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Clinical phenotypes in COVID-19 patients admitted to intensive care units. A Cuban study

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Abstract

Purpose: To identify clinical phenotypes based on age, symptoms and co-morbidities in COVID-19 patients in intensive care units (ICU).

Methods: Data included 1504 patients admitted to ICU in Cuba between January and August 2021. In order to identify clinical patterns related to symptoms, comorbidities and age, the unsupervised classification, K-means algorithm based on unsupervised learning was used.

Results: Six phenotypes using a modified v-fold crossvalidation for the use of K means algorithm were identified: Phenotype class 1: mean age 72.3 years(ys)-- hypertension, coronary artery disease, alongside typical COVID-19 symptoms, class 2: mean age 63 ys -- asthma, cough and fever; class 3: mean age 74.5 ys -- hypertension, diabetes and cough; class 4: mean age 67.8 ys -- hypertension and no symptoms; class 5: mean age 53 ys -- cough and no comorbidities; class 6: mean age 60 ys - without symptoms and comorbidities. The mortality rate totaled 358 (23,8%). Of this number 73 (20.39 %) had preexisting CND. The highest in-hospital mortality rates were found in phenotypes 1 (37, 22 %), and 3 (33, 98%). Ratio between deaths and survival was 0.34. Only phenotypes 1 and 3 exceeded the overall rate of the cohort. Consistently, Kaplan-Meier distributions showed the lowest survival probability in cluster 1 on day 8, followed by cluster 3. In contrast, patients in cluster 2 displayed the highest survival probability on the same day.

Conclusions: The identification of clinical phenotypes using a robust statistical methodology based on age, comorbidities and symptoms could help stratify patients to personalize therapy, rationally focus health services and vaccination strategies

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Introduction

The COVID-19 pandemic remains to impact healthcare systems all over the world. To date, October 16, 2021, the World Health Organization has recorded 241 578 403 cases worldwide, and more than 4 900 000 confirmed deaths. World Health Organization (WHO) Coronavirus Disease (COVID-19) Dashboard Available at, https://covid19.who.int (accessed October 16, 2021). In this respect, Cuba reports more than 8000 deaths with more than 900 000 cases, of this around 9000 have been in Intensive care units. Dashboard Available https://www.paho.org › reportes-situacion-covid-19-cuba.

The clinical spectrum of COVID-19 is broad and complex, ranging from asymptomatic infection, symptoms that spread outside the respiratory system, and unpredictable clinical worsening, which can lead to severe pneumonia with respiratory failure. Elderly individuals and underlying chronic conditions (or comorbidities) rise the risk of severe COVID-19, hospitalization, admittance to intensive care units (ICUs), and death [1-3].

Intensive care units (ICU) have an important role in managing the sickest of these patients [4,5]; nevertheless, mortality is prominently high in this group. A recent systematic review and meta-analysis of 52 observational studies [6] published by April 2021, which included 43,128 patients admitted to ICU with COVID-19, revealed that in most geographical regions, the mortality rate is 30–40%, with some differences in two geographical regions. Death rate was higher in the Middle East (61.9%), and according to a single study , lower in Australasia (10.6%) [4].

Several chronic conditions have proved to be associated with a more severe disease and death, such as heart diseases, hypertension, diabetes mellitus, chronic pulmonary disease, obesity and cancer [1,7,8]. Other conditions including asthma, pregnancy, and slight immunosuppressant conditions are affected by mixed or more limited evidence. Conditions like chronic renal diseases and cytokine activation syndrome may be exacerbated due to COVID-19, and extra care is required for such patients [9].

Even though a large number of investigations have been conducted around the world in a very short time, several problems remain unsolved, including the clinical and biological heterogeneity of COVID-19. This has led to incomplete categorization of disease phenotypes and hampered stratification of key patients in pandemic control. Cluster analysis has been used to investigate the heterogeneity of some diseases in order to identify clinical phenotypes with similar trait mixtures. Previous research approach in asthma, cancer and acute respiratory distress syndrome has been able to identify disease phenotypes with significant therapeutic implications [10-12].

This article aims to identify clinical phenotypes based on age, symptoms and comorbidities in COVID-19 patients admitted to ICU.

Materials and methods

Study design, patient selection, and data collection

A structured database was created and completed by the Cuban Health Ministry experts group from January to August 2021. Data were collected from 1504 ICU patients with COVID-19 in all Cuban hospitals (Collaborators are shown in Appendix A). COVID-19 diagnosis was confirmed by positive high through put sequencing or real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay for nasal and pharyngeal swab specimens.

Definition of variables

Symptoms and comorbidities of all patients were collected upon admission. For all subjects, clinical, radiological, and laboratory examinations were performed during the first 24 h of ICU admission. The collection of clinical data from each patient, treatments, and outcomes were verified by the leading researcher LMCh.

Demographic variables included age, sex, and race. Clinical symptoms encompassed fever, cough, nasal congestion, headache, fatigue, dyspnea, rhinorrhea, nausea and vomiting, diarrhea, arthralgia, myalgia, ageusia, anosmia, chilliness, chest pain as well as unconsciousness.

Regarding comorbidities, we analyzed the presence of hypertension-- described as systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥ 140/90 mmHg, and/or the use of antihypertensive agents--, diabetes-- defined as fasting blood glucose ≥ 126 mg/dL on two occasions, and/or the use of antidiabetic agents--, smoking habit (current or in the preceding 6 months), coronary artery disease, chronic obstructive pulmonary disease (COPD), asthma, cancer, obesity, psychiatric diseases, chronic renal diseases, alcoholism, pregnancy, immunocompromised state (congenital or acquired) as well as chronic neurological disorders (CND).

Imaging results involved chest radiography (CXR) abnormality. Laboratory examinations, on the other hand, included white blood, lymphocytes and neutrophil count, platelet number, mean platelet volume, and Neutrophil to lymphocyte ratio. Other variables embraced ventilation type and illness severity at ICU admission.

Patients were treated in accordance with the Cuban protocol version 1.6 available at the pandemic period https://covid-19cubadata.github.io/protocolos/protocolo-version-6.pdf. The primary outcome of the study was in-hospital mortality.

Statistical analysis

Qualitative and ordinal variables are indicated in terms of frequency and percentage. Continuous variables are shown as medians, minimum-maximum value or mean and standard deviation (SD).

Statistical analysis involved Chi2 test or Fisher's Exact test for contrasting categorical variables, adjusting p-value by Bonferroni method for multiple comparisons correction. The normality of distribution was assessed using the Shapiro–Wilk test. Due to the exploratory nature of the study, the sample size was not calculated. Further, the level of significance threshold was set in 0.05, after adequate adjustment.

Missing data was managed by a complete case analysis. To deal with this drawback, the deletion technique, known as case deletion or complete-case analysis was used. The missing data calculation was less than 20% of the sample size.

In order to identify clinical patterns related to symptoms, comorbidities and age, the unsupervised classification, commonly known as clustering, was performed. A sample of 1258 cases was used for the analysis. All patients with no available variables were left out (16%).

K-means algorithm based on unsupervised learning was used [13]. The optimal number of six clusters (K) was estimated

using a modified v-fold cross-validation for the use of K means algorithm.

The steps of the algorithm include:

1. Determining the number of clusters K

2. Setting centroids by first shuffling the dataset, and then randomly selecting in data points for the centroids without replacement

3. Calculating the distance between data points and all centroids

4. Allocating each data point to the closest cluster (centroid)

5. Updating the position of the centroid according to the assigned data

6. Retaining iterating until there is no change to the centroids

At this point the values are assigned into K clusters without any hierarchical structure by optimizing the minimum distance between points with each of the available clusters, applying Euclidean distance between data points and centroids as distance criterion.

All the analyses were completed using Statistics software (version 12). Modules utilized for the analyses encompassed Generalized EM & k-Means Cluster Analysis, included in the Data Mining.

The Kaplan-Meier method and log-rank test were used to compare the prognosis of COVID-19 patients in different phenotypes. The elapsed time from ICU admission to death or discharge was also evaluated.

Results

The mean age of the patients admitted to the ICU was 66,13 ± 16,33 years (age range: 19-104 years old). Eight hundred and seventy-five (58.3%) of whom were male, and 41.6% had at least one coexisting condition. The top 8 comorbidities were hypertension (1051/1460 [71.99%]), diabetes (423/1459 [28,9%]), cardiovascular disease (334/1458 [23.7%]), CND (237/1504 [15.75%]), obesity (139/1458 [9.5%]), chronic obstructive pulmonary disease (COPD) (132/1459 [9%]), asthma (114/1456 [7.8%]) and cancer (77/1458 [5.2 %]). According to the Cuban Emergency Society guideline, 31,88 % were considered to be critically ill, whereas 68,11% were reported to be in grave condition.

The mortality rate in the patient cohort was 23.8%. Table 1 provides a summary of demographic characteristics of the cohort.

Dry cough, fever (454/1294 [35%]), (608/1298 [46,8%]), dyspnea (366/1295 [28.2%]), cephalic (96/1296 [7.4%]), rhinorrhea (91/1297 [7%]), and fatigue (83/1295 [6.4%]) were acknowledged to be the most common presenting symptoms. Additionally, most patients 88.8 % had abnormal chest radiography (CXR) findings. (Laboratory results of the whole cohort are shown in table 1).

Table 1: Clinical and demographic data of patient cohorts admitted to UCI.

Variables	N and /or (percentage) n=1496
Age (range)	
18 - 30 years	33 (2,20)
31 - 40 years	73 (4,88)
41 – 50 years	151 (10,09)
51 – 60 years	309 (20,65)
61 – 70 years	279 (18,65)
71 – 80 years	332 (22,19)
81 – 90 years	249 (16,64)
90 – 100 years	67 (4,48)
+ 100 years	3 (0,20)
Sex	
Female	624(41,63)
Male	875 (58,37)
Race	
White	(80,12)
Black	(9,87)
Others	(4,75)
Disease Severity	
Critical Illness	(31,88)
Grave Condition	(68,11)
Ventilation Modality	
Invasive Mechanical Ventilation	(66,46)
Non Invasive Mechanical Ventilation	(33,54)
Laboratory examinations	
Neutrophil to lymphocyte ratio> 4	(38,23)
Mean platelet volume > 9	(36,71)
Chest radiography (CXR)	
Non abnormality	(88,80)
abnormality	(11,20)
Treatments	
Antibiotic	(55,92)
Steroids	(52,28)
Anticoagulantes	(53,97)
Jusvinza (Péptido CIGB 258)	(77,6%)
AcMc (Itolizumab)	141 patients
AcMc (Nimotuzumab)	9 patients

Table 2 : Summarizes survival in patients in each phenotype class.

Days in UCI	Phenotype 1 N (%)	Phenotype 2 N (%)	Phenotype 3 N (%)	Phenotype 4 N (%)	Phenotype 4 N (%)	Phenotype 6 N (%)
0	193 (71,8)	58 (87)	233 (73,1)	132 (84,45)	119 (81,28)	175 (89,25)
4,33	63 (74,15)	14 (90,9)	89 (75,38)	46 (83,87)	36 (95,91)	54 (78,66)
8,66	18 (57,14)	7 (100)	25 (74,35)	11 (86,66)	12 (88,88)	13 (73,33)
13	4 (33,33)	1 (0)	9(100)	3 (100)	5 (77,77)	0
17,33	0	0	5 (100)	1 (100)	3 (100)	0
21,66	0	0	2 (100)	0	3(100)	0
26	0	0	1(100)	0	1(100)	0
30,33	0	0	0	0	1(100)	0
34,6	0	0	0	0	1 (0)	0
39	0	0	0	0	0	0

Characteristics of K means algorithm-defined phenotypes for COVID- 19 patients in ICU based on fifteen symptoms, fourteen comorbidities and age

The optimal number of six clusters (K) was estimated using a modified v-fold cross-validation for the use of K means algorithm. One demographic variable (age), fifteen symptom variables, and fourteen comorbidity variables were used to define clinical phenotypes below Figure 1 :

phenotype class 1: mean age 72.3 years -- hypertension, coronary artery disease, cough and fever; n=223 (17.74% of the sample)

phenotype class 2: mean age 63 years -- asthma, cough and fever; n=68 (5.3% of the sample)

phenotype class 3: mean age 74.5 years -- hypertension, diabetes and cough; n=256 (20.3% of the sample)

phenotype class 4: mean age 67.8 years -- hypertension and no symptoms; n=395 (31.4% of the sample)

phenotype class 5: mean age 53 years -- cough and no comorbidities; n=124 (9.8% of the sample)

phenotype class 6: mean age 60 years -- without symptoms and comorbidities; n= 192 (15.2% of the sample)

Comorbidities were more common in mean age 70 years than in younger adult classes (phenotypes 5 and 6). Phenotypes class 1 and class 3 combined two comorbidities and comprised individuals with median ages 72 and 74 years, respectively. Conversely, phenotypes class 5 and class 6 embraced 50 year- mean age patients.

Defined Phenotypes for COVID- 19 patients in ICU and mortality rate

The mortality rate of the sample totaled 358 (23, 85%). The chi square χ^2 analysis indicated a significant association between the cluster analysis -defined phenotypes, illness severity and inpatient mortality χ^2 (5)=12,601, p=,027, χ^2 (5)= 51,211, p=,000 respectively. The inpatient mortality rates for the six phenotypes were 37,22 %,14.93%,33.98%,22.28%,18.55% and 13.02% correspondingly. The highest in-hospital mortality rates were found in phenotypes 1 and 3 (Figure 2). In contrast, phenotypes 6 y 2 displayed the lowest fatality rates.

Ratio between deaths and survival in the cohort was 0.34: cluster 1 (0.59), cluster 2 (0.17), cluster 3 (0.51), cluster 4 (0.28), cluster 5 (0.22), and cluster 6 (0.14). As can be observed, only phenotypes 1 and 3 exceeded the overall rate of the cohort

Consistently, Kaplan-Meier distributions in Figure 2 showed the lowest survival probability on day 8 in ICU in cluster 1 followed by patients in cluster 3. In contrast, patients in cluster 2 displayed the highest survival probability on the same day. In addition, Kaplan-Meier survival curve also indicated a shorter overall survival time in clusters 2 and 6. The table 2 summarizes survival in patients in each phenotype class.

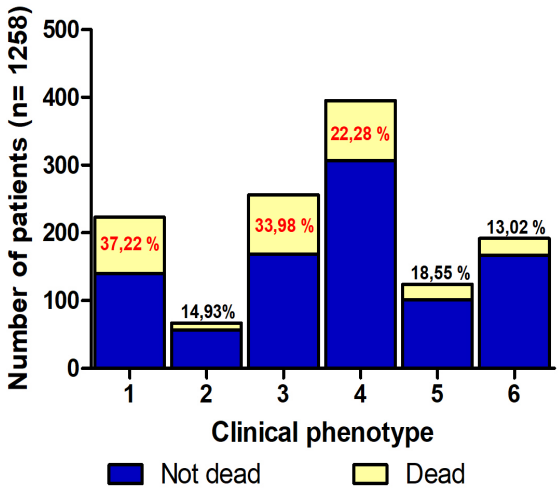

Figure 1: The figure shows the six K means Algorithm -defined phenotypes and associated mortality in each phenotypes. Phenotype class 1 (mean age 72.3 years: hypertension, coronary artery disease, and symptoms, such as cough and fever; 17.74% of the sample), phenotype class 2 (mean age 63 years: asthma, cough and fever; 5.3% of the sample), phenotype class 3 (mean age 74.5 years: hypertension and diabetes, cough; 20.3% of the sample). Phenotype class 4 (mean age 67.8 years: hypertension and no symptoms; 31.4% of the sample), phenotype class 5 (mean age 53 years: cough and no comorbidities; 9.8% of the sample). Patients in class 6 (mean age 60 years: without symptoms and comorbidities; 15.2% of the sample). Inpatient mortality rates for the six phenotypes are presented in yellow. The rates of inpatient mortality for the six phenotypes were 37, 22 %,14.93%,33.98%,22.28%,18.55% and 13.02% correspondingly.

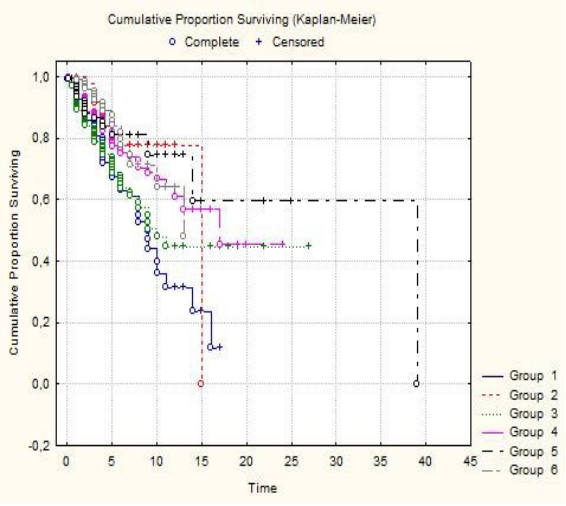

Figure 2: lustrates Kaplan-Meier plots of the ICU admission period. p values of log-rank tests were <0.001 in the six phenotypes comparisons. In this plot, the survival times are indicated with circles, and the censored observations are marked with crosses. Chi-square (5)= 25,11, p = 0 ,0001. Note that patients in cluster 1 display the lowest survival probability on day 8 in UCI, followed by patients in cluster 3. Conversely, patients in cluster 2 show the highest survival probability ont the same day. Group: phenotype class. Time: Days from ICU admission to death or discharge.

Discussion

The current study used a large cohort of COVID-19 patients admitted to ICU, focused on an objective disease classification into clinical phenotypes. Six clinical phenotypes based on age, symptoms and comorbidities were defined using a modified v-fold cross-validation for the use of K means algorithm.

In this study, phenotypes 1 and 3, including elderly people with respiratory symptoms alongside two different comorbidity patterns hypertension with diabetes or with artery coronary disease emerged as important clinical phenotypes. On the other hand phenotype class 4 was characterized by hypertension, no symptoms and mean age 67.8 years. We showed that advanced age, hypertension associated with diabetes or with coronary artery disease was strongly related to a high rate of inhospital mortality in patents admitted to ICU.

The findings in this study offer insights into the clinical spectrum of COVID-19 patient admitted to ICU and comprise distinct phenotypes based on patients' clinical information available in hospital admission. A number of previous studies have identified isolated predictors of severe disease progression, and have developed clinical risk score, but such information has limited impact on clinical practice [14-16].

Recently, some approaches to phenotype clusters in COVD-19 have been described [17,18]. One recent study developed a predictive equation based on symptoms, comorbidities and demographic data. These variables provided fair ability to discriminate severe vs. non-severe outcomes [19].

This study has demonstrated that the phenotypic cluster approach is a better predictor of mortality in ICU than risk assessment merely based on age, symptoms and comorbidities. This provides an incremental benefit to our model over existing knowledge that are also concordant with the country-wide pattern of COVID-19 associated comorbidities in hospitalized and deceased patients. Heart diseases, including hypertension along with cardiovascular diseases are the most frequent associations with SARS-CoV2 infection in most countries (Italy, France, Spain, and Sweden) except for the Netherlands [20].

Similar reports of high prevalence of cardiovascular diseases and hypertension among hospitalized patients were demonstrated in case reports from China and the United States [21-23]. In other studies approximately 25% of COVID-19 cases had at least one associated comorbidity [24,25]. Our results corroborates the ideas that COVID-19 is associated with various comorbidities often linked to endothelial deterioration indicating that endothelium can be the target of SARS-CoV2 such as cardiovascular diseases, hypertension, diabetes, liver, renal and lung diseases, obesity as well as neurological illnesses [20,26,27].

The findings from this study also suggest other potentially relevant clinical implications. For example, phenotype class 2 (mean age 63, asthma, cough and fever) , phenotype class 6 (60 mean age, no symptoms and no comorbidities) as well as phenotype class 5 (53 age mean, cough and no comorbidities showed the-highest survival probability .These results should be considered among the high rates of asymptomatic COVID-19 patients reported in the literature to date [28]. Moreover, young age was found to be the only factor associated with an asymptomatic course [29]. On the other hand, low fatality in phenotype class 2; including patients with asthma raises the hypothesis that asthma may not increase mortality from COVID-19. The first meta-analysis analyzing the influence of asthma on outcomes of COVID-19 patients suggests that it may not have a major role in prolongation of the hospital stay or an increase in the risk of ICU transfer [30].

As to respiratory symptoms in the phenotypes, the results of this study support previous research in which cough, dyspnea and/or fever were considered to be the most common symptoms [17,18].

There is some evidence based on the SARS and MERS epidemics that these comorbidities predispose risk factors for severe infections, leading to critical care and fatality. The same trend has been observed with SARS-CoV-2 and COVID-19 disease [14,31-33]. The results of this study indicated that the mortality rate at ICU has been considerably high for patients who suffer from at least two comorbidities such as coronary artery disease and diabetes. Like in the case of SARS and MERS, the Angiotensin Converting Enzyme-2 (ACE 2) receptors play a crucial role in determining the severity of the disease, and the upregulation of ACE2 [34-36].

In summary the death rate of COVID-19 patients in ICU in the current study was 23.8%, which is lower than in other countries [6]. Yet, this figure is relevant when compared to the usually described mortality rates of community-acquired pneumonia of about 16.6%-18% [37,38]. It is important to highlight that the Cuban health care system provides the elderly population with a broad range of health services. It also stresses prevention and control of chronic diseases from primary healthcare, which is crucial to mitigate the impact of severe COVID-19 and fatality on this age group [39].

The results from this study emphasize that elderly patients with at least two other comorbidities (hypertension with diabetes and hypertension with coronary artery disease) are a high-risk population for severe COVID-19, needing careful health follow-up.

Conclusions

The identification of clinical phenotypes using a robust statistical methodology based on age, comorbidities and symptoms make several noteworthy contributions to basic and clinical investigations to distinguish the COVID-19 spectrum. Recognizing different phenotypes could help stratify patients to personalize therapy, rationally focus health services and vaccination strategies.

Limitations

The findings in this study are subject to certain limitations. First, these findings are limited by the use of a retrospective cohort design. Secondly, the study did not include radiologic and laboratory examinations in the algorithm. Notwithstanding these limitations, the current study constitutes a novel approach to the heterogeneous clinical spectrum of COVID- 19 using more feasible variables.

Taking into account that a number of clinical studies are still on going in Cuba and in many other countries, responses to treatment based on phenotypes could vary. Hence, this study might help update future randomized controlled trials of innovative therapies for COVID-19.

Declarations

Data availability statement: The datasets produced for this study are available on request to the corresponding author.

Ethics statement: This study involving human participants was revised and approved by the scientific and the ethics committee of the Innovative commission of the Cuban Health Ministry. Written informed consent was waived owing to the use of de identified retrospective data. All the procedures performed followed the rules of the Declaration of Helsinki of 1975 for human research.

Author contributions: LMCH designed the study, analyzed the results and wrote the manuscript. LGG participated in the statistical analysis of the results. OMCH revised the English and contributed to the organization of the manuscript .NPF and TCH played a part in the layout of the manuscript. EAM created the database. IMS contributed to the organization of the manuscript, NMP, CMR, CMA, RGG, RPG and OLP took part in the collection of data.

Conflicts of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G et al: Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020, 180(10):1345-1355. doi: 1310.1001/jamainternmed.2020.3539.

2. Jain V, Yuan JM: Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health 2020, 65(5):533-546. doi: 510.1007/s00038-00020-01390-00037. Epub 02020 May 00025.

3. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, Armistead I, Bennett NM, Billing L, Como-Sabetti K et al: Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis 2021, 72(9):e206-e214. doi: 210.1093/cid/ciaa1012.

4. Armstrong RA, Kane AD, Cook TM: Decreasing mortality rates in ICU during the COVID-19 pandemic. Anaesthesia 2021, 76(Suppl 3):10. doi: 10.1111/anae.15230. Epub 12020 Aug 15210.

5. Alban A, Chick SE, Dongelmans DA, Vlaar APJ, Sent D: ICU capacity management during the COVID-19 pandemic using a process simulation. Intensive Care Med 2020, 46(8):1624-1626. doi: 1610.1007/s00134-00020-06066-00137. Epub 02020 May 00137.

6. Armstrong RA, Kane AD, Cook TM: Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia 2020, 75(10):1340-1349. doi: 1310.1111/anae.15201. Epub 12020 Jul 15215.

7. Aboueshia M, Hussein MH, Attia AS, Swinford A, Miller P, Omar M, Toraih EA, Saba N, Safah H, Duchesne J et al: Cancer and COVID-19: analysis of patient outcomes. Future Oncol 2021, 17(26):3499-3510. doi: 3410.2217/fon-2021-0121. Epub 2021 Jul 3415.

8. Drake TM, Riad AM, Fairfield CJ, Egan C, Knight SR, Pius R, Hardwick HE, Norman L, Shaw CA, McLean KA et al: COVID19-related and all-cause mortality risk among middle-aged and older adults across the first epidemic wave of SARS-COV-2 infection: a population-based cohort stuJune 2020.dy in Southern Catalonia, Spain, March. Lancet 2021, 398(10296):223-237. doi: 210.1016/S0140-6736(1021)00799-00796.

9. Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, Ibironke O, Hanna A, Ranski A, Halalau A: Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020, 288(4):469-476. doi: 410.1111/joim.13119. Epub 12020 Jun 13122.

10. Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvärinen A, Kaulek V, Roduit C, Weber J, Schaub B, Lauener R et al: Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med 2014, 189(2):129-138. doi: 110.1164/rccm.201307-201198OC.

11. Reddy K, Sinha P, O'Kane CM, Gordon AC, Calfee CS, McAuley DF: Subphenotypes in critical care: translation into clinical practice. Lancet Respir Med 2020, 8(6):631-643. doi: 610.1016/S2213-2600(1020)30124-30127.

12. Sinha P, Calfee CS: Phenotypes in acute respiratory distress syndrome: moving towards precision medicine. Curr Opin Crit Care 2019, 25(1):12-20. doi: 10.1097/MCC.0000000000000571.

13. DLaDC W: Clustering Academic Press Library in Signal Processing (Signal Processing Theory and Machine Learning) 2004, 1:1115-1149.

14. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, Li Y, Guan W, Sang L, Lu J et al: Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med 2020, 180(8):1081-1089. doi: 1010.1001/jamainternmed.2020.2033.

15. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E,

Bonten MMJ, Dahly DL, Damen JAA, Debray TPA et al: Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ 2020, 369:m1328.(doi):10.1136/bmj.m1328.

16. Aghagoli G, Gallo Marin B, Soliman LB, Sellke FW: Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. J Card Surg 2020, 35(6):1302-1305. doi: 1310.1111/jocs.14538. Epub 12020 Apr 14519.

17. Wang X, Jehi L, Ji X, Mazzone PJ: Phenotypes and Subphenotypes of Patients With COVID-19: A Latent Class Modeling Analysis. Chest 2021, 159(6):2191-2204. doi: 2110.1016/j.chest.2021.2101.2057. Epub 2021 Feb 2126.

18. Rubio-Rivas M, Corbella X, Mora-Luján JM, Loureiro-Amigo J, López Sampalo A, Yera Bergua C, Esteve Atiénzar PJ, Díez García LF, Gonzalez Ferrer R, Plaza Canteli S et al: Predicting Clinical Outcome with Phenotypic Clusters in COVID-19 Pneumonia: An Analysis of 12,066 Hospitalized Patients from the Spanish Registry SEMI-COVID-19. J Clin Med 2020, 9(11):3488. doi: 3410.3390/jcm9113488.

19. Ryan C, Minc A, Caceres J, Balsalobre A, Dixit A, Ng BK, Schmitzberger F, Syed-Abdul S, Fung C: Predicting severe outcomes in Covid-19 related illness using only patient demographics, comorbidities and symptoms. Am J Emerg Med 2021, 45:378-384.(doi):10.1016/j.ajem.2020.1009.1017. Epub 2020 Sep 1019.

20. Jakhmola S, Indari O, Baral B, Kashyap D, Varshney N, Das A, Chatterjee S, Jha HC: Comorbidity Assessment Is Essential During COVID-19 Treatment. Front Physiol 2020, 11:984.(doi):10.3389/fphys.2020.00984. eCollection 02020.

21. Zhou J, Zhang J, Zhou J, Yi H, Lin Z, Liu Y, Zhu M, Wang H, Zhang W, Xu H et al: Clinical characteristics of re-positive COVID-19 patients in Huangshi, China: A retrospective cohort study. PLoS One 2020, 15(11):e0241896. doi: 0241810.0241371/journal.pone.0241896. eCollection 0242020.

22. Wu Z, Wang Q, Zhao J, Yang P, McGoogan JM, Feng Z, Huang C: Time Course of a Second Outbreak of COVID-19 in Beijing, China, June-July 2020. JAMA 2020, 324(14):1458-1459. doi: 1410.1001/jama.2020.15894.

23. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X 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(10229):1054-1062. doi: 1010.1016/S0140-6736(1020)30566-30563. Epub 32020 Mar 30511.

24. Guan Q, Liu M, Zhuang YJ, Yuan Y, Wang SS, Li J, Chen Z, Yang XL, Tang ZR, Jia HJ et al: [Epidemiological investigation of a family clustering of COVID-19]. Zhonghua Liu Xing Bing Xue Za Zhi 2020, 41(5):629-633. doi: 610.3760/cma.j.cn112338-20200223-20200152.

25. Chen G, Wu MZ, Qin CJ, Wu BB, Luo WR, Liu L, Liu JY: Epidemiological analysis of 18 patients with COVID-19. Eur Rev Med Pharmacol Sci 2020, 24(23):12522-12526. doi: 12510.26355/eurrev_202012_224049.

26. Jakhmola S, Baral B, Muduli K, Suar M, Das P, Patnaik PK, Mohakud NK, Jha HC: The interrelation of COVID-19 and neurological modalities. Neurol Sci 2021, 42(6):2157-2160. doi: 2110.1007/s10072-10021-05177-10073. Epub 12021 Mar 10012.

27. Sardu C, Maggi P, Messina V, Iuliano P, Sardu A, Iovinella V, Paolisso G, Marfella R: Could Anti-Hypertensive Drug Therapy Affect the Clinical Prognosis of Hypertensive Patients With COVID-19 Infection? Data From Centers of Southern Italy. J Am Heart Assoc 2020, 9(17):e016948. doi: 016910.011161/JAHA.016120.016948. Epub 012020 Jul 016947.

28. Mizumoto K, Kagaya K, Chowell G: Early epidemiological assessment of the transmission potential and virulence of coronavirus disease 2019 (COVID-19) in Wuhan City, China, January-February, 2020. BMC Med 2020, 18(1):217. doi: 210.1186/s12916-12020-01691-x.

29. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, Ma H, Chen W, Lin Y, Zheng Y et al: Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci 2020, 63(5):706-711. doi: 710.1007/s11427-11020-11661-11424. Epub 12020 Mar 11424.

30. Wang Y, Chen J, Chen W, Liu L, Dong M, Ji J, Hu D, Zhang N: Does Asthma Increase the Mortality of Patients with COVID-19?: A Systematic Review and Meta-Analysis. Int Arch Allergy Immunol 2021, 182(1):76-82. doi: 10.1159/000510953. Epub 000512020 Sep 000510922.

31. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, Guo GY, Du J, Zheng CL, Zhu Q 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(5):2000524. doi: 2000510.2001183/13993003.13900524-13992020. Print 13992020 May.

32. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T et al: Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020, 55(5):2000547. doi: 2000510.2001183/13993003.13900547-13992020. Print 13992020 May.

33. Kim HJ, Hwang H, Hong H, Yim JJ, Lee J: A systematic review and meta-analysis of regional risk factors for critical outcomes of COVID-19 during early phase of the pandemic. Sci Rep 2021, 11(1):9784. doi: 9710.1038/s41598-41021-89182-41598.

34. Elrashdy F, Redwan EM, Uversky VN: Why COVID-19 Transmission Is More Efficient and Aggressive Than Viral Transmission in Previous Coronavirus Epidemics? Biomolecules 2020, 10(9):1312. doi: 1310.3390/biom10091312.

35. Sahai A, Bhandari R, Koupenova M, Freedman J, Godwin M, McIntyre T, Chung M, Iskandar JP, Kamran H, Aggarwal A et al: SARS-CoV-2 Receptors are Expressed on Human Platelets and the Effect of Aspirin on Clinical Outcomes in COVID-19 Patients. Res Sq 2020, 1(23).

36. Messina F, Giombini E, Agrati C, Vairo F, Ascoli Bartoli T, Al Moghazi S, Piacentini M, Locatelli F, Kobinger G, Maeurer M et al: COVID-19: viral-host interactome analyzed by network based-approach model to study pathogenesis of SARS-CoV-2 infection. J Transl Med 2020, 18(1):233. doi: 210.1186/s12967-12020-02405-w.

37. Cillóniz C, Rodríguez-Hurtado D, Torres A: Characteristics and Management of Community-Acquired Pneumonia in the Era of Global Aging. Med Sci (Basel) 2018, 6(2):35. doi: 10.3390/medsci6020035.

38. Lu H, Zeng N, Chen Q, Wu Y, Cai S, Li G, Li F, Kong J: Clinical prognostic significance of serum high mobility group box-1 protein in patients with community-acquired pneumonia. J Int Med Res 2019, 47(3):1232-1240. doi: 1210.1177/0300060518819381. Epub 0300060518812019 Feb 0300060518819387.

39. Mas Bermejo P, Sánchez Valdés L, Somarriba López L, Valdivia Onega NC, Vidal Ledo MJ, Alfonso Sánchez I, Seuc Jo A, Almeida Cruz Y, Morales Ojeda R: Equity and the Cuban National Health System's response to COVID-19. Rev Panam Salud Publica 2021, 45:e80.(doi):10.26633/RPSP.22021.26680. eCollection 22021.