Mortality and bleeding complications of COVID-19 critically ill patients with venous thromboembolism

Critical COVID-19 and venous thrombosis

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ABSTRACT

BACKGROUND: VTE disease in COVID-19 patients is a remarkable issue, especially its relationship with bleeding events and mortality. The objective of this study was to describe the outcomes of critically ill patients with COVID-19 hospitalized in ICU in relationship with VTE during their stay.

METHODS: Prospective cohort study of critically ill COVID-19 patients in two hospitals that underwent a venous ultrasound at the beginning of follow-up of both lower limbs in April 2020. When clinical suspicion of new VTE during the 30-day follow-up, additional ultrasound or thoracic CT were performed. Global VTE frequency, major bleeding events and survival were collected, and their predictors were studied.

RESULTS: We included 230 patients. After 30 days of follow-up, there were 95 VTE events in 86 patients (37,4%). 13 patients (5,7%) developed major bleeding complications and 42 patients (18,3%) died. None of the comorbidities or previous treatments were related with bleeding events. D-dimer at admission was significantly related with VTE development and mortality. Independent predictors of mortality in the regression model were an older age (>66 years), D-dimer at admission (>1 500ng/mL) and low lymphocyte count (<0,45x10^9/L) with an AUC in the ROC curve of 0,81 (95%CI: 0,73-0,89). Patients presenting these three conditions presented a mortality of a 100% in the predictive model.

CONCLUSIONS: VTE frequency in ICU COVID-19 patients is high and risk of major bleeding is low. Comorbidities and laboratory parameters of admission in these patients can be a useful tool to predict mortality.

Key words: SARS-CoV-2 infection; COVID19; Venous thromboembolism; Deep venous thrombosis; mortality; bleeding

Introduction

The Coronavirus disease of 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus (SARS-CoV2) is a pandemic disease, with more than 108 million confirmed cases and 2,38 million deaths on February 2021. Since the pandemics' beginning, COVID-19 has been related with an increased thrombotic risk and coagulopathy[1,2]. Several studies and metanalysis have described an increased incidence of venous thromboembolic events (VTE) in COVID-19 patients, higher in those requiring Intensive Care Unit (ICU) hospitalization [3-8]. VTE has been widely described as to be directly related to mortality in severe COVID-19 patients[9-13].

Initially, standard dose thromboprophylaxis with low molecular weight heparin (LMWH) was proposed, but several groups reported a high incidence of VTE despite prophylactic anticoagulation. For this reason, risk stratification for VTE[4] and tailoring of anticoagulation doses were proposed in the literature[14].

Ying-Feng[15] et al reported that anticoagulation was not associated with an increased risk of mortality. Three randomized clinical trials (RCTs) are trying to evaluate the relationship between higher doses of anticoagulation and major bleeding complications as well as with mortality, VTE, hospital stay and other major adverse events (ACTIV-4, ATTAC, REMAP-CAP). Currently, due to lack of evidence and lack of results of the bleeding RCTs in these patients the global recommendation is to use prophylactic doses[2,16.]

Increased D-dimer has been related with higher incidence of VTE[3-17] and mortality in critically ill COVID-19 patients[10-11-18].

The first aim of this study was to describe the outcomes of critically ill patients with COVID-19 hospitalized in ICU in relationship with VTE during their stay, with special focus in bleeding events and survival. The secondary objective was to describe prognostic factors in relation with these outcomes.

Materials and methods

Patients and data collection

This was a prospective cohort study of patients with COVID-19 admitted to the ICUs of two Spanish university hospitals: Hospital Universitari Vall d'Hebron (HUVH), in Barcelona, and Hospital Universitari Germans Trias i Pujol (HUGTiP), in Badalona.
We included all patients with severe COVID-19 infection (confirmed by positive result on polymerase chain reaction test of a nose/throat sample) hospitalized in both ICUs the same

day of April 2020, regardless the previous length of stay in ICU. We excluded patients with age under 18 years, active therapy with extracorporeal membrane oxygenation (ECMO) and pregnancy. Study protocol was approved by local Ethics Committee (PR(AG)213/202), on April 6th, 2020. Informed consent was waived in patients that were in mechanical ventilation, and patients that were awake were informed and verbally accepted to participate in the study.

This study is focused on 30-days follow-up of an already published cohort screened for DVT and followed 7 days [8]. Those patients were all the patients admitted to the ICU on the same day of April 2020 (regardless the length of stay) and were studied with a single ultrasound scan of both limbs on the first 72h after the day of selection, to assess the prevalence of deep vein thrombosis (DVT), to detect asymptomatic DVT. In addition, we registered symptomatic DVT detected pre-screening and up to 30-d follow-up. To know the overall VTE frequency, we also included confirmed pulmonary embolisms (PE) by computed tomography angiography (CTA) performed pre-screening and 30 days post-screening. These CTAs were performed in patients with sudden respiratory or cardiovascular deterioration, not explained by other causes, and with clinic suspicion of PE. PE in CTA was defined using the classic radiological diagnostic criteria: intraluminal large filling defect inside the pulmonary arteries and its branches; a partial filling defect surrounded by contrast material; peripheral intraluminal filling defect that forms acute angles with the arterial wall.

We did not repeat screening ultrasound to all the selected patients to avoid unnecessary exposure of the investigators and to avoid wasting the scarce personal protective equipment during the first wave.

All DVT diagnosis were done with duplex ultrasound (DUS) performed by certified vascular surgeons. In the screening phase, both limbs were examined, including iliac, femoral, popliteal and distal veins. DVT was diagnosed when it was not possible to fully compress a venous segment, absence of flow augmentation with calf squeeze or hyperechoic intraluminal defect partially or fully occluding the venous segment.

Demographic variables, comorbidities and previous treatments were recorded through medical records and confirmed with the patients at their arrival or with their family. Blood tests at hospital admission were used to define basal values for each patient and included: full hemogram, coagulation test (with D-dimer and fibrinogen), liver and kidney profile, interleukin-6, lactate dehydrogenase, ferritin and C-reactive protein. Major

bleeding and minor clinically relevant bleeding were defined according to the International Society on Thrombosis and Haemostasis classification[19]. ICU stay and time in hospitalization ward were also recorded in addition to the number of patients discharged from the ICU and the deaths occurred both in the ICU and during hospitalization or after hospital discharge up to 30 days.

Regarding thromboprophylaxis treatment during the whole follow-up, the protocol in each hospital during the first COVID outbreak was: in HUVH all patients in ICU with DDimer > 1 500ng/mL plus raised inflammatory markers plus severe acute respiratory failure (PaO_2/FiO_2< 150) and without bleeding risk, received preferably full dose anticoagulation as well as those with confirmed VTE; in HGTiP, the patients that received full dose anticoagulation were only the ones with confirmed VTE. On the other hand, standard dose or intermediate dose thromboprophylaxis were prescribed in HUVH under medical criteria and in HGTiP depending on BMI plus DDimer (BMI > 35 kg/m^2 or DDimer > 2 000 ng/mL received intermediate doses). Because of this, each patient received different doses of thromboprophylaxis during their whole stay, so we were not able to group the patients in different dosage levels. This was the reason why we did not include this parameter in the analysis.

Statistical analysis

Descriptive and frequency statistical analysis were obtained, and comparisons were made with the software SPSS Statistics 26.0. Categorical variables were reported as frequencies (percentages) and continuous variables as mean±standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Normality assumption of quantitative variables was checked with the use of quantile-quantile (Q-Q) plots. In VTE analysis, statistical significance was assessed by Pearson's chi-square for categorical variables -except in case that at least one expected frequency in the contingency table was less than 5, where the Fisher's exact test was used-, the Student's t test when comparing with continuous variables that followed approximately a normal distribution, and the Mann-Whitney U test for the rest of quantitative variables. Mortality and severe bleeding during follow-up were analyzed with the Kaplan-Meier product limit survival method, using the log-rank test to determine statistical significance between different groups and performing simple Cox proportional hazard models to assess differences in continuous variables. Patients who were alive were censored at the last follow-up. Receiver characteristic

operator curves (ROC) were configured in order to calculate cut-off points for continuous variables with best sensitivity and specificity to predict mortality; the optimal cut-off point was obtained using the maximum value of Youden Index (Sensitivity+Specificity-1). Variables with a p-value<0.1 on univariate analysis were entered into multiple Cox regression models to identify factors independently associated with mortality and bleeding over follow-up. Results are shown as hazard ratios (HR) with the 95% confidence interval (CI). A ROC curve was obtained to evaluate the performance of the model and determine its capability to predict mortality and bleeding. Finally, a scale based on the regression model coefficient values (β coefficients) was designed to score patients according to their risk of mortality and bleeding.

Bonferroni correction was applied using the Dubey/Armitage-Parmar (D/AP) method[20] to take into account the correlation between the biomarkers assessed in the study. Since the mean correlation coefficient was 0,177, to achieve statistical significance at 0,05 level, it was necessary to obtain a p-value <0,007. Given the exploratory nature of the study, we also reported results reaching p-values < 0,05 as findings of potential interest.

Results

230 patients with severe COVID-19 in ICU were included (118 in HUVH and 112 in HUGTiP). Demographic variables and blood tests, depending on the presence of VTE, are displayed in **Table I.** Mean age was 60,1 (SD 9,9) years and 77% of them were men. 182 patients (79,5%) had been in invasive mechanical ventilation at some point during their stay.

The day of the screening ultrasound, patients had a median ICU stay of 12 days (interquartile range 5-19 days). Therefore, after the 30-day follow-up, the median total time after ICU admission was 46 days (range 38-53 days). At that moment, 42 (18,3%) patients had died, 33 (14,3%) patients were still on ICU, 34 (14,8%) patients were on hospitalization ward and 121 (52,6%) had been discharged from the hospital.

All patients were using stockings except the ones that had an arterial ischaemia or history of peripheric arterial disease. In patients that suffered a severe bleeding which forced to suspend anticoagulation treatment, intermittent pneumatic compressions (IPC) were used until anticoagulation treatment could be started again.

VTE frequency

During the whole ICU stay, there were 95 events of VTE in 86 patients (37,4%) in both hospitals, 60 patients (69,8%) presenting DVT, 17 patients with PE (19,8%) and 9 patients with DVT and PE (10,5%). VTE patients tended to be older and more in invasive mechanical ventilation (p=0,064 and p=0,065 respectively). In VTE patients, basal D-dimer was higher (786 mg/dL vs 531 mg/dL, p=0,007) and basal activated partial thromboplastin time (aPTT) was lower (29,1 sec vs 30,7 sec, p=0,007).

VTE was associated with a longer hospital stay, with a median of 3 days (IQR: 0 - 6 days). VTE patients had a hospital stay of 50,3 days and non-VTE patients of 47,2 days (p=0,014).

Patients with DVT had a slightly longer admission in ICU before the DVT screening (14 days with IQR 7-20 days) than patients without DVT (10 days with IQR 5-19), but this difference was not significant (p=0,205).

Bleeding complications

During the 30-day follow-up, 13 patients (5,7%) developed major bleeding complications. 6 patients had pulmonary bleedings, 3 had a gastrointestinal bleeding, 2 urinary bleedings, 1 cerebral bleeding and 1 pericardial bleeding. None of the demographic variables or previous treatments were related with a higher risk of major bleeding. The only variables significantly related with patients that had a major bleeding were a lower basal aPTT (27 sec vs 30,2 sec, p=0,005) and DVT in the first seven days of follow-up (11,9% vs 3,5%, p=0,043) in patients with major bleeding versus patients without bleeding, respectively.

The obtained results in the statistical analysis did not allow us to perform a bleeding risk scale nor a prediction model, as we had planned in methods.

Mortality

42 patients (18,3%) died during the 30-day follow-up. Variables associated with mortality are depicted in **Table II**: older age (67,4 vs 58,4 years), lower weight (77,9 vs 87,5 kg), lower body mass index (BMI) (28,2 vs 30,8 kg/m^2) and hypertension (43,1% vs 69% of patients).

Basal biochemic risk factors for mortality were lymphocyte count at admission lower than 0,45 $x10^9$/L (32,7% vs 14,4%, p=0,003) (normal lymphocyte count 1.3-3.5 $x10^9$/L) and D-Dimer at admission higher than 1 500ng/mL (29,1% vs 16%, p=0,014) and higher than 6 200 ng/mL (45,5% vs 16,4%, p=<0,001). Furthermore, the hazard ratio for mortality with a DD > 1 500ng/mL was 2.15 (95%CI 1,15-4) and with a DD > 6 200 ng/mL was 3,68 (95%CI: 1.81-7.50).

Patients with VTE at any moment during the follow-up tended to die more frequently (21 of 42 patients (50%)) than non-VTE patients (65 of 188 patients (34,6%)), but this difference was not statistically significant (p=0,062). On the other hand, patients with major bleeding events during follow-up died more than other patients (38,5% vs 17,1%, p=0,034), with a hazard ratio of 2,63 (95%CI 1,03 – 6,07).

Age and weight had an inverse relation: younger patients had more weight, and older patients were thinner: 185 patients (86%) had a BMI higher than 25 kg/m^2 and had a mean age of 59,0 years old (SD 10,2) and patients with BMI lower than 25 kg/m^2 had a mean age of 66,4 years old (SD 6,4). Mortality prediction models were built controlled by weight due to this inverse relation, and independent predictors of mortality finally were age, lymphocyte count and D-dimer at admission.

Using a Cox regression model to assess mortality, the best ROC curve had AUC of 0,81 (95%CI: 0,73-0,89), the cut off value for age was >66 years old with HR=6,46 (95%CI 3,14-13,28, p<0,001), the cut off value for lymphocyte count was <0,45 x 10^9/L with a HR: 3,1 (95%CI 1,57-6,10, p=0,001) and the cut off value for D-dimer was >1 500 with a HR: 2,14 (95%CI 1,09-4,21, p=0,007 **(Figure 1).**

There were several cut-off values for D-dimer, but the one with the highest overall accuracy (83,9%) in the prediction model for mortality was 1 500 ng/mL, with a sensibility of 26,2% and a specificity of 97,7% and a Youden index of 0,237. The VPP of the model was 73,3% and the VPN 84,6%.

With the beta coefficients of the regression model, a mortality risk score scale was performed with its Kaplan-Meier graph and its mortality rates depending on the score, as shown in **table III and figure 2A-2B.** It should be noted that a score of four points in the mortality scale implies a 100% of mortality.

Discussion

We hereby present one of the largest prospective series in ICU COVID-19 patients focused on venous thromboembolic disease. As previously published, there is a high incidence of VTE among these patients[8] and it is directly associated with D-Dimer value at admission to the hospital. A not irrelevant number of major bleedings were found, but without detecting a strong relationship with a clinical variable. Finally, we did not find a significant association between mortality and VTE in these patients, but with the variables directly related with survival we built a mortality risk score that can be useful in clinicians' daily practice.

Cumulative prevalence of VTE in our series was 37,4% in 30 days of follow-up among 230 patients. Several studies have published VTE incidence in ICU patients, but with absolutely different diagnostic designs and follow-ups, which leads to non-comparable similar incidences. Systematic reviews and metanalysis report VTE incidence in ICU patients in a range between 24 and 31%[3,4,13,15,17], which is a little bit less than our findings. We used a mixed design, performing a DUS screening at the beginning of the study in all patients and, after that, collecting only the symptomatic VTE routinely diagnosed.

We found, as described in our previous work[8] and by other authors, a direct relationship between total VTE frequency and D-Dimer at admission[7]. We did not find a relation with other described parameters such as platelet count[21,22] and albumin[12]. Age has also been found by some authors[3,9,10] to be related with VTE, but in our case there was a non-significant trend.

Conversely to other studies, we found that activated partial thromboplastin time[9,10,23] was lower, instead of higher, in patients with VTE. In these studies, it was not stated when was the aPTT determination performed during the whole stay of the patients. In our study, lab tests were on the first day of ICU admission and the difference was statistically-significant but clinically not relevant (30,7 sec vs 29,1 sec, p=0.007), and being both parameters inside its normal range. Increased aPTT time is well described in COVID-19 patients[24], as well as in MERS and SARS-COV-1 infection[23].

Regarding bleeding complications, 13 of 230 patients (5,7%) had a major bleeding event. The fact that this was a prospective and not a cross sectional study made us impossible to summarize the doses of anticoagulant treatment that patients received, because it changed along the hospitalization period. The anticoagulation regime that each

patient received was decided using the current hospital protocols described previously and the patients' individualised VTE risk by the physician in charge of the patient. Al Samkari et al[22] reported an incidence of 5,6% major bleeding events in ICU patients, and it was related with D-Dimer peak and procalcitonin as well as low platelet count. They recommended, basing it in previous studies in ICU non COVID-19 patients with similar rate of major bleeding events, that increasing doses of anticoagulation therapy in critically ill COVID-19 patients should be done cautiously.

Jimenez et al[25], in their metanalysis, reported a higher incidence of clinically relevant bleedings among patients in intermediate-full dose anticoagulant therapy than in those in prophylactic doses, emphasizing the importance of randomised clinical trials. In this same line, one guideline on treatment of VTE in COVID-19 patients[16], recommends treatment with low molecular weight heparin or fondaparinux in prophylactic doses, and suggests against individualised VTE risk assessment.

The first published RCT, published by Bertoldi in December 2020[26], with 10 patients per arm, did not register any bleeding and reported improved O2 exchange and successful liberation from mechanical ventilation with therapeutic enoxaparin over prophylactic doses. Other ongoing trials (ACTIV-4, REMAP CAP and ATTACC), which have not been published yet, reported concerns about safety of therapeutic anticoagulation during enrolment of ICU patients, and are currently on pause.

Regarding survival, VTE in critically ill COVID-19 patients has been related with a higher mortality since the beginning of the pandemic[7,11,27]. In our study, this relationship was not statistically significant, but there was a trend. A possible explanation to that is the low mortality in COVID-19 patients in Spanish Intensive Care Units[28,29]. The independent predictors of mortality that we found have also been described before (older age, low lymphocyte count and higher D-Dimer at admission) [11,27,30,31]. Other authors have reported high sensibility and specificity for D-Dimer test and VTE in these patients and its relationship with mortality[10]. The most reported cut-off value in literature for D-Dimer is 1 500 ng/mL to predict VTE frequency[8,10,31].

Because of D-Dimer importance in these patients, it has been included in our mortality predicting model, that has a global accuracy of 83,9%, and high values of VPP and VPN. The model groups important risk factors in patients with critically ill COVID that have been well described before[11,27] and reports a 100% of mortality if the 3 criteria are accomplished.

Other authors have also found medical comorbidities (diabetes, chronic pulmonary disease) as well as other biochemic parameters at admission (such as increased ferritin and low platelet count) that we did not find significant. Another reported parameter of worse prognosis in COVID-19 patients is weight[32]. Conversely, we found, that "thinner" patients died more but, at the same time, they were significantly much older. Therefore, mortality was more influenced by age, and weight was a confounding factor.

Our study has some limitations. Firstly, the VTE diagnosis protocol during the 30 days was different, which may have led to underestimate the real VTE frequency. Secondly, when including the patients at the beginning of the follow-up, some had been in ICU for 1-2 days, but others had been there for more than a week, and this can imply that patients were in different stages of the disease. Nevertheless, there were no differences between patients with DVT and patients without DVT in terms of length of stay before the ultrasound screening. Thirdly, we failed to summarize the overall anticoagulation therapy that patients received during the whole hospitalization, because doses were different along the 30 days of follow-up in each patient, so it could not be compared with the bleeding data. At the beginning of the COVID-19 outbreak some authors and protocols suggested full-dose anticoagulation therapy in patients with very high D-Dimer values, and nowadays there are some concerns about this recommendation, and protocols have changed. Finally, we have applied a multiple hypothesis testing to detect significant parameters in order to define a model for predicting mortality. This can lead to the detection of spurious relationships, not really significant. However, the application of the Bonferroni's correction, not commonly used in other publications, tried to correct possible errors.

Conclusions

In conclusion, frequency of VTE in ICU COVID-19 patients is very high during the whole hospitalization period. Comorbidities and laboratory parameters of admission in these patients can be a useful tool to predict mortality. Randomised studies are needed to unveil the unclear role of higher doses over standard thromboprophylaxis in these patients to prevent VTE as well as their effect in global outcomes.

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TABLE I – Global demographic and biochemic variables and separated according to their relationship with VTE disease

Values are shown as median and Interquartile range (IQR) except "*" which are shown as mean (sd)

		VTE		p
Variables	**N=230**	**No (n=144)**	**Yes (n=86)**	
Demographic variables				
Gender (Men)	177 (77%)	108 (75%)	69 (80,2%)	,362
Age*	60,1 (9,9)	59,1 (10,2)	61,6±9,3	,064
Weight*	85,7 (16,3)	85,6 (16,8)	86,0±15,4	,837
Height*	1,68 (0,09)	1,67 (0,09)	1,70±0,09	,103
Body mass index (BMI) *	30,3 (5,1)	30,5 (5,4)	30,0 (4,6)	,449
Risk factors				
Smoker	17 (7,4%)	11 (7,6%)	6 (7,0%)	,982
Pneumopathy	35 (15,2%)	20 (13,9%)	15 (17,4%)	,468
Hypertension	110 (47,8%)	66 (45,8%)	44 (51,2%)	,434
Diabetes	51 (22,2%)	30 (20,8%)	21 (24,4%)	,527
Dyslipidaemia	77 (33,5%)	45 (31,3%)	32 (37,2%)	,354
Chronic kidney disease	21 (9,1%)	14 (9,7%)	7 (8,1%)	,687
Atrial fibrillation	4 (1,7%)	3 (2,1%)	1 (1,2%)	1,000
Coronaropathy	9 (3,9%)	7 (4,9%)	2 (2,3%)	,489
Stroke	8 (3,5%)	4 (2,8%)	4 (4,7%)	,476
Peripheric Arterial disease	5 (2,2%)	5 (3,5%)	0 (0%)	,160
Venous thromboembolism	3 (1,3%)	2 (1,4%)	1 (1,2%)	1,000
Treatments				
Antiplatelet	24 (10,4%)	15 (10,4%)	9 (10,1%)	,991
Anticoagulant	6 (2,6%)	4 (2,8%)	2 (2,3%)	1,000
Immunotherapy	9 (3,9%)	6 (4,2%)	3 (3,5%)	1,000
ICU treatments				
Invasive mechanical ventilation	182 (79,5%)	109 (75,7%)	73 (85,9%)	,065
Prone position	30 (13,1%)	19 (13,2%)	11 (12,9%)	,956

		VTE		
Basal Biochemics	**N=230**	**No (n=144)**	**Yes (n=86)**	**p**
Lymphocyte (x10^9/L)	0,7 (0,5-1)	0,8 (0,5-1,0)	0,7 (0,4-0,9)	,190
Platelet (x10^9/L)	203 (152-281)	191 (145-280)	231 (164-285)	,059
Prothrombin time (sec)	13,3 (12,5-14,8)	13,2 (12,5-14,4)	13,6 (12,6-15)	,115
Fibrinogen (g/L)	6,5 (5,3-8,1)	6,6 (5,3-8)	6,4 (5,3-8,2)	,892
aPTT (sec)	30,1 (27,5-32,4)	30,7 (28-32,9)	29,1 (26,9-31,7)	**,007**
D-Dimer (ng/mL)	601 (294-1 661)	531 (274-1 289)	786 (336-2 296)	**,007**
Glomerular filtrate (mL/min/1,73 m^2)	86 (70-90)	90 (73-90)	83,5 (63,7-90)	,072
Lactate (UI/L)	451 (346-567)	430 (345-559)	482 (347-596)	,131
C-reactive protein (mg/dL)	14,1 (88,1-23)	13,9 (8-22,9)	14,4 (8,9-23,9)	,535
Ferritin (ng/mL)	1120 (575-1 779)	1020 (552-1 648)	1286 (648-2 184)	,077
Interleukin-6 (pg/mL)	94 (49,5-203,6)	93,3 (50,9-199)	100,4 (46,4-265,9)	,513

TABLE II: Demographic and biochemic variables according to mortality
Values are shown as median and Interquartile range (IQR) except "*" which are shown as mean (sd)

	Mortality		p
Variables	**No (n=188)**	**Yes (n=42)**	
Demographic variables			
Gender (Men)	145 (77,1%)	32 (76,2%)	,806
Age*	58,4 (10,1)	67,4 (4,8)	**<,001**
Weight*	87,5 (16.1)	77,9 (14,7)	**<,001**
Height*	1,69 (0.09)	1,66 (0.1)	,093
BMI*	30,8 (5.0)	28,2 (5.0)	**,006**
Risk factors			
Smoker	14 (7,4%)	3 (7,1%)	,975
Pneumopathy	27 (14,4%)	8 (19%)	,424
Hypertension	81 (43,1%)	29 (69%)	**,002**
Diabetes	42 (22,3%)	9 (21,4%)	,858
Dyslipidaemia	66 (33,0%)	15 (35,7%)	,746

Chronic kidney disease		18 (9,6%)	3 (7,1%)	,678
Atrial fibrillation		2 (1,1%)	2 (4,8%)	,077
Coronaropathy		8 (4,3%)	1 (2,4%)	,667
Stroke		6 (3,2%)	2 (4,8%)	,700
Peripheric Arterial disease		5 (2,7%)	0 (0%)	,325
Venous thromboembolism		3 (1,6%)	0 (0%)	,427
Treatments				
Antiplatelet		18 (9,6%)	6 (14,3%)	,337
Anticoagulant		5 (2,7%)	1 (2,4%)	,840
Immunotherapy		7 (3,7%)	2 (4,8%)	,921
ICU treatments				
Invasive mehanical ventilation		146 (77,7%)	36 (87,8%)	,183
Prone position		22 (11,7%)	8 (19,5%)	,150
VTE		65 (34,6%)	20 (50%)	,057
DVT		53 (28,1%)	16 (38,1%)	,194
PE		19 (10,1%)	7 (16,7%)	,215
		Mortality		**p**
Basal biochemics		**No (n=188)**	**Yes (n=42)**	
Lymphocyte ($x10^9$/L)		0,8 (0,5-1,0)	0,6 (0,3-0,8)	,061
	<=0.45	33 (17,6%)	16 (38,1%)	**,003**
Platelets ($x10^9$/L)		199 (148-274)	221 (168-301)	,209
Prothrombin time (sec)		13,2 (12,6-14,8)	13,4 (12,5-14,7)	,160
Fibrinogen (g/L)		6,5 (5,3-8)	6.9 (5,0-8,2)	,816
aPTT (sec)		30,2 (27,6-32,2)	29,8 (26,2-33,6)	,871
D-Dimer (ng/mL)		577 (277-1 410)	706 (351-4 519)	,053
	>6 200	12 (6.,9%)	10 (23,8%)	**<,001**
	>1 500	39 (22,3%)	16 (38,1%)	**,014**
Glomerular filtrate ($mL/min/1,73m^2$)		87 (70,7-90)	80,5 (64-90)	,337
Lactate (UI/L)		454 (349-566)	426 (315-595)	,962
C-reactive protein (mg/dL)		14,1 (8.2-22.8)	14,3 (6,8-24,2)	,816
Ferritin (ng/mL)		1120 (604-1 793)	1110 (556-1 633)	,970
Interleukin-6 (pg/mL)		94 (46,3-94,0)	130,4 (56,9-230,5)	,588

TABLE III: COVID19 mortality risk score in ICU patients

Variable	Cut-off	Score
Age (years old)	< 66	0
	> = 66	2
Lymphocyte count (10^9/L)	> 0,45	0
	< = 0,45	1
D-dimer (ng/mL)	< =1500	0
	> 1500	1
Total Risk Score		**0 - 4 points**

TITLES OF FIGURES

Figure 1.— Cox Regression model and ROC curve with independent risk factors of mortality

FIGURE 2A. — Kaplan Meier survival curves according to COVID-19 mortality risk scale

FIGURE 2B. — Frequency of mortality depending on resulting score in the COVID-19 mortality risk scale