PREDICTORS OF PNEUMONIA AND SEVERE PNEUMONIA IN PATIENTS WITH CORONAVIRUS DISEASE 2019 AT A TERTIARY-CARE HOSPITAL, THAILAND

Sirawat Srichatrapimuk[1], Kulapong Jayanama[1], Suppachok Kirdlarp[2], Kanin Thammavaranucupt[1], Supawadee Suppadungsuk[1], Thananya Wongsinin[1], Nithita Nanthatanti[1], Watchara Lohawijarn[2], Thanyakamol Phongnarudech[2], Katathep Wiputhanuphongs[2], Sithakom Phusanti[1], Dhanesh Pitidhammabhorn[1] and Somnuek Sungkanuparph[1]

[1]Ramathibodi Medical School, [2]Ramadhibodi Chakri Naruebodindra Hospital, Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand

Abstract. Clinical spectrum of coronavirus disease 2019 (COVID-19) encompasses asymptomatic to severe pneumonia. Clinical characteristics of pneumonia and severe pneumonia in patients with confirmed COVID-19 infection admitted to a university hospital in Thailand were recorded and factors predicting pneumonia and severe pneumonia were determined using a Cox-regression analysis. Of 144 patients, mean ± SD age was 39 ±13 years, with 42% males. Following admission, 51% of patients developed pneumonia within median period of 7 days from onset of illness, among whom 27% progressed to severe pneumonia. Multivariate analysis showed age ≥40 years, body mass index ≥25 kg/m^2, absolute lymphocyte count <1500 cells/mm^3, and serum lactate dehydrogenase (LDH) level ≥200 U/l at admission were significant factors associated with pneumonia, while severe pneumonia was associated with male gender, room-air oxygen saturation <97% and serum LDH level ≥300 U/l at admission. These findings should be of assistance in predicting COVID-19 patients at risk of developing pneumonia and those progressing to the severe form, allowing preparation for close monitoring and prompt management of such patients.

Keywords: coronavirus, COVID-19, pneumonia, predicting factor.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 (Valencia *et al*, 2020). As of 12 May 2020, more than 200 countries have reported COVID-19 and more than 4.2 million infections and 280,000 deaths have been reported globally (Center for Systems Science and Engineering at Johns Hopkins University, 2020). A vast majority of COVID-19 patients have good

Correspondence: Prof Somnuek Sungkanuparph, Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 111 Moo 14, Bang Phli, Samut Prakan 10540, Thailand.
Tel: +66 (0) 2839 6000; Fax: +66 (0) 2839 5147
Email: somnuek.sun@mahidol.ac.th

prognosis with mild clinical symptoms of respiratory tract infection, such as cough, sore throat, myalgia, headache and low-graded fever (Guan *et al*, 2020). Alterations in smell and/or taste have also been reported in mildly symptomatic COVID-19 patients and often are the first apparent symptoms (Spinato *et al*, 2020). However, there are a substantial number of patients who develop pneumonia, some of whom have progressed to severe pneumonia and become critically ill and even die (Goyal *et al*, 2020; Guan *et al*, 2020; Spinato *et al*, 2020; Wang *et al*, 2020). The majority of these critically ill patients do not develop severe clinical manifestations in the early stage of the disease; however, their conditions suddenly deteriorate in the later stage of the disease, presenting as acute respiratory distress syndrome (ARDS) and rapid onset of multi-organ failure. The majority of these severely ill patients need intensive care and mechanical ventilation, some of whom needs renal replacement therapy (Goyal *et al*, 2020; Zhou *et al*, 2020). Up to now, there is no specific treatment regimen for COVID-19 patients (Berlin *et al*, 2020; Gandhi *et al*, 2020), but key to COVID-19 care is early detection of the severe cases and prompt proper respiratory support.

Studies in predicting severity of COVID-19 are increasingly available; however, these studies do not focus on factors at admission that predict subsequent pneumonia and progression to severe pneumonia (Dong *et al*, 2020; Ji *et al*, 2020; Mo *et al*, 2020). The ability to better predict patients who will develop pneumonia and severe pneumonia once they are admitted is crucial for clinical care and preparedness for medical personnel, medical supplies, protective equipment, medication, and other resources. Here, clinical characteristics of COVID-19 patients at admission were determined and predictive factors of pneumonia severe pneumonia were evaluated.

MATERIALS AND METHODS

Study site, design and patients

A single-center prospective cohort study was conducted among patients with confirmed COVID-19, >15 years of age and admitted to Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand, between 12 March and 22 April 2020. All patients with confirmed COVID-19 were admitted to the Institute even if presenting with mild symptoms or asymptomatic. Diagnosis of COVID-19 was established by detecting SARS-CoV-2 RNA in nasopharyngeal and throat swab specimens using quantitative RT-PCR amplification of SARS-CoV-2 ORF1AB and N gene fragments (Sansure Biotech Inc, Changsha, PR China).

The study protocol was approved by the Institutional Review Board, Faculty of Medicine Ramathibodi Hospital, Mahidol University (approval no. MURA2020/673).

Data collection

Baseline clinical characteristics of patients at admission including demographic data, medical history (symptoms and risk exposures), physical examinations, and results of laboratory investigations were collected. Risk exposures to SARS-CoV-2 were identified by contact tracing (WHO, 2020b). Physical examination was performed by trained physicians on the day of admission, and blood tests and chest radiography (interpreted by two independent radiologists) were carried out. Rates of pneumonia (primary outcome), defined

as clinical symptoms of respiratory tract infection with abnormal lung imaging compatible with pneumonia, and of severe pneumonia (secondary outcome), defined as having one of the following criteria: respiratory rate >30 breath/minute, severe respiratory distress or SpO_2 ≤93% at room air (WHO, 2020a) were noted. Length of time to pneumonia and severe pneumonia were measured from date of first onset of a symptom to that of pneumonia and severe pneumonia event respectively.

Data analysis

Continuous variables are presented as mean ± SD and categorical variables as frequency (%). Student's *t*-test was used to compare means between the two groups and chi-square test to analyze categorical variables. Predictive factors for pneumonia and severe pneumonia were determined using a Cox regression model and presented as hazard ratio (HR) and 95% confidence interval (CI). Variables identified by univariate analysis with *p*-value <0.050 were subsequently subjected to multivariate analysis. Proportions of patients without pneumonia were illustrated by a Kaplan-Meier curve stratified by groups of significant predictive factors, and significance of differences between the two groups were determined using a Log-rank test. Statistical significance is accepted at two-sided *p*-value <0.050. Statistical analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 24.0 (IBM Corp, Armonk, NY).

RESULTS

Patients (*n* = 1,155) during the study period presenting symptoms of respiratory tract infection or history of exposure to patients with COVID-19 were tested for SARS-CoV-2 RNA from nasopharyngeal and throat swab specimens, and patients (*n* = 144, 12.5%) diagnosed with COVID-19 were recruited in the study, mean ± SD age of 39 ± 13 years and 42% males (Table 1). Thirty-one percent of these patients had a body mass index (BMI) of ≥25 kg/m^2, 9% with diabetes mellitus and 10% with hypertension. The three most common presenting symptoms were cough (46%), productive sputum (32%) and shortness of breath (29%). Among patients with available information, 22 (41%) reported anosmia. All COVID-19 patients reported being present in places with risk of exposure to SARS-CoV-2 (Table 1). Factors at admission significantly associated with subsequent development of pneumonia were higher age, higher body mass index, higher body temperature, lower blood oxygen saturation, lower absolute lymphocyte counts, higher lactate dehydrogenase (LDH) and alanine aminotransferase levels, (marginally) lower albumin concentration, and (marginally) shorter days of illness prior to admission (Table 1). Univariate analysis confirmed these characteristics as risk factors for pneumonia except the latter and included hypertension to the list; however, multivariate analysis showed only increased age, higher BMI, lower absolute lymphocyte count and higher serum LDH level as independent risk factors (Table 2).

During hospital stay, 74 (51%) patients succumbed to pneumonia, with a median time from onset of illness to development of pneumonia of 7 days (Fig 1A). Kaplan-Meier plots, categorized according to the four independent risk factors, indicated significantly higher proportion of patients ≥40 years of age, BMI ≥25 kg/m^2, absolute lymphocyte count <1,500 cells/mm^3, or serum LDH level ≥200 U/l with

Table 1
Demographic profile, clinical characteristics and pneumonia status of COVID-19 patients at Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (12 March to 22 April 2020).

Characteristic	Total Number (%) (*n* =144)	With pneumonia Number (%) (*n* = 74)	Without pneumonia Number (%) (*n* = 70)	*p*-value*
Age (years), mean ± SD	39 ± 13	43 ± 13	33 ± 11	<0.001
Being male	61 (42)	36 (49)	25 (36)	0.116
Underlying condition				
Diabetes	13 (9)	10 (14)	3 (4)	0.053
Hypertension	14 (10)	12 (16)	2 (3)	0.007
Active smoker	30 (20)	14 (19)	16 (23)	0.081
Active alcohol drinker	81 (56)	40 (55)	41 (58)	0.856
Exposure site				0.455
Night club	44 (31)	24 (32)	20 (29)	
Boxing stadium	29 (20)	16 (22)	13 (19)	
Pub	20 (14)	7 (9)	13 (19)	
Taxi driver	7 (5)	5 (7)	2 (3)	
Others	44 (31)	22 (30)	22 (31)	
Days of illness prior to admission, mean ± SD	7 ± 4	6 ± 3	8 ± 5	0.050
Symptom				
Cough	66 (46)	36 (49)	30 (43)	0.486
Productive sputum	46 (32)	23 (31)	23 (33)	0.819
Shortness of breath	42 (29)	22 (30)	20 (29)	0.879
Myalgia	41 (28)	20 (27)	21 (30)	0.693
Sore throat	38 (26)	17 (23)	21 (30)	0.339
Headache	34 (24)	21 (28)	13 (19)	0.166
Running nose	33 (23)	13 (18)	20 (28.6)	0.116
Diarrhea	25 (17)	17 (23)	8 (11)	0.068
Fever	18 (12)	16 (22)	2 (3)	0.001
Anosmia (*n* = 54)	22 (41)	17 (47)	5 (28)	0.170
Body temperature (°C), mean ± SD	36.9 ± 0.7	37.0 ± 0.8	36.7 ± 0.5	0.001
Systolic BP (mmHg), mean ± SD	123 ± 15	124 ± 15	121 ± 14	0.173
Diastolic BP (mmHg), mean ± SD	82 ± 10	81 ± 10	82 ± 10	0.869
Pulse rate (/minute), mean ± SD	86 ± 13	88 ± 14	85 ± 13	0.128
Respiratory rate (/minute), mean ± SD	20 ± 1	20 ± 2	20 ± 3	0.081

Table 1 (Continued)

Characteristic	Total Number (%) (*n* =144)	With pneumonia Number (%) (*n* = 74)	Without pneumonia Number (%) (*n* = 70)	*p*-value*
Oxygen saturation RA (%), mean ± SD	97 ± 2	96 ± 2	98 ± 1	<0.001
BMI (kg/m^2), mean ± SD	23 ± 5	25 ± 6	21 ± 3	<0.001
Blood test (mean ± SD)				
Hemoglobin (g/dl)	13 ± 2	14 ± 1	13 ± 2	0.635
White blood cells (/mm^3)	5,804 ± 1,735	5,913 ± 1,796	5,689 ± 1,673	0.437
Absolute neutrophil counts (/mm^3)	3,386 ± 1,409	3,577 ± 1,357	3,183 ± 1,444	0.093
Absolute lymphocyte counts (/mm^3)	1,916 ± 768	1,780 ± 811	2,060 ± 697	0.028
Platelet (/mm^3)	251,007 ± 72,394	243,351 ± 75,334	259,100 ± 68,761	0.193
Lactate dehydrogenase (U/l)	201 ± 85	238 ± 98	161 ± 38	<0.001
D-Dimer (ng/ml)	467 ± 485	541 ± 592	361 ± 229	0.091
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	0.042
Aspartate aminotransferase (U/l)	33 ± 21	40 ± 25	25 ± 10	<0.001
Alanine aminotransferase (U/l)	32 ± 24	37 ± 27	26 ± 19	0.008
Alkaline phosphatase (U/l)	68 ± 41	72 ± 49	63 ± 31	0.180
Total bilirubin (mg/dl)	0.4 ± 0.3	0.5 ± 0.3	0.4 ± 0.2	0.346
Direct bilirubin (mg/dl)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.132
Total protein (g/l)	78 ± 6	78 ± 6	78 ± 6	0.662
Albumin (g/l)	42 ± 4	41 ± 4	43 ± 3	0.011

*Significant at <0.050; BMI: body mass index; BP: blood pressure; RA: room air.

chance to have pneumonia (Figs 1B, C, D, and E). Twenty patients (27%) with pneumonia went on to the severe form. Thirteen characteristics were identified by univariate analysis as risk factors for progression to severe pneumonia, but multivariate analysis indicated only three as independent risk factors, namely, being male, room air oxygen saturation <97% and serum LDH level ≥300 U/l (Table 3).

All SARS-CoV-2-positive patients were admitted in three cohort wards and cared according to the national guidelines for diagnosis and treatment of COVID-19 in Thailand (Department of Disease Control, 2020). Patients with pneumonia were treated with hydroxychloroquine and lopinavir/ritonavir or darunavir/ritonavir, and those with severe pneumonia favipiravir was also considered. Fourteen patients (10%) were admitted to intensive care unit and eight (6%) required intubation and mechanical ventilator support. As of

Table 2
Univariate and multivariate analyses of predictive factors for pneumonia in 144 COVID-19 patients at Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (12 March to 22 April 2020).

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value*	HR (95% CI)	*p*-value*
Age (years)	1.03 (1.02-1.05)	<0.001	1.02 (1.01-1.04)	0.043
Hypertension	2.40 (1.29-4.47)	0.006	-	-
BMI (kg/m^2)	1.09 (1.05-1.13)	<0.001	1.08 (1.03-1.13)	0.003
Body temperature (^{o}C)$^\#$	1.60 (1.19-2.13)	0.002	-	-
Oxygen saturation at room air (%)$^\#$	0.86 (0.78-0.95)	0.002	-	-
Absolute lymphocyte count (per 100/mm^3)$^\#$	0.84 (0.76-0.92)	<0.001	0.92 (0.81-0.99)	0.049
Lactate dehydrogenase (U/l)$^\#$	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.02)	0.047
Alanine aminotransferase (U/l)$^\#$	1.01 (1.00-1.02)	0.042	-	-
Albumin (g/l)$^\#$	0.93 (0.88-0.99)	0.017	-	-

*Significant at <0.050; $^\#$At admission; BMI: body mass index; 95% CI: 95% confidence interval; HR: hazard ratio.

Table 3
Uni- and multivariate analyses of predictive factors for severe pneumonia in 74 COVID-19 patients at Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (12 March to 22 April 2020).

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value*	HR (95% CI)	*p*-value*
Age ≥40 years	4.67 (1.37-15.95)	0.014	-	-
Male	2.86 (1.09-7.14)	0.033	15.27 (2.85-81.75)	0.001
Diabetes mellitus	3.54 (1.36-9.24)	0.010	-	-
Hypertension	4.62 (1.86-11.45)	0.001	-	-
Contact at boxing stadium	3.50 (1.45-8.47)	0.006	-	-
History of shortness of breath	4.88 (1.98-11.99)	0.001	-	-
Body temperature ≥37.8 ^{o}C$^\#$	4.38 (1.82-10.57)	0.001	-	-
Respiratory rate ≥24/minute$^\#$	6.05 (2.13-17.85)	0.001	-	-
Oxygen saturation RA <97%$^\#$	6.39 (2.29-17.85)	<0.001	7.22 (1.79-29.08)	0.005
Absolute neutrophil count ≥3,500/mm$^{3\#}$	1.66 (1.05-2.63)	0.029	-	-
Absolute lymphocyte count <1,500/mm$^{3\#}$	3.81 (1.46 -9.95)	0.006	-	-
Lactate dehydrogenase ≥300 U/l$^\#$	10.12 (3.71-27.64)	<0.001	12.47 (3.10-50.16)	<0.001
Serum albumin <36 g/l$^\#$	5.99 (2.27-15.80)	<0.001	-	-

*Significant at <0.050; $^\#$At admission; BMI: body mass index; 95% CI: 95% confidence interval; HR: hazard ratio; RA: room air.

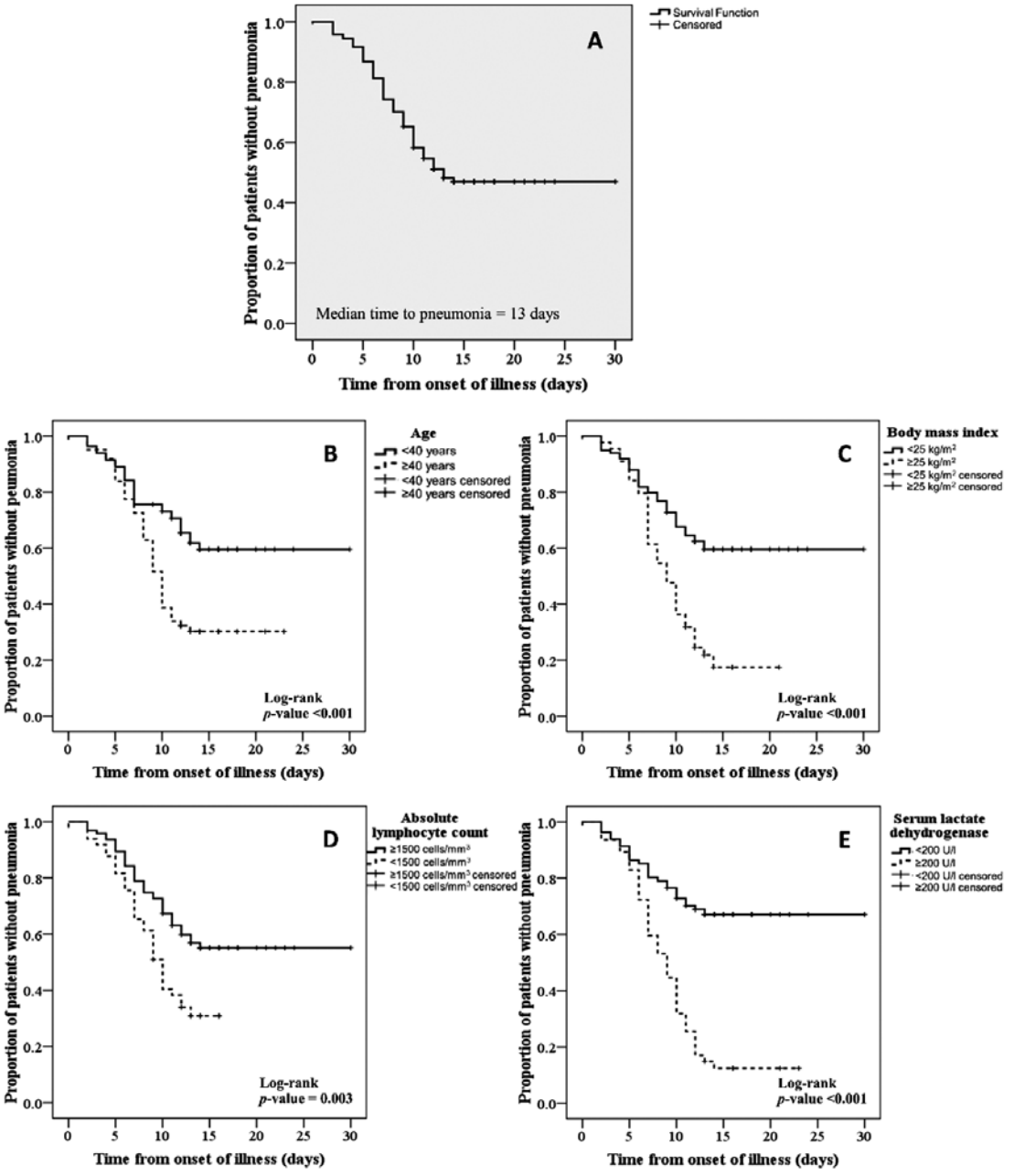

Fig 1-Kaplan-Meier plot of proportion without pneumonia of (A) all patients, (B) patients <40 or ≥40 years of age, (C) patients with body mass index <25 or ≥25 kg/m^2, (D) patients with absolute lymphocyte count <1,500 or ≥1,500 cells/mm^3, and (E) with serum lactate dehydrogenase <200 or ≥200 U/l, Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (12 March to 22 April 2020).
Censored data are shown as crosses.

12 May 2020, 142 patients had improved clinical conditions and were subsequently discharged, while two died due to severe COVID-19 and multiorgan failure.

DISCUSSION

The present study included all patients diagnosed with confirmed COVID-19 admitted to the study institute during the period of interest regardless of severity of symptoms and should be a more representative cohort of the natural course of COVID-19. Independent predictors of pneumonia among the study COVID-19 patients were higher age, higher BMI, lower absolute lymphocyte count and higher serum LDH, and those for progression to severe pneumonia were male gender, room air oxygen saturation <97% and serum LDH level ≥300 U/l. Patients developed pneumonia within 14 days from onset of illness but none after this period, suggesting that future COVID-19 care guidelines should include close monitoring for signs/symptoms of this complication during this critical two-week window.

Previous studies have shown age as an important independent predictor of disease severity as well as mortality in COVID-19 patients, owing to such patients having weaker immune response and more comorbid conditions (Du *et al*, 2020; Wang *et al*, 2020; Zhou *et al*, 2020). Comorbidities were not found to be a significant predictor of pneumonia, possibly due to the low proportion of patients having comorbidities in the study cohort. Male COVID-19 patients have been reported having higher mortality (Grasselli *et al*, 2020).

This is the first observation of BMI as an independent predictor of pneumonia in COVID-19 patients. Obesity is an important predictive factor of poor outcome in any respiratory disease (Murugan and Sharma, 2008). High BMI alters airway resistance, pattern of breathing, respiratory drive, gas exchange, pulmonary blood volume, and ventilation-perfusion mismatch. Furthermore, overweight also decreases lung volume and compromises muscle strength due to an increase in elastic load posed by excess weight on thorax and abdomen (Murugan and Sharma, 2008; Stefan *et al*, 2020). Obesity also leads to dysregulated immune response, impaired chemotaxis, altered macrophage differentiation, and eventual susceptibility for infection, including pneumonia (Huttunen and Syrjänen, 2013).

A low PaO_2/FiO_2 ratio (indicator of hypoxia severity) is associated with severity and mortality of COVID-19 pneumonia (Yang *et al*, 2020). To the best of our knowledge, the present study is the first to identify oxygen saturation at room air below 97% on hospital admission as an independent predictor of severe pneumonia in COVID-19 patients, suggesting use of pulse oximetry as an early indicator of progression to severe pneumonia. Furthermore, this screening test can minimize exposure of healthcare workers to SARS-CoV-2.

Low absolute lymphocyte counts at admission are associated with severity and mortality of pneumonia among COVID-19 patients (Wang *et al*, 2020; Zhou *et al*, 2020). Lymphocytes, especially B-cells and T-cells, are members of the adaptive immune response, which plays a crucial role in host defense mechanism and inflammatory response during viral infection (Chaplin, 2010). Although the mechanism of lower absolute lymphocyte count in COVID-19 remains unclear, it is of interest to note that lymphocytopenia has been reported in SARS and MERS

(Middle East respiratory syndrome) (Li *et al*, 2004; Chu *et al*, 2016; Chen *et al*, 2020; Wang *et al*, 2020).

Du *et al* (2020), Grasselli *et al* (2020), Wang *et al* (2020), Wu *et al* (2020), Yang *et al* (2020), and Zhou *et al* (2020) reported that serum LDH level is associated with pneumonia and severe pneumonia in COVID-19 patients. LDH catalyzes conversion of lactate to pyruvate in the glycolysis pathway (Drent *et al*, 1996). LDH level can be significantly increased due to leakage of the enzyme from damaged cells caused by either inflammation or cell death. The observation that high LDH level at hospital admission is an indicator of pneumonia and progression to severe pneumonia might imply that in such patients inflammation processes have already occurred prior to detection of SARS-CoV-2. However, LDH is not only present in lung tissues but can also be found in other organs. Thus, the inflammation process might not specifically exist in the lungs but also occur in other tissues.

The case fatality rate in our study is lower than in previous reports (11% to 22%) (Chen *et al*, 2020; Huang *et al*, 2020, Wu *et al*, 2020), probably as a result of differences in the proportion of disease severity in the study cohort. Prompt diagnosis and treatment might also have contributed to the reduced fatality rate.

The present study has two major limitations. Firstly, the survey was conducted at a single-center hospital with a moderately small sample size. Secondly, the history of anosmia was only available in 25% of the patients as recognition of this symptom was reported after the study had commenced.

In conclusion, the study allows assessment of predictive factors of pneumonia and progression to severe pneumonia in patients with COVID-19, and is the first study in Thailand to uncover perdictors of COVID-19 pneumonia and severe pneumonia from data collected at time of hospital admission. The most important strategy in COVID-19 care plan is to predict the disease severity at the earliest opportunity to allow assessment for hospitalization and appropriate treatment at the proper time, particular in situations of constrained resources.

ACKNOWLEDGEMENTS

The authors thank all study patients and attending staff, fellows, residents and nurses of Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University for their kind assistance and cooperation.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020; 10.1056/NEJMcp2009575. doi:10.1056/NEJMcp2009575N. [published online ahead of print]

Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 dashboard, 2020 [cited 2020 May 12]. Available from: URL: https://coronavirus.jhu.edu/map.html

Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol* 2010; 125 (2 Suppl 2): S3-23.

Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507-13.

Chu H, Zhou J, Wong BH, *et al*. Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. *J Infect Dis* 2016; 213: 904-14.

Department of Disease Control. Guidelines for clinical practice, diagnosis, treatment and prevention of healthcare-associated infection in response to patients with COVID-19 infection, 2020 [cited 2020 May 12]. Available from: URL: https://ddc.moph.go.th/viralpneumonia/eng/file/guidelines/g_CPG.pdf

Dong Y, Zhou H, Li M, *et al*. A novel simple scoring model for predicting severity of patients with SARS-CoV-2 infection. *Transbound Emerg Dis* 2020; 10.1111/tbed.13651. doi: 10.1111/tbed.13651. [published online ahead of print]

Drent M, Cobben NA, Henderson RF, Wouters EF, van Dieijen-Visser M. Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. *Eur Respir J* 1996; 9: 1736-42.

Du RH, Liang LR, Yang CQ, *et al*. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: A prospective cohort study. *Eur Respir J* 2020; 55: 2000524.

Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med* 2020; 10.1056/NEJMcp2009249. doi:10.1056/NEJMcp2009249. [published online ahead of print]

Goyal P, Choi JJ, Pinheiro LC, *et al*. Clinical characteristics of Covid-19 in New York City. *N Engl J Med* 2020; 382: 2372-4.

Grasselli G, Zangrillo A, Zanella A, *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; 323: 1574-81.

Guan WJ, Ni ZY, Hu Y, *et al*. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382: 1708-20.

Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.

Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. *Int J Obes* (Lond) 2013; 37: 333-40.

Ji D, Zhang D, Xu J, *et al*. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL score. *Clin Infect Dis* 2020; ciaa414. doi: 10.1093/cid/ciaa414. [published online ahead of print]

Li T, Qiu Z, Zhang L, *et al*. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. *J Infect Dis* 2004; 189: 648-51.

Mo P, Xing Y, Xiao Y, *et al*. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020; ciaa270. doi: 10.1093/cid/ciaa270. [published online ahead of print]

Murugan AT, Sharma G. Obesity and respiratory diseases. *Chron Respir Dis* 2008; 5: 233-42.

Spinato G, Fabbris C, Polesel J, *et al*. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 2020; 323: 2089-90.

Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. *Nat Rev Endocrinol* 2020; 16: 341-2.

Valencia DN. Brief review on COVID-19: The 2020 pandemic caused by SARS-CoV-2. *Cureus* 2020; 12: e7386.

Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061-9.

World Health Organization (WHO). Clinical management of COVID-19: interim guidance, 2020a [cited 2020 Apr 15]. Available from: URL: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

World Health Organization (WHO). Contact tracing in the context of COVID-19, 2020b [cited 2020 May 12]. Available from: URL: https://www.who.int/publications/i/item/contact-tracing-in-the-context-of-covid-19

Wu C, Chen X, Cai Y, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 13: e200994. doi: 10.1001/jamainternmed.2020.0994. [published online ahead of print]

Yang X, Yu Y, Xu J, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475-81.

Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-62.