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# Plasminogen as a Marker for Assessing Thrombotic Risk During Hepatitis in Cameroon: Case–Control Study

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## ABSTRACT

**Background and Aims:** The liver synthesizes coagulation factors, anticoagulants, proteins involved in fibrinolysis, and the platelet production regulator, thrombopoietin, from megakaryocytes. Importantly, hepatic dysfunction that arises from hepatitis may perturb the clotting process. This study aims to determine these patients' plasminogen levels and hemostasis disorders to assess the thrombotic risk.

**Methods:** An analytical case-control study was carried out over 6 months. The study included hepatitis B, C, and D patients from Bafoussam Regional Hospital and Laquinitie Hospital in Douala-Cameroon, compared to healthy controls, to evaluate differences in hemostasis and thrombotic risk. Control tests were performed using the immunochromatographic and ELISA methods. Blood Count was performed by flow cytometry method. And determination of D-dimer and plasminogen by nephelometry and ELISA respectively; finally the evaluation of the enzymatic activity of alanine aminotransferase and aspartate aminotransferase (ALT and AST) by the spectrophotometric kinetic method. The results were recorded in an Excel spreadsheet and analyzed using the statistical software R version 4.1.1.

**Results:** The population size was 340 participants including 162 controls (47.7%) and 178 (52.3%) cases of which 136 cases of hepatitis B (76.4%), 26 cases of hepatitis C (14.6%), and 16 cases of hepatitis D (9%). The sex ratio was 3.15 in favor of men; including 1.7 in cases and 9.1 in controls. All patients had a thrombotic risk characterized by a decrease in plasminogen levels compared to controls ($p < 0.001$). 13.5% of the population had thrombocytopenia compared to none among controls ($p < 0.001$). The following parameters are associated with risk of developing thrombosis in this study in particular Hepatitis (aOR = 3; 95% CI [1.01–5.2]; $p < 0.03$), plasminogen decrease (aOR = 3; 95% CI [1.01–5.2]; $p < 0.03$), shortening cephalin time activator (CTA) (aOR = 1.5; 95% CI [1.1–5.2]; $p < 0.04$), and decreased hemoglobin (aOR = 2.1; 95% CI [1.1–5.1;]; $p < 0.03$).

**Conclusion:** This study shows a decrease in plasminogen in patients during hepatitis. It suggests it is an important element to evaluate the thrombotic risk although the exploration of other coagulation tests should be associated with it for a complete and exhaustive evaluation and a better final diagnosis.

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## 1 | Introduction

Any disruption in the integrity of the vascular circuit, causing blood leakage, triggers a series of cellular and biochemical processes ensuring the closure of the breach and the control of the hemorrhage or, failing that, the prevention of thrombus formation [1]. Hemostasis responds to all of these physiological mechanisms and includes several interrelated and interdependent steps including primary hemostasis which targets the formation of platelet thrombus, plasma coagulation for the consolidation of the previously formed thrombus, and finally fibrinolysis [2]. Fibrinolysis studies the mechanisms of destruction of the fibrin thrombus to permeabilize a thrombosed vessel [3]. The homeostasis of this process is carried out by the liver. Indeed, the liver plays a central role in hemostasis thanks to the synthesis of several factors and coagulation inhibitors, synthesis of fibrinolytic proteins and their inhibitors [4]. Moreover, the hepatic reticuloendothelial system is responsible for the removal of all activated clotting factors, coagulation, and fibrinolysis activation complexes, as well as fibrin and fibrinogen breakdown products. It is also involved in the synthesis of molecules such as plasminogen (which, when transformed into plasmin, will split fibrin), as well as fibrinolysis activators and inhibitors [5]. Tissue plasminogen activator (tPA), which induces the transformation of plasminogen into plasmin, is eliminated by the liver [6]. However, its functions can be disrupted during liver damage.

Indeed, hepatic cirrhosis is an irreversible disease of the liver resulting from a diffuse process, characterized by mutilating fibrosis that destroys normal liver architecture and isolates hepatocyte nodules of abnormal structure [7]. It is the consequence of chronic liver disease. The main reported causes of cirrhosis in adults are prolonged and excessive alcohol consumption (50%–75% of cases) associated in at least 10% of cases with chronic hepatitis C virus infection, chronic hepatitis C virus infection (15%–25% of cases), metabolic syndrome, chronic hepatitis B virus infection (5% of cases), possibly superinfected with hepatitis D virus [8, 9]. It is estimated that about 20%–30% of patients with chronic hepatitis C progress to cirrhosis within 20 years, and about 15%–20% of patients with chronic hepatitis B can do so within 5 years [10]. Patients with established cirrhosis have a poor prognosis because they are at high risk of hepatic decompensation and/or the development of hepatocellular carcinoma (HCC) [11]. In addition, hepatic cirrhosis is a major risk factor for coagulopathy and venous thromboembolism (VTE) [12]. Hepatic cirrhosis can increase thrombotic risk through a variety of mechanisms. Chronic hepatitis can induce inflammatory changes in the surrounding tissues, especially the endothelium of the portal vein system, resulting in activation of the coagulation system through inflammation and increasing the risk of portal vein thrombosis (PVT). In addition, antiphospholipid antibodies (aPLs) may be involved in the pathogenesis of thrombosis [13]. These antibodies, along with other autoimmune phenomena, have been associated with chronic hepatitis C virus infection. Therefore, special attention must be paid to chronic hepatitis. Although it is classically considered a coagulopathy resulting in bleeding, there is recent evidence to suggest that in bleeding coagulopathy, the risk of thrombosis may even outweigh that due to bleeding [14]. On the atherothrombotic side, similarly, viral infections can contribute to atherosclerosis either through direct infection of endothelial cells or indirectly through cytokines or acute-phase proteins induced by systemic inflammation. A recent review of the literature suggests a relationship between different infectious pathogens and atherothrombosis; here, she suggests that the global burden of chronic infections may contribute to atherosclerosis and thrombotic complications [15].

From the above, the relationship between the fibrinolytic and hepatic systems in humans remains complex, particularly concerning the susceptibility of patients with liver damage and the predisposition to thrombotic risk, which has given rise to much controversy among several authors [13–15]. Hepatitis is a highly prevalent infection in the world in general and in Cameroon in particular, and the symptoms intrinsic to the disease are the cause of an increase in mortality [15]. Associated with this, the thrombotic risk constitutes an aggravating factor of mortality in this population group [10]. This study therefore aims to shed some light on the subject in the Cameroonian context based on the evaluation of plasminogen levels in these patients and hemostasis disorders in the latter and thus contribute to the prevention of thrombotic risk; and improve patient care.

## 2 | Materials and Methods

### 2.1 | Study Design and Subjects

An analytical case–control study was carried out over 6 months. Participants were recruited at the Bafoussam Regional Hospital (BRH) and Hospital Laquitinie in Douala. These two hospitals are located in Cameroon and represent second category of hospitals according to the Cameroon health pyramid. Patients were recruited from the gastroenterology department of the hospitals and/or those regularly followed in said hospitals on a consecutive basis. Cases consisting of patients with hepatitis B, C, or D; and control of people of apparent good health. A total of 340 participants were included in the study registry to the Lorentz formula, including 178 patients including 136 cases of hepatitis B, 26 cases of hepatitis C and 16 cases of hepatitis D. The selection of the latter was done under the basis of a consecutive sample. Furthermore, the selection of the control population was made in the same socioeconomic environment as cases, and in total, 162 healthy were included.

Information on the study was given to the potential participants and their legal guardians (if need be) in their first official languages. Patients read and signed the informed consent form. For each participant, demographic, and clinical data were obtained and noted on a pre-structured data collection sheet. Any participant who had received an immunochromatographic and enzyme-linked immunosorbent assay to monitor hepatitis status was included in the study.

Moreover, participants with the following characteristics were not included: participants with pathologies that could influence the physiological process of hemostasis according to the literature, in particular those on anticoagulant treatment (antivitamin K, heparin), patients with a history of alcoholism and smoking, patients with a current bacterial infection or with human immunodeficiency virus (HIV) infection, patients on systemic steroid treatment, pregnant women and those on oral contraceptives and/or estrogen treatment.

### 2.2 | Data Collection Tools and Methods

A volume of blood was collected in two tubes from each of the study participants. Each tube of blood sample collected was transported to the Hematology and Medical Biochemistry laboratories of "Hôpital Regional de Bafoussam" and "Hôpital Laquitinie de Douala."

For hematological analysis, a Complete Blood Count was performed on the HumaCount 30TS hematology automaton. Besides this later, blood smears were done to assess the quality of blood cells and the vital staining to classify the type of anemia. The slides colored with May Grunwald Giemsa were read under a binocular microscope from the manufacturer "Irmerco."

Rapid diagnostic and enzyme-linked immunosorbent assay (ELISA) tests were performed for the case population to confirm the participants' status. Regarding the biochemical and immunological analyses, the concentration of the D-dimer was determined according to the method of the "Genrui" Kit, using the semi-automatic protein analyzer "PA50" calibrated by a magnetic card whose operating principle is nephelometry. Furthermore, the plasminogen concentration was determined in patients according to the reagent Elabscience® protocol (of the batch number *ER020N407972)* and on the system Mindray *MR-96A ELISA* chain.

Subsequently, the determination of fibrinogen and Quick's Time were carried out by automatic method using the coagulometer "Sinothinker" (according to the kit "CYPRESS" and Biolabo respectively). The Prothrombin level was deduced from the Quick Time from the Thivolle calibration curve. The determination of the Cephalin Time Activator was carried out automatically (according to the "Biolabo" kit). Finally, the determination of the enzymatic activity of transaminases aspartate aminotransferase and alanine aminotransferase (AST and ALT) was done (according to the "Chronolab" kit) using the spectrophotometric method, the principle of which was kinetics.

Plasminogen cut-off values are 5–22 μg/mL. Thrombotic risk in patients was defined for plasminogen levels < 5 μg/mL. The prothrombin level ranged from 70% to 100% and TCA ranged from 25 to 35 s. Hemostasis disorders in favor of thrombotic risk have been defined for people with a cephalin time activator (CTA) and/or decreased prothrombin level.

### 2.3 | Data Analysis

The data collected were saved in Microsoft Excel 2016 software. Statistical analysis was performed using the statistical tool R version 4.1.1. The qualitative variables studied were the clinical history of participants and sex; and quantitative variables were age, D dimer concentration, plasminogen concentration, prothrombin time (PT), CTA, hemoglobin concentration, platelets cells, red blood cells, white blood cells, ALT, and AST enzyme activity. Each of the biochemical, hematological, hemostasis parameters, and immunological parameters studied has been dichotomized and grouped into "normal, high, or low" according to the reference values and cutoff defined by the WHO, the manufacturer of each reagent used and the scientific literature. Qualitative variables were presented as frequency, while quantitative variables were presented as averages and standard deviation. The comparison of proportions was made with the chi-square test. The student *t*-test was used to compare the mean between different groups. Univariate and multivariate logistic regression analyses were used to identify associated factors with thrombotic risk in patients. All these tests were done at a risk threshold of $\alpha = 5\%$.

### 2.4 | Ethical Considerations

This study was approved by the *Université des Montagnes* Research Ethics Committee (N°2022/175/UdM/PR/CEAQ) and the Ethics Committee of the University of Douala (N°3624 CEI-UDo/05/2023/M). Authorization to collect the data was obtained from the Regional Hospital of Bafoussam (N° 005/L/MINSANTE/SG/DRSPO/HRB/D) and the Regional Delegate of Health of the Littoral (Authorization N°2448/ACD/MINSANTE/DHC/SG). Before initiating the study, participants were given a newsletter about the objectives of the study, its benefits, and its risks. We obtained their free and informed consent through their signatures for eligible participants. The confidentiality of the research results was respected by the use of a unique code for each patient.

The following Figure 1 describes the sampling dynamics and sample flow during this study:

According to this figure, patients with hepatitis (case population) had a higher thrombotic risk compared to healthy negative controls (control population) who did not have it.

## 3 | Results

### 3.1 | Distribution of the Study Population by Sociodemographic Characteristics and Clinical History

Tables 1 and 2 present respectively the socio-demographic characteristics and clinical history of the study population during the study period.

From Table 1, the mean age of participants in the study population was $32.10 \pm 10.66$ years: $34.64 \pm 11.81$ years old in the

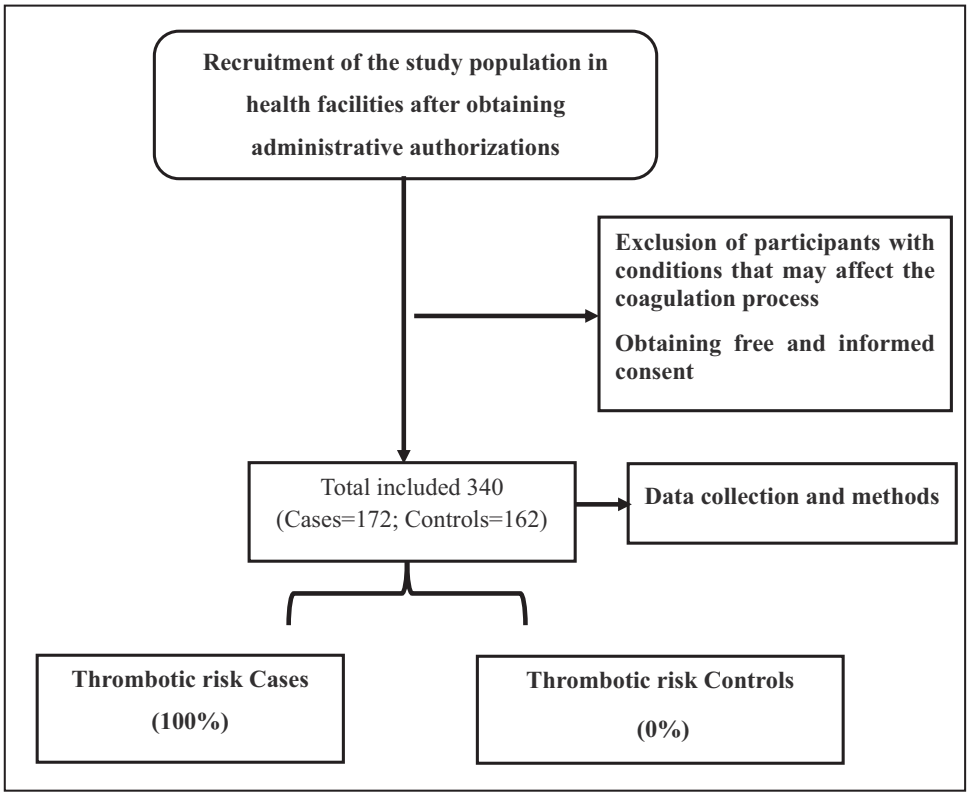


**FIGURE 1** | Data flow diagram.

**TABLE 1** | Distribution of the study population by sociodemographic characteristics.

| Parameters | Cases $N = 178$ *n* (%) | Controls $N = 162$ *n* (%) | Total $N = 340$ *n* (%) | *p*-value |
|---|---|---|---|---|
| Sex | | | | |
| F | 66 (37.1) | 16 (9.9) | 82 (24.1) | 0.017* |
| M | 112 (62.9) | 146 (90.1) | 258 (75.9) | |
| Age, mean ± SD | 34.64 ± 11.81 | 29.31 ± 8.43 | 32.10 ± 10.66 | 0.461 |
| BMI, mean ± SD | 26.37 ± 4.57 | 25.57 ± 4.61 | 26.12 ± 4.58 | 0.186 |
| Marital status | | | | |
| Married | 78 (43.8) | 62 (38.3) | 140 (41.2) | 0.942 |
| Single | 96 (53.9) | 100 (61.7) | 196 (57.6) | |
| Widow | 4 (2.23) | / | 4 (1.2) | |

*Note:* Population originating from the West and Littoral region of Cameroon and their surroundings.
Abbreviations: F, female; M, male; SD, standard deviation.
*Chi-square test; significant difference at $p < 0.05$.

hepatitis group and 29.31 ± 8.43 years old in the control group. 75.6% of the study population was male. Participants were mainly single (53.9%).

From Table 2, 136 cases of hepatitis B (76.4%), 26 cases of hepatitis C (14.6%), and 16 cases of hepatitis D (9%) have been reported. Clinical analysis of the data showed that 50 (28.1%) patients were suffering from chronic hepatitis, while 116 (65.2%) were at the acute hepatitis stage. Hepatitis patients at the clinical stage of cirrhosis were 2, which represented 1.1% of the hepatitis group (Table 2).

## 3.2 | Distribution of the Study Population According to Thrombotic Risk, Profile, and Hemostasis Disorders and Biological Parameters

### 3.2.1 | Thrombotic Risk and Hemostatic Disorders in the Population

All patients with hepatitis in this study had thrombotic risk compared to none in controls ($p < 0.001$). Table 3 presents the profile and disorders of hemostasis parameters and biologicals in the population.

**TABLE 2** | Distribution of study population by characteristics of clinical history.

| Parameters | Clinical data Cases $N = 178$ $n$ (%) |
|---|---|
| Hepatitis type | |
| B | 136 (76.4) |
| C | 26 (14.6) |
| D | 16 (9.0) |
| Hepatitis phase | |
| Chronic hepatitis | 50 (28.1) |
| Acute hepatitis | 116 (65.2) |
| Occult hepatitis | 12 (6.7) |
| Hepatic cirrhosis | |
| Yes | 2 (1.1) |
| No | 176 (98.9) |
| Diabetes | |
| No | 176 (98.9) |
| Yes | 2 (1.1) |

*Note:* Population originating from the West and Littoral region of Cameroon and their surroundings.

From the above Table 3, the cases population showed disorders of hemostasis parameters compared to the control population characterized by a decrease of the PT ($p < 0.001$), and a shortening of the CTA ($p < 0.001$). In addition, 74 (41.6%) patients (cases) had an elevation in ALT compared to none in controls ($p < 0.001$). And 82 (24.1%) cases had an elevation in AST compared to none in controls ($p < 0.001$).

### 3.3 | Population Profile and Disorders of Blood Counts

The following Table 4 presents the profile and disorders of blood count in the population.

From Table 4, 144 (80.9%) patients presented anemia compared to no anemia in controls ($p < 0.001$). Moreover, cases of thrombocytosis and thrombocytopenia were reported in the case population compared to none in controls ($p < 0.001$).

The following Table 5 describes the profile of the hemogram in the population.

From Table 5, the mean white blood cell count in cases population was $8.2 \pm 4.9$ g/L and $5.3 \pm 1.1$ G/L in controls ($p < 0.001$). The mean red blood cell count in cases population was $3.7 \pm 0.9$ T/L and $4.6 \pm 0.4$ T/L in controls ($p < 0.001$).

### 3.4 | Factors Associated with Thrombotic Risk

All patients with hepatitis in this study had thrombotic risk characterized by decreased plasminogen levels. Table 6 describes the factors associated with thrombotic risks in the population during the study in univariate and multivariate analyses.

From Table 6 above, hepatitis, plasminogen decrease, shortening CTA, decreased hemoglobin and leukocytosis are associated at risk of developing thrombosis in this study with respectively (aOR = 3; 95% CI [1.01–5.2]; $p < 0.03$), (aOR = 3; 95% CI [1.01–5.2]; $p < 0.03$), (aOR = 1.5; 95% CI [1.1–5.2]; $p < 0.04$), (aOR = 2.1; 95% CI [1.1–5.1]; $p < 0.03$) and (aOR = 1.1; 95% [0.00–1,2]; $p < 0.06$).

## 4 | Discussion

Venous thromboembolism is a condition characterized by the formation of a blood clot (thrombus) that blocks a vein or artery and blocks the flow of blood [16]. Thrombosis and subsequent embolism are the result of blood stasis, venous wall damage, and hypercoagulability. This is a situation encountered during several pathologies including hepatitis [16, 17]. This study aimed to assess plasminogen levels and hemostasis disorders during liver disease and to infer thrombotic risk in liver diseases to prevent the occurrence of venous thromboembolism. The results of this study showed that all cases had a thrombotic risk characterized by a decrease in plasminogen levels, while controls did not present a thrombotic risk ($p < 0.001$). Several authors also report low levels of plasminogen in hepatitis and also present it as an element in favor of thrombotic risk and suggest the hypothesis of its use as a parameter for assessing liver function [11, 18]. This study also raises the possibility of using plasminogen levels as a test of liver function; also suggested by some authors. Plasminogen levels were abnormal in a large proportion of patients with liver disease and is associated with worsening of disease pathophysiology and increased mortality in this population group [19].

Of the population of cases, the high proportion of hepatitis B (76.4%) is explained by the fact that it is the most common viral hepatitis in the world and therefore the most frequent in health facilities. Several authors also report a higher frequency of viral hepatitis B compared to other types in their studies [20, 21]. The sex ratio was 3.15 in favor of men; including 1.7 in cases and 9.1 in controls. The high proportion of males in patients compared to females can be explained by the fact that males are more prone to factors in favor of the onset and aggravation of hepatitis: alcohol consumption, and multiplication of sexual partners. The study population consisted primarily of young adults with a mean age of $34.64 \pm 11.81$ years. These results are consistent with data from the literature and similar to those of Diallo et al. [21] who also reported young adults during their study [22].

Cases of chronic, acute, and hepatic cirrhosis were reported during this study. This study also reported high AST and ALT concentrations in cases compared to controls ($p < 0.001$) (Table 3). These symptoms are those commonly encountered during hepatitis. Indeed, this could be explained by the fact that viral replication favors the chronicity of the disease; and the consequence being hepatic cytolysis hence the hyperactivity of transaminases; although ALT is the most commonly used

**TABLE 3** | Thrombotic risk, biological parameters, and hemostasis disorders in the population study.

| Variables/parameters | Cases $N = 178$ $n$ (%) | Controls $N = 162$ $n$ (%) | Total $N = 340$ $n$ (%) | $p$-value |
|---|---|---|---|---|
| Plasminogen | | | | |
| Mean ± SD | 1.5 ± 0.5 | 22.3 ± 9.3 | 11.4 ± 10.3 | < 0.001[b,*] |
| Low | 178 (100) | 0 (0) | 178 (52.4) | < 0.001[a,*] |
| Normal | 0 (0) | 100 (47.6) | 100 (47.6) | |
| Thrombotic risk | | | | |
| Yes | 178 (100) | 0 (0) | 178 (52.4) | *< 0.001*[a,*] |
| No | 0 (0) | 162 (47.6) | 162 (47.6) | |
| D-dimer | | | | |
| Mean ± SD | 5.3 ± 3.3 | 4.9 ± 2.9 | 5.1 ± 3.3 | 0.3[b] |
| High | 66 (37.07) | 30 (18.5) | 96 (28.2) | 0.14[a] |
| Normal | 112 (62.9) | 132 (81.5) | 244 (71.8) | |
| CTA | | | | |
| Mean ± SD | 28.2 ± 2.4 | 39.2 ± 5.5 | 33.9 ± 9.5 | < 0.001[b,*] |
| Shortening | 124 (69.7) | 0 (0) | 124 (36.5) | < 0.001[a,*] |
| Normal | 54 (30.3) | 162 (100) | 216 (63,5) | |
| PT | | | | |
| Mean ± SD | 68.5 ± 6.3 | 88.9 ± 5.5 | 78 ± 11.72 | < 0.001[b,*] |
| Low | 98 (55.1) | 0 (0) | 98 (28.8) | < 0.001[a,*] |
| Normal | 80 (44.9) | 162 (100) | 242 (71.2) | |
| AST | | | | |
| Mean ± SD | 42.7 ± 35.4 | 18.4 ± 2.3 | 31.2 ± 25.5 | < 0.001[b,*] |
| High | 82 (24.1) | 0 (0) | 82 (24.1) | < 0.001[a,*] |
| Normal | 96 (28.2) | 162 (47.6) | 258 (75.9) | |
| ALT | | | | |
| Mean ± SD | 53.2 ± 45.5 | 24 ± 1.9 | 38.6 ± 33.5 | < 0.001[b,*] |
| High | 74 (41.6) | 0 (0) | 74 (21.8) | < 0.001[a,*] |
| Normal | 104 (58.4) | 162 (47.6) | 266 (78.2) | |

Abbreviations: ALT(UI/L), alanine aminotransferase; AST(UI/L), aspartate aminotransferase; CTA, cephalin time activator; M, mean; PT, prothrombin level; SD, standard deviation.
*Significant difference at $p < 0.05$.
[a]Chi Square Pearson test.
[b]Student test.

surrogate indicator reflecting liver cell damage [23–25]. Transaminase elevations (ALT and AST) are considered evidence of hepatocyte T-cell-mediated cytolytic clearance [26]. This observation has also been made by several authors [23, 26].

Furthermore, the fibrinolysis parameters evaluated during this study revealed a decrease in plasminogen in patients compared to controls ($p < 0.001$) and an elevation of D-dimer in cases (37.07%) compared to controls (18.5%); results in favor of fibrinolytic hyperactivity during hepatitis. Indeed, the decrease in plasminogen levels can be explained by the fact that plasminogen is a protein synthesized by the liver, so the presence of the virus in the liver not only destroys hepatocytes but also cause of the failure and inability of the liver to synthesize plasminogen normally [17]. This result is consistent with that found by Wu et al. [26] where a significant decrease in plasminogen synthesis was observed during acute and chronic liver failure compared to controls ($p < 0.001$) [27]. Davis et al. [18] report 75% of patients with decreased plasminogen in hepatitis. On the other hand, the elevation of D-dimers in patients could be explained by the fact that D-dimers are degradation products of fibrin and are markers of coagulation activation. They are therefore always elevated in the presence of thrombosis in the acute phase and is an argument in favor of thromboembolic venous disease [19]. Authors also report elevated D-dimer concentrations during liver disease [28–30]. Indeed, it is well known that deep vein thrombosis is a possible complication of liver cirrhosis and liver transplantation. The main risk factors for deep vein thrombosis are portal hypertension and the resulting venous stasis. Recently, however, there has been a focus on the possible role of the prothrombotic state related to chronic liver disease. This resulted in a state of

**TABLE 4** | Blood count disorders in the population.

| Variables/parameters | Cases $N = 178$ $n$ (%) | Controls $N = 162$ $n$ (%) | Total $N = 340$ $n$ (%) | $p$-value |
|---|---|---|---|---|
| RBC | | | | |
| Low | 100 (56.2) | 0 (0) | 100 (29.4) | < 0.001[a,*] |
| High | 6 (3.4) | 0 (0) | 6 (1.8) | |
| Normal | 72 (40.5) | 162 (100) | 234 (68.8) | |
| HB | | | | |
| Low | 144 (80.9) | 0 (0) | 144 (42,4) | < 0.001[a,*] |
| Normal | 34 (19.1) | 162 (100) | 196 (57.6) | |
| Hematocrit | | | | |
| Low | 178 (100) | 0 (0,0) | 142 (95.3) | < 0.001[a,*] |
| Normal | 0 (0.0) | 162 (100) | 5 (3.36) | |
| MCV | | | | |
| Microcytosis | 40 (22.5) | 0 (0.0) | 6 (1.8) | < 0.001[a,*] |
| Normocytosis | 132 (74.2) | 162 (100) | 294 (86.5) | |
| Macrocytosis | 6 (3.4) | 0 (0.0) | 6 (1,8) | |
| MCH | | | | |
| Low | 72 (40.44) | 0 (0.00) | 72 (21,2) | < 0.001[a,*] |
| Normal | 104 (58.4) | 162 (100) | 266 (66.4) | |
| High | 2 (1.1) | 0 (0) | 2 (0,6) | |
| MCHC | | | | |
| Hypochromia | 80 (44.9) | 0 (0.00) | 80 (23.5) | < 0.001[a,*] |
| Normal | 98 (55.1) | 162 (100) | 260 (76.5) | |
| WBC | | | | |
| Leukocytosis | 50 (28.1) | 0 (0.00) | 50 (14.7) | < 0.001[a,*] |
| Normal | 106 (59.5) | 162 (100) | 268 (78.8) | |
| Leucopenia | 22 (12.4) | 0 (0.00) | 22 (6.5) | |
| Granulocytes | | | | |
| Low | 40 (22.5) | 0 (0.00) | 40 (11.8) | < 0.001[a,*] |
| High | 28 (15.7) | 0 (0.00) | 28 (8.2) | |
| Normal | 110 (61.8) | 162 (100) | 272 (80.0) | |
| Lymphocyte | | | | |
| Lymphocytosis | 42 (23.6) | 0 (0.00) | 42 (12.4) | < 0.001[a,*] |
| Lymphopenia | 6 (3.4) | 0 (0.00) | 6 (1.8) | |
| Normal | 130 (73.0) | 162 (100) | 292 (85.9) | |
| Monocyte | | | | |
| Monocytosis | 22 (12.4) | 0 (0.00) | 22 (6,5) | < 0.001[a,*] |
| Normal | 156 (87.6) | 162 (100) | 318 (93.5) | |
| Thrombocyte | | | | |
| Thrombocytopenia | 24 (13.5) | 0 (0) | 24 (7.1) | < 0.001[a,*] |
| Thrombocytosis | 56 (31.5) | 0 (0) | 56 (16.5) | |
| Normal | 98 (55.0) | 162 (100) | 260 (76.5) | |

Abbreviations: RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin content; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cells.
*Significant difference at $p < 0.05$.
[a]Chi square pearson test.

**TABLE 5** | Complete blood count profile.

| Variables/parameters | Cases $N = 178$ Mean ± SD | Controls $N = 162$ Mean ± SD | Total $N = 340$ Mean ± SD | *p*-value |
|---|---|---|---|---|
| RBC (T/L) | 3.7 ± 0.9 | 4.6 ± 0.4 | 4.1 ± 0.9 | < 0.001[b,*] |
| HB (g/dL) | 10.3 ± 2.1 | 13.5 ± 0.8 | 11.8 ± 2.3 | < 0.001[b,*] |
| HTE (%) | 31.5 ± 6.3 | 46.7 ± 1.7 | 38.8 ± 8.9 | < 0.001[b,*] |
| MCV (fL) | 85.8 ± 10.9 | 88.2 ± 1.9 | 86.9 ± 8.1 | 0.007[b,*] |
| MCHC (pg/c) | 27.6 ± 7.9 | 28.7 ± 0.7 | 28.1 ± 5.7 | 0,43[b] |
| MCH (g/L) | 32.8 ± 8.1 | 33.3 ± 0.9 | 33.1 ± 5.9 | 0.06[b] |
| WBC (G/L) | 8.2 ± 4.9 | 5.3 ± 1.1 | 6.9 ± 3.9 | < 0.001[b,*] |
| Lymphocytes (G/L) | 3.3 ± 3.2 | 2.7 ± 0.2 | 3.1 ± 2.9 | 0.024[b,*] |
| Monocytes (G/L) | 0.8 ± 0.7 | 1.2 ± 0.2 | 1.1 ± 0.6 | < 0.001[b,*] |
| Granulocytes (G/L) | 4.1 ± 3.1 | 5.4 ± 0.5 | 4.7 ± 2.3 | < 0.001[b,*] |
| Thrombocytes (G/L) | 247.7 ± 135.1 | 250.1 ± 92.5 | 248.8 ± 116.6 | 0.85[b] |

Abbreviations: G/L, Giga/Liter; M, mean; MCH, mean corpuscular hemoglobin content; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDB, red blood cell; SD, standard deviation; T/L, Tera/Liter; WBC, white blood cells.
*Significant difference at $p < 0.05$.
[b]Student test.

hypercoagulability similar to that conferred by congenital protein C deficiency or a factor V Leiden mutation. It is uncertain whether HBV and HCV themselves cause deep vein thrombosis. Evidence suggests that chronic viral infection is a risk factor for thrombosis, possibly through infection-mediated inflammation and hemostatic insufficiency. Indeed, it is now appreciated that there exists a delicate hemostatic balance between reduced production of procoagulant factors and platelets and decreased levels of anticoagulants (such as protein C and antithrombin) in cirrhosis. Authors have demonstrated in vitro that the activated protein C (APC) resistance test is impaired in cirrhotic patients and worsens with progressive deterioration of liver disease from Child Pugh class A to C [14]. Also, antiphospholipid antibodies and the prothrombotic state associated with chronic liver disease appear to play an important role in virus-associated thrombosis [12, 31, 32].

In addition, evaluation of coagulation parameters showed coagulation disorders in patients during hepatitis characterized by a shortening of the CAT in cases population (69.7%) compared to none in controls ($p < 0.001$) and a decrease of the PT in cases (55%) compared to none in controls ($p < 0.001$). Authors also report coagulation disorders during hepatitis; in particular, Zhang et al. [33] report a decrease prothrombin level during hepatitis (72 ± 12%). Pawlak et al. [8] and Ozier et al. [10] also report disorders of coagulation parameters in hepatitis. Indeed, hepatocellular insufficiency leads to a decrease in the synthesis of clotting factors (except FVIII and Willebrand factor), but also in that of natural coagulation inhibitors such as protein C and antithrombin (formerly anti-thrombin III) [34]. However, a growing body of evidence suggests that prothrombin levels (and other congener tests) poorly reflect hemostatic balance in cirrhosis. In these patients, the reduction in procoagulant levels is counteracted by a parallel reduction in their anticoagulant counterparts [34].

In this study, cases of thrombocytopenia were reported in cases population compared to none in controls ($p < 0.001$). Thrombocytopenia is a common complication of cirrhosis of the liver. Many factors may contribute to the development of thrombocytopenia in patients with liver cirrhosis, such as splenic sequestration, reduced hematopoietic growth factor thrombopoietin (TPO) activity, cirrhotic coagulopathy, direct HBV cytokaryocyte/platelet cytotoxicity, and interferon-based antiviral therapy (IFN) [24, 35, 36]. Zhang et al. [33] also report cases of thrombocytopenia during hepatitis.

Moreover, 80.9% cases of anemia were also reported during this study in patients compared to none in controls ($p < 0.001$). Liver disease is associated with a wide range of hematologic abnormalities, including anemia, reduced clotting factor activity, hypersplenism, and thrombocytopenia. Several authors also report cases of anemia during hepatitis, and hemolytic anemias [37, 38].

In addition, after multivariate regression analyses, hepatitis, plasminogen decrease, shortening CTA, decreased hemoglobin, and leukocytosis are associated at risk of developing thrombosis in this study with respectively (aOR = 3; 95% CI [1.01–5.2]; $p < 0.03$), (aOR = 3; 95% CI [1.01–5.2]; $p < 0.03$), (aOR = 1.5; 95% CI [1.1–5.2]; $p < 0.04$), (aOR = 2.1; 95% CI [1.1–5.1]; $p < 0.03$) and (aOR = 1.1; 95% [0.00–1.2]; $p < 0.06$). Indeed, as reported above in the course of hepatitis, the intrinsic consequences of the disease as reported above are the main factors in favor of and associated with the disease. These elements have also been reported by several authors to be associated with hepatitis [24, 37].

In short, in addition to the synthesis of proteins related to coagulation, the liver is also intimately involved in the regulation of coagulation. The clearance of activated or fibrinolytic clotting factors, activation complexes, and end products of fibrinogen-to-fibrin conversion is facilitated by the reticuloendothelial system of the liver [1]. In-depth studies of other coagulation parameters and factors would provide a better understanding of the mechanisms by which they are regulated in the maintenance of homeostasis.

**TABLE 6** | Factors associated with thrombotic risk: Univariate and multivariate analyses.

| Parameters | Thrombotic risk positive $N = 178$ (52.4%) | Thrombotic risk negative $N = 162$ (47.6%) | Univariate analysis OR [IC 95%] | *p*-Value | Multivariate analysis: aOR [IC 95%] | *p*-value |
|---|---|---|---|---|---|---|
| Status | | | | | | |
| Cases | 178 (52.4) | 0 (0) | 6 [2.07–11.2] | 0.001* | 3 [1.01–5.2] | 0.03 |
| Control | 0 (0) | 162 (47.6) | Ref | Ref | Ref | Ref |
| Diabetes | | | | | | |
| Yes | 2 (1.1) | 0 (0) | 1.09 [0.094–1.5] | 0.386 | / | / |
| No | 176 (98.9) | 162 (47.6) | Ref | Ref | / | / |
| Sex | | | | | | |
| Female | 66 (37.1) | 16 (9.9) | Ref | Ref | / | / |
| Male | 112 (62.9) | 146 (90.1) | 0.45 [0.13–1.59] | 0.233 | / | / |
| D-dimer | | | | | | |
| High | 66 (37.1) | 70 (43.2) | 1.2 [0.8–1.9] | 0.2 | / | / |
| Normal | 112 (62.9) | 92 (56.8) | *ref* | *ref* | / | / |
| Plasminogen | | | | | | |
| Low | 178 (100.0) | 0 (0.0) | 6 [2.07–11.2] | 0.001* | 3 [1.01–5.2] | 0.03 |
| Normal | 0 (0.0) | 162 (100.0) | Ref | Ref | Ref | Ref |
| ALT | | | | | | |
| High | 74 (41.6) | 0 (0.0) | 0.0 [0.00;] | 0.99 | / | / |
| Normal | 104 (58.4) | 162 (100.0) | *ref* | *ref* | / | / |
| AST | | | | | | |
| High | 82 (46.1) | 0 (0.0) | 0.0 [0.00;] | 0.99 | / | / |
| Normal | 96 (53.9) | 162 (100.0) | *ref* | *ref* | / | / |
| CTA | | | | | | |
| Shortening | 124 (69.7) | 0 (0.0) | 3 [2.1–11.2] | < 0.001* | 1.5 [1.1–5.2] | 0.04 |
| Normal | 54 (30.3) | 162 (100.0) | *ref* | *ref* | *ref* | *ref* |
| Prothrombin level | | | | | | |
| Low | 98 (55.1) | 0 (0.0) | 0.0 [0.00;] | 0.9 | / | / |
| Normal | 80 (44.9) | 162 (100.0) | *ref* | *ref* | / | / |
| Hemoglobin | | | | | | |
| Low | 144 (80.9) | 0 (0.0) | 4.7 [2.3–10.1] | < 0.001* | 2.1 [1.1–5.1] | 0.03 |
| Normal | 34 (19.1) | 162 (100.0) | *ref* | *ref* | *ref* | *ref* |
| Platelets | | | | | | |
| Low | 24 (13.5) | 0 (0.0) | / | / | / | / |
| High | 56 (31.5) | 0 (0.0) | 1.6 [0.00;] | 1 | / | / |
| Normal | 98 (55.1) | 162 (100.0) | *ref* | *ref* | / | / |
| WBC | | | | | | |
| Low | 22 (12.4) | 0 (0.0) | 0.0 [0.00;] | 0.9 | / | / |
| High | 50 (28.1) | 0 (0.0) | 1.5 [0.00–2.2] | 0.001 | 1.1 [0.00–1.2] | 0.06 |
| Normal | 106 (59.6) | 162 (100.0%) | *ref* | *ref* | *ref* | *ref* |
| Monocyte | | | | | | |

(Continues)

**TABLE 6** | (Continued)

| Parameters | Thrombotic risk positive $N = 178$ (52.4%) | Thrombotic risk negative $N = 162$ (47.6%) | Univariate analysis OR [IC 95%] | *p*-Value | Multivariate analysis: aOR [IC 95%] | *p*-value |
|---|---|---|---|---|---|---|
| High | 22 (12.4) | 0 (0.0%) | 1.03 [0.00;] | 0.7 | / | / |
| Normal | 156 (87.6) | 162 (100.0%) | *ref* | *ref* | / | / |

Abbreviations: aOR, adjusted odd ratio multivariate analysis; 95% CI , 95% confidence interval; CTA, cephalin time activator; MCH, mean corpuscular hemoglobin content; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDB, red blood cell; WBC, white blood cells.
[b]Student test.
*Significant difference at $p < 0.05$.

This study is interest in improving the management of patients with hepatitis because it mainly focuses on plasminogen and other plasma coagulation exploration markers to assess the thrombotic risk. In addition, a comprehensive exploration of other tests for example physiological inhibitors of fibrinolysis may be considered and will be the subject of future studies.

## 5 | Conclusion

This study aimed to determine plasminogen's level and hemostasis disorders in patients with liver disease to assess the thrombotic risk. We reported disorders of coagulation parameters characterized by a shortening of the CTA and a statistically different decrease in TP in patients compared to controls. We also report a high frequency of thrombotic risk characterized by a significant decrease in plasminogen in patients compared to controls. These observations raise the need for exploration of hemostasis in general and determination of plasminogen levels in particular for better management of patients with hepatitis because the latter are associated with a risk of thrombosis; which is a factor in increased mortality in this population group.

### Author Contributions

**Romaric De Manfouo Tuono:** conceptualization, investigation, writing – review and editing, methodology, project administration, supervision, writing – original draft. **Marius Mbiandjeu Tchoumke:** methodology, writing – review and editing, formal analysis. **Winy Asdrid Djoumeni Tepe:** methodology, writing – review and editing. **Winnie Ketcha Jeuta:** methodology, writing – review and editing. **Simon Ngamli Fewou:** supervision, writing – review and editing.


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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Transparency Statement

The lead author Romaric Tuono De Manfouo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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