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Latent profile analysis identified COVID-19 ARDS phenotypes in Thai patients: Research protocol and preliminary report

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ABSTRACT:

Background: Clinical heterogeneity was observed among COVID-19 patients with acute respiratory distress syndrome (CARDS). The heterogeneity of disease was contributed to different clinical progression, responses to treatment, and mortality.

Objective: We aim to study the phenotype and associated mortality of COVID-19 respiratory failure in Thai patients.

Methods: We conducted a single-center, retrospective observational study. The data were collected in CARDS who received an invasive mechanical ventilator in ICU. Patient-related data were collected at admission before the onset of respiratory failure. The main features include demographics data, SOFA score, laboratory, CXR severity score, treatment during hospitalization, and the following data at the onset of respiratory failure during invasive mechanical ventilator. We also collected patients' status at 28-day, in-hospital complications, and ventilator-free days at 28-day after intubation. The latent profile analysis was performed to identify distinct phenotypes. After identifying phenotypes, characteristics and clinical outcomes were compared between phenotypes. The primary outcome was the phenotype and associated mortality of COVID-19 respiratory. Secondary outcomes include characteristics of phenotype, ventilator-free days, response to treatment, and complications in each phenotype.

Discussion: This study aims to identify the phenotype of COVID-19 Respiratory Failure in Thai Patients The different phenotypes may be associated with varying responses to treatment and outcomes that the result of this study may be useful for determining treatment and predicted prognosis of COVID-19 Respiratory Failure In Thai Patients.

Ethics and dissemination: The study protocol was approved by the Institution Review Board of Ramathibodi Hospital, Mahidol University, Thailand (No. MURA2021/740). We plan to disseminate the results in peer-reviewed critical care medicine or pulmonology related journal, conferences nationally and internationally

Keywords: Phenotype, SARS-CoV-2, COVID-19, Acute respiratory distress syndrome

BACKGROUND

COVID-19 ARDS (CARDS) is an infectious disease caused by SARS-CoV-2 that mainly affects the respiratory tract system. The global pandemic of COVID-19 is associated with high morbidity and mortality [1]. Thailand was the first country to report a case outside China. Throughout most of 2020, Thailand was relatively successful in controlling the pandemic of disease but has been uncontrolled the new outbreak since April 2021, causing high morbidity and mortality due to respiratory failure. Among CARDS patients, we found the difference in the progression of the disease, response to treatment [2,3], in-hospital complications, and mortality. Previous studies found two phenotypes, namely hyper and hypo inflammation, in ARDS that might be useful for prognostic and predictive response in ARDS [4-6]. A recent prospective observational study in CARD found hypoinflamatory phenotype had lower mortality than the hyperinflammatory phenotype. But this study has limitations due to the low study population (39 patients) [7]. Another large study tries to identify clinical and biochemical phenotypes in acute respiratory distress syndrome secondary to COVID-19 but has the limitation due to cannot characterize the phenotype and missing data for class defining variables were imputed[8].

We hypothesized that different phenotypes are associated with varying responses to treatment and outcome. Therefore, we aim to study the phenotype and associated mortality of COVID-19 respiratory failure in Thai Patients.

KEY MESSAGES:

- To study the phenotype and associated mortality of SARS-CoV-2 Respiratory Failure in Thai Patients.

MATERIALS AND METHODS

Study design

We conducted a single-center, retrospective observational study. The data was collected in COVID-19 respiratory failure patients who received invasive mechanical ventilators in medical ICU Ramathibodi Chakri Naruebodindra Hospital from1 April 2021 to the present. The study protocol was approved by the Institution Review Board of Ramathibodi Hospital, Mahidol University, Thailand (No. MURA2021/740)

Objectives of the study

The primary objective is to identifies the phenotype of COVID-19. Respiratory Failure in Thai Patients. The different phenotypes may associated with varying responses to treatment and outcome that the result of this study may useful for determine treatment and predicted prognosis of COVID-19Respiratory Failure In Thai Patients.

Selection of participants

All Thai patients aged ≥ 18 years old who were positive for COVID-19 with hypoxic respiratory failure ($PaO_2 \leq 60$ mmHg on ≥ 60% Oxygen) that required an invasive mechanical ventilator were included in this study. Patients with pregnancy, under complete palliative care, or tracheostomy were excluded.

Study procedure

Patient-related data were collected at admission before the onset of respiratory failure. The main features include demographics, underlying disease, history of vaccination, day of illness, day of admission, SOFA score, laboratory investigation, CXR severity score[9], and treatment medications during hospitalization such as anti-viral, venous thromboembolic prophylaxis, systemic steroid, interleukin-6 inhibitor, a kinase inhibitor, and cytokine removal. In addition, following data at the onset of respiratory failure during invasive mechanical ventilator including laboratory investigation, change in inflammatory markers, lung mechanics, and intervention during invasive mechanical ventilation such as recruitment maneuver, PEEP titration, and prone position We also collected patients' status at 28-day, in-hospital complications, and ventilator-free days at 28-day after intubation. Table 1 shows the variables data recording and time point. Figure 1 shows a timeline of data recording

The chest x-ray at the first 24 hours of admission and the first 24 hours of intubation were reviewed and evaluated by a pulmonologist. We use the chest x-ray scoring system (named the Brixia score)[9] grades lung abnormalities on an 18-point severity scale

All the related variables will be considered at the preliminary stage. The latent profile analysis was performed on the shortlisted variables to identify distinct phenotypes of patients with COVID-19 respiratory failure. After the identification of phenotypes, comparison between phenotypes was conducted using T-test or Mann-Whitney U test for continuous variables, and Z- test was used for categorical variables.

Study endpoints

The primary outcome was the phenotype and associated mortality of COVID-19 respiratory failure in Thai patients. Secondary outcomes include characteristics of phenotype, ventilator-free days, response to treatment, and complications in each phenotype.

Statistical analysis

The data of 80 patients with COVID-19 ARDS were collected from medical ICU Ramathibodi Chakri Naruebodindra Hospital from 1 April 2021 to the present

Clinical variables in the study cohort (n=80) included baseline characteristic features, laboratory investigation and biomarker at baseline, data of treatment medication, intervention and respiratory parameter during invasive mechanical ventilation, change of inflammatory markers on the day of endotracheal intubation compare with baseline (delta NLR, delta LDH, delta CRP), change of CXR severity score at the day of endotracheal intubation compare with baseline(delta CXR severity score), complication during the hospital, length of hospital stay, 28 days of ventilator-free day and mortality are presented in table 2. The mean and the standard deviation are reported for continuous variables with a roughly mound-shaped distribution, whereas the median and interquartile range

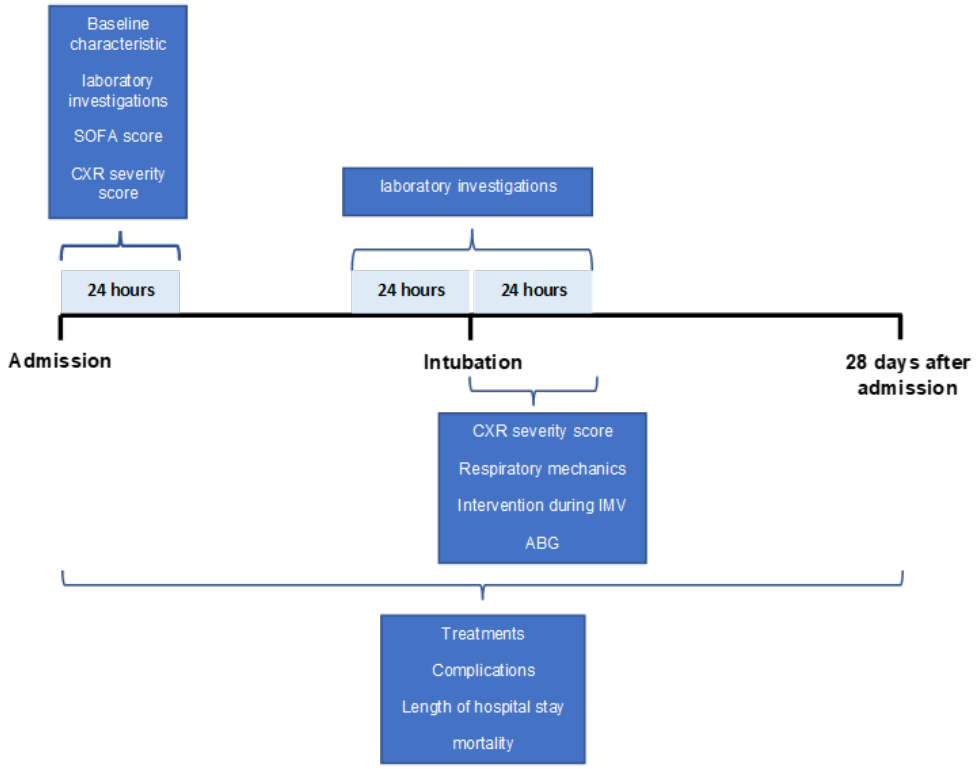

Figure 1. Shows a timeline of data recording
Abbreviation: ABG, Arterial blood gas; CXR, Chest x-ray; SOFA score, Sequential Organ Failure Assessment Score

Table 1. Shows the variables data recording and time point

Variables	Timepoint Collection method	The first 24 hours of admission	During hospitalization	The date of the intubation period	At 28 days
Age/Sex	Chart review	√			
History of vaccination	Chart review	√			
Comorbidity - Hypertension - Diabetic mellitus - Lung disease	Chart review	√			
Day of illness/ day of admission	Chart review	√			
COVID-19 PCR cycle threshold	Ramathibodi laboratory program	√			
SOFA score	Ramathibodi laboratory program	√			
Laboratory investigations - Complete blood count - C-reactive protein - D-dimer - Lactate dehydrogenase(LDH) - Interleukin 6(IL-6) - liver function test - Creatinine/glomerular filtration rate(GFR)	Ramathibodi laboratory program	√		√	

Table 1. (Continued) Shows the variables data recording and time point

Variables	Timepoint Collection method	The first 24 hours of admission	During hospitalization	The date of the intubation period	At 28 days
The chest x-ray severity score	Picture Archiving and Communication System	√		√	
Treatment medications - Antiviral - VTE prophylaxis - Systemic steroid - Pulse methylprednisolone - interleukin-6 inhibitor - kinase inhibitor - cytokine removal	Chart review		√	√	√
Respiratory mechanics - PEEP setting - Peak inspiratory pressure - tidal volume - minute ventilation - lung compliance	Chart review			√	
Intervention during the invasive mechanical ventilation - Recruitment maneuver - PEEP titration - Prone position	Chart review			√	
Arterial blood gas	Ramathibodi laboratory program			√	
Complications - Bacterial pneumonia - Pneumothorax or pneumomediastinum - CMV pneumonitis - IPA - AFOP - VTE - Septic shock - Bleeding (gastrointestinal bleeding/ intramuscular bleeding) - Tracheostomy	Chart review		√	√	√
Length of hospital stay	Chart review				√
Ventilator free day after 28 days of intubation	Chart review				
Mortality	Chart review				√

Abbreviation: AFOP, Acute fibrinous and organizing pneumonia; CMV, Cytomegalovirus; COVID-19, Coronavirus Disease of 2019; IPA, Invasive pulmonary aspergillosis; PCR, Polymerase chain reaction; PEEP, Positive End-Expiratory Pressure; SOFA Score, Sequential Organ Failure Assessment Score; VTE, Venous Thromboembolism

are presented for highly skewed data. Categorical variables such as treatment medication or intervention received by patients were shown in proportions (percentages). It is important to note that the missing data were not imputed.

To identify latent subgroups within this group of patients, the latent profile analysis (LPA) is adopted[10]. LPA is a mixture model that is underpinned by the assumption that observations can be grouped together with varying degrees of probabilities according to a certain set of variables. In this study, we identify five key variables at the primary stage of analysis. Specifically, PCR-N, NLR, CRP, D-DIMER, and LDH were deemed to be the key attributes used in the classification because the previous study has shown these variables are associated with disease severity[11-15] and no missing variable data. The variables chosen for the primary stage of analysis must be complete and have no missing data. However, due to the limited sample size of 80 and the fact that the data imputation is not performed, no more than three variables should be included in the LPA model[16].

To identify an appropriate set of variables in this study, we perform LPA on all possible combinations in which three out of five variables are chosen at a time. In our experiment, a two-class model is chosen to ensure the accurate and complete analysis of the results. This is because the number of observations in different classes will be very sparsely distributed if three classes or more are employed.

All ten combinations of the variables and their corresponding fit index values are exhibited in Table 3. Since we consider only two-class model, there is no need to consider the penalty terms incurred by the additional number of classes. Hence, the log-likelihood function (LL)[17], the approximate weight of evidence (AWE)[18], entropy (reverse-coded)[19], and integrated completed likelihood (ICL)[20] are adopted as fit indicators in our experiments. It can be seen from Table 3 that three out of four indicators concur that NLR, CRP, and LDH should be employed as variables for LPA. More precisely, this combination leads to the highest LL, lowest AWE, and highest ICL as well as results in the second-best model based on entropy. The results signify that the LPA model with NLR, CRP, and LDH offers a better fit to the data than do others. Thus, further analyses in this study will be based on the latent profiles shown in Figure 2. After the identification of phenotypes, comparison between phenotypes was conducted using T-test or Mann-Whitney U test for continuous variables, and Z- test was used for categorical variables.

Table 2. Shows clinical variables in the study cohort (n=80).

Clinical variable	Study cohort	N
Female, n (%)	38 (47.5%)	80
Male, n (%)	42 (52.5%)	80
Age in years, mean (SD)	62.0 (13.2)	80
BMI (kg/m^2), mean (SD)	30.2 (13.5)	79
Diabetes mellitus, n (%)	43 (54%)	80
Hypertension, n (%)	52 (65%)	80
Complete vaccination, n (%)	0	80
Lung disease, n (%)	15 (19%)	80
DOI to DOA (days), mean (SD)	6 (2.1)	80
DOI to ETT (days), mean (SD)	10 (4.4)	80
COVID-19 qualitative RT-PCR, mean (SD)	21.5(5.6)	80
% O_2 saturation(RA), mean (SD)	90 (8.9)	79
SOFA score, mean (SD)	2 (1.3)	79
Neutrophil-lymphocyte ratio, median [IQR]	4.9 [2.9;7.9]	80
C-Reactive Protein (mg/L), median [IQR]	81.9 [32.7;137.4]	80
Lactate Dehydrogenase (U/L), median [IQR]	363.0 [247;541.5]	80
Interleukin 6 (pg/mL), median [IQR]	41.5 [24.6;85.8]	32
D-dimer (ng/mIFEU), median [IQR]	625.5 [402;1222.8]	80
Aspartate aminotransferase (U/L), median [IQR]	52.0 [27.0;79.0]	79
Alanine aminotransferase (U/L), median [IQR]	32 [22;52]	79
Alkaline phosphatase (U/L), median [IQR]	74 [60;88]	79
Total bilirubin (mg/dL), median [IQR]	0.4 [0.4;0.7]	79
Albumin (g/L), mean (SD)	37.7 (4.9)	79
Glomerular filtration rate (ml/min/1.73/m^2), mean (SD)	64.7 (27.8)	80
Chest X-ray severity score, median [IQR]	5 [2;10]	80

Table 2. (Continued) Shows clinical variables in the study cohort (n=80).

Treatment variable	Study cohort	
Anti-viral - Favipiravir, n (%) - Remdesivir, n (%)	 59 (74%) 21 (26%)	 80
VTE prophylaxis, n (%)	67 (84%)	80
Corticosteroid, n (%)	79 (98%)	80
Pulse methylprednisolone, n (%)	69 (86%)	80
Interleukin 6 inhibitor, n (%)	39 (49%)	80
Kinase inhibitor, n (%)	11 (14%)	80
Anti-tumor necrosis factor, n (%)	1 (1%)	80
Cytokine removal, n (%)	15 (19%)	80
Recruitment maneuver, n (%)	36 (45%)	80
PEEP titration, n (%)	63 (79%)	80
Prone, n (%)	38 (48%)	80
Clinical variable on the day of endotracheal tube intubation	**Study cohort**	
Delta NLR, median [IQR]	7.4 [0.0;18.9]	80
Delta CRP, median [IQR]	0.0 [-42.1;30.2]	79
Delta LDH, median [IQR]	47 [0.0;194]	75
Delta CXR severity score, median [IQR]	5 [2;8]	80
Tumor necrosis factor (pg/mL), median [IQR]	47.2 [19.3;129..0]	60
Lung compliant, median [IQR]	23.2 [18.6;30]	79
Peak inspiratory pressure (cmH_2O), mean (SD)	29.4 (5.7)	76
PEEP setting (cmH_2O), mean (SD)	12 (3.3)	80
Arterial blood gas after ETT PH, mean (SD) PaO_2/FiO_2 ratio (mmHg), mean (SD) PCO_2 (mmHg), mean (SD)	 7.36 (0.08) 236.5 (83) 37.5 (8.5)	 80
Complication	**Study cohort n (%)**	
HAP/VAP, n (%)	54 (68%)	80
Pneumothorax/ Pneumomediastinum, n (%)	19 (24%)	80
CMV Pneumonitis, n (%)	14 (18%)	80
IPA, n (%)	9 (11%)	80
AFOP, n (%)	14 (18%)	80
VTE, n (%)	20 (25%)	80
Septic shock, n (%)	39 (49%)	80
Bleeding, n (%)	25 (31%)	80
Tracheotomy, n (%)	7 (8%)	80
Clinical variable	**Study cohort**	
Ventilator free day (days), median [IQR]	0.0 [0.0;15.0]	80
Length of hospital stay (days), median [IQR]	26.0 [20.2;40.8]	80
Death, n (%)	31 (39%)	80

The mean and the standard deviation(SD) are reported for continuous variables with a roughly mound-shaped distribution, whereas the median and interquartile(IQR) range are presented for highly skewed data. Abbreviation: AFOP, Acute fibrinous and organizing pneumonia; BMI, Body Mass Index; CMV, Cytomegalovirus; COVID-19, Coronavirus Disease of 2019; Delta CRP, Difference of C-reactive protein value on the day of intubation compared with baseline; Delta CXR severity score, Difference of Chest x-ray severity score on the day of intubation compared with baseline; Delta LDH, Difference of lactate Dehydrogenase value on the day of intubation compared with baseline; Delta NLR, Difference of neutrophil-lymphocyte ratio value on the day of intubation compared with baseline; DOI to DOA, Day of illness to day of admission; DOI to ETT,Day of illness to endotracheal intubation; ETT, endotracheal intubation; HAP, Hospital-acquired pneumonia; IPA, Invasive pulmonary aspergillosis; PCR, Polymerase chain reaction; PEEP, Positive End-Expiratory Pressure; SOFA Score, Sequential Organ Failure Assessment Score; VAP, Ventilator-associated pneumonia; VTE, Venous thromboembolism

Table 3. Fit statistics for latent profile analysis model.

Variables						Fit indicators			
Model	PCR-N	NLR	CRP	D-dimer	LDH	LL	AWE	Entropy	ICL
1	✓	✓	✓			-282.24	677.71	0.87	-611.96
2	✓	✓		✓		-284.79	682.78	0.88	-616.85
3	✓	✓			✓	-285.92	685.06	0.88	-619.19
4	✓		✓	✓		-285.12	683.45	0.89	-617.14
5	✓		✓		✓	-270.90	654.98	0.89	-588.76
6	✓			✓	✓	-285.10	683.41	0.89	-617.07
7		✓	✓	✓		-282.04	677.32	0.87	-611.57
8		✓	✓		✓	-264.61	642.35	0.92	-574.70
9		✓		✓	✓	-268.58	650.15	0.99	-579.86
10			✓	✓	✓	-270.38	653.94	0.90	-587.79

Abbreviation: AWE, The approximate weight of evidence; CRP, C-Reactive Protein; ICL, Integrated completed likelihood; LDH, Lactate Dehydrogenase; LL, The log-likelihood function; NLR, Neutrophile Lymphocyte ratio; PCR-N, Polymerase chain reaction N

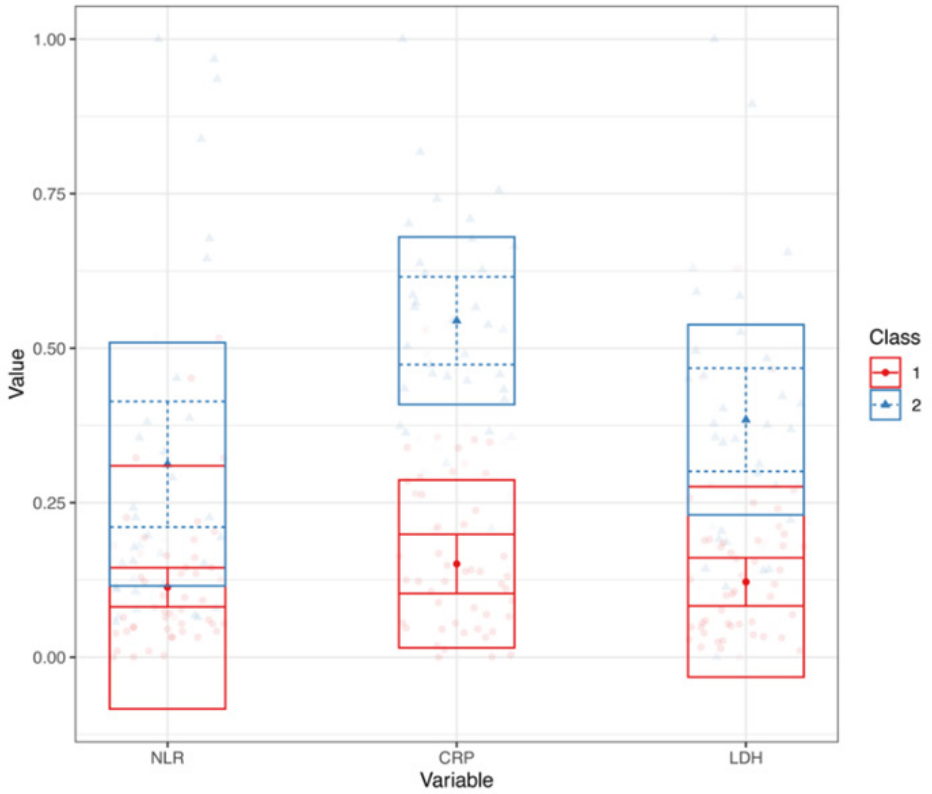

Figure 2. Shows Class analysis by Latent profile analysis.
Abbreviation: CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, Neutrophil-lymphocyte ratio

All the aforementioned statistical analyses will be implemented in R 4.1.2 using poLCA [21] and nnet [22] packages.

RESULTS

From figure 3, 103 COVID-19 patients who received invasive mechanical ventilator were recruited from1 April 2021 to the present. 85 COVID-19 patients met the inclusion criteria. Excluding 5 patients who met the inclusion criteria due to incomplete variables for the class analysis. 80 patients underwent latent profile analysis.

Clinical variables in the study cohort were present in table 2. The mean age was 62 years old and the mean BMI was 30.2 kg/m^2. No one has been fully vaccinated. The mean time from the onset of symptoms to hospital admission (DOI to DOA) was 6 days. The average oxygen saturation was 90% and the SOFA score was 2 points. Overall laboratory investigation and biomarker at baseline were collected within 24 hours of admission. All patients received antiviral drugs, either Favipiravir or Remdesivir. Most patients received Favipiravir (74%). Almost all patients received systemic corticosteroids (98%). PEEP titration was performed in most of the patients (79%) during an invasive mechanical ventilator. The average PEEP setting was 12 cmH2O. Laboratory investigations and some biomarkers were collected within 24 hours of the intubation period. We offer a change in the mean value of variables compared

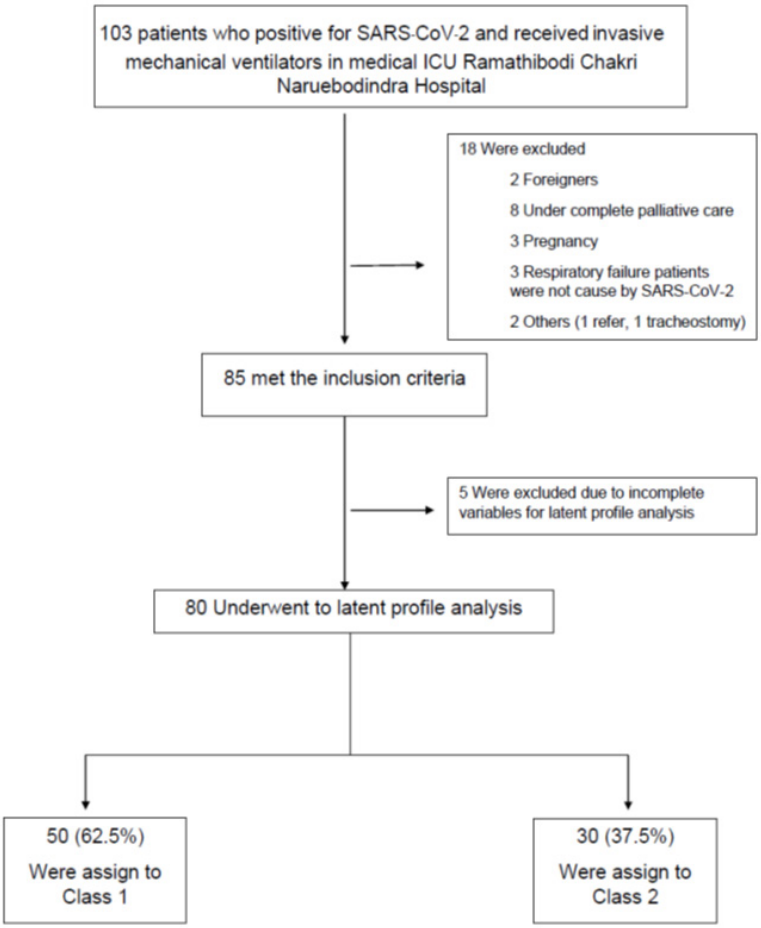

Figure 3. Enrollment and inclusion in the latent profile analysis.

to baseline measurements such as delta NLR, delta CRP, delta LDH, delta CXR severity score shown in the table, and the lower value or negative value represents a decrease in variable values during the intubation period compared to baseline. The most common complication was pneumonia (68%). The mean ventilator-free days and hospital stay were 6, 30 days, respectively. 31 of 80 patients died (39%).

Based on the class analysis, we can divide the study cohort into 2 classes by using 3 variables (CRP, LDH, and NLR). We compared the data between class 1 and class 2 the main result will be reported in a full paper.

DISCUSSION

In previous studies [4-6,23,24], a latent class analysis was used to classify the ARDS subphenotype, indicating that there was a high inflammatory group and a less inflammatory group. Due to the situation of the COVID-19 outbreak, there are many patients with covid ARDS, and the severity of the disease is related to the inflammatory cytokine[25-31]. Therefore, many anti-inflammatory drugs have been used. We choose latent profile analysis for the clustering group of a cohort study. Latent profile analysis is a statistical technique that aims to identify subgroups from observed data regardless of the outcome. Latent profile analysis is similar to latent class analysis, but the two methods differ in that Latent profile analysis is suitable for subgroups based on the mean of continuous variables and latent class analysis which does the same for categorical variables. Therefore, choosing a latent profile analysis was probably more appropriate for using inflammatory marker values (continuous variables) in clustering. Our study aims to identify the phenotype of COVID-19 respiratory failure in Thai Patients.

Trial status

At the time of submission, we still enroll the patients and review the data to record in case record form.

ETHICS

The study is no funding sponsor. The study protocol was approved by the Institution Review Board of Ramathibodi Hospital, Mahidol University, Thailand (No. MURA2021/740)

DISSEMINATION POLICY

When the study is concluded, We plan to disseminate the results in peer-reviewed critical care medicine or pulmonology related journal, conferences nationally and internationally

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Namsai Pukiat, Pongdhep Theerawit, Yuda Sutherasan, Detajin Junhasawasdikul; (II) Data curation: Namsai Pukiat, Supawadee Suppadungsuk; (III) Methodology: Namsai Pukiat, Pongdhep Theerawit, Sanyapong Petchrompo; (IV) Statistic analysis: Namsai Pukiat, Pongdhep Theerawit, Sanyapong Petchrompo; (V) Writing: Namsai Pukiat, Pongdhep Theerawit, Sanyapong Petchrompo.

SUPPLEMENTARY MATERIALS

None

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