Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS
Pharmacy

Risk Factors, Bleeding Disorder and COVID-19 in Bamako, Mali

Yaya Goïta[1, 2*], Boubacar Sidiki Ibrahim Dramé[2, 3], Doumbia Nanko[4, 5] Abdoulaye Dabo[2], Klétigui Casimir Dembélé[1], Aboubacar Tiétié Bissan[1], Adama Koné[2], Djibril Mamadou Coulibaly[1], Seydou Sassou Coulibaly[1], Yacouba Diallo[4, 5] Pascal Reynier[6]

[1]Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako, Mali
[2]Medical Biology and Anatomopathology Laboratory Department, Centre Hospitalier Universitaire Hôpital du Mali, Bamako, Mali
[3]Faculty of Medicine and Odontostomatology, University of Sciences, Techniques and Technologies of Bamako, Mali
[4]Department of Medicine, and Endocrinology, University Hospital Center Hospital of Mali, Bamako, Mali
[5]National Center for Scientific and Technological Research (CNRST)
[6]Department of Biochemistry and Molecular Biology, University Hospital Center, Angers, France

DOI: 10.36347/sajp.2022.v11i05.001 | **Received:** 30.03.2022 | **Accepted:** 05.05.2022 | **Published:** 10.05.2022

***Corresponding author:** Yaya Goïta
Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako, Mali

Abstract **Original Research Article**

Introduction: Patients with COVID_19 infection have been shown to have an increased thrombotic risk, due to activation of coagulation secondary to sepsis. ***Objective*:** To study biological markers correlated with blood clotting disorders in hospitalized patients with COVID_19. ***Method*:** This was a retrospective descriptive and analytical cross-sectional study conducted at the Mali Hospital between September 2020 and January 2021. The markers being biologically monitored were: PT, ACT, INR, D-dimer and Troponin-I. ***Result*:** A total of 134 patients were enrolled in our study. Male was in the majority than female with 62.68% male and 37.31% female**.** The age group from 20 to 50 years was the most represented, at 58.21%. Biological markers showed plasma D-dimer concentration > 0.5 µL, PT < 70, INR > 3; an ACT > 40 seconds and a Troponin > 0.1 µL for 76.11%, 10.44%, 15.67%, 16.41% and 1.49% of the study population respectively. The rate of cured patients was 94.02% and that of deceased patients was 5.97%, with all deceased patients having a high D-dimer level. ***Conclusion*:** Blood clotting disorders and elevated D-Dimer are important biomarkers predicting complications of COVID_19 infection.

Keywords: Covid_19, D-dimer, PT, ACT, INR, Troponin-I, Mali.

Copyright © 2022 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

I. INTRODUCTION

The SARS_COV_2 virus, or COVID_19, is a virus of the Coronaviridae family responsible for the global pandemic of respiratory infection since December 2019. This pandemic poses an unprecedented threat to global public health [1, 2].

Respiratory symptoms are at the forefront with a possible progression to acute respiratory distress syndrome (ARDS) leading to many hospitalizations in intensive care settings [9]. The COVID_19 virus [3] is excreted through the respiratory tract and is found in aerosols expelled by the infected person. Depending on their size, these particles are deposited in the nose, throat, bronchi, up to the pulmonary alveoli. Most infected people develop a mild or moderate form of the disease and recover without hospitalization [4].

Epidemiological data [5] from the first wave of the epidemic have made it possible to better understand the development of the epidemic and the prognostic factors of Covid_19. These data facilitated the understanding of the evolution of 2 main criteria, hospitalization and hospital mortality. It has been reported [6] that of all hospitalized patients, 8.16% were aged 30 to 50 years and 30.48% were 50 to 70 years of age and that these deaths, 93% occurred in people under 60 years of age. In Mali [7], 30,484 Covid_19 positive cases including 727 deaths with a case-fatality rate of 2.38% were reported in the daily report at the end of the first trimester 2022.

One of the important characteristics of the disease is its severity and the risk of death it causes [4, 8]. The recognition of the disease offers the opportunity to screen at the individual level the entire population and vascular risk factors.

Patients with COVID_19 have an increased risk of thrombotic events due to activation of

coagulation secondary to sepsis. Venous thromboembolic disease complicates severe hospitalizations especially in patients hospitalized in intensive care [10]. The study of a prospective Canadian cohort showed that more than 7% of patients in intensive care were at risk of developing proximal venous thrombosis or pulmonary embolism despite heparin-based anticoagulant prophylaxis [11]. Several Retrospective Chinese cohorts have also explored this coagulopathy which is biologically characterized by an increase in markers of fibrin degradation such as D-Dimers. These studies showed that the increase in D-Dimers was a corollary to complications of COVID_19. Prolonged prothrombin (PT) time, decreased platelets and fibrinogen levels were also observed in the same patients COVID_19 severe. Overall, these results demonstrate intravenous hypercoanutility in patients COVID_19 [10].

We present here a retrospective study of coagulation biomarkers in patients hospitalized at the Mali Hospital in Bamako, which is one of the centers specializing in the management of the disease in Mali, in order to better understand and prevent vascular complications.

MATERIALS AND METHODS

Ethical Aspects

The study was conducted in accordance with the ethical standards set out in the Declaration of Helsinki (1983). The inclusion in the study was carried out according to the rules of the legislation in force at the hospital of Mali and the strict respect of the confidentiality of the identity of the patients and their results of analysis.

Study type and participants

It was a retrospective descriptive and analytical cross-sectional study that takes place in the department of the laboratory of medical biology and anatomical pathology and the center for the management of patients Covid_19 of the hospital of Mali. This study included 134 patients who tested positive for Covid_19 from September 2020 to January 2021. Eligible Patients were selected according to the inclusion criteria set as follows: Patient tested positive for covid_19 by RT-PCR, hospitalized, of any age group and having benefited from a blood coagulopathy assessment (PT, INR, ACT, D-dimer) and Troponin-I cardiac marker.

The non-inclusion criteria were all patients who tested negative at the COVID_19 by the RT-PCR method and all suspected patients whose pulmonary artery angioscan was not in favor of lesions typical of COVID-19 pneumonitis.

Sample Collection

Samples were taken on an empty stomach, in the absence of heparin treatment or drugs that could increase the anticoagulant effect. Hemolysis samples, which may alter the determination of activated cephalin time (ACT), have been ruled out. Blood samples were taken in the laboratory of medical biology and anatomical pathology analysis of the Hospital of Mali, in tubes containing sodium citrate of 0.5 mL for 4.5 mL of whole blood, lithium heparinate and dry tubes using a vacutainer and centrifuged at +4 ° C immediately for 10 minutes at 3000 g and before recovery of plasma and serum. Sampling with the syringe was prohibited in order to avoid the formation of micro-blood clots. The blood samples taken were taken directly to the medical biology analysis laboratory. The biological test assays were carried out no more than 4 hours within the sampling at room temperature (15 to 25 ° C).

Diagnosis of Covid-19

The diagnosis of Covid-19 was carried out by the RT-PCR method at the Laboratory of the Hospital of Mali.

Prothrombin rate (PT)

The BIOLABO SOLEA-4 hemostasis machine was used for the determination of PT, APTT and INR. The technique used is based on the work of Quick *et al*., [12]. Clotting time was measured at 37°C in the presence of tissue thromboplastin and calcium. This test reflects the activity of Factors II (Prothrombin), V (Pro accelerin) VII (Proconvertin), X (Stuart Factor) and fibrinogen. The measured time was converted to PT (%) or INR. Calibration was performed using plasma collected with Thromboplastin and reference Thromboplastin to obtain a calibration curve. Quality controls were performed after calibration and after each reagent vial change. The Bio-TP reagent (reference 13880) and calcium chloride (reference 13565), the Biocal calibrant (reference 13970) and the quality control (reference 13962) were purchased from the supplier representing Biolabo S.A.S in Mali.

Activated Cephalin Time (ACT)

The reagent is Cephalin, an extract of brain phospholipids, used as a substitute for platelet factors. Micronised silica has been used as an activator of factor XII. The factors of the intrinsic coagulation pathway are activated by the addition of these reagents and calcium chloride. The reagent used for the ACT assay is Biolabo S.A.S. Bio-CK reagent (reference 13570), purchased from the supplier representing Biolabo S.A.S. in Mali, for testing the intrinsic pathway of blood coagulation

D-dimer and Troponin I

The Snibe MAGLUMI-800 sandwich chemiluminescence immunoassay (CLIA) was applied for the determination of D-dimers and Troponin I. The membrane-bound serum binds to anti-D-dimer or anti-Troponin I monoclonal antibodies. Buffer and magnetic beads coated with another monoclonal anti-Dimer or anti-Troponin I antibody were carefully mixed and incubated at 37°C for the sandwich reaction. The light

signal was measured by a photomultiplier within 3 seconds as relative light units, which is proportional to the concentration of D-dimer or Troponin l present in the sample. The same principle was applied to the control and calibrator samples of the MAGLUMI-800 system. Reagents, Calibrators and Internal Quality Control used for the D_dimer assay are D_dimer (CLIA) reagent (part number 130206008M) and Troponin I (CLIA) reagent (part number 130206002M) were all purchased from the representative supplier Shenzhen new industries biomedical engineering Co. in Mali.

Parameters explored in the study

The socio-demographic data explored are age and gender. The biological parameters measured were the prothrombin rate (PT) with INR, Actvated Cephalin active, D-dimer and Troponin-I. Markers of coagulopathy were considered normal when PT is between 70 and 100%, INR between 2 and 3; APTT between 25 and 40 and D-dimer less than 0.5 µl/ml. Troponin-I was considered normal when it was below 0.1 µl/ml.

Analyses statistiques univariées

The non-parametric Mann-Whitney-Wilcoxon test was used to compare the means of quantitative variables while χ 2 tests or Fisher's exact test, depending on the numbers, were used for qualitatives variables. Differences were considered significant if the probability (p) of the observed difference under the null hypothesis was $p \leq 0.05$.

V. RESULTS

The coagulation and cardiac markers are presented in Tables I to VII. Our study population was predominantly male, with 62.69% male and 37.31% female, and a ratio of 0.59 in favour of males. The majority of patients were between 20 and 50 years old, with 4.48% between 14 and 20 years old, 58.21% between 20 and 50 years old and 37.31% more than 50 years old.

1. Marqueurs biologiques et gravité de la maladie à covid_19

Statistically significant differences were obtained between the different stages of disease progression with INR (P=0.0002), ACT (P= 0.0259) and D-dimer (P=0.0060). There were also no statistically significant differences in disease progression with PT (P=0.3996) and Troponin-I, (P=0.9714). Mean D-dimer levels were elevated at all stages of the disease with a significant difference for the more severe forms compared to the moderate forms (P = 0.0060).

Table I: Biological markers according to disease severity.

Markers	Severity	Mean ± Ecart-type	*P value*
TP	Moderate	89.35±11.12	*0.3996*
	Severe	84.81±11.77	
	Stable	85.86±12.57	
INR	Moderate	2.43±0.71	*0.0002*
	Severe	3.14±1.62	
	Stable	1.47±0.92	
ACT	Moderate	33.88±3.84	*0.0259*
	Severe	38.30±7.11	
	Stable	34,82±7,18	
D-dimer	Moderate	1.03±0.88	*0.0060*
	Severe	2.14±2.15	
	Stable	1.13±1.14	
Troponin-I	Moderate	0.02±0.04	*0.9714*
	Severe	0.02±0.01	
	Stable	0.01±0.02	

Only 10.44% of our population had low PT with 0.74% deaths while the majority (89.55%) had normal PT but with 5.22% deaths.

Table II: Stages of Severity according to Prothrombin Levels (TP)

Markers	Reference values	Stages of Severity (%)			Total Severity (%)
		Moderate	Severe	Stable	
TP	< 70%	2 (1.49%)	2 (1.49%)	10 (7.46%)	14 (10.44%)
	≥ 70%	21 (15.67%)	18 (13.43%)	81 (60.44%)	120 (89.55%)
	Total	23 (17.16%)	20 (14.92%)	91 (67.91%)	134 (100%)

Some 58.20% of the patients had an INR below normal with 1.49% of deaths, while 15.67% of them had an INR above normal with 2.23% of deaths.

Table III: Severity stage according to INR values

Markers	Reference values	Stages of Severity (%)			Total Severity (%)
		Moderate	Severe	Stable	
INR	< 2	3 (2.23%)	5 (3.73%)	70 (52.23%)	78 (58.20%)
	2 ≤ 3	16 (11.94%)	3 (2.23%)	16 (11.94%)	35 (26.11%)
	>3	4 (2.98%)	12 (8.95%)	5 (3.73%)	21 (15.67%)
	Total	23 (17.16%)	20 (14.92%)	91 (67.91)	134 (100%)

Prolongation of TCA was observed in 16.41% of patients with 2.23% of deaths, while 80.59% of patients had a normal TCA with 3.73% of deaths.

Table IV: Severity stages according to TCA values

Markers	Reference values	Stages of Severity (%)			Total Severity (%)
		Moderate	Severe	Stable	
ACT	< 25 s	0	0	4 (2.98%)	4 (2.98%)
	25 ≤ 40 s	21 (15.67%)	12 (8.95%)	75 (55,97%)	108 (80.59%)
	> 40 s	2 (1.49%)	8 (5.97%)	12 (8.95%)	22 (16.41%)
	Total	23 (17.16%)	20 (14.92%)	91 (67.91%)	134 (100%)

Increased D-dimer values were observed in 76.12% of patients with a death rate of 5.97% in our study population.

Table V: Severity stages according to D-dimer values

Markers	Reference values	Stages of Severity (%)			Total Severity (%)
		Moderate	Severe	Stable	
D-dimer	≤ 0.5 µl	5 (3.73 %)	2 (1.49 %)	25 (18.65 %)	32 (23.88 %)
	> 0.5 µl	18 (13.43 %)	18 (13.43 %)	66 (49.25 %)	102 (76.11 %)
	Total	23 (17.16 %)	20 (14.92 %)	91 (67.91 %)	134 (100 %)

Only 1.49% of patients had an increase in cardiac troponin but with a death rate of 5.97% in the population with a normal troponin-I value.

Table VI: Severity stages according to Troponin-I values

Markers	Reference values	Stages of Severity (%)			Total Severity (%)
		Moderate	Severe	Stable	
Troponin I	≤ 0.1 µl	22 (1.49 %)	20 (14.92 %)	90 (67.16 %)	132 (98.50 %)
	> 0.1 µl	1 (0.74 %)	0	1 (0.74 %)	2 (1.49 %)
	Total	23 (17.16 %)	20 (14.92 %)	91 (67.91 %)	134 (100 %)

2. Morbidity and mortality factors

Among the different biomarkers studied, only D-dimer appears to be a negative factor with a death rate of 5.97% observed in patients with high D-dimer levels.

Table VII: Biological markers related to disease progression

Markers	Reference values	Deaths %	Healthy %	Total %
PT	< 70	1 (0.74 %)	13 (9.70 %)	14 (10.44 %)
	≥ 70	7 (5.22 %)	113 (84.32 %)	120 (89.55 %)
INR	< 2	2 (1.49 %)	76 (56.71 %)	78 (58.20 %)
	2-3	3 (2.23 %)	32 (23.8 %)	35 (26.11 %)
	> 3	3 (2.23 %)	18 (13.43 %)	21 (15.67 %)
ACT	< 25 s	0	4 (2.98 %)	4 (2,98 %)
	25 - 40 s	5 (3.73 %)	103 (76.86 %)	(80.59 %)
	> 40 s	3 (2.23 %)	19 (14.17 %)	22 (16.41 %)
D-dimer	≤ 0.5 µl	0	32 (23.88 %)	(23.88 %)
	≥ 0.5µl	8 (5.97 %)	94 (70.14 %)	102 (76.11 %)
Troponin-I	≤ 0.1 µl	8 (5.97 %)	124 (92.53 %)	132 (98.50 %)
	> 0.1µl	0	2 (1.49%)	2 (1.49 %)

DISCUSSION

We conducted a descriptive and prospective cross-sectional study conducted from September 2020 to January 2021. It concerned patients tested positive for COVID_19 by RT-PCR and hospitalized at the Covid_19 management center at Mali Hospital. The study population consisted of 134 patients. We recorded 50 female and 84 male patients. The sex ratio was 0.64 in favor of males. One in six severe cases was observed in the age range of 14 to 20 years. Male sex has been reported as a significant risk factor for hospitalization and mortality [14]. Indeed, several studies have found that COVID-19 infects more men than women [15, 16].

The age group between 20 and 50 years represented the majority with 78 patients or 58.21% of the total with 10 severe cases out of the 20 patients who developed the severe form of the disease. This data is certainly explained by the fact that this age group represented the most active layer of society due to daily occupations. These data are similar to the study report published by the Institut National de Santé Publique (INSP) in Mali where 70% of positive cases were in the age group 15-54 years [18]. Other studies report juvenile factors, population genetics and the lack of a case reporting system in Africa [19].

Age is an important risk factor for the severe clinical course of the infection and this study recorded 9 severe cases out of 50 patients in the age group of more than 50 years including 6 deaths, all of them male.

In the entire study population, 14 patients out of 134 had a prothrombin level (PT) below the normal value, namely 10.45%. On the other hand, 120 patients had a level greater than or equal to 70% of the normal value, namely 89.55%. One case of death was recorded (7.14%) compared to 13 cases of recovery (92.86%) out of the 14 patients with a low prothrombin level. On the other hand, there were seven cases of death (5.22%) versus 113 cured cases (84.32%) out of 120 patients with high prothrombin level.

The prothrombin time and activated thromboplastin time are routine elements of hemostasis analysis. We have seen that they can be modified by the activation of coagulation cascades by the infectious process. Prolonged prothrombin time (PT), decreased platelet count and decreased fibrinogen level have been commonly reported in severe COVID-19 patients [20]. Several international, national or local learned societies have issued recommendations for the management of coagulopathy in COVID-19 patients [21, 22], and our data are similar to those reported by [23] in Wuhan province who recorded a decrease in PT in 30% of their cohort of 99 patients hospitalized with SARS-CoV2 pneumonia.

There were no deaths in patients with a ACT of less than 25 seconds. On the other hand, those with a ACT between 25 and 40 seconds recorded 5 deaths (4.63%) against 103 cases of cure (95.37%) out of a total of 108 cases (80.60%). Patients with a TCA greater than 40 seconds, we recorded 3 deaths (13.64%) with 19 cured patients (86.36%). We observed a significant difference in ACT values in our patients ($p = 0.0259$). Coagulation disorders were frequently observed in patients with COVID-19. This coagulation disturbance can be explained by the complications of Covid_19, which leads mainly to the risk of thrombosis. As in any inflammatory pathology, such as sepsis, the fibrinogen (coagulation factor I) level is also strongly increased in COVID-19 patients, especially in the most severe forms [24, 13]. A correlation with the risk of thrombosis, as in other pathologies, has been suggested [25]. A deficiency in vitamin K or in certain proteins necessary for coagulation could lead to a longer coagulation time. This study did not evaluate the level of fibrinogen or vitamin K, which could in part provide further support for the prolongation of the ACT related to the coagulation disorders observed in our patients. The severity of the disease is more variably associated with a change in prothrombin time or active thromboplastin time [26]. These disorders increase the risk of death during the course of the disease. Among the biological markers, weobserve an increase in D-dimer, a decrease and or increase in PT and ACT which characterize the coagulopathy syndrome frequently associated with a poor prognosis.

The population with an INR of less than 2 (INR < 2) was 58.21% with two cases of death (2.56%) against 76 cases of cure of 56.71%. In patients with an INR between 2 and 3, we recorded 3 cases of death or 2.23% for a cure rate of 23.88%. Similarly, those with an INR greater than 3, we recorded 3 cases of death or 2.23% for 18 cases of cure 13.43%. Prolonged INR values were significantly associated with severity and mortality of COVID-19 reported in a study [27]. Prolonged INR and D-dimer elevations may be useful in diagnosing COVID-19- associated coagulopathy and predicting clinical outcomes. A correlation was found in our study between INR and D-dimer elevations with significant differences ($p = 0.0002$ *and* $p = 0.0060$) for INR and D-dimers, respectively. Data from a meta-analysis [27] reported that INR was significantly associated with C-reactive protein ($p = 0.048$) and D-dimers ($p = 0.001$) [28] which corroborates with our results.

Patients with a Troponin-I level less than or equal to 0.1 µl/ml (≤ 0.1 µl) were 132 (98.51%) with 8 cases of death (6.06%) against 124 cured patients (93.94%). On the other hand, those with a Troponin-I level greater than 0.1 µl/ml were a total of two patients or 1.49%, and no cases of death recorded. Myocardial necrosis is common in patients hospitalized in

emergency and intensive care units; it is estimated to be present in 8% to 28% of patients hospitalized with coronavirus disease (COVID_19) [29]. Defined by an elevation of troponin beyond the 99e percentile of a healthy reference population [30], myocardial injury associated with COVID_19 may be due to ischemic or nonischemic myocardial injury [31]. In the absence of muscle necrosis, the troponin concentration is very low or even zero [30]. Although it is useful for emergency physicians to show that myocardial necrosis is a predictive factor for poor prognosis in patients with COVID_19, it is not specific for this disease. However, the correlation between troponin elevation and increased mortality has been described previously in populations of patients testing positive for Covid_19. The deaths seen in the study population with normal troponin-I levels could be explained by the frequency of comorbid factors such as diabetes, hypertension, and age >50 years reported in our study. The fact that our study reported no deaths in the population with elevated troponin may result from the fact that patients in the group with elevated troponin were more stable, which may partly explain the differences in mortality found.

Together, these biological data show us that an elevated plasma D-dimer level in a patient with COVID_19 is suggestive of a severe case because all the patients who died in our study had an elevated D-dimer level and this is the only common parameter that could explain the pathology related to the severity and mortality rate in our sample. More interestingly, elevated fibrinogen and D-dimer levels identify patients at high risk for thromboembolic complications. This confirms the hypothesis established by Wang D *et al*., [32] that the most important disturbances were related to the elevation of D-dimer in patients admitted to intensive care. There was considerable heterogeneity in the results for all-cause death and determinants of death or major thrombotic event. In severe COVID-19, specific coagulation-related mortality is not established. However, an impact on prognosis is suggested in a retrospective Chinese series of 183 patients in which 71.4% of the deceased patients had evidence of coagulation related disorders [13]. Moreover, from the beginning of the epidemic, some authors pointed out a decrease in mortality for patients on heparin [33]. The elevation of D-dimer could therefore serve as a risk marker for the severity of the disease, which is specific to COVID-19 and could be used for risk stratification related to coagulopathy. Clinical signs such as respiratory distress associated with increased D-dimer levels in patients who test positive should aid in rapid decision making in the hospital and intensive care setting.

VII. CONCLUSION AND PERSPECTIVES

Monitoring of biological parameters of hemostasis in patients with COVID_19 allows the detection of abnormalities related to the disruption of hemostasis to prevent thrombotic events or pulmonary embolisms that could lead patients to develop severe forms of the infection.

Their control would also allow health workers to ensure better management of patients and to predict cases of complications in order to reduce hospitalizations in the critical care sector. It would be desirable to combine the determination of fibrinogen, platelet count, C-reactive protein and D_dimer with the biological diagnosis in the diagnosis and monitoring of Covid_19 disease.

What is known about this subject?

It is a public health problem

What's new about your study

Combine fibrinogen, Troponinin-I, PT, ACT, and D_dimer assays with biological diagnosis in the diagnosis and monitoring of Covid_19 disease**.**

Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions

All authors participated in the development of the study clinically than biologically, in the statistical analysis and in the writing.

Acknowledgements: We would like to thank the Mali Hospital, Mali.

REFERENCES

1. WHO. Estimated mortality from COVID-19. WHO/2019 nCoV/Sci_Brief/Mortality/2020.1
2. Mohamed, M. F., Abuo-Rahma, G. E. D. A., Hayallah, A. M., Aziz, M. A., Nafady, A., & Samir, E. (2020). Molecular docking study reveals the potential repurposing OF histone deacetylase inhibitors against COVID-19. *International Journal of Pharmaceutical Sciences and Research*, 4261-4270.
3. Dhama, K., Khan, S., Tiwari, R., Sircar, S., Bhat, S., Malik, Y. S., ... & Rodriguez-Morales, A. J. (2020). Coronavirus disease 2019–COVID-19. *Clinical microbiology reviews*, *33*(4), e00028-20.
4. Chilamakuri, R., & Agarwal, S. (2021). COVID-19: characteristics and therapeutics. *Cells*, *10*(2), 206.
5. https://www.santepubliquefrance.fr/maladies-et traumatismes/maladies-et-infections-respiratoires/infection-a_coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-22-octobre 2020. Santé publique France. Covid-19.
6. https://www.hcsp.fr/explore.cgi/avisrapportsdomaine. Avis du 20 avril 2020 relatif à l'actualisation de l'avis relatif aux personnes à risque de forme grave de Covid-19 et aux mesures barrières.
7. http://www.sante.gov.ml/index.php/actualites/communiques. Rapport journalier Covid_19 n°759.
8. https://www.hcsp.fr/explore.cgi/avisrapportsdomaine. Avis du 31 mars 2020 relatif à la prévention et à la prise en charge des patients à risque de formes graves

de COVID-19 ainsi qu'à la priorisation des tests diagnostiques
9. Wu, C., Chen, X., Cai, Y., Zhou, X., Xu, S., Huang, H., ... & Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA internal medicine*, *180*(7), 934-943.
10. Casini, A. (2020). Risque thrombotique veineux induit par le SARS-CoV-2 : prévalence, recommandations et perspectives. *Rev Med Suisse*, 16, 951-954.
11. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. (2011). Dalteparin versus unfractionated heparin in critically ill patients. *New England Journal of Medicine*, *364*(14), 1305-1314.
12. Quick, A. J. (1938). The nature of the bleeding in jaundice. *Journal of the American Medical Association*, *110*(20), 1658-1662.
13. Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis*, *18*(4), 844-847.
14. EL Kettani, Z. (2020). Méta-analyse La maladie COVID 19: Facteurs de risque et l'intérêt pronostic des D-dimères.
15. Sharma, G., Volgman, A. S., & Michos, E. D. (2020). Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected?. *Case Reports*, *2*(9), 1407-1410.
16. Jin, J. M., Bai, P., He, W., Wu, F., Liu, X. F., Han, D. M., ... & Yang, J. K. (2020). Gender differences in patients with COVID-19: focus on severity and mortality. *Frontiers in public health*, 152.
17. https://sante.journaldesfemmes.fr/fiches-maladies/2622115-victime-covid-france-profil-age-plus-jeune-celebre-nombre-bilan-cas-deces
18. https://reliefweb.int/sites/reliefweb.int/files/resources/mali_sitrep_covid_19_n82_14_juin.pdf
19. Ogunleye, O. O., Basu, D., Mueller, D., Sneddon, J., Seaton, R. A., Yinka-Ogunleye, A. F., ... & Godman, B. (2020). Response to the novel corona virus (COVID-19) pandemic across Africa: successes, challenges, and implications for the future. *Frontiers in pharmacology*, 11, 1205.
20. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*, *395*(10229), 1054-1062.
21. Lu, Y. F., Pan, L. Y., Zhang, W. W., Cheng, F., Hu, S. S., Zhang, X., & Jiang, H. Y. (2020). A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. *International journal of infectious diseases*, *100*, 34-41.
22. Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of thrombosis and haemostasis*, *18*(5), 1094-1099.
23. Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., ... & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The lancet*, *395*(10223), 507-513.
24. Helms, J., Tacquard, C., Severac, F., Leonard-Lorant, I., Ohana, M., Delabranche, X., ... & Meziani, F. (2020). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive care medicine*, *46*(6), 1089-1098.
25. Ageno, W., Squizzato, A., Garcia, D., & Imberti, D. (2006, October). Epidemiology and risk factors of venous thromboembolism. In *Seminars in thrombosis and hemostasis* (Vol. 32, No. 07, pp. 651-658). Copyright© 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA..
26. Bikdeli, B., Madhavan, M. V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., ... & Lip, G. Y. (2020). COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *Journal of the American college of cardiology*, *75*(23), 2950-2973.
27. Zinellu, A., Paliogiannis, P., Carru, C., & Mangoni, A. A. (2021). INR and COVID-19 severity and mortality: a systematic review with meta-analysis and meta-regression. *Advances in Medical Sciences*, *66*(2), 372-380.
28. Iba, T., Warkentin, T. E., Thachil, J., Levi, M., & Levy, J. H. (2021). Proposal of the definition for COVID-19-associated coagulopathy. *Journal of clinical medicine*, *10*(2), 191.
29. Calvillo-Argüelles, O., & Ross, H. J. (2020). Cardiac considerations in patients with COVID-19. *CMAJ*, *192*(23), E630-E630.
30. https://www.eurofins-biomnis.com/referentiel/liendoc/precis/troponines.pdf
31. Driggin, E., Madhavan, M. V., Bikdeli, B., Chuich, T., Laracy, J., Biondi-Zoccai, G., ... & Parikh, S. A. (2020). Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *Journal of the American College of Cardiology*, *75*(18), 2352-2371.
32. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, *323*(11), 1061-1069.
33. Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of thrombosis and haemostasis*, *18*(5), 1094-1099.