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Coagulation disorders in Covid-19 patients

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Abstract

So far the pathophysiology of infection due to coronavirus 2019 (covid 19) is not well elucidated, however, several studies suggest that there is a link between the coagulation system and Sars-coV2. The objective of this work is to study the variability of coagulation parameters in patients infected with covid-19. Patients and methods: We have collected 102 confirmed Covid 19 infected patients (group 1), hospitalized at the Covid 19 center of the CHU Mohamed VI of Marrakesh, we have studied the coagulation parameters in these patients and comparing them with a group of control patients (group 2) who did not present any coronavirus infection. Results: The mean age was 46 years in group 1 and 40 years in group 2, with male predominance in both groups (55.4% in G1 and 52.8% in G2). D-dimer (1.35±2.1 vs 0.18±0.05, p<0.001) and fibrinogen (4.04 (±1.85) vs 2.13 (±0.308), p <0.001) levels in G1 are elevated relative to G2, while prothrombin levels are decreased (84.7 (±16.9) vs 93.1 (±6.60), p<0.01). We did not observe a significant difference between the two groups with respect to platelet count, International Normalized Ratio (INR) and APTT (p >0.05). D-dimer and fibrinogen values in severe Covid 19 patients were higher than in non-severe Covid 19 patients (p<0.001). Conclusion: Clotting factors in Sars cov 2 patients are significantly impaired compared to those in the control group. The high level of fibrinogen and D-dimer may be a marker for the early identification of severe cases.

Keywords: Blood coagulation; Sars-Cov 2; D-dimer; Fibrinogen

1. Introduction

As of December 2019, a new type of pneumonia, now defined as Coronavirus 2019 (COVID-19), has spread widely in China and even to many foreign countries [1]. It is an emerging infectious disease of viral zoonosis type. In a context that became epidemic within a few weeks, on March 11, 2020, the World Health Organization (WHO) declared the Covid-19 pandemic [2].

This coronavirus, initially called nCOV-2019, then renamed SARS-Cov-2, was isolated from upper respiratory tract epithelial cells by RT-PCR on a deep nasal swab [1]. The increasing number of infected patients in many Chinese cities, as well as in other countries around the world, clearly reflects the high risk of human-to-human transmission [3].

A significant proportion of infected people have no symptoms but can transmit the disease. The most common clinical signs of Covid-19 are those of acute respiratory infection, ranging from pauci-symptomatic forms or suggestive of mild pneumonia, to very severe forms with acute respiratory distress syndrome (ARDS) and even multi-visceral failure and death. Forms with digestive symptoms (anorexia, nausea, diarrhea, abdominal pain) or initially non-febrile may be at the forefront. Other reported symptoms include headache, sore throat and rhinorrhea. Sudden anosmia without nasal

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obstruction and dysgeusia are described from day 6-7. In the elderly, deceptive neurological forms are described (concentration disorders, confusion...) [2, 4-5, 7].

Although a good analysis of the clinical features of COVID-19 has been acquired, less clear information has been provided on biological abnormalities, in particular, on the potential deregulation of hemostasis factors.

Therefore, in order to better understand the pathophysiology of Sars Cov 2 infection, we have studied the correlation between coagulation factor disruption and the severity of COVID 19 infection.

2. Patients and methods

2.1. Diagnostic Criteria

A total of 140 patients were included.

2.1.1. Inclusion criteria:

- Patients over 18 years of age
- Patients admitted for suspicion of COVID infection 19 who were hospitalized at the Covid services of the CHU Mohamed VI of Marrakesh between March and June 2020.
- Patients who have benefited from a SARS CoV-2 RT-PCR

2.1.2. According to the results of the RT-PCR, we divided our population into groups:

- Group 1 (G1) corresponds to confirmed Covid-19 patients
- Group 2 (G2) are the control patients whose SARS CoV-2 RT-PCR sample tested negative.

2.1.3. The group of SARS-CoV-2 patients was divided into subgroups according to disease severity:

Severity criteria:

- Disorders of consciousness
- Breathing rate greater than 30 cycles per minute
- Systolic blood pressure less than 90 mmHg
- Heart rate greater than 120 beats per minute
- Oxygen saturation lower than 92 % under 4l/ min O2

2.2. Exclusion criteria:

- patients under 18 years of age
- patients on anticoagulant therapy
- patients with a history of hemopathy
- patients who have had a blood transfusion

The coagulation blood tests performed include: platelet count (PQ), prothrombin (TP), D-dimer, fibrinogen, International Normalized Ratio (INR) and activated partial thromboplastin time (APTT).

Data entry was performed on Excel 2013, quantitative variables were compared using the Student's t-test and the Mann-whitney U-test, and results were presented as mean, standard deviation and percentage. The software used for the p-value is epi info 7.2. A value of $p<0.05$ is considered statistically significant.

3. Results

The average age was 46 years in Group 1 and 40 years in Group 2, with a male predominance in both groups (55.4 per cent in G1 and 52.8 per cent in G2). We found that the rate of D-dimer (1.35±2.1 vs 0.18±0.05, $p<0.001$) and fibrinogen (4.04 (±1.85) vs 2.13 (±0.308), $p <0.001$) in G1 are elevated compared to G2, while the rate of prothrombin is decreased (84.7 (±16.9) vs 93.1 (±6.60), $p<0.01$). We did not observe a significant difference between the two groups with respect to platelet count, International Normalized Ratio (INR) and APTT (p 0.05) (Table 1).

Table 1 Comparison of coagulation parameters between patients and controls

coagulation parameters	G1 (n=102)	G2 (n= 38)	P value
Platelets *10^3 /mm3	251 (±89.3)	266 (±50.6)	0.3
D-dimer mg/l	1,35±2.1	0.18±0.05	<0.001
Fibrinogen g/L	4.04 (±1.85)	2.13 (±0.308)	<0.001
TP %	84.7 (±16.9)	93.1 (±6.60)	<0.01
INR	1.06± 0.05	1.08±0.3	0.75
APTT	27.5±4.5	27±5	0.14

Group 1 was divided into two subgroups according to severity criteria. The mean age of the severe patients was 61.4 years and 86. 6% were male. Statistical analysis of coagulation parameters showed that there was no significant difference between the two subgroups in platelet count, APTT and INR, but a comparison of fibrinogen, D-dimer and prothrombin levels between severe and non-severe patients showed a statistically significant difference ($p < 0.05$) between the two subgroups and that the rate of the first two and more parameters increased in patients who represented a severe Covid-19 infection, whereas it decreased for TP in the same patients (Table 2).

Table 2 Comparison of clotting factors by severity of Covid 19

coagulation parameters	Non-severe patients	Severe patients	Group control
Platelets *10^3 /mm3	255 (±90)	240.2 (±100)	266 (±50.6)
D-dimer mg/l	0.6±1.1	6± 6	0.18±0.05
Fibrinogen	4.10 ± 1.06	6±2	2.13 (±0.308)
TP %	84.56 ± 12.20	62,7	93.1 (±6.60)
INR	1.1 ± 0.08	1.26	1.08±0.3
APTT	28.3	33,5	27±5

4. Discussion

Since December 12, 2019, cases of pneumonia related to a new coronavirus have been reported in China [8]. Although mortality appears to be relatively low, patients with severe or critical conditions are at high risk of developing acute respiratory distress syndrome (ARDS) and being admitted to the intensive care unit. Therefore, accurate diagnosis and rigorous monitoring of disease progression from the earliest stages has become imperative for the rapid and effective management of these patients and the reduction of mortality [9].

On admission, many patients with pneumonia have neutrophil polynucleosis and relatively deep lymphopenia, reported in 84% of cases, with CRP increasing with disease severity [5,10]. In addition to these "standard" abnormalities, certain biological abnormalities are associated with a poorer prognosis or imminent worsening, including coagulopathy, which is also central to the process of degradation of the patient's clinical condition [5, 11-13].

During the Chinese epidemic, coagulopathy was initially described in the first severe cases of SARS-Cov-2 infection, and this was confirmed in European countries [5, 11-14]. The first abnormalities described were a very marked rise in D-dimer (DD) and a rather moderate thrombocytopenia, correlated with a higher risk of resuscitation admission and a higher death rate [5].

Returning to the clinical-biological chronology of the evolution of this disease, the rapid worsening of respiratory symptoms is accompanied by systemic signs (fever > 40°, deterioration of general condition) and an extremely marked rise in proinflammatory cytokines (IL-2, IL6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α), commonly known as "cytokine storm" [7, 14, 16, 27]. The explosive and uncontrolled release of these pro-inflammatory cytokines results in a significant increase in the biological parameters of inflammation (CRP, fibrinogen, ferrit<inemia, LDH). This acute inflammatory phenomenon can affect coagulation and fibrinolysis in several ways and amplify hypercoagulability [15-

17]. It is more a coagulopathy than a true disseminated intravascular coagulation (DIC) observed in sepsis of infectious origin. This notion is corroborated by the conclusions of a thromboelastography (TEG) analysis of hemostasis in Covid-19 patients who noted a state of hypercoagulability associated with major inflammation and a significant elevation of DDD. The study by Helms et al. also supports this finding and reports that compared to non-Covid ARDS, patients with ARDS in relation to SARS-Cov-2 infection have a higher DD rate (4300 vs 2300 ng/mL, $p < 0.001$), mild APTT and antithrombin abnormalities and higher fibrinogen levels (7.0 vs 5.6 g/L, $p < 0.001$) [19]. 19] Thus, coagulopathy-Covid-19 associated with major inflammation is more commonly referred to as coagulopathy-Covid-19 associated with major inflammation than post-sepsis DIC.

Clinical and biological data from a cohort of 201 pneumonia patients admitted to Jinyintan Hospital in Wuhan, of whom 42% developed ARDS and 22% died. Deceased patients with ARDS had a significant increase in DD compared to surviving patients with ARDS (890 vs 5270 ng/mL; 95% CI, $p = 0.001$), suggesting that coagulopathy was implicated in the clinical deterioration and death of these patients [20].

In our study, PT values in COVID-19 patients were decreased more remarkably in severe patients, while D-dimer, fibrinogen values were higher than controls and were significantly increased in patients with ARDS, confirming earlier similar results.

5. Conclusion

There is an obvious hypercoagulability of severe forms of Covid-19, a high level of DD (> 1000 ng/ mL) is associated with aggravation of pneumonia and progression to ARDS, it is a predictor of thrombotic complications and death, this coagulopathy accompanies and complicates a major inflammatory state.

A careful and dynamic thrombotic risk assessment should be performed in all Covid-19 patients, whether hospitalized or not. This assessment includes the classical thrombotic risk factors, but also biological parameters such as DD and fibrinogen.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest

Statement of informed consent

Permission to conduct the study was obtained from Cadi Ayyad University, Department of Pneumology, ARRAZI Hospital, Mohamed VI University Hospital Center, Marrakesh. Informed consent was obtained from patients. All patients' information including raw data was be kept confidential during and after study period.

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