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Coagulopathy and COVID-19: About 102 cases

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Abstract **Review Article**

Introduction: The SARS-COV 2 virus, in particular in its severe form, appears to be associated with a large number of thromboembolic events, an incidence all the higher as the patients are admitted to intensive care units or intensive care units. The objective of our work is to identify the prognostic factors for the occurrence of thromboembolic complications of covid 19 in intensive care. ***Material and method*:** It is a single-center retrospective study, carried out in the intensive care unit of the IBN TOFAIL hospital in Marrakech. We included all covid 19 patients hospitalized from November 15, 2020 to January 10, 2021 confirmed by RT-PCR or by compatible CT lesions. The qualitative variables were expressed in% and compared by Chi-square test or Fisher's test. The quantitative variables were expressed as a mean (± standard deviation) or as a median (Percentile), and compared by Student's or Mann-Whitney t-test. For multivariate analysis, we used multiple logistic regressions using SPSS version 19 for Windows. A $p < 0.05$ is considered significant. ***Results:*** We collected 102 patients hospitalized with SARS-COV 2 pneumonia during the study period. The mean age was 61.81 ± 11 with a predominance of men (65.7%), 45.4% of the patients had a BMI between 30-34.9 Kg / m². Diabetes predominates in 59.8% followed by hypertension in 40.2%, heart disease, dysthyroidism and renal failure were observed in 8.8%, 3.9% and 3.2% of cases, respectively. Forty-two percent of patients presented with coagulopathy on admission, defined by D-Dimer levels> 0.5µg / ml, fibrinogen> 4g / l and thrombocytopenia. The occurrence of an arterial or venous thromboembolic event was found in 24.5% of cases with mainly venous manifestations, i.e. thirteen pulmonary embolisms, three catheter thromboses and two deep vein thromboses and five arterial accidents represented by three ischemic strokes, two limb ischemia and one myocardial infarction. The presence of this coagulopathy associated with cardiovascular risk factors present prognostic factors independent of the occurrence of a thrombotic event. ***Conclusion:*** Covid 19 is a systemic infection having a significant impact on hemostasis, requires regular biological monitoring in order to identify the patients most at risk.

Keywords: Coagulopathy, Covid-19.

INTRODUCTION

In December 2019, a new coronavirus was identified in the city of Wuhan, Hubei Province in China, in patients who presented with severe unexplained pneumonia [1]. In 2020, the World Health Organization (WHO) assigned the name Covid 19 to designate the disease caused by this virus [2]. Coronavirus disease 2019 (Covid-19) is a viral infection caused by "severe Acute respiratory syndrome" (SARS-COV2) responsible for a pandemic with a global health crisis. SARS-COV2 is a single-stranded RNA virus that enters body cells via the angiotensin-converting enzyme receptor widely expressed in pulmonary alveoli and vascular endothelium [3].

Covid-19 is increasingly characterized by diffuse damage affecting many tissues and organs, secondary to systemic endothelial dysfunction. It appears to be a systemic disease with a prothrombotic state causing thromboembolic complications (pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular accident (stroke), myocardial infarction (IDM)), the frequency of which is increasing [4].

The current pandemic context, accompanied by a multitude of scientific publications, leads to a large and rapidly evolving literature. We propose here to synthesize the prognostic parameters of the occurrence of thromboembolic complications of Covid-19 and to report the main thromboembolic complications observed in severely affected patients.

RESULTS

Single-center retrospective study, carried out in the intensive care unit of the IBN TOFAIL hospital in Marrakech. We included all covid-19 patients hospitalized from November 15, 2020 to January 10, 2021 confirmed by RT-PCR or by compatible CT scan lesions.

The statistical analysis of the data was based on the SPSS version 19 software. The descriptive analysis consisted in the calculation of the absolute and relative frequencies, and of the positioning and dispersion parameters for the quantitative variables (mean standard deviation). The normal distribution of the variables was studied by the Kolmogorov-Smirnov test. In bivariate analysis, the comparison of the qualitative variables used the statistical Chi-square test of Pearson and that of Fisher if necessary. The quantitative variables were compared by Student's test and Mann Whitney test. Multivariate analysis by binary logistic regression was used to model predictors of the onset of thromboembolic complications in Covid-19 patients. The variables whose association was significant at the 20% threshold in bivariate analysis were included in a multivariate model. The variables retained in the final model were selected using a stepwise forward method with an entry threshold of 0.2 and an exit threshold of 0.05.

The Hosmer Lemeshow test was used to examine the quality of the final statistical regression model. The significance level was retained for a $p < 0.05$.

One hundred and two patients were collected during the study period. The breakdown by age group showed that the most affected group was that of 51-74 years, estimated at 47% of cases. (Mean age 61.83 ± 11), with an estimated male predominance of 65.7%. 43.10% of patients were overweight (25-29.9 cm / m²) and 45.10% were obese 30-34.9 cm / m². Diabetes is the most frequent comorbidity and observed in 59.8% followed by hypertension, heart disease and dysthyroidism (Table 1).

On admission, 88.2% of the patients were dyspneic with 62.2% were in stage III of NYHA. 61.80% of patients were hypoxic on admission with SpO2 ranged from 79-89%.

Regarding the coagulopathy markers on admission, the platelet count was normal (150-450000 / mm²) in 46.8% and thrombocytopenia was only observed in 13.5% of cases (<150,000 mm²). The fibrinogen level was elevated above 4 g / l in 60.9% of patients. D-Dimers were measured in all patients on admission and in 87.9% were elevated. (> 0.5µg / mL) (Table 2). The presence of this coagulopathy was an independent factor for the occurrence of a thrombotic event. *(Fibrinogen: OR = 1.5, 95% CI [1.03-1.7]; DD: OR = 9.1, 95% CI [4.12-12]).*

The mortality rate was estimated at 45.1%, and the evolution was favorable in 54.9%. During hospitalization; 84.5% of patients developed complications of which 24.5% were thromboembolic, followed by inflammatory complications, i.e. 24%, and then renal, cardiac and septic complications, respectively 15.7%, 8.8% and 18.6 % of cases.

Among the patients who developed thromboembolic complications. We observed 18 venous thromboembolic events, in 13 EP, 3 catheter thrombosis, 2 deep vein thrombosis, and 6 arterial TE events, in 3 ischemic stroke, 2 limb ischemia and one myocardium infartus.

DISCUSSION

According to the literature published to date in the context of the pandemic linked to the new coronavirus SARS-CoV-2, it would appear that the COVID-19 disease is associated with a significant procoagulant state, leading to an increased risk of arterial and venous thrombosis [5]. Up to 30% of patients admitted to intensive care settings develop a thromboembolic complication, with a majority of pulmonary embolisms (16–25%) [6, 7]. The occurrence of ischemic stroke is described between 5–9% [7, 4]. These thromboembolic complications are fraught with significant mortality and occur despite prophylactic anticoagulation [6].

Published data from a cohort of 183 patients infected with SARS-CoV-2 and hospitalized revealed a mortality rate of 11.5%. The increase in D-dimers has been observed in more than 71% of the patients who died with an adult acute respiratory distress syndrome (ARDS) [5]. The authors describe these abnormalities as disseminated intravascular coagulation (DIC) as defined by the CIVD score of the ISTH (International Society on Thrombosis and Haemostasis [8].However, unlike the abnormalities noted in classic DIC associated with other sepsis or in multiple trauma patients, in patients with severe COVID-19, the prolongation of the TCA and / or PT is minimal and the thrombocytopenia moderate [9].

The study by Zhou *et al*. compared 54 deceased patients and 137 survivors; in-hospital mortality was associated in multivariate analysis with several variables including advanced age, a SOFA score> 5 and DD rate greater than 1000 ng / mL ($p = 0.003$). For a DD rate greater than 1000 ng / mL, the OR of death was 18.4 ($p = 0.003$) [10].

A recent meta-analysis, including six original studies of inpatients with moderate or critical forms of COVID-19 (n = 1355), concludes that DD levels are

significantly associated with a high risk of mortality, (95% CI 2.79–4.40 µg / L) (P <0.00001) [11] (Table3).

3 resumes the studies evaluating the correlation between the rate of DD and the clinical course of patients hospitalized for Covid-19.

Thrombocytopenia is often considered an indicator of severity in sepsis. This also appears to be the case for SARS-CoV2 infection. A meta-analysis of 9 Asian studies described admission thrombocytopenia in the most severe patients (weighted mean difference −31 × 10ˆ9 / L; 95% confidence interval [CI], −35 −29 × 10ˆ9/ L). In subgroup analysis, thrombocytopenia was associated with a 5 times higher risk of severe form (OR = 5.1; 95% CI, 1.8 - 14.6) [12].

The first descriptions show clinical observations in the field, with thrombotic complications all the more frequent as the disease was severe. These descriptions were very varied, ranging from classic deep vein thrombosis (DVT) and pulmonary embolism (PE), to completely unusual thromboses of central or arterial catheters, to very early thromboses of extra-renal purification filters and ECMO cannulas. Conversely, very few hemorrhagic complications have been reported, which reinforces the idea of hypercoagulability complicating COVID-19.

In a prospective Dutch cohort of 184 patients with COVID-19 pneumonia, the occurrence of an arterial or venous thromboembolic event was found in 31% of cases with again mainly venous manifestations (25 PE, 1 deep vein thrombosis, 2 thromboses catheters) and only 3 arterial accidents (ischemic strokes). Thirty-eight percent of patients presented with coagulopathy on admission to intensive care, defined as prolongation of PT> 3 sec or APT> 5 sec. The presence of this coagulopathy was an independent factor for the occurrence of a thrombotic event (aHR 4.1, 95% CI 1.9-9.1) [8].

In France, Helms *et al*. report on a prospective cohort of 150 COVID-19 patients admitted to the ICU for ARDS, an overall incidence of VTE of 18%, mainly PE. Compared to a historical cohort of matched patients hospitalized for ARDS unrelated to COVID-19, the risk of PE is significantly higher in COVID-19 patients (OR: 6.2, 11.7% vs. 2.1 %, p <0.01) [6].

The frequency of VTE in COVID-19 patients thus appears to be much higher than in other severe respiratory infections. In a meta-analysis of seven studies including 1,783 patients with ARDS from causes other than COVID-19, the incidence of VTE was 12.7% [13].

Due to the heterogeneity of studies, differences in inclusion criteria, and high risk of selection bias, it is difficult to determine an accurate rate of VTE in patients with COVID-19. In all observational studies, VTE is reported in 30 to 35% of ICU hospital patients. When DVT screening is systematic, the rate of VTE can be greater than 50% in the ICU. Table 4 summarizes the data from the different studies analyzing the incidence of thromboembolic events during COVID-19.

Observations concerning the hypercoagulant state of patients with COVID-19 have led to the development of recommendations recommending prophylactic anticoagulation at higher doses than usual [14], or even at therapeutic doses depending on the presence of certain factors. Risk or significant hypercoagulability [15]. The benefit of anticoagulant therapy is reported by Tang et al. in 99 patients who received Low Molecular Weight Heparin Thromboprophylaxis (LMWH). Despite several important limitations, the authors concluded that treatment with LMWH appeared to be associated with lower mortality in patients with six-fold higher than normal DD or≥ 3000 ng / mL (32.8% vs 52.4%, p = 0.017) [16].

CONCLUSION

Infection with SARS-CoV2 probably constitutes a predisposition to the onset of VTE, the frequency of thrombotic events, in particular in severe forms, requires regular biological monitoring of the parameters of inflammation and hemostasis at the end of " identify patients at risk.

Systematic intrahospital thromboprophylaxis is necessary to prevent thromboembolic disease and dose escalation may be considered in severely affected patients.

The occurrence of thromboembolic events in COVID-19 patients should not be underestimated, even in the presence of effective anticoagulation.

Table-1: Epidemiological and clinical characteristics of patients admitted to intensive care (BMI: Body mass index, HR: Heart rate, RF: Respiratory rate).

Variable	Frequency	P
Median age)	61.7 ± 11	0.03
Male (n, %)	65.7	0.132
BMI	[30-34.9] 45.10	0.05
Diabetes (n, %)	59.8	0.001
HTA (n, %)	40.2	0.029
Heart disease (n, %)	8.8	0.17
Dysthyroidism (n, %)	3.9	0.45
NYHA III-IV	62.2	0.001
SpO2 [79-89%]	61.8%	0.799
FC [80-99bpm]	54.9%	0.506
FR> 30cpm	57.8%	0.193

Table-2: Miltivariate analysis: markers of coagulability on admission. P: significance level of the Wald test, OR: Odds Ratio, CI: Confidence interval.

Coagulopathy markers	P	GOLD	95% CI for OR
Pq rate 150-40000 / mm²	0.53	0.91	0.09-3.2
D-Dimers> 0.5µg / ml	0.001	9.1	4.12-12
Fibrinogen> 4g / l	0.03	1.5	1.03-1.7

Table-3: Studies evaluating the correlation between the level of D-Dimer and the clinical course of patients hospitalized for Covid-19

Author	Median DD Level (Median Deviation) µg / mL		P value
Chen *et al*. [17].	Healed (n = 161)	Deceased (n = 113)	<0.05
	0.6 (0.3-1.3)	4.6 (1.3-21.0)	
Zhou *et al*. [10].	Survivor (n = 137)	Deceased (n = 54)	<0.0001
	0.6 (0.3-1)	5.2 (1.5-21.1)	
Zhrang *et al*. [3].	Survivor	Deceased	<0.001
	0.41 (0.15-0.69)	4.76 (2.99-11.9)	
Tang *et al*. [5].	Survivor (n = 162)	Deceased (n = 21)	<0.001
	0.6 (3.5-12.9)	21.2 (7.1-52.70)	
El Aidaoui *et al*. [18].	Survivor	Deceased	0.001
	0.54 (0.30-0.87)	0.42 (0.26-0,) 68	

Table-4: Incidence of Thromboembolic Events and Characteristics of Studies in Covid-19 Patients.

Author	Type of study	Venous TE event	Arterial TE event
Helms *et al*. (n = 150) 18% [6].	Prospective	25 Pulmonary embolism	- 2 ischemic stroke - 1 MI ischemia - 1Mesenteric ischemia
Klok *et al*. (n = 184) 36% [4].	Observational	- 25 pulmonary embolism - 1 TVP - 2 catheter thromboses	- 3 ischemic stroke
Poissy *et al.* (n = 107) [19].	Observational	- 21 EP	-
Thomas *et al*. (n = 63) [20].	Observational	- 1 jugular thrombosis	-
Ren *et al*. (n = 48) [21].	Retrospective	- 5 proximal DVT - 36 distal DVT	-

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