, sensitivity 83.1% (95% CI, 75.3-89.2), specificity 64.3% (95% CI, 46.6-55.4), PPV 51.0% (95% CI, 46.6-55.4) and NPV 89.4% (95% CI, 85.0-92.7).

Patients with severe COVID-19 pneumonia had the following complication: septic shock (12.1%), pneumothorax (2.4%), they needed a mechanical ventilator (16.1%) and they died (9.7%). Those with non-severe COVID-19 pneumonia that had none of these complications and they survived.

Discussion

Many reportedly elder patients especially those aged above 60 years were more likely to have severe COVID-19 infections and

Table 5: AUC and cutoff value of initial laboratory results related with COVID-19 pneumonia.

Laboratory results	Area under the curve (AUC) (95%CI)	Cutoff value	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Absolute lymphocyte count	0.755 (0.706, 0.804)	< 1.20 x 10^9 /L	63.7 (54.6, 72.2)	71.5 (65.8, 76.7)	50.0 (44.3, 55.7)	81.5 (77.5, 84.9)
Neutrophil/Lymphocyte (N/L) ratio	0.781 (0.731, 0.831)	> 2.4	81.4 (73.5, 87.9)	58.1 (52.1, 64.0)	46.5 (42.5, 50.6)	87.5 (82.7, 91.1)
C-reactive protein (CRP)	0.783 (0.735, 0.832)	> 12 mg/L	79.0 (70.8, 85.8)	60.3 (54.3, 66.1)	47.1 (42.3, 51.4)	86.5 (81.8, 90.2)
CRP/Lymphocyte ratio	0.817 (0.772, 0.862)	> 10	83.1 (75.3, 89.2)	64.3 (46.6, 55.4)	51.0 (46.6, 55.4)	89.4 (85.0, 92.7)

rapidly progressive clinical deterioration [13,14]. Obese patients, especially with a BMI of more than 30 kg/m^2 were recognized to develop serious complications from COVID-19 infection [15,16].

In the study, severe COVID-19 pneumonia was more likely to occur in elderly and obese patients. In multivariable analyses, an age above 60 years and obesity of a BMI more than 30 kg/m^2 were not found to be independent predictors for severe pneumonia. These results that differ in this study were probably due to low number of patients aged above 60 years (n=74, 18.4%) and obesity with a BMI of more than 30 kg/m^2 (n=59, 14.7%) in the study period.

Multiple comorbidities occurred in elderly patients more than in the younger age group that may relate to severe infections. In this study, as reported elsewhere [13], it was found that pre-existing chronic kidney disease was the only statistically significant entity related to severe COVID-19 pneumonia. Some studies regarding obesity and COVID-19 infections reported that patients with higher BMI were more likely to be younger patients and have fewer comorbidities, these were the reasons to explain COVID-19 pneumonia in obesity not increase hospital mortality [17,18].

A clinical presentation with dyspnea, an increased respiratory rate, and pulse oxygen less than 96% with ambient air were the independent predictors for severe pneumonia in this present study. Clinical presented of dyspnea had limited accuracy for detecting hypoxemia in COVID-19 pneumonia; the sensitivity of dyspnea was 50% when a cut-off $\leq$ 92% was used to define hypoxemia [19]. The difference of COVID-19 pneumonia from other infectious pneumonia was that patients usually had silent hypoxemia due to endothelial capillary injury before chest radiography showed abnormal infiltrates [20]. In this present study, 8% of COVID-19 pneumonia patients had a normal initial chest radiograph, but progressed later after admission. Then patients may have had no clinical dyspnea even though having oxygen desaturation. It is still possible, however, to perform this early detection of silent hypoxemia in COVID-19 pneumonia by using pulse oximetry monitoring; oxygen saturation in healthy individuals ranges from 95-100%, it's mean that if SpO_2 < 96% patients clinically have silent hypoxemia [21]. In this present study, severe COVID-19 pneumonia was more likely to have bilateral ground glass opacity on chest radiography than non-severe COVID-19 pneumonia. In multivariable analysis, however, bilateral ground glass opacity on chest radiography was not found to be an independent predictor for severe pneumonia.

The ROC-analysis of initial blood tests in this study showed that the CRP/L ratio had the highest accuracy related to severe COVID-19 pneumonia, followed by CRP, N/L ratio and absolute lymphocyte count (ALC). All of these biomarkers at admission were useful to triage severe COVID-19 pneumonia patients with close monitoring and prompt appropriate treatment [22].

A retrospective and observational study found that a C-reactive protein-to-lymphocyte (CRP/L) ratio at day 1 was independently associated with higher probability for ICU admission (both direct admission and transfer to ICU) and the need of an invasive mechanical ventilator (IMV) during the course of hospitalization admission [23]. As described elsewhere [24], CRP/L (AUC = 0.787, 95% CI 0.698-0.860) and CRP (AUC = 0.781, 95% CI

0.693-0.856) had a higher accuracy than lymphocyte (AUC = 0.643, 95% CI 0.545-0.733) to assess severe COVID-19. No one has reported so far the cut off value of CRP/L ratio that related to severe COVID-19 pneumonia. This study was the first study that determined the CRP/L with a cut off value of 10 that exhibited a sensitivity of 83.1% and specificity of 64.3%.

Many studies reported that a CRP on admission was a predictor for severe COVID-19 infection [13,25,26]. The elevated CRP level might be linked to the over production of inflammatory cytokines and lung damage in severe COVID-19 pneumonia. Moreover, the serum CRP levels increased during disease progression [26]. A retrospective study found that the CRP level at admission was independently associated with COVID-19 severity (critically ill patients), with the cut off value of 10 mg/L; CRP exhibited a sensitivity of 86.36% and specificity of 70.3% [27]. In the present study, CRP at admission at the cut off value of 12 mg/L was related to severe COVID-19 pneumonia with a sensitivity of 79% and specificity of 60.3%.

The N/L ratio was another biomarker to determine COVID-19 pneumonia severity [28]. An increased N/L was the early signal for severe COVID-19 [28]. A meta-analysis of thirty studies published between January 2020 and July 2021 found that the accuracy of N/L ratio to determine the severity of COVID-19 was high with an AUC 0.87 (95% CI, 0.84-0.90) [29]. The cut off value of N/L ratio, however varied from 1.0 to 13.39 [29]. In this study, the N/L ratio at admission at the cut off value of 2.4 mg/L was related to severe COVID-19 pneumonia, exhibited a sensitivity of 81.4% and specificity of 58.1%. A previous study showed that the N/L ratio was strongly correlated with the CRP level and the N/L ratio might be used to differentiate between severe on non-severe COVID-19 infection [30-32].

The lymphocyte count might be related to severe COVID-19 infection more than total white blood cell count (WBC) [33]. Lymphopenia usually occurred in a cytokine storm syndrome (CSS) in COVID-19 infection and reflected disease progression [33]. A meta-analysis of twenty-four studies published before March, 2020 showed that lymphopenia on admission was associated with severe COVID-19 infection and poor outcomes with varying cut off values in the studies of 1.0 x 10^9 /L, 1.1 x 10^9 /L, 1.2 x 10^9 /L and 1.5 x 10^9 /L [34]. A study showed an absolute lymphocyte count had a lower accuracy than the N/L ratio; the AUC for an absolute lymphocyte count was 0.780 and an AUC for the N/L ratio was 0.856 for COVID-19 severity [35]. This finding was same as this current study showing that the absolute lymphocyte count on admission had lower accuracy than the N/L ratio, CRP, and the CRP/L ratio was associated with severe COVID-19 pneumonia. The cut off value of absolute lymphocyte count in this study was less than 1.2 x 10^9 /L that was related to severe COVID-19 pneumonia; exhibiting a sensitivity of 63.7% and specificity of 71.5%.

This current study has some limitations: first this was a single center, cross-sectional study. Second, it may have selection bias due to a referral center of this hospital. Then it might be difficult to generalizability of these findings. The strengthening of this study was the first study to determine the cut off value of initial laboratory results on admission related to severe COVID-19 pneumonia. The early recognition of severe COVID-19 pneumonia by easily obtainable markers upon hospital admission such as absolute lymphocyte count (ALC), CRP, N/L ratio, and CRP/L ratio can be implemented at all levels of a healthcare institution. These could help the physician to identify and prioritize patients with a higher probability for intensive care monitoring and prompt initial appropriate treatment. Future studies are needed to determine applicability of these findings to differentiate severe from non-severe COVID-19 pneumonia.

In conclusion, factors significantly associated with severe COVID-19 pneumonia in this present study were: pre-existing chronic kidney disease ≥ stage 3, presented with clinical dyspnea, high respiratory rate (> 24/min) and low SpO_2 at ambient air (< 96%). In patients who did not have clinical features as mentioned above in this study were found on admission to have initial laboratory findings including absolute lymphocyte count (<1.2 x 10^9 cells/L), CRP (>12 mg/L), N/L ratio (>2.4) and CRP/L ratio (>10) had high that possibility were associated with severe COVID-19 pneumonia. Of these results, CRP/L ratio had the highest accuracy related to severe COVID-19 pneumonia. All are simplified and useful in primary care to triage severe COVID-19 pneumonia patients to early initiate aggressive treatment to decrease morbidity and mortality.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Author's Contributions

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