A Differential Therapeutic consideration for use of Corticosteroids according to Established COVID-19 Clinical Phenotypes in Critically ill Patients

Supplementary Online Content

e-Methods. Supplemental Methods

Data Collection and Validation

Data were collected using a paper CRF (case Report Form). CRF collect and record all protocol-required information, which is transcribed from patient source documents, such as hospital records and laboratory reports during the patient's participation in the study. Before being sent to the Study Coordinator (AR) this data was de-identified (not traceable to the patient) by removing the patient's name, medical record number, etc., and giving the patient a unique study number. We implemented a double data entry model for potential errors in real-time. Data was entered twice by two different Data Entry personnel based on the same set of data collected in the paper CRFs. All data were reviewed, and values that appeared incongruent or out of range were manually validated by confirming the accuracy of the data with the Study Coordinator (AR). The database was validated and cleaned before the statistical analysis and finally, the study database was locked to prevent any further changes, and to ensure data consistency and integrity for the statistical reporting and analysis.

Study population

The study enrolled consecutive adult patients (>16 years) with laboratory confirmed SARS-CoV-2 infection, detected by RT-PCR positive test of nasopharyngeal, oropharyngeal swab or invasive respiratory samples according to the WHO recommendations. The follow-up of patients was scheduled until August 11, 2020, which confirmed ICU discharge or death whichever occurred first. The study was approved by the reference institutional review board at Joan XXIII University Hospital (IRB# CEIM/066/2020) and each participating site with a waiver of informed consent.

Outcomes The primary outcome included all-causes of ICU mortality. Patients who were discharged alive from ICU were evaluated in the data as alive considering mortality was defined as any in-ICU death. All complications and outcomes were followed during ICU admission.

Approach to missing data

Continuous variables with missing data > 30% were excluded of database. Missing data for continuous variables were imputed using R-package "missForest" for the statistical software R/CRAN. The imputation was applied to impute the missing values of D dimer (20%), Ferritin (20%), D-Lactate dehydrogenase (17%), Procalcitonin (17%), creatinine (16%), SOFA score (16%), APACHE II score (10%) and C-reactive protein (CRP) (5%). Categorical data (including ICU mortality) were available for all patients.

Study definitions

Community-acquired pneumonia (CAP) was defined in accordance with current American Thoracic Society and Infectious Diseases Society of America guidelines (ATS/IDSA)(4).

Primary viral pneumonia due to SARS-CoV-2 infection was defined by the presence of acute respiratory failure and unequivocal alveolar opacities involving one or more lobes, with negative respiratory and blood bacterial cultures at ICU admission.

Shock was defined in accordance with the Surviving Sepsis Campaign guidelines (5); that is, patients in whom adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability.

Acute Kidney injury (AKI) was defined according to Consensus Conference of the Acute Dialysis Quality Initiative (6).

Acute respiratory distress syndrome (ARDS) was defined according Berlin definition (7) in 3 categories based on degree of hypoxemia: mild (PaO2/FIO2 ≤ 300 mm Hg), moderate (PaO2/FIO2 ≤ 200 mm Hg), and severe (PaO2/FIO2 ≤ 100 mm Hg)

References

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5.- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580-637. https://www/doi/10.1097/CCM.0b013e31827e83af.

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7.- Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: The Berlin Definition ARDS Definition Task Force. JAMA 2012;307(23):2526-33. https://doi/10.1001/jama.2012.5669.

Statistical analysis

To determine if a significant inter-hospital variation in corticosteroids is present, multilevel conditional logistic modelling with patients nested in hospital to characterize hospital-level variation of ICU mortality was done. We built a model with corticosteroids (treatment) and hospital as random variable, to assess the variation of the log-odds from one hospital to another and calculate the intraclass correlation coefficient (ICC) for one-way random-effects model.

The ICC quantifies the degree of homogeneity of the outcome within clusters and represents the proportion of the between-hospital variation in the total variation. When the ICC is not different from zero or negligible, indicates perfect independence of residuals and traditional one level regression analysis can be done (6). The ICC obtained when considering all hospital (n=63) was 0.04. This ICC represents that the hospital-level variation was very poor (4%).

```
model_cov<- lmer(muereUCI ~ cortis +(1|hospital), REML = FALSE, data=covid_mis)

summary(model_cov)

confint(model_cov)
```

```
Linear mixed model fit by maximum likelihood  ['lmerMod']

Formula: muereUCI ~ cortis + (1 | hospital)

Data: covid_mis

     AIC      BIC   logLik deviance df.resid

  2661.9   2684.4  -1327.0   2653.9     2018

Scaled residuals:

    Min      1Q  Median      3Q     Max

-1.0293 -0.7188 -0.5961  1.2942  1.7045
```

```
Random effects:
 Groups   Name        Variance Std.Dev.
 hospital (Intercept) 0.006893 0.08302
 Residual             0.213283 0.46183
 Number of obs: 2022, groups:  hospital, 63
 Fixed effects:
             Estimate Std. Error t value
(Intercept)  1.32097    0.02068  63.872
cortissi     0.01084    0.02210   0.491
Correlation of Fixed Effects:
        (Intr)
cortissi -0.643
Computing profile confidence intervals ...
                        2.5 %     97.5 %
.sig01        0.05308768 0.11813691
.sigma        0.44775260 0.47664905
(Intercept)  1.28038742 1.36242446
cortissi    -0.03273725 0.05431544
Show in New Window
[1] 0.009727901

intraclass correlation coefficient
icc <- model_cov@theta[1]^2/ (model_cov@theta[1]^2 + (3.14159^2/3))
icc
[1] 0.009727901
```

e-Table 1: Definitions of variables recorded, Comorbidities, Treatments, and Outcomes Collected in patients

General characteristics and severity of illness	
Hospital type	According to beds number (<200 ; 200-500 and > 500 beds)
Sex	1:Male; 0: Female
Age	Number of years of age at the time of ICU admission
Date of Hospital admission	Per chart review
Data of ICU admission	Per chart review
Data of ICU discharge	Per chart review
Data of Hospital discharge	Per chart review
GAP ICU	Time in days from Hospital to ICU admission
GAP diagnosis	Time in days from onset of symptoms to diagnosis
GAP antiviral treatment	Time in days from onset of symptoms to first dose of antiviral
APACHE II score	Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated for all patients within the first 24 h of ICU admission
SOFA score	Sequential Organ Failure Assessment (SOFA) scoring system was calculated for all patients within the first 24 h of ICU admission.
Health worker	People who work in the hospital or other areas of health care
Comorbidities and coexisting conditions	
9.- Asthma	Per chart review
10.- Chronic Pulmonary Obstructive Disease	Per chart review
11.- Arterial Hypertension	Per chart review
12.- Chronic Heart disease	Per chart review. New York Heart Association (NYHA) Functional Classification III and IV
13.- Chronic kidney disease	Baseline eGFR< 60 on at least two consecutive values at least 12 weeks apart prior or hemodialysis
14.- Hematologic disease	Per chart review, included acute leukemia, myelodysplastic syndrome and Lymphomas.
15.- Pregnancy	Per chart review
16.- Obesity	Body mass index > 30
17.- Diabetes mellitus	Per chart review
18.- HIV/AIDS	Per chart review
19.- Coronary artery disease	Per chart review
20.- Neuromuscular disease	Per chart review
21.- Immunological disease	Per chart review
22.- Other Immunodeficiency disorders	Per chart review
Laboratory findings	
D-Lactate dehydrogenase	U/L, Per laboratory report
White blood cell	$x10^9$ Per laboratory report
Serum Creatinine	mg/dL, Per laboratory report
C-Reactive Protein (CRP)	mg/mL, Per laboratory report
Procalcitonin (PCT)	ng/mL, Per laboratory report
Serum lactate	mmol/L, Per laboratory report
D dimer	ng/mL, Per laboratory report
Ferritin	ng/mL, Per laboratory report
Arterial blood gas (ABG) test	Per laboratory report
Treatment at ICU admission	
Corticosteroids	Per chart review
Antibiotics	Per chart review
Lopinavir/ritonavir	Per chart review
Hydroxychloroquine	Per chart review
Tocilizumab	Per chart review
Interferon β	Per chart review
Anti-hypertensive treatment	ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin receptor blockers
Oxygenation and ventilator support at ICU admission and at first 24 hours	
Oxygen mask	Per chart review
High Flow nasal cannula	Per chart review
Non-invasive ventilation	Per chart review
Invasive mechanical ventilation	Per chart review
Oxygen mask	Per chart review
High Flow nasal cannula	Per chart review

Complications at ICU admission	
Shock	Per chat review
Acute kidney dysfunction	Per chat review
Myocardial dysfunction	Per chat review
Community-acquired co-infection	Per chat review
> 2 Quadrant infiltrates in chest x-ray	Per chest x-ray review
Outcome	
ICU crude mortality	Per chart review

Development of phenotypes

All consecutive cases admitted to the ICU were collected. There were no patients excluded from the analysis that were enrolled based on the participating ICUs' established criteria. The ICU admission criteria, use of antiviral, antibiotic or co-adjuvant treatment, and also the measures that would determine the need to intubate and type of ventilator support required (oxygenation, high flow nasal cannula [HFNC], noninvasive [NIMV] or invasive [IMV] mechanical ventilation) were not standardized between centers. These guidelines were left to the discretion of the attending physician, according to SEMICYUC and National Ministry of Health and were included in the case report form and confirmed by the medical records. Defining variables recorded, comorbidities, treatments, and outcomes collected in all patients are shown in e-Table 1 in supplementary online content.

The analysis plan for the development of the phenotypes was carried out through the following steps:

In a first step, a multilevel conditional logistic modelling and the intraclass correlation coefficient (ICC) was calculated with patients nested in hospital to characterize hospital-level variation of ICU mortality and not a significant inter-hospital variation was observed.

In a second step, to determine presence of distinct clinical phenotypes in our population of COVID-19 patients, an unsupervised clustering analysis was applied to the database at ICU admission. In order to carry out this analysis, a discretization of the numerical variables into categorical ones was done. The information provided by each variable regarding ICU mortality was defined using the Information Value (IV). A IV greater than 0.03 was considered clinically important and this variable was included in the multivariate logistic regression analysis.

Model performance was examined using accuracy test, Sensitivity, Specificity and AUC modeling. Subsequently, the unsupervised cluster analysis was performed using the important variables. The Podani distance was used to calculate the distance between patients and the "partition around medoids" (PAM) algorithm to perform the clustering. Three was the optimal number of clusters determined after studying the silhouette and the PAM objective. Each of these clusters represent a specific patient's phenotype. We obtain important variables by the IV for each phenotype, and the OR of these variables were obtained after applying a GLM analysis. Multinomial regression models were fit to further compare patient comorbidities across phenotype classification. Model performance in each phenotype was examined using accuracy test, Sensibility, Specificity and AUC.

Lastly, a traditional multivariate analysis (GLM: Generalized linear Regression model) was performed to investigate the association between baseline (on ICU admission) variables and ICU-mortality. The GLM model comprised factors of clinical interest and all significant covariates ($p<0.05$) in the univariate analysis of ICU mortality and presence of collinearity was studied by variance inflation factors (VIF). To determine our model, we checked adequate model performance between groups with a cross validation model (K-fold=10) and the model with better performance was chosen.

For all model validation, database was randomly split into two subsets: (a) a "training set" (80%), and (b) a "validation set" (20%). Model performance was examined using accuracy test, precision, sensitivity,

specificity and area under ROC curve (AUC). Data analysis was performed using R software (cran.r-project.org).

Of the 50 variables considered, only 25 were considered as predictors according to the IV and were included in the model. Remarkably, no treatment option was a predictive factor for ICU-mortality (e-Table 2).

e-Table 2: Ranking of variables according to the information value to select important variables in a predictive model. Highly and somewhat predictive variables were included in the model.

(ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin receptor blockers; WBC: White blood cells; HFNC: High Flow nasal cannula, NIV: non-invasive ventilation, MV: invasive mechanical ventilation, CRP: C-Reactive Protein; PCT: Procalcitonin; GAP antiviral: Time from the symptoms onset to the first dose of antiviral, GAP diagnostic: Time from the symptoms onset to diagnosis, GAP ICU: time from the symptoms onset to ICU admission.)

## VARIABLES	Information Value	HSTRENGTH
## 1 Hospital type	4.041964e-03	Not Predictive
## 2 Male	9.730608e-03	Not Predictive
## 3 Influenza vaccine	2.719595e-02	Not Predictive
## 4 shock	1.025376e-01	Highly Predictive
## 5 Health worker	3.939070e-02	Somewhat Predictive
## 6 ACEI	5.176515e-02	Somewhat Predictive
## 7 ARB	1.407840e-02	Not Predictive
## 8 asthma	4.023492e-04	Not Predictive
## 9 COPD	4.605924e-02	Somewhat Predictive
## 10 Chronic Cardiac Dis	3.472710e-03	Not Predictive
## 11 Chronic Renal Dis	2.721800e-02	Not Predictive
## 12 Hematological Dis	2.144353e-02	Not Predictive
## 13 Pregnancy	2.253727e-03	Not Predictive
## 14 Obesity	2.452981e-03	Not Predictive
## 15 Diabetes	4.266095e-02	Somewhat Predictive
## 16 HIV	9.368383e-04	Not Predictive
## 17 Neuromuscular Dis	8.444705e-03	Not Predictive
## 18 Autoimmune Dis	5.088465e-04	Not Predictive
## 19 Coronary Dis	5.313002e-02	Somewhat Predictive
## 20 Hypertension	9.908557e-02	Somewhat Predictive
## 21 Infiltrates chest x-ray	3.931693e-02	Somewhat Predictive
## 22 Corticosteroids	4.460850e-03	Not Predictive
## 23 Antibiotics	7.133596e-05	Not Predictive
## 24 Empiric treatment	1.926115e-04	Not Predictive
## 25 Lopinavir/ritonavir	2.828696e-03	Not Predictive
## 26 interferon beta-1	1.351955e-02	Not Predictive
## 27 Hydroxychloroquine	8.557354e-03	Not Predictive
## 28 Tocilizumab	9.848787e-03	Not Predictive
## 29 O2	7.471572e-03	Not Predictive
## 30 Bacterial coinfection	6.317831e-03	Not predictive
## 31 HFNC	6.584694e-02	Somewhat Predictive
## 32 NIV	1.044679e-03	Not Predictive
## 33 MV	1.195287e-01	Highly Predictive
## 34 Myocardial Dysf.	1.020782e-01	Highly Predictive
## 35 Acute Kidney injury	4.267500e-01	Highly Predictive
## 36 Age	5.583901e-01	Highly Predictive
## 37 APACHE II	5.038235e-01	Highly Predictive
## 38 SOFA	3.964658e-01	Highly Predictive
## 39 Lactate dehydrogenase	1.623883e-01	Highly Predictive
## 40 WBC	5.118266e-02	Somewhat Predictive
## 41 Creatinine	2.605650e-01	Highly Predictive
## 42 CRP	5.374965e-02	Somewhat Predictive
## 43 PCT	1.590328e-01	Highly Predictive
## 44 Lactate	1.674733e-01	Highly Predictive
## 45 D Dimer	1.728036e-01	Highly Predictive
## 46 Ferritin	3.332789e-01	Highly Predictive
## 47 Gap antiviral	0.000000e+00	Not Predictive
## 48 PaO2/FiO2	6.116536e-02	Somewhat Predictive
## 49 Gap diagnostic	1.738805e-02	Not Predictive
## 50 Gap ICU	5.325043e-02	Somewhat Predictive

The categorized variables independently associated with ICU-mortality in each phenotype are shown in e-Table 3. The performance of the model was adequate with an accuracy of 0.77, sensitivity of 0.88, specificity of 0.54 and AUC of 0.82.

e-Table 3: Ranking of variables according to the information value to select important variables in each phenotype. Variables highlighted in red were included in each model. (ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin receptor blockers; WBC: White blood cells; HFNC: High Flow nasal cannula, NIV: non-invasive ventilation, MV: invasive mechanical ventilation, CRP: C-Reactive Protein; PCT: Procalcitonin; GAP antiviral: Time from the symptoms onset to the first dose of antiviral, GAP diagnostic: Time from the symptoms onset to diagnosis, GAP ICU: time from the symptoms onset to ICU admission.)

	A Phenotype		B Phenotype		C Phenotype	
Variables	IV	PREDICTIVE	IV	PREDICTIVE	IV	PREDICTIVE
## 1 Hospital type	9.132863e-03	No	1.559446e-03	No	2.944340e-02	No
## 2 Male	1.444146e-04	No	2.590207e-02	No	3.869809e-03	No
## 3 Influenza vaccine	9.431129e-02	Somewhat	2.126550e-02	No	3.765656e-02	Somewhat
## 4 shock	3.964703e-02	Somewhat	5.164118e-03	No	4.618684e-04	No
## 5 Health worker	7.215440e-02	Somewhat	6.021809e-02	Somewhat	9.813392e-03	No
## 6 ACEI	1.684165e-01	Highly	6.080522e-03	No	1.076237e-02	No
## 7 ARB	1.828984e-02	No	2.404218e-04	No	1.177667e-03	No
## 8 asthma	1.227356e-02	No	2.533545e-04	No	1.092745e-04	No
## 9 COPD	1.749341e-01	Highly	7.302773e-02	Somewhat	6.691157e-03	No
## 10 Chronic Cardiac Disease	6.204765e-02	Somewhat	1.492305e-03	No	2.960268e-05	No
## 11 Chronic Renal Disease	1.738024e-01	Highly	1.492305e-03	No	1.146307e-02	No
## 12 Hematological Disease	2.654456e-02	No	3.754947e-03	No	4.883194e-02	Somewhat
## 13 Pregnancy	9.222784e-03	No	1.283035e-02	No	0.000000e+00	No
## 14 Obesity	3.637363e-02	Somewhat	6.145638e-07	No	2.066138e-04	No
## 15 Diabetes	1.866242e-01	Highly	5.704696e-03	No	2.479443e-02	No
## 16 HIV	1.819062e-02	No	4.376645e-03	No	8.041982e-05	No
## 17 Neuromuscular Disease	3.325893e-02	Somewhat	4.106090e-03	No	4.524557e-03	No
## 18 Autoimmune Disease	1.319137e-05	No	7.433381e-03	No	3.870564e-03	No
## 19 Coronary Disease	1.340642e-01	Highly	2.627084e-03	No	1.221929e-01	Highly
## 20 Hypertension	2.210587e-01	Highly	1.186944e-02	No	1.223492e-02	No
## 21 Infiltrates chest x-ray	2.817873e-02	No	1.564487e-01	Highly	3.578773e-02	Somewhat
## 22 Corticosteroids	1.229703e-03	No	1.560437e-04	No	1.635793e-03	No
## 23 Antibiotics	6.889626e-03	No	3.134299e-03	No	2.975869e-04	No
## 24 Empiric treatment	5.959459e-03	No	4.937022e-03	No	2.287937e-03	No
## 25 Lopinavir/ritonavir	1.598323e-03	No	5.711297e-02	Somewhat	1.005827e-04	No
## 26 interferon beta-1	2.656602e-02	No	2.371890e-02	No	8.530341e-03	No
## 27 Hydroxychloroquine	4.276412e-02	Somewhat	2.599639e-04	No	3.468705e-02	Somewhat
## 28 Tocilizumab	1.916296e-02	No	2.610744e-03	No	1.415470e-02	No
## 29 O2	2.146274e-05	No	3.402079e-02	Somewhat	4.340230e-03	No
## 30 HFNC	2.353027e-03	No	7.516552e-04	No	1.157880e-03	No
## 31 NIV	1.070219e-02	No	3.063022e-02	Somewhat	3.737383e-05	No
## 32 MV	3.057185e-03	No	1.653186e-01	Highly	2.370305e-08	No
## 33 Myocardial Dysfunction	2.228904e-01	Highly	6.177601e-02	Somewhat	6.055540e-02	Somewhat
## 34 Acute Kidney injury	6.306028e-01	Highly	3.646921e-01	Highly	2.337694e-01	Highly
## 35 Age	6.513748e-01	Highly	7.408417e-01	Highly	4.622984e-01	Highly
## 36 APACHE II	4.310389e-01	Highly	2.986345e-01	Highly	2.939476e-01	Highly
## 37 SOFA	4.038444e-01	Highly	2.953304e-01	Highly	1.487510e-01	Highly
## 38 Lactate dehydrogenase	5.366081e-02	Somewhat	1.041057e-01	Highly	3.504073e-02	Somewhat
## 39 WBC	4.581520e-02	Somewhat	2.181871e-03	No	3.820653e-02	Somewhat
## 40 Creatinine	5.615214e-01	Highly	2.412052e-01	Highly	9.217995e-02	Somewhat
## 41 CRP	7.164503e-02	Somewhat	8.547374e-02	Somewhat	3.204018e-03	No
## 42 PCT	3.048025e-01	Highly	8.008344e-02	Somewhat	0.000000e+00	No
## 43 Lactate	6.190517e-02	Somewhat	1.543924e-01	Highly	2.290830e-01	Highly
## 44 D Dimer	2.521748e-01	Highly	4.644420e-01	Highly	8.243056e-02	Somewhat
## 45 Ferritin	4.180265e-01	Highly	3.490296e-01	Highly	1.818192e-01	Highly
## 46 Gap antiviral	2.766619e-01	Highly	0.000000e+00	No	0.000000e+00	No
## 47 PaO2/FiO2	0.000000e+00	No	0.000000e+00	No	1.018619e-01	Highly
## 48 Gap diagnostic	0.000000e+00	No	0.000000e+00	No	0.000000e+00	No
## 49 Gap ICU	6.204765e-02	Somewhat	0.000000e+00	No	7.482980e-02	Somewhat

Patients with the cluster A phenotype (mild COVID-19 disease) had <65 years, lower severity of illness, fewer abnormal laboratory values and less development of complications, with a crude ICU mortality of 20.3%; those with the cluster B phenotype (moderate COVID-19 disease) had similar characteristics as seen in the A phenotype but were more likely to present shock at ICU admission with a crude ICU-mortality of 25.5%. Patients with the cluster C phenotype (severe COVID-19 disease) had >65 years, a high level of severity of illness, more likely to have elevated measures of inflammation (e.g. D dimer, LDH and ferritin), high frequency of shock, AKI and myocardial dysfunction, with a crude ICU mortality of 45.4%

A detailed description of the development and analysis of clusters can be found in the original paper (3).

References

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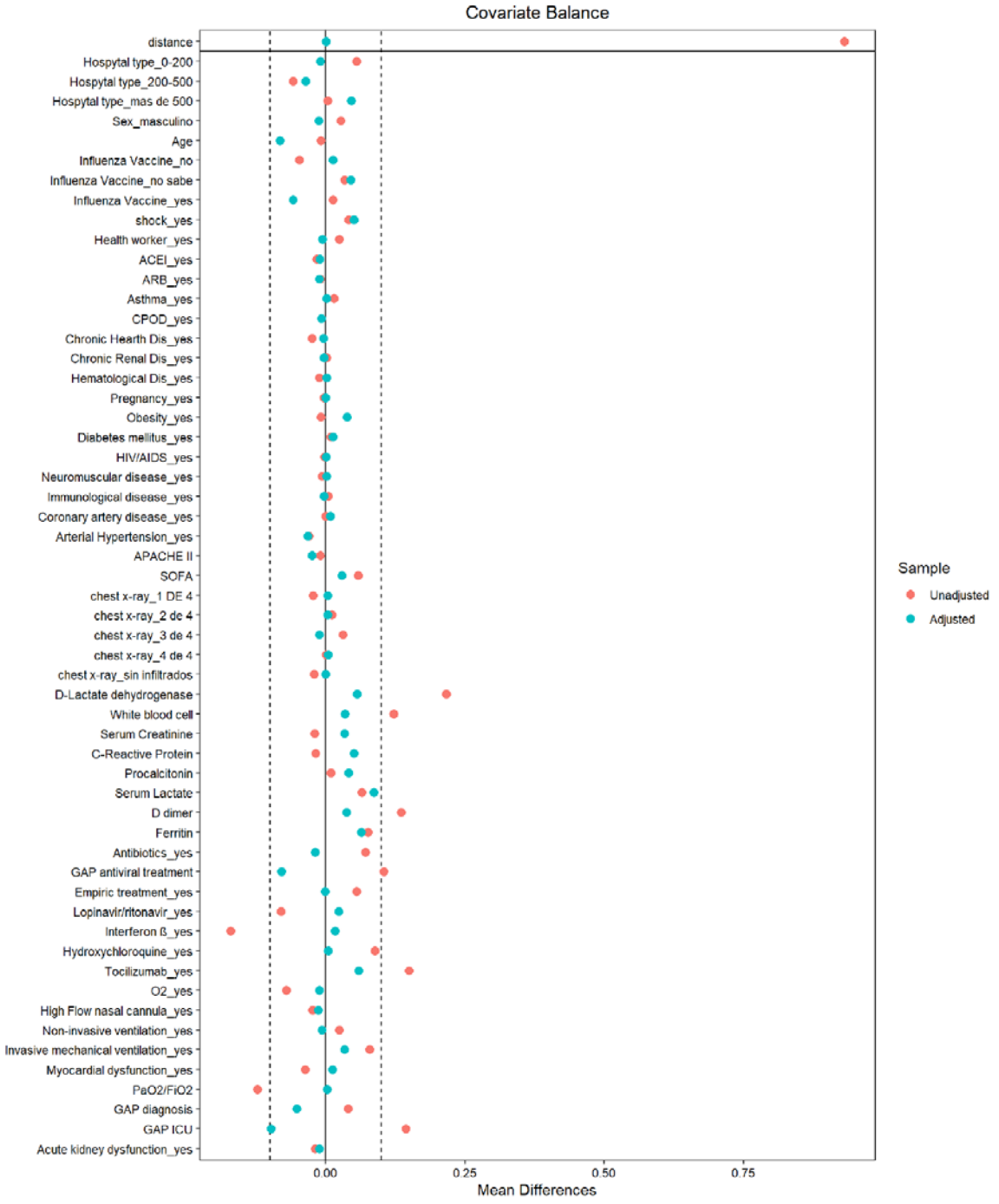
ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin receptor blockers; WBC: White blood cells; HFNC: High Flow nasal cannula, NIV: non-invasive ventilation, MV: invasive mechanical ventilation, CRP: C-Reactive Protein; PCT: Procalcitonin ; GAP antiviral: Time from the symptoms onset to the first dose of antiviral, GAP diagnostic: Time from the symptoms onset to diagnosis, GAP ICU: time from the symptoms onset to ICU admission.

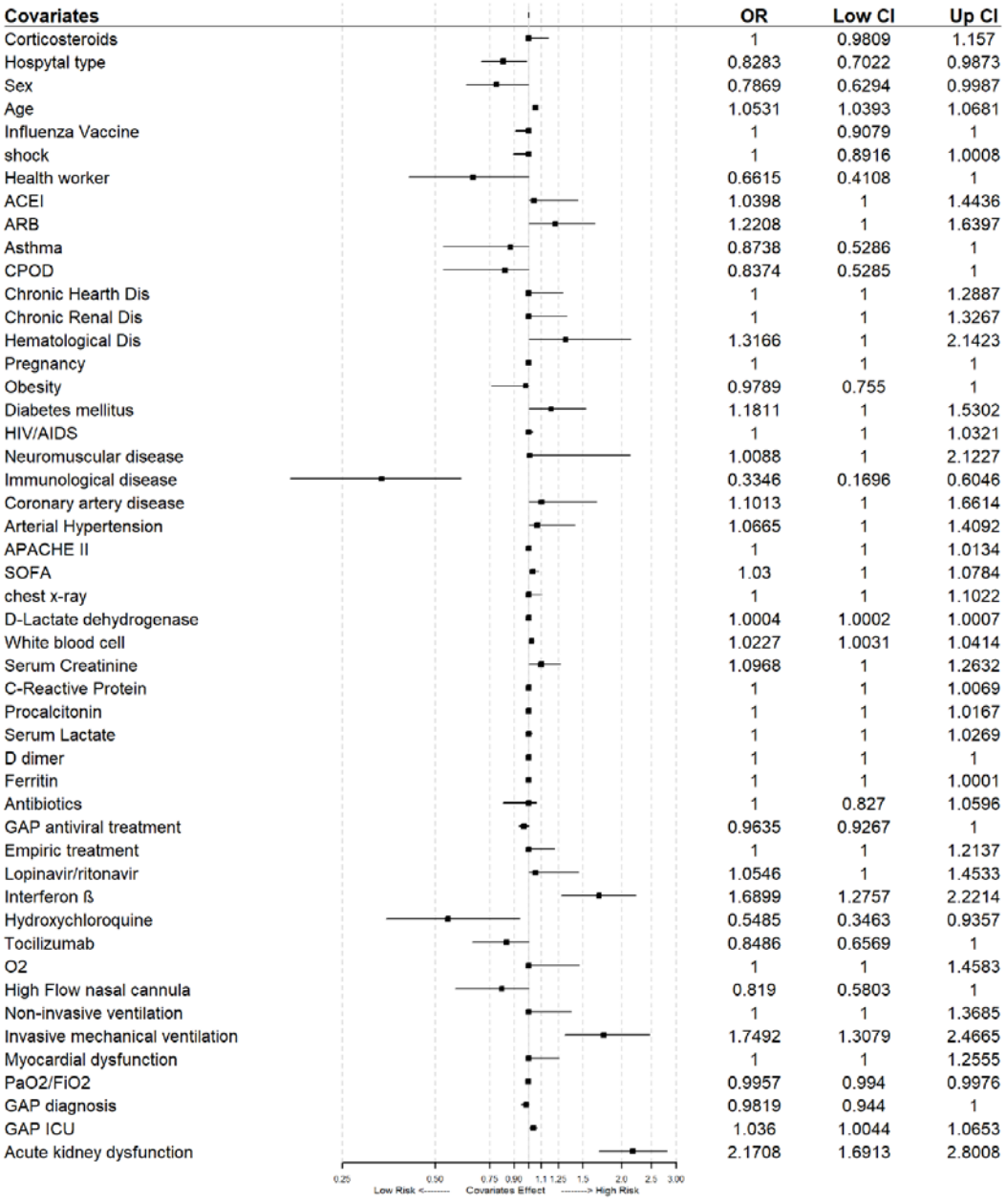
e-Table 4: Characteristics of whole population and different phenotypes according corticosteroid treatment

	Whole Population (n=2017)		A Phenotype (n= 537)			B Phenotype (n=623)			C Phenotype (n=857)		
Variable	**Corticosteroid= NO n=846**	**Corticosteroid= YES n=1171**	**Corticosteroid = NO n=239**	**Corticosteroid= YES n=298**	**p-value**	**Corticosteroid = NO n= 285**	**Corticosteroid= YES n=338**	**p-value**	**Corticosteroid = NO n= 322**	**Corticosteroid= YES n=535**	**p-value**
General characteristics and severity of illness											
Age, median (p25-75), year	65(55-72)	64(56-88)	63(53-69)	63(54-71)	0.61	64(50-73)	63(55-71)	0.71	66(58-73)	65(58-71)	0.05
Male, n(%)	582(68.8)	837(71.5)	163 (68.2)	214(71.8)	0.41	189(66.3)	227(67.2)	0.89	230(71.4)	396(74.0)	0.45
APACHE II [b], median (p25-75),	14(11-18)	14(11-18)	12(9-16)	11.5(9-15)	0.39	13(10-17)	12(10-16)	0.36	17(14-22)	17(14-21)	0.24
SOFA [c], median(p25-75),	5.0(3-7)	5.7(4-8)	4(3-5)	4(3-5)	0.61	5(3-7)	5(3-6)	0.88	7(5-9)	7(6-8)	0.95
GAP diagnosis[d], median(p25-75),	6(4-9)	7(4-9)	7 (5-9)	6.6(4-8)	0.35	6(4-8)	6(3-8)	0.89	6(4-8)	7(5-8)	0.01
Laboratory findings											
D-lactate dehydrogenase, median (p25-75), U/L	509(405-640)	570(434-765)***	478(381-547)	463(359-576)	0.49	451(358-543)	492(400-587)	**0.001**	605(504-800)	708(576-990)	**0.001**
White blood cell, median (p25-75), x10^9	8.3(6.0-11.6)	9.2(6.4-12.8)***	7.2(5.6-10.2)	8.3(6.0-10.2)	**0.04**	8.2(5.8-10.8)	9.2(6.2-12.4)	**0.005**	9.6(6.7-12.7)	10.2(7.0-14.0)	0.08
Serum creatinine, median (p25-75), mg/dL	0.88(0.70-1.16)	0.85(0.70-1.12)	0.80(0.66-1.03)	0.80(0.66-1.01)	0.98	0.82(0.65-1.02)	0.79(0.66-0.97)	0.36	1.0(0.78-1.36)	0.98(0.74-1.37)	0.22
C-Reactive Protein , median (p25-75), mg/dL	15.7(9.8-24)	15.3(8.9-25.0)	15(9-21)	14(7-22)	0.36	14.5(8.7-21.4)	14.4(8.0-23.0)	0.82	18(11-27)	18(10-26)	0.25
Procalcitonin, median (p25-75), ng/mL	0.33-(0.15-0.85)	0.31(0.14-0.87)	0.29(0.14-0.60)	0.27(0.10-0.68)	0.36	0.21(0.12-0.62)	0.23(0.10-0.50)	0.67	0.61(0.24-1.39)	0.50(0.20-1.30)	0.06
Serum lactate, median (p25-75), mmol/L	1.5(1.1-2.0)	1.6(1.2-2.2)*	1.5(1.2-1.9)	1.5(1.1-2.0)	0.94	1.3(1.0-1.8)	1.5(1.1-2.0)	**0.002**	1.6(1.2-2.1)	1.7(1.3-2.2)	0.32
D dimer, median (p25-75), ng/mL	1590(720-3880)	1700(723-5990)	1160(592-2025)	1058(571-2370)	0.87	1340(670-2830)	1305(615-3980)	0.55	2200(1000-4846)	2330(1023-5099)	0.30
Ferritin, median (p25-75), ng/mL	1577(1300-2150)	1668(1300-2300)*	1509(1264-1825)	1596(1300-2038)	**0.03**	1528(1267-1829)	1580(1276-2016)	0.27	1780(1445-2290)	1860(1375-2440)	0.37
Coexisting condition and comorbidities											
Arterial hypertension, n(%)	283(33.4)	526(44.9)	90(37.7)	121(40.6)	9.54	83(29.1)	90(26.6)	0.54	233(72.4)	315(58.9)	**0.001**
Obesity (BMI>30), n(%)	278(32.8)	375(32.0)	80(33.5)	79(26.5)	0.09	88(30.9)	112(33.1)	0.60	110(34.2)	184(34.4)	1.00
Diabetes, n(%)	171(20.2)	247(21.0)	44(18.4)	68(22.8)	0.25	56(19.6)	52(15.4)	0.19	71(22.0)	127(23.7)	0.62
Coronary arterial disease, n(%)	52(6.1)	72(6.1)	10(4.2)	25(8.4)	0.07	22(7.7)	19(5.6)	0.37	20(6.2)	28(5.2)	0.65
COPD, n(%)	66(7.8)	82(7.0)	16(6.7)	21(7.0)	1.00	19(6.7)	19(5.6)	0.70	31(9.6)	42(7.9)	0.43
Chronic renal disease, n(%)	35(4.1)	50(4.2)	12(5.0)	19(6.4)	0.62	4(1.4)	6(1.8)	0.96	19(5.9)	25(4.7)	0.52
Hematologic disease, n(%)	36(4.2)	36(3.0)	12(5.0)	8(2.7)	0.23	12(4.2)	10(3.0)	0.53	12(3.7)	18(3.4)	0.93
Asthma, n(%)	43(5.0)	77(6.6)	13(5.4)	28(9.4)	0.12	21(7.4)	24(7.1)	1.00	9(2.8)	25(4.7)	0.23
HIV, n(%)	3(0.3)	2(0.1)	1(0.4)	1(0.3)	1.00	1(0.4)	0(0.0)	0.93	1(0.3)	1(0.2)	1.00
Pregnancy, n(%)	3(0.3)	1(0.08)	0(0.0)	1(0.3)	1.00	3(1.1)	0(0.0)	0.19	0(0.0)	0(0.0)	NA
Autoimmune disease, n(%)	29(3.4)	46(3.9)	5(2.1)	15(5.0)	0.11	11(3.9)	7(2.1)	0.27	13(4.0)	23(4.3)	0.99
Chronic heart disease, n(%)	36(4.2)**	21(1.8)	14(5.9)	7(2.3)	0.06	8(2.8)	2(0.6)	0.06	14(4.3)	12(2.2)	0.12
Neuromuscular disease, n(%)	10(1.2)	6(0.51)	2(0.8)	1(0.3)	0.84	4(1.4)	1(0.3)	0.27	4(1.2)	4(0.7)	0.71
Oxygenation and ventilator support											
Oxygen mask, n(%)	171(20.2)***	154(13.1)	61(25.5)	63(21.1)	0.27	68(23.9)	37(10.9)	**0.001**	42(13)	54(10.1)	0.22
High flow nasal cannula, n(%)	169(19.9)	206(24.3)	152(63.6)	193(64.8)	0.84	2(0.7)	1(0.3)	0.88	15(4.7)	12(2.2)	0.07
Non-invasive ventilation, n(%)	47(5.5)	93(7.9)	21(8.8)	43(14.4)	0.06	8(2.8)	18(5.3)	0.17	18(5.6)	32(6.0)	0.93
Invasive mechanical ventilation, n(%)	453(53.5)	719(61.4)***	2(0.8)	1(0.3)	0.84	200(70.2)	275(81.4)	**0.002**	251(78.0)	443(82.8)	0.09
PaO2/FiO2, median (p25-75),	130(100-170)	130(93-162) **	116(81-136)	106(83-130)	0.13	167(148-220)	162(135-209)	0.05	124(88-157)	126(88-154)	0.54
Complications and outcome											
Shock, n(%)	359(42.4)	545(46.5)	24(10)	32(10.7)	0.90	95(33.3)	101(29.9)	0.40	240(74.5)	412(77.0)	0.45
AKI, n(%)	252(29.8)	327(27.9)	54(22.6)	57(19.1)	0.38	54(18.9)	64(18.9)	1.00	144(44.7)	206(38.5)	0.08
Myocardial dysfunction, n(%)	89(10.5)	80(6.8)	17(7.1)	13(4.4)	0.23	28(9.8)	15(4.4)	**0.01**	44(13.7)	52(9.7)	0.09
>2 quadrant infiltrates in chest x-ray, n(%)	542(64.0)	788(67.2)	141(58.9)	203(68.1)	**0.02**	179(62.8)	234(69.2)	0.09	222(68.9)	351(65.6)	0.31
Ventilator associated pneumonia n(%)	116(13.7)	210(17.9)	35(14.6)	38(12.8)	0.61	34(11.9)	63(18.6)	**0.02**	47(14.6)	109(20.4)	**0.04**
ICU LOS, median(p25-75)	13(5.4-23)	15(9.0-27)***	12(5-26)	11(6-21)	0.65	13(5-20)	14(8-25)	**0.001**	15(7.0-24.0)	19(11-30)	**0.001**
ICU crude mortality, n(%)	261(30.8)	396(33.8)	47(19.7)	62(20.8)	0.82	72(25.3)	87(25.7)	0.96	142(44.1)	247(46.2)	0.60

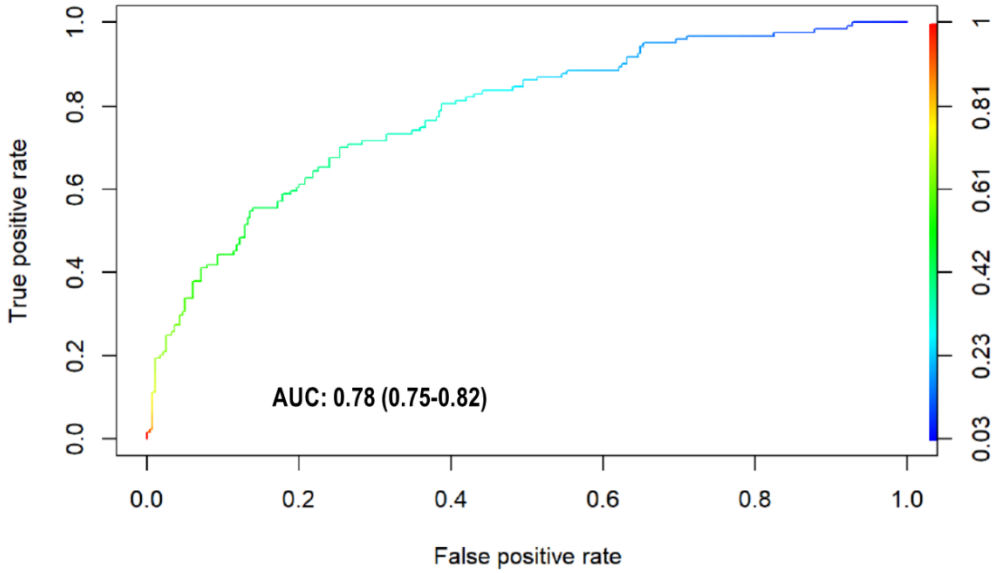
e-Figure 1: Mean differences plot of variables before and after propensity full matching



e-Table 5: Forest plot of variables associated with ICU mortality in the multivariate analysis in whole population



e-Figure 2: Area under ROC curve for ICU mortality multivariate model in the whole population



e-Table 6: Characteristics of 537 A phenotype patients according to ICU mortality

Variable [a]	Survivors n=428	Non- survivors n=109	p-value
General characteristics and severity of illness			
Age, median (p25-75), year	60.5(51-68)	70(64-74)	**0.001**
Male, n(%)	300 (70.1)	77(70.6)	1.00
APACHE II [b], median (p25-75),	11(8-15)	15(11-18)	**0.001**
SOFA [c], median(p25-75),	3(3-5)	5(3-7)	**0.001**
Laboratory findings			
D-lactate dehydrogenase, median (p25-75), U/L	467(369-549)	488(384-582)	0.07
White blood cell, median (p25-75), $x10^9$	7.6(5.8-10.2)	8.0(5.8-10.8)	0.93
Serum creatinine, median (p25-75), mg/dL	0.79(0.64-0.94)	0.96(0.77-1.42)	**0.001**
C-Reactive Protein , median (p25-75), mg/dL	14(7-22)	15 (10-22.7)	0.09
Procalcitonin, median (p25-75), ng/mL	0.25(0.10-0.53)	0.55(0.20-1.28)	**0.001**
Serum lactate, median (p25-75), mmol/L	1.5(1.1-1.9)	1.7(1.2-2.2)	**0.03**
D dimer, median (p25-75), ng/mL	1960(512-1965)	1620(875-3770)	**0.001**
Ferritin, median (p25-75), ng/mL	1500(1260-1820)	1820(1390-2190)	**0.001**
Coexisting condition and comorbidities			
Arterial hypertension, n(%)	148(34.6)	63(57.8)	**0.001**
Obesity (BMI>30), n(%)	119(27.8)	40(36.7)	0.08
Diabetes, n(%)	73(17.1)	39(35.8)	**0.001**
Coronary arterial disease, n(%)	19(4.4)	16(14.7)	**0.001**
COPD, n(%)	19(4.4)	18(16.5)	**0.001**
Chronic renal disease, n(%)	15(3.5)	16(14.7)	**0.001**
Hematologic disease, n(%)	13(3.0)	7(6.4)	0.16
Asthma, n(%)	30(7.0)	11(10.1)	0.37
HIV, n(%)	2(0.5)	0(0.0)	1.00
Pregnancy, n(%)	1(0.2)	0(0.0)	1.00
Autoimmune disease, n(%)	16(3.7)	4(3.7)	1.00
Chronic heart disease, n(%)	12(2.8)	9(8.3)	**0.01**
Neuromuscular disease, n(%)	1(0.2)	1(0.3)	0.84
Oxygenation and ventilator support			
Oxygen mask, n(%)	99(23.1)	25(22.9)	1.00
High flow nasal cannula, n(%)	277(64.7)	68(62.4)	0.73
Non-invasive ventilation, n(%)	48(11.2)	16(14.7)	0.40
Invasive mechanical ventilation, n(%)	2(0.5)	1(0.9)	1.00
PaO2/FiO2, median (p25-75),	114(85-136)	98(70-122)	**0.001**
Treatment			
Corticosteroids, n(%)	236(55.1)	62(56.9)	0.82
Antibiotics, n(%)	370(86.4)	91(83.5)	0.52
Lopinavir/ritonavir, n(%)	359(83.9)	93(85.3)	0.82
Hydroxychloroquine, No.(%)	396(92.5)	94(86.2)	0.06
Tocilizumab , No.(%)	107(25.0)	21(19.3)	0.25
Interferon β, No.(%)	143(33.4)	45(41.3)	0.15
Complications and Outcome			
Shock, n(%)	39(9.1)	17(15.6)	0.08
AKI, n(%)	58(13.6)	53(48.6)	**0.001**
Myocardial dysfunction, n(%)	13(3.0)	17(15.6)	**0.001**
>2 quadrant infiltrates in chest x-ray, n(%)	271(63.3)	73(66.9)	0.50
LOS UCI, median (p25-75), days	11(5.7-22)	14.5(7-29)	0.10

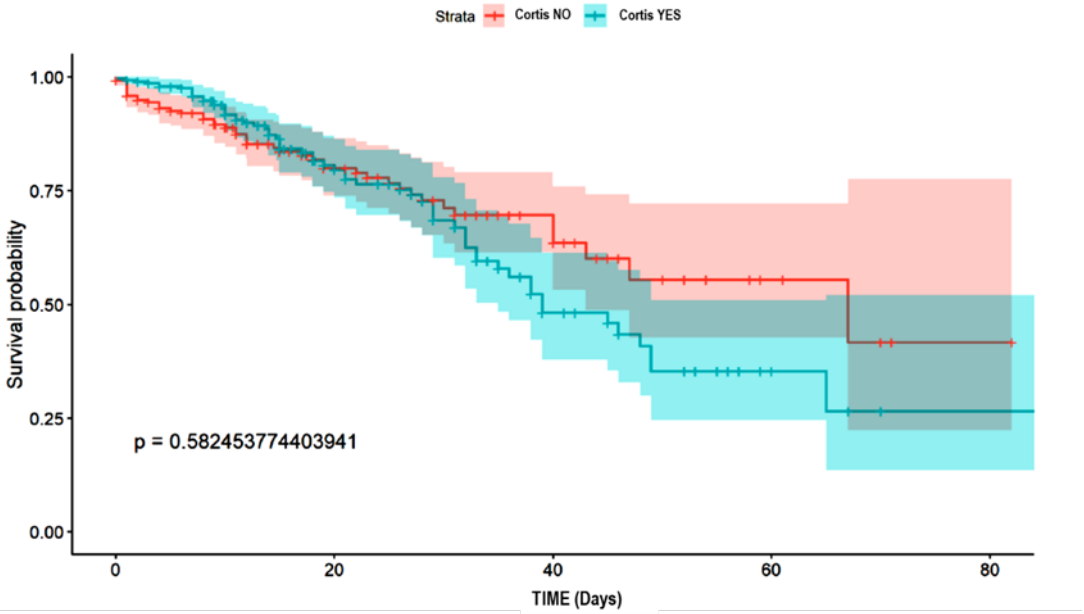
Abbreviations: (p25-75): percentile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses; PaO2/FiO2, Partial pressure arterial oxygen/ fraction of inspired oxygen

a Corresponds to minimum or maximum value, as appropriate, within 12 hours of ICU admission. The variables in this Table were no transformed for your comparison.

b APACHE II score to the severity of illness, the score is obtained by adding the following components 1) 12 clinical and laboratory variables each with a score range of 0 to 4 points (APS). The APS is determined from the worst physiologic values during the initial 24 h after ICU admission, 2) age with a range 0 to 6 points and 3) Chronic health points if the patients has history of severe organ system insufficiency or is immunocompromised assign 5 points if the patients is no operative or emergency postoperative and 2 points for elective postoperative patients with a total score range of 0 to 71.

c SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24,

e-Figure 3: Unadjusted survival plot (Kaplan-Meier) for A phenotype patients according to corticosteroids treatment (cortis)

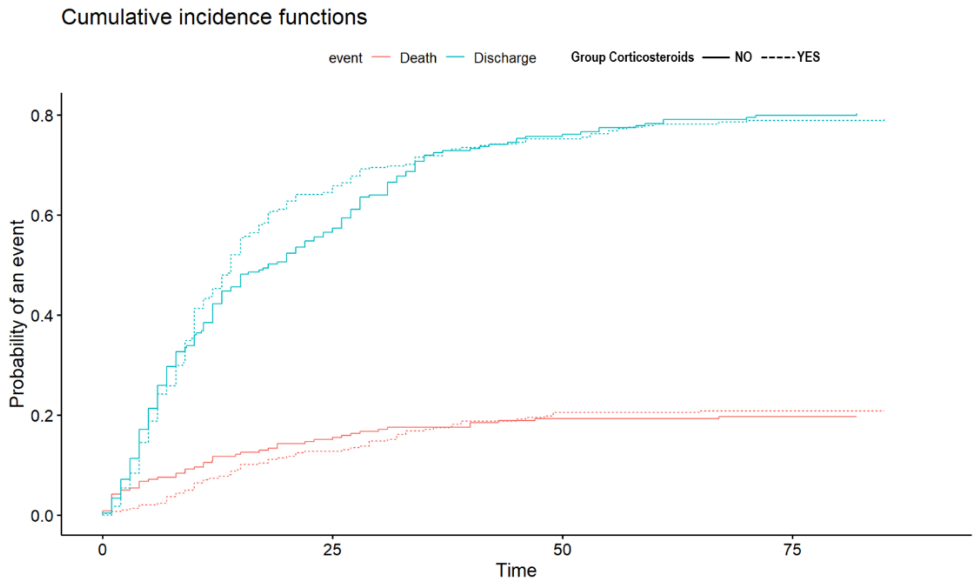


e-Table 7: Ranking of variables according to the information value to select important variables in each phenotype. Variables highlighted in red were included in each model.

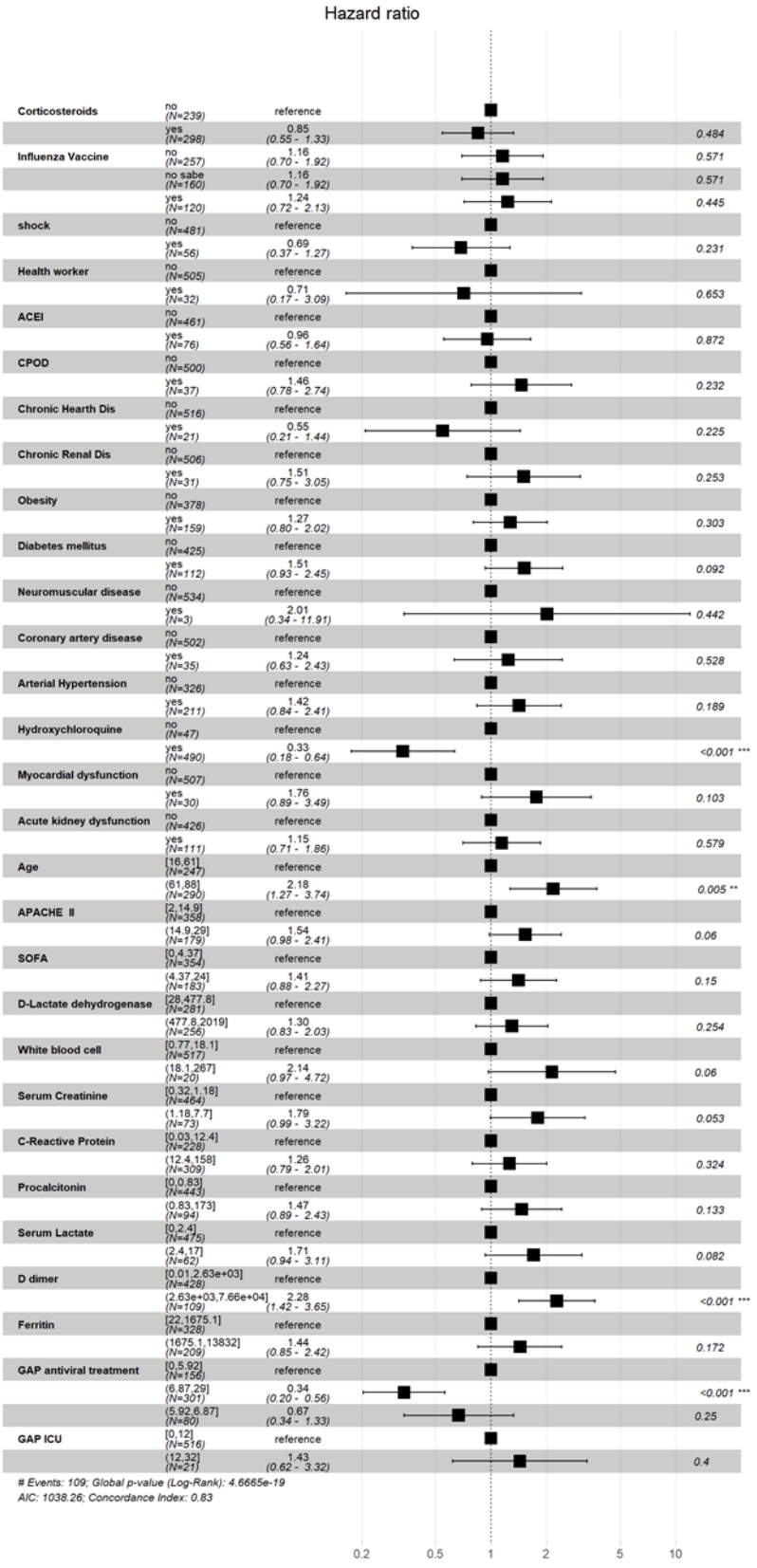
	A Phenotype		B Phenotype		C Phenotype	
Variables	IV	PREDICTIVE	IV	PREDICTIVE	IV	PREDICTIVE
## 1 Hospital type	9.132863e-03	No	1.559446e-03	No	2.944340e-02	No
## 2 Male	1.444146e-04	No	2.590207e-02	No	3.869809e-03	No
## 3 Influenza vaccine	9.431129e-02	Somewhat	2.126550e-02	No	3.765656e-02	Somewhat
## 4 shock	3.964703e-02	Somewhat	5.164118e-03	No	4.618684e-04	No
## 5 Health worker	7.215440e-02	Somewhat	6.021809e-02	Somewhat	9.813392e-03	No
## 6 ACEI	1.684165e-01	Highly	6.080522e-03	No	1.076237e-02	No
## 7 ARB	1.828984e-02	No	2.404218e-04	No	1.177667e-03	No
## 8 asthma	1.227356e-02	No	2.533545e-04	No	1.092745e-04	No
## 9 COPD	1.749341e-01	Highly	7.302773e-02	Somewhat	6.691157e-03	No
## 10 Chronic Cardiac Disease	6.204765e-02	Somewhat	1.492305e-03	No	2.960268e-05	No
## 11 Chronic Renal Disease	1.738024e-01	Highly	1.492305e-03	No	1.146307e-02	No
## 12 Hematological Disease	2.654456e-02	No	3.754947e-03	No	4.883194e-02	Somewhat
## 13 Pregnancy	9.222784e-03	No	1.283035e-02	No	0.000000e+00	No
## 14 Obesity	3.637363e-02	Somewhat	6.145638e-07	No	2.066138e-04	No
## 15 Diabetes	1.866242e-01	Highly	5.704696e-03	No	2.479443e-02	No
## 16 HIV	1.819062e-02	No	4.376645e-03	No	8.041982e-05	No
## 17 Neuromuscular Disease	3.325893e-02	Somewhat	4.106090e-03	No	4.524557e-03	No
## 18 Autoimmune Disease	1.319137e-05	No	7.433381e-03	No	3.870564e-03	No
## 19 Coronary Disease	1.340642e-01	Highly	2.627084e-03	No	1.221929e-01	Highly
## 20 Hypertension	2.210587e-01	Highly	1.186944e-02	No	1.223492e-02	No
## 21 Infiltrates chest x-ray	2.817873e-02	No	1.564487e-01	Highly	3.578773e-02	Somewhat
## 22 Corticosteroids	1.229703e-03	No	1.560437e-04	No	1.635793e-03	No
## 23 Antibiotics	6.889626e-03	No	3.134299e-03	No	2.975869e-04	No
## 24 Empiric treatment	5.959459e-03	No	4.937022e-03	No	2.287937e-03	No
## 25 Lopinavir/ritonavir	1.598323e-03	No	5.711297e-02	Somewhat	1.005827e-04	No
## 26 interferon beta-1	2.656602e-02	No	2.371890e-02	No	8.530341e-03	No
## 27 Hydroxychloroquine	4.276412e-02	Somewhat	2.599639e-04	No	3.468705e-02	Somewhat
## 28 Tocilizumab	1.916296e-02	No	2.610744e-03	No	1.415470e-02	No
## 29 O2	2.146274e-05	No	3.402079e-02	Somewhat	4.340230e-03	No
## 30 HFNC	2.353027e-03	No	7.516552e-04	No	1.157880e-03	No
## 31 NIV	1.070219e-02	No	3.063022e-02	Somewhat	3.737383e-05	No
## 32 MV	3.057185e-03	No	1.653186e-01	Highly	2.370305e-08	No
## 33 Myocardial Dysfunction	2.228904e-01	Highly	6.177601e-02	Somewhat	6.055540e-02	Somewhat
## 34 Acute Kidney injury	6.306028e-01	Highly	3.646921e-01	Highly	2.337694e-01	Highly
## 35 Age	6.513748e-01	Highly	7.408417e-01	Highly	4.622984e-01	Highly
## 36 APACHE II	4.310389e-01	Highly	2.986345e-01	Highly	2.939476e-01	Highly
## 37 SOFA	4.038444e-01	Highly	2.953304e-01	Highly	1.487510e-01	Highly
## 38 Lactate dehydrogenase	5.366081e-02	Somewhat	1.041057e-01	Highly	3.504073e-02	Somewhat
## 39 WBC	4.581520e-02	Somewhat	2.181871e-03	No	3.820653e-02	Somewhat
## 40 Creatinine	5.615214e-01	Highly	2.412052e-01	Highly	9.217995e-02	Somewhat
## 41 CRP	7.164503e-02	Somewhat	8.547374e-02	Somewhat	3.204018e-03	No
## 42 PCT	3.048025e-01	Highly	8.008344e-02	Somewhat	0.000000e+00	No
## 43 Lactate	6.190517e-02	Somewhat	1.543924e-01	Highly	2.290830e-01	Highly
## 44 D Dimer	2.521748e-01	Highly	4.644420e-01	Highly	8.243056e-02	Somewhat
## 45 Ferritin	4.180265e-01	Highly	3.490296e-01	Highly	1.818192e-01	Highly
## 46 Gap antiviral	2.766619e-01	Highly	0.000000e+00	No	0.000000e+00	No
## 47 PaO2/FiO2	0.000000e+00	No	0.000000e+00	No	1.018619e-01	Highly
## 48 Gap diagnostic	0.000000e+00	No	0.000000e+00	No	0.000000e+00	No
## 49 Gap ICU	6.204765e-02	Somewhat	0.000000e+00	No	7.482980e-02	Somewhat

ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin receptor blockers; WBC: White blood cells; HFNC: High Flow nasal cannula, NIV: non-invasive ventilation, MV: invasive mechanical ventilation, CRP: C-Reactive Protein; PCT: Procalcitonin; GAP antiviral: Time from the symptoms onset to the first dose of antiviral, GAP diagnostic: Time from the symptoms onset to diagnosis, GAP ICU: time from the symptoms onset to ICU admission.

e-Figure 4: Competing risk analysis (Fine and Grey) for A Phenotype patient's

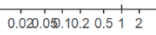


e-Table 8: Factors associated with ICU mortality in Cox Hazard regression analysis for patients among A phenotype



e-Table 9: Factors associated with corticosteroids use in A phenotype patients'

Variable		N	Odds ratio	p
White blood cell		537	1.04 (1.00, 1.08)	0.07
Ferritin		537	1.00 (1.00, 1.00)	0.25
>2 quadrants in chest x-ray	2 or less	193	Reference	
	more than 2	344	1.51 (1.05, 2.16)	0.03
APACHE II		537	0.97 (0.94, 1.01)	0.13
SOFA		537	1.04 (0.96, 1.13)	0.33
Age		537	1.01 (0.99, 1.02)	0.42
Invasive mechanical ventilation	no	534	Reference	
	yes	3	0.27 (0.01, 3.01)	0.30
Obesity	no	378	Reference	
	yes	159	0.73 (0.50, 1.07)	0.10
C-Reactive Protein		537	0.99 (0.98, 1.01)	0.29



e-Table 10: Characteristics of 623 B phenotype patients according to ICU mortality

Variable [a]	Survivors n=464	Non- survivors n=159	p-value
General characteristics and severity of illness			
Age, median (p25-75), year	61(51-69)	71(63-75)	**0.001**
Male, n(%)	301(64.9)	115(72.3)	0.10
APACHE II [b], median (p25-75),	12(9-16)	15(12-18)	**0.001**
SOFA [c], median(p25-75),	4.5(3-6)	6.(4-7.5)	**0.001**
Laboratory findings			
D-lactate dehydrogenase, median (p25-75), U/L	463(366-555)	511(418-650)	**0.001**
White blood cell, median (p25-75), $x10^9$	8.3(5.9-11.3)	9.6(6.4-13.7)	**0.01**
Serum creatinine, median (p25-75), mg/dL	0.78(0.64-0.94)	0.88(0.7-1.18)	**0.001**
C-Reactive Protein , median (p25-75), mg/dL	13.8(7.7-21.3)	17.3(10.0-25.5)	**0.001**
Procalcitonin, median (p25-75), ng/mL	0.21(0.10-0.45)	0.27(0.14-0.79)	**0.002**
Serum lactate, median (p25-75), mmol/L	1.4(1.0-1.8)	1.7(1.1-2.2)	**0.001**
D dimer, median (p25-75), ng/mL	1140(575-2790)	1870(790-5780)	**0.001**
Ferritin, median (p25-75), ng/mL	1500(1200-1760)	1775(1480-2350)	**0.001**
Coexisting condition and comorbidities			
Arterial hypertension, n(%)	123(26.5)	50(31.4)	0.27
Obesity (BMI>30), n(%)	149(32.1)	51(32.1)	1.00
Diabetes, n(%)	77(16.6)	31(19.5)	0.47
Coronary arterial disease, n(%)	29(6.2)	12(7.5)	0.70
COPD, n(%)	20(4.3)	18(11.3)	**0.003**
Chronic renal disease, n(%)	8(1.7)	2(1.3)	0.97
Hematologic disease, n(%)	15(3.2)	7(4.4)	0.65
Asthma, n(%)	34(7.3)	11(6.9)	1.00
HIV, n(%)	1(0.2)	0(0.0)	1.00
Pregnancy, n(%)	3(0.6)	0(0.0)	0.72
Autoimmune disease, n(%)	15(3.2)	3(1.9)	0.54
Chronic heart disease, n(%)	8(1.7)	2(1.3)	0.97
Neuromuscular disease, n(%)	3(0.6)	2(1.3)	0.81
Oxygenation and ventilator support			
Oxygen mask, n(%)	86(18.5)	19(11.9)	0.07
High flow nasal cannula, n(%)	2(0.4)	1(0.6)	1.00
Non-invasive ventilation, n(%)	23(5.0)	3(1.9)	0.15
Invasive mechanical ventilation, n(%)	335(72.2)	140(88.1)	**0.001**
PaO2/FiO2, median (p25-75),	169(147-220)	154(130-206)	**0.001**
Treatment			
Corticosteroids, n(%)	251(54.1)	87(54.7)	0.96
Antibiotics, n(%)	425(91.6)	148(93.1)	0.67
Lopinavir/ritonavir, n(%)	368(79.3)	140(88.1)	**0.02**
Hydroxychloroquine, No.(%)	421(90.7)	145(91.2)	0.98
Tocilizumab , No.(%)	160(34.5)	51(32.1)	0.64
Interferon β, No.(%)	158(34.1)	66(41.5)	0.11
Complications and Outcome			
Shock, n(%)	142(30.6)	54(34.0)	0.49
AKI, n(%)	58(12.5)	60(37.7)	**0.001**
Myocardial dysfunction, n(%)	24(5.2)	19(11.9)	**0.006**
>2 quadrant infiltrates in chest x-ray, n(%)	292(62.9)	121(76.1)	**0.001**
LOS UCI, median (p25-75), days	13(6.7-23.0)	14(8.0-23.0)	0.29

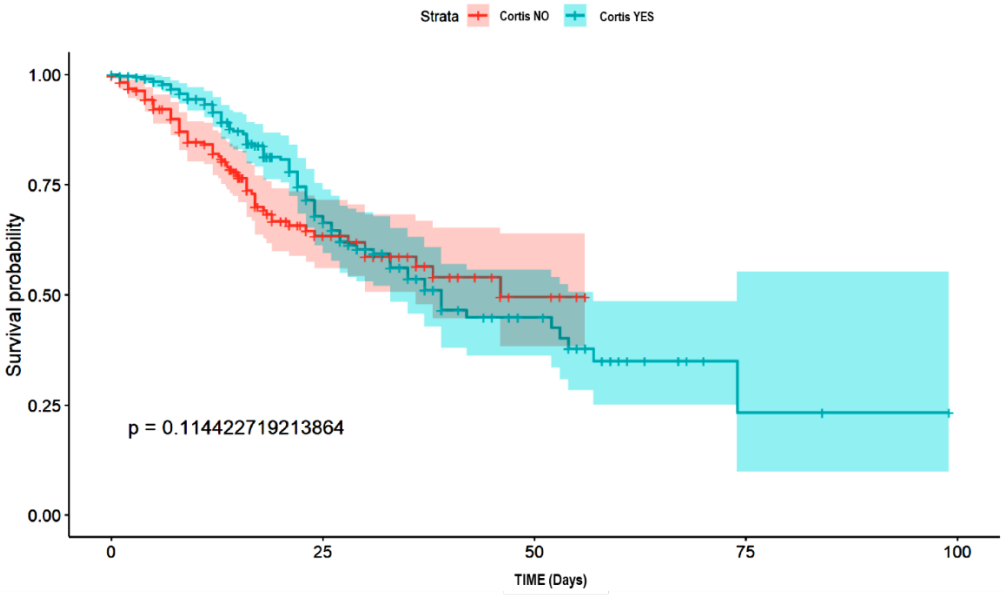
Abbreviations: (p25-75): percentile range, range; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses; PaO2/FiO2, Partial pressure arterial oxygen/ fraction of inspired oxygen

a Corresponds to minimum or maximum value, as appropriate, within 12 hours of ICU admission. The variables in this Table were no transformed for your comparison.

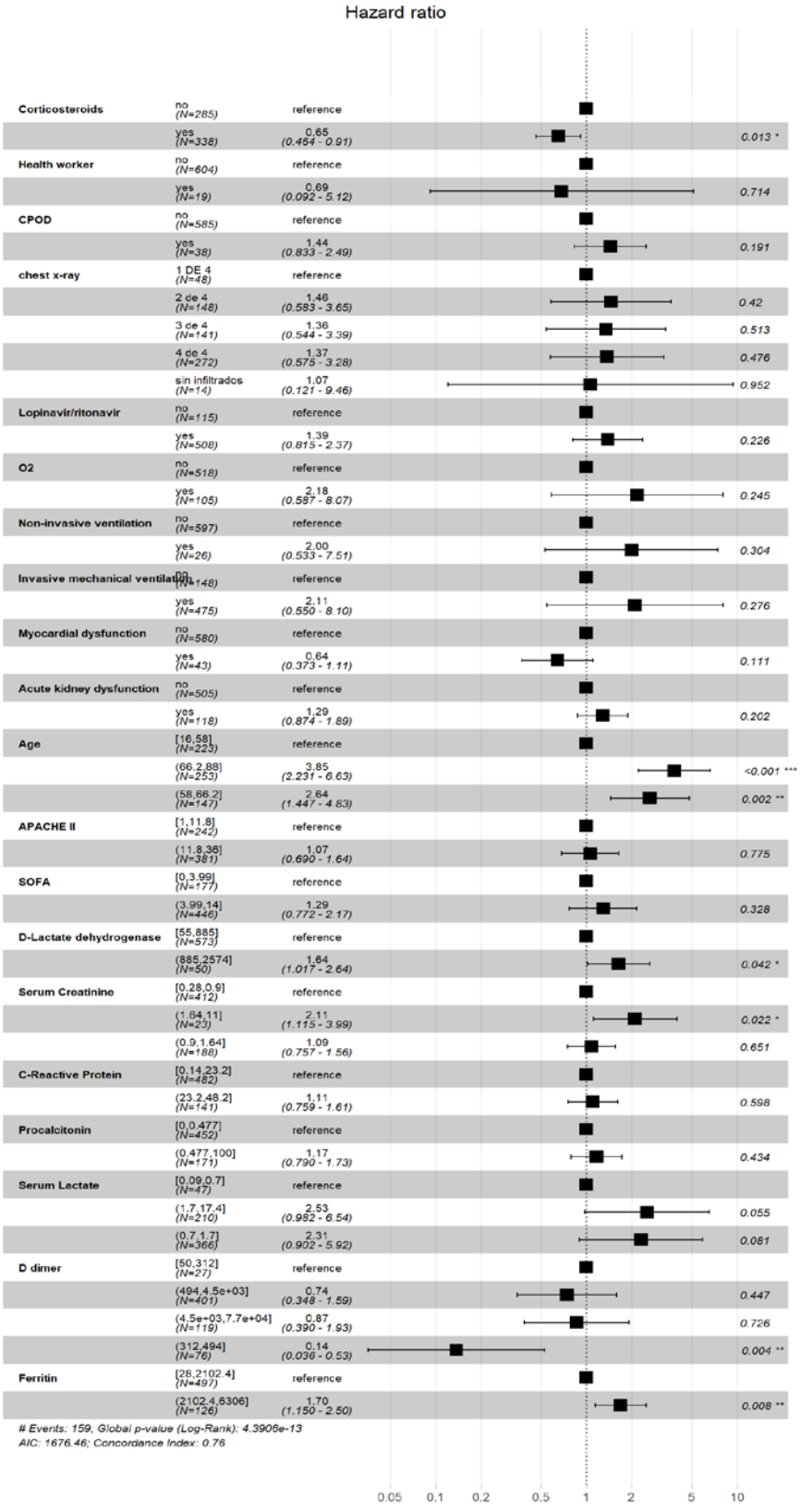
b APACHE II score to the severity of illness, the score is obtained by adding the following components 1) 12 clinical and laboratory variables each with a score range of 0 to 4 points (APS). The APS is determined from the worst physiologic values during the initial 24 h after ICU admission, 2) age with a range 0 to 6 points and 3) Chronic health points if the patients has history of severe organ system insufficiency or is immunocompromised assign 5 points if the patients is no operative or emergency postoperative and 2 points for elective postoperative patients with a total score range of 0 to 71.

c SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24,

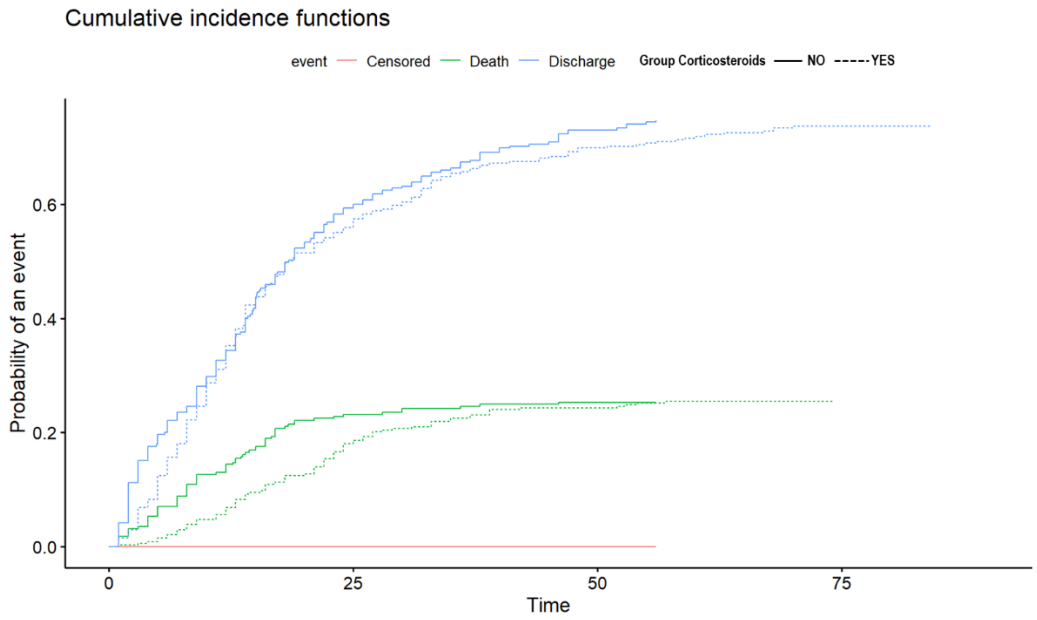
e-Figure 5: Unadjusted survival plot (Kaplan-Meier) for B phenotype patients according to corticosteroids treatment



e-Table 11: Factors associated with ICU mortality in Cox Hazard regression analysis for patients among B phenotype



e-Figure 6: Competing Risk analysis plot (Fine and Gray) for B phenotype patient's



e-Table12: Factors associated with corticosteroids use in B phenotype patient'

Variable		N	Odds ratio	p
D-Lactate dehydrogenase		623	1.00 (1.00, 1.00)	0.023
Serum Lactate		623	1.13 (1.02, 1.26)	0.023
White blood cell		623	1.04 (1.01, 1.08)	0.016
O2	no	518	Reference	
	yes	105	0.38 (0.18, 0.78)	0.008
Myocardial dysfunction	no	580	Reference	
	yes	43	0.37 (0.18, 0.75)	0.006
APACHE II		623	0.99 (0.95, 1.02)	0.526
SOFA		623	0.95 (0.88, 1.02)	0.165
Age		623	1.01 (0.99, 1.02)	0.478
Invasive mechanical ventilation	no	148	Reference	
	yes	475	0.88 (0.46, 1.68)	0.710
Obesity	no	423	Reference	
	yes	200	1.09 (0.76, 1.56)	0.637
C-Reactive Protein		623	1.00 (0.99, 1.02)	0.792

e-Table 13: Characteristics of 857 C phenotype patients according to ICU mortality

Variable [a]	Survivors n=468	Non-survivors n=389	p-value
General characteristics and severity of illness			
Age, median (p25-75), year	63(55-69)	68(63-74)	**0.001**
Male, n(%)	336(71.8)	290(74.6)	0.40
APACHE II [b], median (p25-75)	15(12-20)	18(15-23)	**0.001**
SOFA [c], median(p25-75)	7.0(5-8)	7.4(6-9)	**0.001**
Laboratory findings			
D-lactate dehydrogenase, median (p25-75), U/L	655(548-909)	680(565-933)	0.07
White blood cell, median (p25-75), $x10^9$	9.6(6.6-13.2)	10.3(7.3-14.3)	**0.01**
Serum creatinine, median (p25-75), mg/dL	0.9(0.7-1.26)	1.0(0.7-1.4)	**0.001**
C-Reactive Protein , median (p25-75), mg/dL	17(10-26)	18(10-27)	0.54
Procalcitonin, median (p25-75), ng/mL	0.5(0.2-1.1)	0.6(0.2-1.6)	0.05
Serum lactate, median (p25-75), mmol/L	1.5(1.1-1.9)	1.8(1.4-2.5)	**0.001**
D dimer, median (p25-75), ng/mL	2046(880-4260)	3060(1250-5820)	**0.001**
Ferritin, median (p25-75), ng/mL	1700(1330-2260)	2000(1530-2690)	**0.001**
Coexisting condition and comorbidities			
Arterial hypertension, n(%)	288(61.5)	260(66.8)	0.12
Obesity (BMI>30), n(%)	162(34.6)	132(33.9)	0.89
Diabetes, n(%)	94(20.1)	104(26.7)	**0.02**
Coronary arterial disease, n(%)	10(2.1)	38(9.8)	**0.001**
COPD, n(%)	35(7.5)	38(9.8)	0.28
Chronic renal disease, n(%)	19(4.1)	25(6.4)	0.15
Hematologic disease, n(%)	8(1.7)	22(5.7)	**0.03**
Asthma, n(%)	19(4.1)	15(3.9)	1.00
HIV, n(%)	1(0.2)	1(0.3)	1.00
Pregnancy, n(%)	0(0.0)	0(0.0)	NA
Autoimmune disease, n(%)	17(3.6)	19(4.9)	0.46
Chronic heart disease, n(%)	14(3.0)	12(3.1)	1.00
Neuromuscular disease, n(%)	3(0.6)	5(1.3)	0.53
Oxygenation and ventilator support			
Oxygen mask, n(%)	48(10.3)	48(12.3)	0.39
High flow nasal cannula, n(%)	16(3.4)	11(2.8)	0.76
Non-invasive ventilation, n(%)	27(5.8)	23(5.9)	1.00
Invasive mechanical ventilation, n(%)	379(81.0)	315(81.0)	1.00
PaO2/FiO2, median (p25-75),	132(96-164)	116(82-144)	**0.001**
Treatment			
Corticosteroids, n(%)	288(61.5)	247(63.5)	0.64
Antibiotics, n(%)	427(91.2)	353(90.7)	0.89
Lopinavir/ritonavir, n(%)	382(81.6)	316(81.2)	0.95
Hydroxychloroquine, No.(%)	449(95.9)	356(91.5)	**0.01**
Tocilizumab , No.(%)	139(29.7)	95(24.4)	0.09
Interferon β, No.(%)	155(33.1)	146(37.5)	0.20
Complications and Outcome			
Shock, n(%)	358(76.5)	294(75.6)	0.81
AKI, n(%)	141(30.1)	209(53.7)	**0.001**
Myocardial dysfunction, n(%)	36(7.7)	60(15.4)	**0.001**
>2 quadrant infiltrates in chest x-ray, n(%)	301(64.3)	272(69.9)	0.08
LOS UCI, median (p25-75), days	20(13-32)	15(8-24)	**0.001**

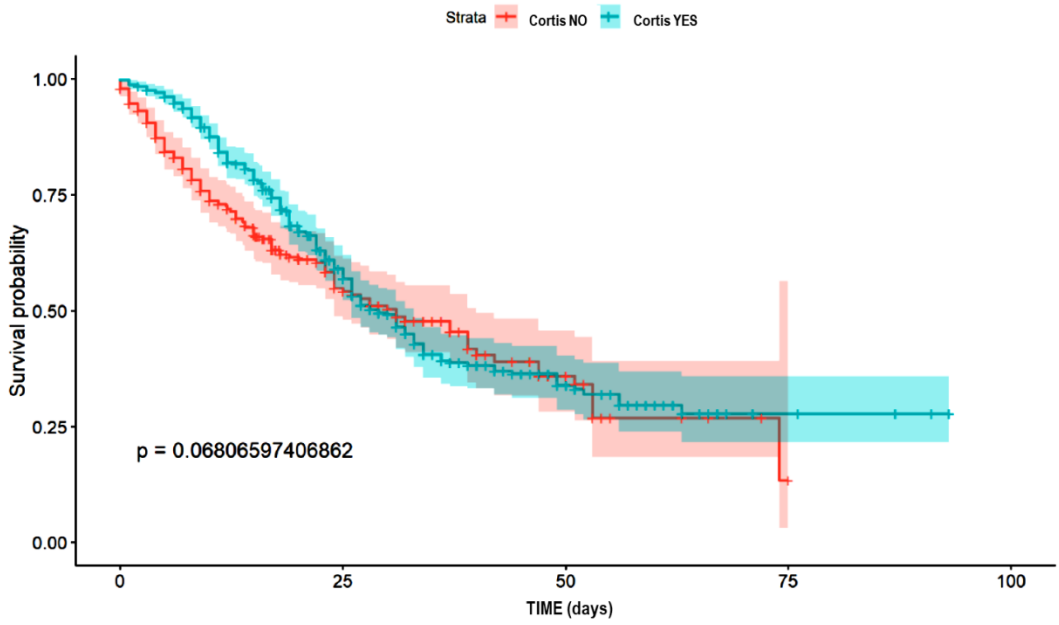
Abbreviations: (p25-75):percentile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses; PaO2/FiO2, Partial pressure arterial oxygen/ fraction of inspired oxygen

a Corresponds to minimum or maximum value, as appropriate, within 12 hours of ICU admission. The variables in this Table were no transformed for your comparison.

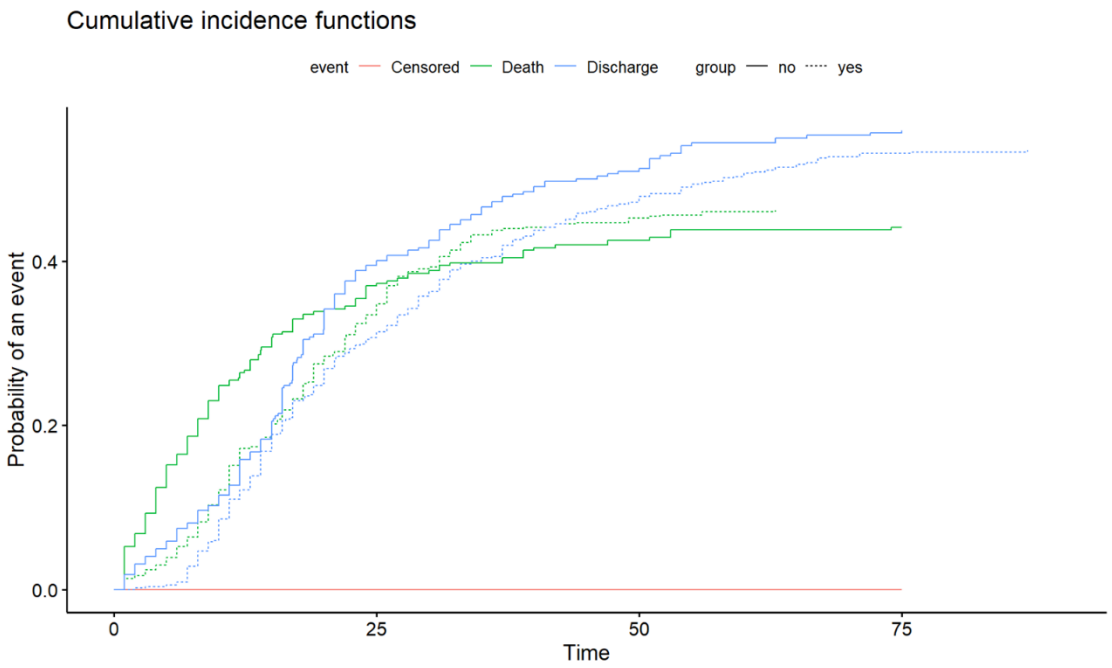
b APACHE II score to the severity of illness, the score is obtained by adding the following components 1) 12 clinical and laboratory variables each with a score range of 0 to 4 points (APS). The APS is determined from the worst physiologic values during the initial 24 h after ICU admission, 2) age with a range 0 to 6 points and 3) Chronic health points if the patients has history of severe organ system insufficiency or is immunocompromised assign 5 points if the patients is no operative or emergency postoperative and 2 points for elective postoperative patients with a total score range of 0 to 71.

c SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24,

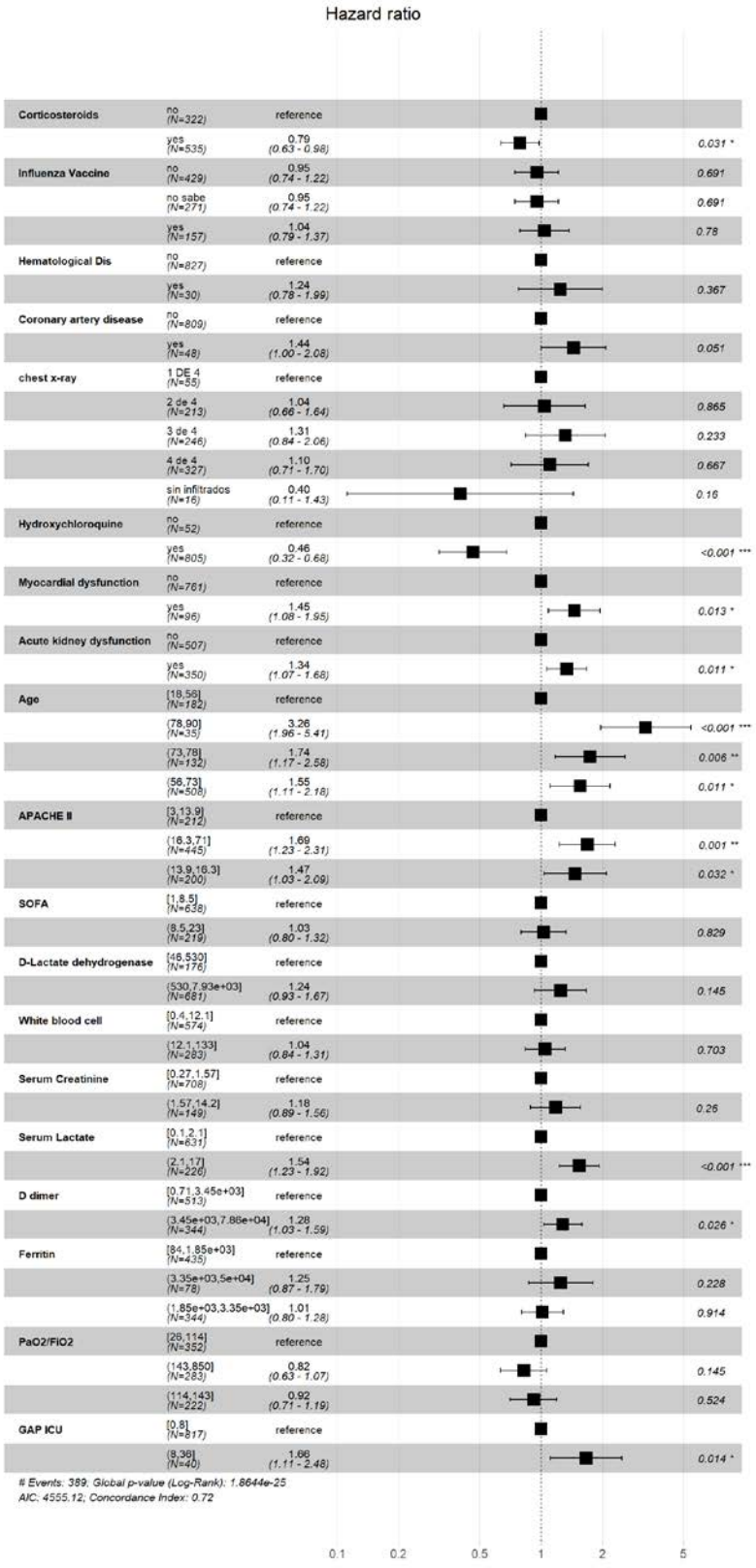
e-Figure 7: Unadjusted survival plot (Kaplan-Meier) for C phenotype patients according to corticosteroids treatment



e-Figure 8: Competing risk analysis plot (Fine and Gray) for C phenotype patient's



e-Table 14: Factors associated with ICU mortality in Cox Hazard regression analysis for patients among C phenotype



e-Table 15: Variables associated with corticosteroid use in C phenotype patients

Variable		N	Odds ratio	p
D-Lactate dehydrogenase		857	1.00 (1.00, 1.00)	<0.001
Arterial Hypertension	no	309	Reference	
	yes	548	0.62 (0.45, 0.85)	0.003
APACHE II		857	0.98 (0.96, 1.01)	0.179
SOFA		857	1.00 (0.94, 1.06)	0.997
Age		857	1.00 (0.98, 1.01)	0.573
Invasive mechanical ventilation	no	163	Reference	
	yes	694	1.24 (0.87, 1.77)	0.234
Obesity	no	563	Reference	
	yes	294	1.04 (0.77, 1.41)	0.786
C-Reactive Protein		857	0.99 (0.98, 1.01)	0.292