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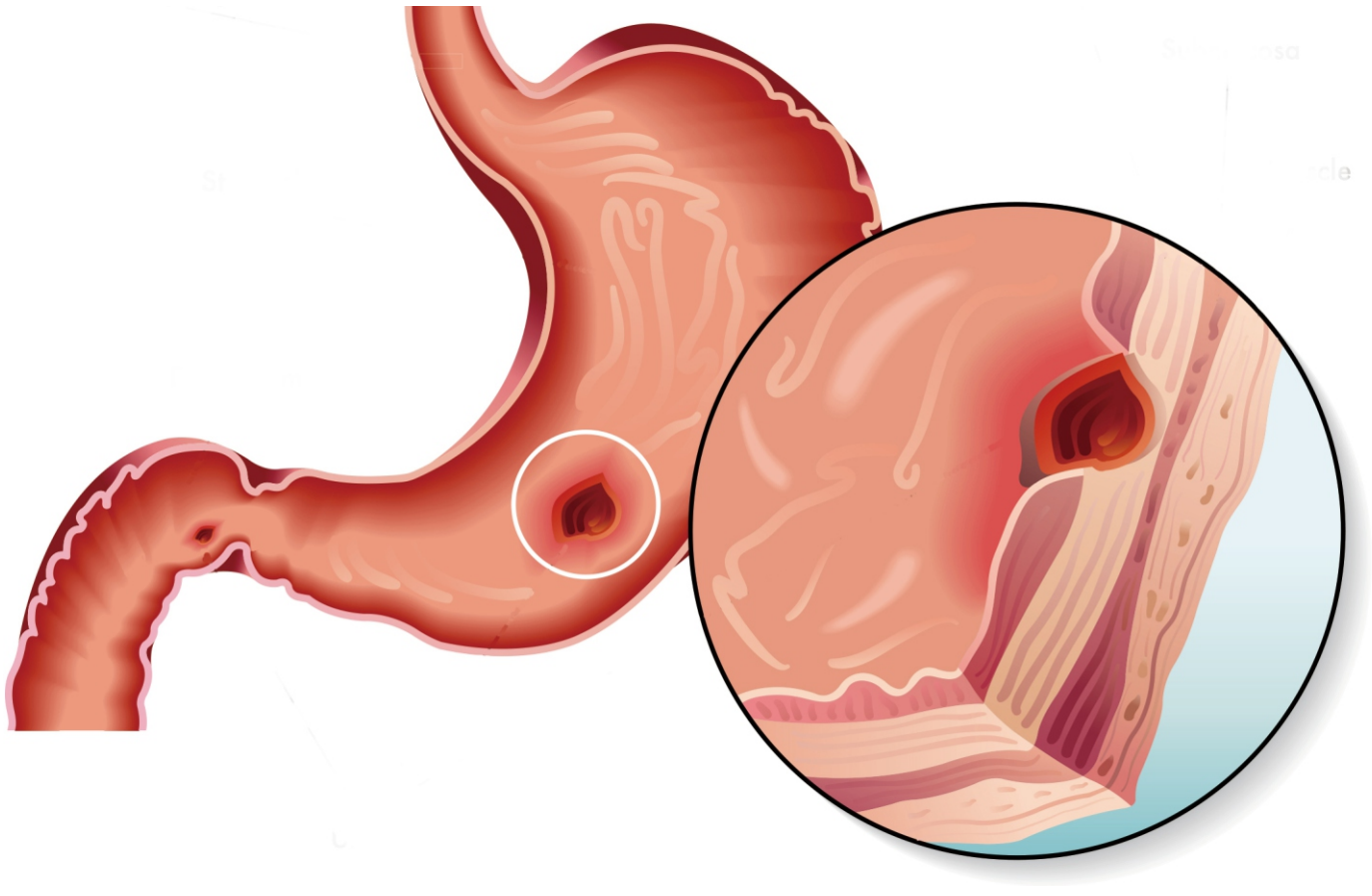

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Spontaneous Infection of Ascites Fluid at the National and University Hospital Hubert Koutoukou Maga in Cotonou: Prevalence and Associated Factors

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Abstract

Background: Spontaneous ascites fluid infection (SAFI) is an extremely serious and frequently encountered complication in cirrhotic patients. We aimed to determine the prevalence of SAFI and the factors associated with it in the largest hospital in Cotonou. **Methods:** This was a retrospective descriptive and analytical study conducted from January 2013 to July 2019, at the National and University Hospital Hubert Koutoukou Maga (CNHU-HKM) in Cotonou, Benin. All patients followed in the University Clinic of Hepato-Gastroenterology and diagnosed with SAFI were included. **Results:** Eighty-two patients were included, predominantly males (69.5%), with a mean age of 51.5 ± 14.5 years. Among them, 32 had SAFI, *i.e.*, a prevalence of 39%. Of the 32 cases of SAFI, the culture of ascites fluid was positive in 6 cases (18.7%). The most frequent germ found in SAFI was *Escherichia coli* (5 patients, 83.3%). The factors associated with SAFI in this study were: abdominal pain ($p = 0.004$), increased bilirubinemia ($p = 0.009$), decreased prothrombin level <50% ($p = 0.007$), cloudy macroscopic appearance of the fluid ($p < 0.001$), ascites protide level <15 g/L ($p = 0.001$), and severe cirrhosis, with a high Child Pugh C score or MELD score >20 ($p = 0.001$). **Conclusion:** SAFI was common in cirrhotic patients in the department. Certain clinical and paraclinical factors were associated with it, as was the severity of cirrhosis. Early diagnosis and aetiological management of cirrhosis could reduce its frequency.

Keywords

Ascites, Infection, Cirrhosis, Cotonou

1. Introduction

Spontaneous ascites fluid infection (SAFI) is a formidable complication during cirrhosis, occurring in approximately 20% - 35% of patients hospitalised with ascites, especially those with cirrhosis [1] [2]. SAFI results from the seeding of ascites fluid by bacteria from the digestive tract; this is favoured by abnormal digestive permeability associated with an increase in microbial proliferation [3]. Patients with reduced antimicrobial activity and reduced opsonising capacity of ascites fluid proteins are more likely to develop spontaneous bacterial peritonitis [4]. The germs most likely to induce SAFI are gram-negative bacilli (especially enterobacteria), probably due to their high adhesion capacity; and gram-positive cocci [3] [5] [6].

SAFI has a poor prognosis, as it is responsible for a worsening of the disease at the origin of the ascites, with a mortality rate of between 10% and 50% [7] [8]. In the West African sub-region, few studies have been carried out on ISLA. In Benin, work by Kom Mogto [3] in 1999 showed that the prevalence of ISLA was 33.3% and that cirrhosis was the most common aetiology among patients with ISLA, accounting for 81.8% of cases. The lack of recent studies in Benin on this serious pathology in cirrhotics justifies the interest of this work.

The aim of this study was to determine the prevalence of SAFI and the germs involved, as well as the clinical and biological characteristics and factors associated with its occurrence.

2. Methods

This was a retrospective descriptive and analytical study conducted from January 2013 to July 2019 (80 months). All patients with ascites who consulted the Hepato-Gastroenterology University Clinic of the CNHU-HKM of Cotonou, aged 15 years or more and with a medical record including a cytobacteriological examination (CBE) of the ascites fluid, were included. Of the 3787 patients seen in the department during this period, 150 presented with ascites. Sixty-eight cases were excluded from this study: those with tuberculosis or peritoneal carcinosis, and incomplete records (absence of CBE of ascites fluid, protein levels in ascites fluid and/or clinical signs).

The dependent variable was spontaneous ascitic fluid infection.

Positive diagnosis of SAFI was retained if the number of neutrophils in ascites was 250/mm^3 with positive ascitoculture (Spontaneous Bacterial Peritonitis: SBP) or negative (neutrocytic ascites with negative culture: ANCN); or the number of neutrophils < 250/mm^3 and bacteriascity. Thus, we had 32 cases of spontaneous infection of ascites fluid.

The independent variables are sociodemographic, variables relating to antecedents, clinical, paraclinical, therapeutic and evolutionary data. Data was collected using a standardised questionnaire.

We searched for possible statistical associations between SAFI (dependent variable) and several other independent variables using the Pearson Chi^2 test or the Fisher test depending on the case or an ANOVA model.

The accepted statistical significance threshold was 5%. If necessary, the student test, the Odds ratio was used with a 95% confidence interval.

The information collected in the medical records was treated in strict confidentiality. Anonymity has been respected in the processing of data.

3. Results

3.1. Characteristics of the Study Population

Overall, the population consisted of 82 patients with ascites. There was a male predominance (69.5%) with a sex ratio of 2.3. The mean age was 51.5 ± 14.5 years. The majority were Fon and related ethnic groups (70.7%). Shopkeepers and the like were the most represented with a percentage of 24.4%.

3.2. SAFI Prevalence and Sociodemographic Characteristics of Patients

Of the 82 patients included, 32 had SAFI, *i.e.* a prevalence of 39%.

The mean age of patients with SAFI was 51.9 18.0 years (with extremes of 19 years and 80 years). Males predominated in this sample of patients with SAFI with a sex ratio of 3.5. Shopkeepers and the like accounted for the majority of the population with SAFI, with a percentage of 31.3%.

3.3. Clinical, Biological and Evolutionary Characteristics of Patients with SAFI

The history of viral hepatitis B (25%, n = 8) and C (15.6%, n = 5) and chronic alcoholism (21.9%, n = 7) are the most represented in the group of patients with SAFI.

The main reason for consultation was ascites (97.5%, n = 80). The associated functional signs were dominated by abdominal pain (78.1%, n = 25), followed by diarrhea (18.8%, n = 6). As general signs, most of the patients had a fever (34.4%, n = 11), with a WHO Performance Status Index of 3 (25.6%, n = 21). Physical examination revealed jaundice in 34.4% (n = 11) of cases and hepatomegaly in 48.8%. Ascites fluid was cloudy in 40.6% (n = 15) of cases; and 86.7% (n = 13) of subjects with a cloudy ascites fluid had infected ascites. Cirrhosis was the main causal disease of ascites in patients (81.2%, n = 26).

Ascites fluid culture was positive in 6 cases. The germs identified were *Escherichia coli* (*E. coli*) in 5 cases and *Staphylococcus aureus* in 1 case. Patients with SAFI had neutrocyte ascites with positive culture (*Spontaneous bacterial peritonitis*), 3.1% had neutrocyte-free monomicrobial bacteriology, and 81.3% of pa-

tients had neutrocyte ascites with negative culture (NANC) (Table 1).

As other biological abnormalities, total bilirubin averaged 54.6 53.4 mg/L, prothrombin 51.1% ± 16.3%, Gamma GT 427.1 ± 794.5 IU/L, AST 220.2 ± 352.5 IU/L, creatinine 16.3 ± 18.2 mg/L, intra ascitic protein 14.6 ± 13.5 g/L and albumin 35.6 ± 3.6 g/L.

Furthermore, 68% (n = 17) of patients had a Child Pugh B score and 71.4% (n = 10) of those with a Child Pugh C score developed SAFI. This was also observed in 81.8% (n = 9) of patients with a Meld Score greater than 20.

At the evolutionary level, SAFI was treated with ceftriaxone in all cases. Cure was obtained in 37.5% (n = 12) of subjects. Among the 32 patients with SAFI, 13 patients (40.6%) died and 11 (34.4%) were lost to follow-up.

Comparatively, there are more deaths in the group of patients with SAFI than in the group of patients without SAFI: 40.6% (n = 13) in the group of SAFI versus 20% (n = 10) in the group without SAFI with p-value = 0.049.

Among patients with SAFI, 40.6% died at the first episode of ascitic fluid infection. However, the exact cause of death could not be proven in this work.

3.4. Factors Associated with SAFI

In univariate analysis, the independent variables associated with SAFI were the existence of abdominal pain (p = 0.004), the risk being increased by 4.2 times compared to an ascitic subject without SAFI (Table 2); ascites cloudy fluid (p = 0.001), increased bilirubinemia (p = 0.009) or Aspartate aminotransferase (ASAT) (p = 0.018), prothrombin rate (PR) less than 50% (p = 0.007), albumin less than 35 g/L (p < 0.001), and ascites fluid protide less than or equal to 15 g/L (p = 0.001) (Table 3). Cirrhosis was also associated with SAFI (p < 0.001), increasing the risk by 8.4 times; 60.5% of cirrhotic subjects had a SAFI against

Table 1. Cytobacteriological characteristics of ascites fluid from patients at the HGE university clinic of CNHU-HKM (2013-2019).

	SIFA		Univariate Analysis		
	Yes	No	OR	CI (95%)	p-value
Neutrophils (/mm^3)					
≥250	32 (100%)	0 (0%)	-	-	<0.001*
<250	0 (0%)	50 (100%)	-	-	-
Culture					
Positive	6 (100%)	0 (0%)	-	-	0.0013*
Negative	26 (34.7%)	49 (65.3%)	1	-	-
Macroscopic Aspect					
Citrine Yellow	10 (25%)	30 (75%)			
Brown	0 (0%)	5 (100%)			
Trouble	13 (86.7%)	2 (13.3%)			
Purulent	0 (0%)	3 (100%)			
Hematic	9 (47.4%)	10 (52.6%)			0.001*

*Statistically significant link.

Table 2. Relationship between spontaneous ascitic fluid infection and clinical characteristics of patients at the CNHU-HKM HGE university clinic (2013-2019).

	SAFI		Univariate analysis		
	Yes	No	OR	CI (95%)	p-value
Mean age (years)	51.9	50.4			0.073
Gender					
Male	25 (43.9%)	32 (56.1%)	-		0.222
Female	7 (28%)	18 (72%)	-	-	
Fever					
Yes	18 (66.3%)	18 (36%)	2.28	0.92 - 5.65	0.11
No	14 (43.8%)	32 (64%)	1		
Abdominal pain					
Yes	25 (78.1%)	23 (46%)	4.19	1.53 - 11.46	0.004*
No	7 (21.9%)	27 (54%)	1		
Jaundice					
Yes	11 (34.4%)	15 (30%)	1.22	0.47 - 3.15	0.808
No	21 (65.6%)	35 (70%)	1		
Hepatic Encephalopathy					
Yes	4 (12.5%)	2 (4%)	-	-	0.28
No	28 (87.5%)	47 (94%)	1		
Cirrhosis					
Yes	26 (60.5%)	17 (39.5%)	8.41	2.90 - 24.35	0.000*
No	6 (15.4%)	33 (84.6%)	1		

*Statistically significant link.

Table 3. Relationship between spontaneous ascitic fluid infection and biological characteristics of patients at the HGE University Clinic of CNHU-HKM (2013-2019).

	SAFI		Univariate analysis		
	Yes	CI (95%)	No	CI (95%)	p-value
Leukocyte in ascites fluid	2438.03	1221.73 - 3654.32	257.58	197.66 - 317.49	0.001*
Intra-ascitic proteins	14.59	9.71 - 19.48	24.81	20.98 - 28.65	0.001*
Total Bilirubin	54.66	35.39 - 73.93	26.22	17.28 - 35.15	0.009*
Prothrombin rate	51.14	45.26 - 57.01	62.96	56.60 - 69.31	0.007*
ASAT	220.24	93.14 - 347.33	62.38	38.94 - 85.81	0.018*
Albumin	35.65	34.27 - 37.02	30.85	30.08 - 31.61	0.000*
Proteinemia	69.56	67.30 - 71.82	61.14	59.42 - 62.85	0.000*
MELD score					
<20	16 (35.6%)	29 (64.4%)	-	-	
>20	9 (81.8%)	2 (18.2%)	-	-	0.005*
No information	7 (26.9%)	19 (73.1%)	-	-	
Child Pugh					
Class A	1 (12.5%)	7 (87.5%)	-	-	
Class B	17 (68%)	8 (32%)	-	-	0.001*
Class C	10 (71.4%)	4 (28.6%)	-	-	
No information	4 (21.1%)	15 (78.9%)	-	-	

*Statistically significant link.

15.4% of non-cirrhotic subjects (Table 2). Patients with a Child Pugh C and B score were more affected by SAFI than classes A, thus showing correlation with cirrhosis severity (p = 0.001). The same was true for patients with a MELD score greater than 20 (p = 0.005) (Table 3).

4. Discussion

SAFI is the second leading cause of bacterial infection in cirrhotics (after urinary tract infection) in western countries [9]. In developing countries, especially in black Africa, there are very few published data available on the subject. The prevalence of SAFI in the University Clinic of Hepato-Gastroenterology during the period of this study was 39%. This result is similar to those of Kom Mogto [3] in Benin in 1999 and Diarra [10] in Mali in 2007, which were 33.3% and 35.9% respectively. It is also close to that of Rimola *et al*. [11] in Barcelona which was 46%. In addition, other studies were conducted in hospitalized ascitic patients where the frequency of occurrence of SAFI was much lower than that found in our study. Thus, the prevalence of SAFI in our study is higher than those found by Laah Njoho [12] in a prospective study in Yaoundé in 1998 which was 17.9%. Our result is higher than that reported in several European studies which is 10% to 30% [8] [13] [14]. This difference in results is related to the fact that patients in our study population had several risk factors for ascites fluid infection that are: advanced age (54% of patients were older than 50 years), severe hepatocellular insufficiency (mean prothrombin rate = 51%, mean albuminemia = 35 g/L), low concentration of intra-ascitic proteins equal to 14 g/L, increased mean bilirubinemia (54 mg/L) and impaired renal function with mean creatinine at 16.36 mg/L.

In our study the factors associated with SAFI were abdominal pain, increased bilirubinemia, a decrease in TP < 50%, a macroscopic cloudy appearance of the fluid, a protide level in ascites < 15 g/L, and a severe cirrhosis score of Child Pugh C or a high Meld score. SAFI is often pauci symptomatic and systematic discovery by biological examinations of ascites fluid [15]. The clinical signs of SAFI are important to consider when they are present but the diagnosis is primarily paraclinical (cytological and bacteriological examination of ascites fluid), especially in asymptomatic patients. Abdominal pain is the only clinical sign associated with SAFI (p = 0.004) in our study. Among subjects with SAFI, 78.1% had abdominal pain. This result is superimposed on that of Bouzaidi *et al*. [16] who found as clinical signs associated with SAFI abdominal pain and thermoregulatory disorders (hypo or hyperthermia) in a respective proportion of 84% and 66%. In our study, the macroscopic aspect of ascites fluid was associated with the occurrence of SAFI (p = 0.001). Indeed, 86.7% of subjects with ascites fluid disorder had infected ascites and among patients with SAFI 40.6% had a cloudy fluid. This result is comparable to that of Maïga *et al*. [17] and that of Diarra [10] who reported respectively a frequency of 45.5% and 42.9% of cloudy fluid in their population of patients with SAFI. However, our result is lower than that of

Attia *et al*. [18] in Abidjan who found a frequency of 66.7%. However, a citrine yellow liquid does not rule out SAFI.

Thus, in our group of patients with SAFI, 81.2% of patients had cirrhosis as the cause of ascites and statistically a cirrhotic subject has 8.4 times the risk of developing SAFI compared to a non-cirrhotic subject. This result is similar to those of Maïga *et al*. [17] and Kom Mogto [3] who noted 87.5% and 81.8% of cirrhotic patients in the group of patients with SAFI, respectively. In cases of cirrhosis, hepatocyte functions are impaired and the body's defense capacity against germs is reduced; this explains the high frequency of SAFI in cirrhotic patients [7]. The group of patients free from SAFI in our study also consists mainly of cirrhotics with a percentage of 34%, we can conclude that SAFI can occur in any patient with ascites, but more particularly in cirrhotics.

The plasma biological disturbances observed in our series are more significant in the group of patients with SAFI than in the group with sterile ascites and there is a statistically significant link between prothrombin rate and SAFI ($p = 0.007$), between albuminemia and SAFI ($p < 0.001$) then between ASAT and SAFI ($p = 0.018$). In patients with SAFI, the mean prothrombin rate value is 51.1% ± 16.3% and the mean serum albumin is 35.6 ± 18.2 g/L. These results are superimposable to those of Kom Mogto [3] in Benin and those of Diarra [10] in Mali who found in their series respectively for average prothrombin rate 41.19% ± 19% and 50.21% ± 14.7% and for mean albuminemia respectively 28.6 ± 7 g/L and 34.8 ± 16.9 g/L. Furthermore, Attia *et al*. [18] in Ivory Coast found that 83.3% of patients with SAFI had a prothrombin rate less than 50% and that 75% of these patients had a serum albumin less than 20 g/L. This shows that ascitic patients with hepatocellular insufficiency have a high risk of developing SAFI, as confirmed by the work of Dever *et al*. [7]. In our series, the average ASAT level in patients with SAFI of 220.2 IU/L is higher than that of patients without SAFI which is 62.4 IU/L. This result is similar to that of Kom Mogto [3] who found that the average ASAT level in patients with infected ascites is higher than that of patients without SAFI (178 IU/L in patients with SAFI compared to 76 IU /L in patients without SAFI). This proves that ascitic patients with hepatic dysfunction are more susceptible to the development of SAFI. According to our study, there was a correlation between the severity of cirrhosis and SAFI. High Child-Pugh and MELD scores are a factor favoring the development of SAFI. Thus, 68% of cirrhotic patients classified as Child-Pugh B and 71.4% of those classified as Child-Pugh C had developed SAFI. In addition, 81.8% of patients with a MELD score greater than 20 had SAFI. These results are in agreement with those of Amoako *et al*. [19] in Accra who found in their study that 80% of patients with infected ascites were classified Child-Pugh C and had a MELD score greater than 15. Furthermore, a study conducted in Portugal by Cristina *et al*. [20] in 2019 also showed that the majority of cirrhotics who developed an ascitic fluid infection were classified Child-Pugh B or C and these patients had a high MELD score (greater than 20). Indeed, patients with high Child-Pugh

scores (B and C) and MELD present a severe alteration of hepatocyte functions with a reduction in the secretion of proteins (Immunoglobulins and albumin) involved in the body's defense against germs [19] [20]; which explains the high risk of occurrence of SAFI in these patients.

The average intra-ascitic protein level in patients with infected ascites is 14.6 g/L, lower than the average in patients with sterile ascites which is 24.8 g/L. In addition, there is a statistically significant link between the intra-ascitic protein level and SAFI ($p = 0.001$). Subjects with low intra-ascitic protein levels are more likely to develop SAFI. This finding is consistent with the literature [1] [2] [20] [21] [22]. For most authors, the risk of SAFI is very high if the protein level in the ascitic fluid is less than 10 g/L.

All patients with SAFI in our series received a 3rd generation cephalosporin (Ceftriaxone). This antibiotic has proven sensitivity to almost all germs that frequently induce ascitic fluid infections according to literature data [8] [23] [24]. But Piroth *et al*. [25] suggested that the combination of 3rd generation cephalosporins + Amoxicillin-clavulanic acid, Cotrimoxazole + Amoxicillin-clavulanic acid are effective options in cases of severe infection or lack of improvement after 48 hours antibiotic therapy.

Among patients with SAFI, 40.6% died at the first episode of ascitic fluid infection. This result is compatible with that found by the European Association for the Study of the Liver in 2010 which was 10% to 50% [8]. Our result is, however, lower than those of Kom Mogto [3], Diarra [10] and Maïga *et al*. [17] who respectively found 90.9% in their series; 69.6% and 75% deaths.

This difference in results could be linked to the fact that 34.4% of patients in our study population were lost to follow-up. This significant rate of loss to follow-up could be explained by the lack of financial means to honor care by patients with the possibility of resorting to traditional medicine. Comparatively, there are more deaths in the group of patients with SAFI than in the group of patients without SAFI (40.6% in the SAFI group versus 20% in the group without SAFI with p-value = 0.049). SAFI therefore worsens the prognosis of the disease-causing ascites with an increased risk of mortality.

5. Conclusion

The prevalence of SAFI is high in our series 39%, with *Escherichia coli* as the most common germ. It would be associated with a low protein level in ascites and severe underlying cirrhosis. The puncture with cytobacteriological examination of the ascitic fluid, which represents the only reliable diagnostic method for SAFI, must be systematic in any patient with ascites; it must be followed by an ascites-culture. The worsening of SAFI seriously impacts the prognosis of cirrhotic patients. Therefore, there is a need for early antibiotic therapy in suspected cases of ascitic fluid infection. Antibiotic prophylaxis must be systematic in cirrhotic patients at high risk of developing SAFI, especially if the protein level in ascites is less than 15 g/L. Prevention and early treatment could reduce mor-

tality in cirrhosis.

Authors' Contributions

All authors participated in the active writing and editing of the article. All authors read and approved the final version of the manuscript.

Limitations of the Study

This was a retrospective study, so a lot of information was missing from the files used. The collection was done using a questionnaire with 7 main sections, there could be information bias. The study was carried out in the largest university hospital in the city of Cotonou; however, the data cannot be generalized on a national scale.

Conflicts of Interest

The authors declare no conflict of interest.

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Portal Venous Thrombosis and Splenic Hemangioma, Secondary to Acute Pancreatitis: Case Report

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Abstract

We present an unusual case of portal vein thrombosis with a splanchnic hemangioma secondary to acute biliary pancreatitis. We report a 45-year-old patient, who has systemic arterial hypertension in treatment, was admitted for abdominal pain in the epigastrium, with irradiation to the right hypochondrium, accompanied by nausea and vomiting of 10 occasions of bile content, physical examination with pain in the right hypochondrium, Murphy positive. We have laboratory studies with a lipase of 788, so a diagnosis of pancreatitis is made with an etiology to be determined. The laboratories suggestive of acute biliary pancreatitis (lipase 788.71); an imaging study was subsequently performed (ultrasonography) with the result of stone in the common bile duct. A laparoscopy was performed with relative improvement, so he was discharged and returned 20 days after surgery due to abdominal pain of the same intensity in the left hypochondrium. Ending his hospitalization with a splenectomy for splenic hemangioma with portal vein thrombosis.

Keywords

Pancreatitis, Esplenic Hemangioma, Esplenectomy, Portal Vein Thrombosis, Surgery

1. Introduction

Acute pancreatitis (AP) is a common condition with a very variable disease pres-

entation, clinically and morphologically, causing significant morbidity and mortality in severe cases [1].

The diagnosis of AP is made when two of the following three features are present: 1) characteristic pain in the upper abdomen; 2) amylase and/or lipase three times the institutional upper limit of normal; and 3) imaging findings consistent with AP. The severity of PA disease is variable: between 75% and 80% have a relatively mild clinical course with a rapid response to conservative management, resulting in complete recovery and a short hospital stay [1].

The term portal venous thrombosis (DVT) should refer to thrombosis that affects only the portal trunk, extending or not to the intrahepatic portal branches [2].

Portal thrombosis is found in approximately 1% of autopsies. In most cases, this thrombosis is related to cirrhosis or liver neoplasms and in only a third of cases it is attributable to a non-cirrhotic and non-tumor origin [2].

Meta-analyses showed a pooled Splanchnic vein thrombosis (SVT) prevalence of 13.6% in pancreatitis. According to the stage of pancreatitis, the pooled prevalence of SVT was 16.6% and 11.6% in patients with acute and chronic pancreatitis, respectively. According to the causes of pancreatitis, the pooled prevalence of SVT was 12.2% and 14.6% in patients with hereditary and autoimmune pancreatitis. Depending on SVT location, the combined prevalence of portal vein, splenic vein, and mesenteric vein thrombosis was 6.2%, 11.2%, and 2.7% in pancreatitis. The prevalence of SVT in pancreatitis was 16.9%, 11.5% and 8.5% in Europe, America and Asia, respectively [3].

Thrombosis of the splanchnic circulation secondary to acute pancreatitis is an entity that has gradually become more relevant to this pathology. The incidence is variable, estimating a prevalence of 10.2% to 17.4% in cohorts with intentional search [4].

The clinical manifestations of splanchnic thrombosis depend on the affected vascular territory. Portal thrombosis: usually accompanying the episode of acute pancreatitis, beyond being able to present silently, persistent or exacerbated abdominal pain after the acute moment of pancreatitis can guide us to the diagnosis. The presentation of fever and dyspepsia, accompanied by pain with a palpable liver edge, is compatible with acute distension of the capsule and make us suspect a possible acute portal thrombosis [4].

Splenic thrombosis: frequently is the one that presents the least signs and symptoms of all, recently appeared splenomegaly is characteristic, described as even more pronounced than in patients who already had a diagnosis of portal hypertension [4].

The diagnosis of acute DVT should be suspected in all patients with recent abdominal pain; especially if you are known to have an underlying prothrombotic disease. Likewise, chronic DVT must be ruled out in all patients with portal hypertension [3].

Abdominal Doppler ultrasound performed by an experienced physician informed about the suspicion of the condition is the technique of choice due to its

high sensitivity and absence of side effects. The diagnosis is demonstrated by the absence, stasis, turbulence, flow reversal, or presence of solid echogenic material within the portal vein. In addition, it allows assessing the existence of collateral vessels and splenomegaly [3].

The objective of this report was investigation of splenic hematoma, it was secondary to splenic hemangioma or pancreatitis since splenic hemangioma was not observed in the first figures or during surgery (**Figure 1**).

2. Case Report

A 45-year-old male patient with a history of systemic arterial hypertension (SAH) under medical treatment, was admitted to the emergency department on 12/27/2021 due to abdominal pain in the epigastrium, with irradiation to the right hypochondrium, accompanied by nausea and vomiting of 10 occasions of bile content, physical examination with pain in the right hypochondrium, Murphy positive.

Laboratory studies were performed with amylase 297 IU/L, lipase 788.71 U/L, Glucose 390.90 mg/dL, Alkaline phosphatase 164 IU/L, Total bilirubin 1.45, mg/dL, Direct bilirubin 0.49 mg/dL, Indirect bilirubin 0.96 mg/dL, Gamaglutamine 87 IU, leukocytes 11.86 × 10^3/uL, Neutrophils 88.6%.

Ultrasonography (USG) of the liver and bile ducts was performed finding Gallbladder with presence of biliary sludge in its lower part, stone diameter of approximately 4 mm, common bile duct of 6.2 mm. Spleen of correct morphology without evidence of splenomegaly.

The patient was admitted to the general surgery service with mild acute pancreatitis of biliary origin and acute lithiasic cholecystitis, medical treatment was given and the pancreatitis condition was resolved and a laparoscopic cholecystectomy was performed, finding the gallbladder under tension, 35 cc of bile content was punctured, parkland 2, with no incidents during the procedure, he was discharged 24 hours after surgery. On 01/19/2022, he went to the emergency department again due to abdominal pain at the level of the left hypochondrium,

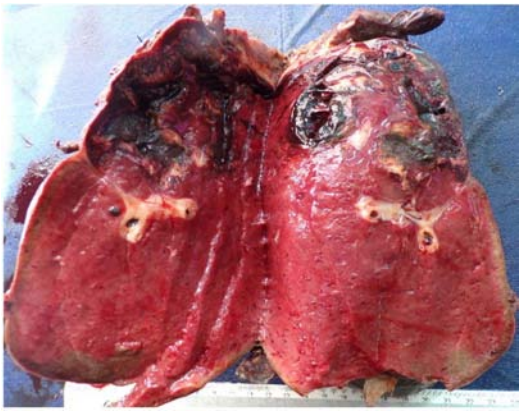

Figure 1. Splenectomy with 1800 mg cross section measuring 22 × 17 × 12 cm with necrotic areas. Necrotic areas are observed in the upper portion.

an increase in temperature quantified at 38˚C, with the presence of myalgia, arthralgia and bilateral parietotemporal headache. Laboratory studies were performed, finding amylase 185 IU/L, lipase 397.72.71 U/L, Glucose 452.20 mg/dL, Alkaline phosphatase 196 IU/L, Total bilirubin 0.38, mg/dL, Direct bilirubin 0.22 mg/dL, Indirect bilirubin 0.17 mg/dL, Gamaglutamine 87 IU, TGP 10.10 IU/L, TGO 7.6 IU/L, ferritin 419.9 ng/mL, leukocytes 7.33 × 10^3/uL, Neutrophils 66.3%, on physical examination abdomen with surgical wounds on the basis of healing, spleen is palpable below the costal margin, with dullness to percussion, with no other important findings. The patient was admitted to the general surgery service with a diagnosis of mild acute pancreatitis. A computed tomography (CT) scan of the abdomen with triple contrast was requested showing perihepatic fluid, splenomegaly marked with density changes, thickened gastric wall, and free fluid in the abdominal cavity. The pancreatitis condition resolves, the patient is tolerating the oral route, but with persistent abdominal pain. Laboratory studies performed 01/26/22: D-dimer 3614 ng/mL,

An elective splenectomy was performed 16 days after admission, after a vaccination schedule based on *Streptococcus pneumoniae* and *Haemophilus*, due to the continuous pain and splenomegaly that the patient presented, finding.

Digestive endoscopy was performed on 02/11/22 due to a suspected diagnosis of gastric varicose veins, finding an esophagus with normal characteristics and a stomach with mucous membrane of the body and antrum with diffuse erythematous dotting, gastric fundus with submucosal venous cord corresponding to isolated gastric fundic varices IGC-1 and mild acute congestive gastropathy.

Pathology results were received on 02/11/22 (**Figure 2**) with a histopathological

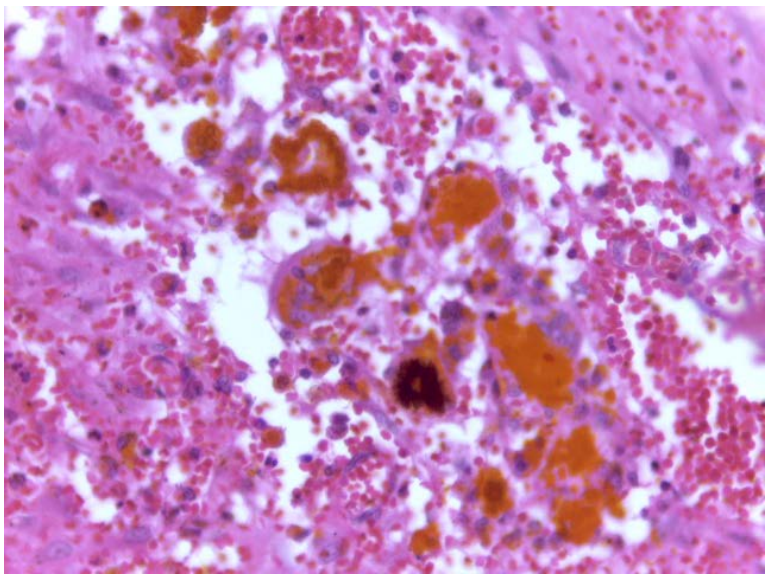

Figure 2. Multiple vascular channels were observed, some of them cavernous in appearance with blood inside, lined by endothelium with normal histological characteristics (simple flat epithelium), without cytological atypia and without mitotic figures. The histopathological appearance is consistent with subcapsular splenic hemangioma.

diagnosis of splenic capillary hemangioma measuring 2.9 × 2 × 2 cm with rupture and formation of a 4.2 mm subcapsular hematoma, splenic parenchyma with ischemic areas associated with thrombosis and splenic chronic passive congestive splenomegaly.

Currently, the patient is stable and is being reviewed every 6 months by an outpatient general surgery clinic in good condition with no complications secondary to surgical procedures.

3. Discussion

D-dimer testing for the diagnosis of thrombosis at unusual sites should not currently be recommended as a first-line diagnostic tool. The development of algorithms that combine biomarkers such as D-dimer and clinical decision tools could improve diagnosis [5].

Splenic hemangioma is the most common benign neoplasm of the spleen in adults, most frequently in ages 35 to 55 years, with no predominance of sex; its clinical behavior is usually indolent, on rare occasions with a palpable mass in the left flank that can cause early satiety or nonspecific abdominal pain due to displacement of adjacent viscera. In more severe conditions, it causes symptoms from cell sequestration inside (Kasabach-Merritt syndrome) or acute abdomen after its spontaneous rupture [6].

Every patient with thrombosis is a patient who requires two lines of management: prevention of complications derived from the clot and behavior to prevent a new episode of formation [4].

A meta-analysis that included 8353 patients in seven studies carried out until December 2020 that compared the use of therapeutic anticoagulation in splanchnic thrombosis, resulted in an RR 1.95 (95% CI 0.98 - 3.88; $I^2 = 0\%$; $p = 0.06$) for hemorrhagic complications between the anticoagulated and non-anticoagulated groups, without being statistically significant. Mortality between both groups was reported with a RR 2.02 (95% CI 0.85 - 4.8) being not statistically significant for the risk of mortality due to a wide confidence interval and a RR 1.6 (95% CI 1.17 - 2.27; $I^2 = 0\%$; $p = 0.004$) in terms of vascular recanalization. The analysis demonstrated that, among patients with AP-associated splanchnic vein thrombosis, therapeutic anticoagulation resulted in recanalization of the involved vessels without significantly increasing the risk of hemorrhagic complications. There were no differences in the RR of death or in the rates of collateral vessel formation during follow-up [7].

In the last decade, the mortality rate from acute DVT has decreased from 30% to approximately 10%. Early diagnosis and anticoagulation are probably the main determinants of improved survival, through prevention or rapid relief of superior mesenteric vein thrombosis. The development of portal hypertension can be prevented if the trunk of the portal vein and at least one of its two branches achieve patency, and this goal can be achieved in up to 40% of patients treated with anticoagulants within the first weeks from onset of acute symptoms.

Currently, 5-year survival in patients without previous liver disease is around 85% and mortality is mainly related to postoperative complications or underlying diseases [8].

4. Conclusions

The primary treatment of acute portal vein thrombosis is anticoagulation and, when possible, treatment of predisposing conditions. The objective of anticoagulation is to prevent the extension of the clot and allow recanalization so that intestinal infarction or portal hypertension does not develop.

In this case, our patient found a splenic hemangioma where clinical improvement was obtained when a splenectomy was performed when changes in the morphology of the wall were found, as well as a hematoma, with resolution of pain completely. Therefore, our first hypothesis was that the patient presented pain due to a splanchnic thrombosis along with a rapidly growing hemangioma since the first two figures did not show splenomegaly and during surgery, no growth of the spleen or any change in the morphology of the spleen was observed.

Although the distal portion of the tail of the pancreas is closely related to the course of the splenic vessels, rupture of the spleen is an unusual complication of acute pancreatitis that should be included in the differential diagnosis of shock during its evolution. Investigation of the splenic hematoma continues, it was secondary to splenic hemangioma or pancreatitis.

Early detection leads to timely management, which has shown structural improvement, but now without clear evidence of a reduction in mortality.

Ethical Considerations

The authors declare that they have met all ethical responsibilities regarding data protection, right to privacy and informed consent.

Authorization from the institution's ethics committee is not necessary since at no time do they fail to comply or violate patient anonymity rules, nor is any experimental procedure performed that puts the patient's integrity at risk.

The authors declare that this article does not contain personal information that would allow the patient described to be identified, which makes the patient's informed consent unnecessary for the publication of the article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Factors Associated with Renal Impairment in Patients on Tenofovir for Chronic Hepatitis B in Yaoundé (Cameroon)

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Abstract

Background: Tenofovir (TFV) is widely used to treat patients with hepatitis B virus (HBV) infection. But kidney abnormalities are the main concern using this drug. Few studies have described the renal impairment due to the TFV in chronic hepatitis B (CHB) in Sub-Saharan Africa. The objective was to evaluate factors associated with renal impairment observed in patients on TFV for CHB. **Method**: It was a hospital based cross sectional prospective study carried out from June 2023 to July 2023 in Yaoundé (Cameroon) and included any patient treated with TFV for CHB during at least a period of 6 months. For each participant, we collected in the medical report socio-demographic data, clinical data, baseline creatinine, treatment information (type of TFV which was Disoproxil Fumarate (TDF) or Alafenamide (TAF), duration). Then, we collected blood samples to measure serum creatinine and phosphate levels and urine dipstick analysis. Factors associated with renal impairment were assessed with the Odds Ratio. A p value of < 0.05 was significant. **Results**: A total of 60 participants were included. The median age was 44 years [36 - 55] and median duration of TFV therapy was 17.5 months [11.7 - 25.7]. The prevalence of reduced eGFR (<60 mL/min/1.73m^2) was 6/60 (10%), the prevalence of hypophosphatemia 6/60 (10%) and the prevalence of albuminuria 24/60 (40%). Factors associated with eGFR reduced were diuretic use (OR 8.5, [1.09 - 9.58], p = 0.042) and duration of TFV ≥ 36 months (OR 34, [4.3 - 266.3], p = 0.001). Those associated with hypophosphatemia

were duration of TFV ≥ 36 months (OR 12.5 [1.88 - 83.3], p = 0.009). While factors associated with albuminuria were TDF prodrug use (OR 8.8 [1.8 - 43.1], p = 0.009), and duration of TFV ≥ 36 months (OR 11.7, [CI 1.3 - 104.5], p = 0.009). **Conclusion**: Kidney function was impaired in some patients receiving TFV for CHB. It should be monitored, particularly after 36 months and for those receiving TDF prodrug.

Keywords

Chronic Hepatitis B, Tenofovir, Factors Associated, Renal Impairment, Cameroon

1. Background

Hepatitis B is a deadly inflammation of the liver caused by the hepatitis B virus (HBV) [1]. Untreated, the infection could lead to liver cirrhosis or hepatocellular carcinoma. The prevalence in Cameroon is estimated to be 11.2%, varying from one region to another [2]. Tenofovir (TFV) is an antiviral widely used in monotherapy to treat patients with hepatitis B virus (HBV) infection [3] [4] [5]. It could be the Tenofovir Disoproxil Fumarate (TDF) at the posology of 300 mg once daily, other the Tenofovir Alafenamide (TAF) 25 mg per day [1]. This last seems to have a lower nephrotoxicity than the first one. The TFV is also prescribed against HIV in an anti-retroviral treatment regimen [6] [7]. The duration of treatment is long, sometimes for life. But kidney abnormalities are the main concern using this drug. Hypophosphatemia is a possible complication in patients. The TFV is associated with a risk of proximal tubular dysfunction and declining estimate glomerular filtration rate (eGFR) [8] [9] [10]. Fanconi syndrome with its complications (bone weakness, dysfunctions in amino acid metabolism and renal lesions) is a possible adverse reaction of TFV treatment, especially in HIV-infected patients [11]. It leads to excessive urinary excretion of solutes handled by the proximal tubule, such as phosphate, glucose, and bicarbonate. Age ≥ 60 years, diabetes mellitus, high blood pressure, and high serum bilirubin have also been described as risk factors for the development of renal insufficiency in chronic hepatitis B (CHB) patients receiving TDF therapy [12]. But, the mechanism of renal impairment in patients with HVB is multifactorial. In addition to the antiviral therapy nephrotoxicity, the kidney disease can be due to the virus itself [13]. The commonest type is membranous glomerulonephritis. Therefore, the monitoring of renal function is recommended during treatment [3] [14]. If there are studies describing renal impairment associated with the use of TFV against HIV in sub-Saharan Africa, few studies have described its effects on renal function in CHB in our area [15] [16] [17].

2. Objective

The objective was to identify factors associated with renal impairment in pa-

tients on TFV for CHB.

3. Materials and Method

A hospital based cross sectional prospective study was carried out over a period of 2 months (June and July 2023) in two referral hepato gastrointestinal units of the Cameroonian capital: Yaoundé General Hospital and Centre Médical la Cathédrale (Yaoundé, Cameroon) and included all consenting patients treated with TFV for CHB during at least 6 months. Patients whose baseline creatinine was not recorded at the start of the treatment were excluded. For each participant, we collected in the medical report socio-demographic data (age, sex), clinical data (BMI, blood pressure readings at rest, comorbidities such as hypertension, diabetes, hepatitis D virus coinfection (HDV), baseline biological characteristics (creatinine, Alanine aminotransferase (ALAT) and Aspartate aminotransferase (ASAT)), treatment (type of TFV which was TDF or TAF, duration of treatment and associated treatment (such as angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEI) and diuretics use). Then, we collected blood samples to measure serum creatinine (to calculate the eGFR) and phosphate levels by spectrophotometry, and midstream urine for dipstick urine analysis.

3.1. Blood Sample and Urine Analysis

1) Serum Creatinine

All samples collected for serum creatinine were centrifuged and stored in the hospital's freezer at −20˚C. We analyzed the samples using a spectrophotometer (HUMAN®). Creatinine was determined using the Jaffe reaction and the GFR is later calculated using the CKD-EPI formula.

2) Serum phosphorus

All samples collected for serum phosphorus were centrifuged and stored in the hospital's freezer at −20˚C. We analyzed the samples using also a spectrophotometer (HUMAN®).

The principle is based on the fact that inorganic phosphate reacts with ammonium molybdate in the presence of sulfuric acid to form a phosphomolybdic complex which is measured at 340 nm. The absorbance at this wavelength is directly proportional to the amount of inorganic phosphorus present in the sample. The procedure described by the fabricant was respected.

3) Dipstick Urine analysis

Urine analysis was realized using a dipstick LABSTIX®. Holding the dipstick at the end opposite to the chemical pads, we dipped it into the freshly collected urine sample for approximately 2 seconds. The dipstick was compared with the colour chart on the dipstick container and each parameter read after its recommended time.

3.2. Data Management and Analysis Plan

At the end of daily data collection, completed forms were assessed, validated,

coded, and stored. Data was entered Access Microsoft and exported Excel. The information was stored on a computer and on an external drive. Data was analyzed according to objectives using the Statistical Package for Social Sciences (SPSS) version 26 and Microsoft Excel.

Renal abnormalities studied were a reduced of eGFR (<60 mL/min/1.73m^2), a hypophosphatemia (Serum phosphorus < 2.5 mg/dL), and an albuminuria (more than 1+ proteinuria on dipstick). Factors associated with renal impairment were assessed with the Odds Ratio (OR). A p-value of < 0.05 was considered significant after bivariate and multivariate analysis.

4. Results

Two hundred and seven (207) files of participants on TFV treatment during at least 6 months for CHB have been recorded during the period. We excluded 101 patients because there was no baseline serum creatinine in their files. After implementing our inclusion criteria, eighty-six participants were eligible to participate in the study for which sixty of them consented to participate.

4.1. Socio Demographic Characteristics of the Study Population

Of the 60 participants, 68.3% (n = 41) were males and the median age [IQR] was 44.0 [36 - 55] years (Table 1).

4.2. Comorbidities in the Study Population

Coinfection with HDV (20 patients, 33.3%), obesity (18 patients, 30%), hypertension (12 patients, 20%), and diabetes mellitus (7 patients, 11.7%) were the most frequent comorbid conditions. We also observed liver cirrhosis (5 patients, 8.3%), HIV (3 patients, 5%), an underweight with BMI < 18 Kg/m^2 (3 patients, 5%) and a hepatocellular carcinoma (1 patient, 1.7%) (Table 1).

4.3. CHB Treatment

The median [IQR] duration of TFV therapy was 17.5 [11.7 - 25.7] months. We noted 53 patients with duration of TFV ≥ 36 months. TDF was the main prodrug observed in 42 patients while TAF was noted in 18 patients.

4.4. Other Medications Used in the Study Population

Herbal African medication (21.7%), angiotensin converting enzyme inhibitors (13.3%) and metformin (11.7%) were the most frequent drugs used. We also noted diuretics (8.3%), angiotensin receptor blocker (8.3%), and non-steroidal anti-inflammatory drugs (6.7%) (Table 1).

4.5. Baseline Biological Characteristics of the Study Population

Of the 60 participants, only 1.7% (1 patient) had a raised serum creatinine at baseline. Until 30 patients (50%) and 29 patients (48.3%) had raised ALAT and ASAT at baseline respectively. We registered 26 patients (43.3%) with Hepatitis

Table 1. Socio demographic characteristics of the study population.

Variable	Category	Frequency (n = 60)	Percentage (%)
Median age[IQR]		44.0 [36 - 55]	
Age groups (years)	[18 - 30]	4	6.7
	[30 - 40]	16	27.7
	[40 - 50]	20	33.3
	[50 - 60[	7	11.7
	≥60	13	21.7
Sex	Male	41	68.3
	Female	19	31.7
Comorbidities	Hepatitis D	20	33.3
	Hypertension	12	20
	Diabetes mellitus	7	11.7
	Liver cirrhosis	5	8.3
	HIV	3	5
	Hepatocellular carcinoma	1	1.7
Medication	Herbal medication	13	21.7
	ACEI	8	13.3
	Metformin	7	11.7
	Diuretics	5	8.3
	ARB	5	8.3
	NSAIDS	4	6.7
Median baseline creatinine [IQR]		0.95 mg/dL [0.80 - 1.10]	
Baseline creatinine	Raised	1	1.7
	Normal	59	98.3
Mean baseline eGFR ± SD		93.18 ± 20.10 mL/min/1.73m^2	
Baseline eGFR	Decreased	1	1.7
	Normal	59	98.3
Median ALAT [IQR]		37.00 IU/L [22.00 - 83.25]	
Baseline ALAT	Raised	30	50
	Normal	30	50
Median ASAT [IQR]		34.00 IU/L [25.50 - 68.75]	
Baseline ASAT	Raised	29	48.3
	Normal	31	51.7
Median baseline viral load [IQR]		1362.00 IU/mL [125.00 - 21642.00]	

ACEI = angiotensin converting enzyme inhibitor, ALAT = alanine aminotransferase, ASAT = aspartate aminotransferase, ARB = angiotensin receptor blocker, HIV = human immunodeficiency syndrome, NSAIDS = non-steroidal anti-inflammatory drugs.

B viral load > 2000 IU/mL (Table 1).

4.6. Renal Function of the Population at Time of the Study

After at least 6 months of TFV treatment, 6 patients (10%) of the participants had an eGFR < 60 mL/min/1.73m^2. There was an increase in mean serum creatinine from baseline (0.95 mg/dL) to after at least 6 months of TFV treatment (1.05 mg/dL) with change in mean serum creatinine being 0.1 mg/dL (p = 0.005) (Figure 1). There was a decrease in mean eGFR from baseline (93.2 mL/min/1.73m^2) to after at least 6 months of TFV treatment (83.6 mL/min/1.73m^2) with change in mean eGFR being 9.6 mL/min/1.73m^2 (p = 0.001) (Figure 1). All 6 participants who had an eGFR < 60 mL/min/1.73m^2 were between the ranges 45 - 59 mL/min/1.73m^2.

The median [IQR] serum phosphorus was 3.3 [2.8 - 3.8] and a total of 6 participants (10%) had hypophosphatemia.

A total of 24 participants (40%) had albuminuria and 5 (20%) were nephrotic range albuminuria (more than 300 mg/dL).

4.7. Factors Associated with Reduced Estimated Glomerular Filtration Rate

In bivariate analysis, factors associated with eGFR reduced were diuretic use (OR 8.5 [1.09 - 9.58], p = 0.042) and duration of TFV ≥ 36 months (OR 34 [4.3 - 266.3], p = 0.001) (Table 2). Sociodemographic characteristics (age and sex),

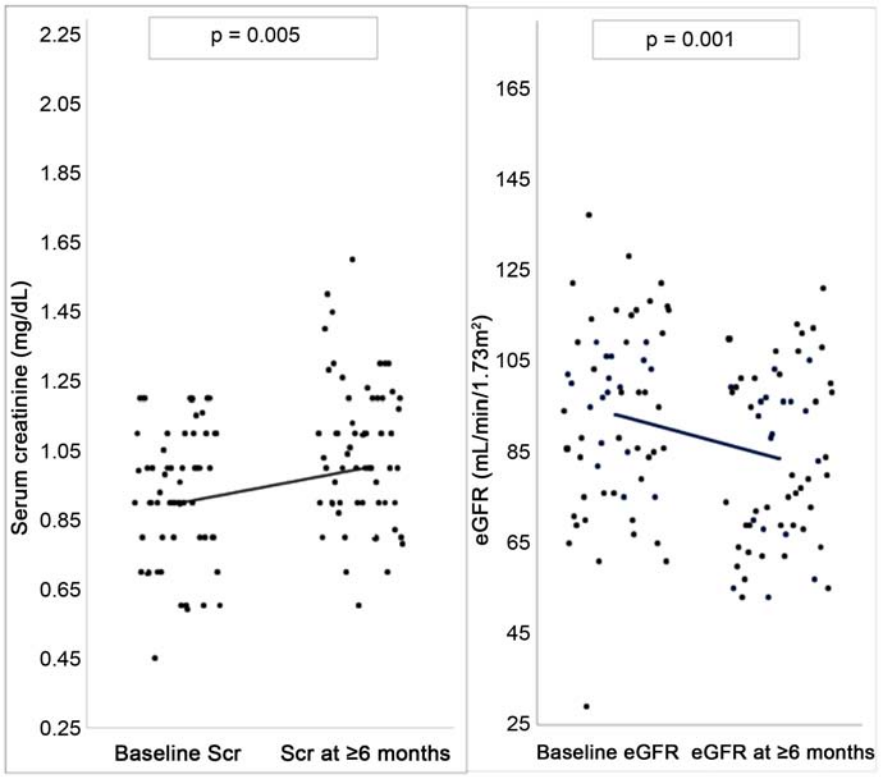

Figure 1. Changes in mean serum creatinine and eGFR of the study population (n = 60).

Table 2. Factors associated with reduced estimated glomerular filtration rate (bivariate analysis) (n = 60).

Variable	Categories	Reduced eGFR		OR (95% CI)	p-value
		Yes (n = 6)	No (n = 54)		
		n (%)	n (%)		
Age (Years)	<60	2 (33.3)	11 (20.4)	1	0.471
	≥60	4 (66.7)	43 (79.6)	1.96 [0.32 - 12.0]	
Sex	Male	3 (50)	38 (70.4)	0.42 [0.08 - 2.31]	0.320
	Female	3 (50)	16 (26.9)	1	
Medication	ARB use	0 (0)	5 (8.4)	Undefined	0.999
	ACEI use	2 (33.3)	6 (11.1)	4.00 [0.60 - 26.68]	0.152
	NSAIDS use	1 (16.7)	3 (5.6)	3.40 [0.30 - 39.10]	0.326
	Diuretics use	**2 (33.3)**	**3 (5.6)**	**8.50 [1.09 - 6.58]**	**0.042**
	Herbal med use	1 (16.7)	12 (22.2)	0.70 [0.07 - 6.58]	0.755
TFV prodrug	TDF	5 (83.3)	37 (40.7)	2.30 [0.25 - 21.2]	0.463
	TAF	1 (16.7)	17 (31.5)	1	
Comorbidities	Hypertension	2 (33.3)	10 (18.5)	2.20 [0.35 - 13.7]	0.399
	Diabetes	0 (0)	7 (13)	Undefined	0.999
	HDV	3 (50)	17 (31.5)	2.18 [0.40 - 1.92]	0.370
BMI (kg/m^2)	<18	1 (16.7)	2 (3.7)	5.20 [0.40 - 7.94]	0.209
	≥18	5 (83.3)	52 (96.3)	1	
Duration of TFV therapy (months)	**<36**	**4 (66.7)**	**3 (5.6)**	**1**	**0.001**
	≥36	**2 (33.3)**	**51 (94.4)**	**34.00 [4.34 - 266.3]**	
ALAT, IU/L	>36	3 (50)	27 (50)	1.00 [0.19 - 5.40]	1.000
	≤36	3 (50)	27 (50)	1	
ASAT, IU/L	>35	3 (50)	26 (48.1)	1.08 [0.20 - 5.82]	0.931
	≤35	3 (50)	28 (51.9)	1	
Hepatitis B viral load, IU/mL	>2000	3 (50)	23 (43.4)	1.30 [0.24 - 7.07]	0.78
	≤2000	3 (50)	30 (56.6)	1	

ACEI = angiotensin converting enzyme inhibitor, ALAT = alanine aminotransferase, ARB = angiotensin receptor blocker, ASAT = aspartate aminotransferase, BMI = body mass index, NSAIDS = non-steroidal anti-inflammatory drugs, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, TFV = tenofovir.

comorbidities (hypertension, diabetes mellitus, coinfection with HVD), other medications (ARB use, ACEI use, NSAIDS use, herbal medication use) and baseline biological characteristics (ASAT, ALAT, and HVB viral load) was not associated with eGFR reduced (Table 2). After controlling for cofounders (diuretics use and TFV duration), only the duration of tenofovir therapy of ≥36 months was independently associated with a reduction in estimated glomerular filtration rate (aOR = 56.6, p-value = 0.002). Therefore, this factor increased the risk to have a reduced eGFR.

4.8. Factors Associated with Hypophosphatemia

Factors associated with hypophosphatemia was duration of TFV ≥ 36 months (OR 12.5 [1.88 - 83.3], p = 0.009) (Table 3). Sex, comorbidities (hypertension), medications (ARB use, ACEI use, diuretics use, herbal medication use) and baseline biological characteristics (ASAT, ALAT, and HVB viral load) was not associated with hypophosphatemia (Table 3). Age ≥ 60 years (p = 0.095) and coinfection with HVD (p = 0.089) were marginally associated with hypophosphatemia (Table 3). After controlling for cofounders (age ≥ 60 years, coinfection with HDV, TFV duration), no factor was independently associated with hypophosphatemia.

Table 3. Factors associated with hypophosphatemia (bivariate analysis) (n = 60).

Variable	Categories	Hypophosphatemia		OR [95% CI]	p-value
		Yes (n = 6) n (%)	No (n = 54) n (%)		
Age (Years)	<60	3 (50)	10 (18.5)	1	0.095
	≥60	3 (50)	44 (81.5)	4.4 [0.77 - 25.10]	
Sex	Male	4 (66.7)	37 (68.5)	0.92 [0.15 - 5.51]	0.926
	Female	2 (33.3)	17 (31.5)	1	
Medication	ARB use	0 (0)	5 (9.3)	Undefined	0.999
	ACEI use	1 (16.7)	7 (13.0)	1.34 [0.14 - 13.25]	0.801
	Diuretics use	1 (16.7)	4 (7.4)	2.50 [0.23 - 26.91]	0.450
	Herbal med use	2 (33.3)	11 (20.4)	1.95 [0.32 - 12.09]	0.471
TFV prodrug	TDF	6 (100)	36 (66.7)	Undefined	0.998
	TAF	0 (0)	18 (33.3)	1	
Comorbidities	Hypertension	1 (16.7)	11 (20.4)	0.78 [0.08 - 7.39]	0.830
	HDV	4 (66.7)	16 (29.6)	4.75 [0.79 - 28.60]	0.089
BMI (kg/m^2)	<18	1 (16.7)	2 (3.7)	5.20 [0.40 - 67.94]	0.209
	≥18	5 (83.3)	52 (96.3)	1	
Duration of TFV therapy (months)	**<36**	**3 (50)**	**4 (7.4)**	**1**	**0.009**
	≥36	**3 (50)**	**50 (92.6)**	**12.50 [1.88 - 83.31]**	
ALAT, IU/L	>35	3 (50)	27 (50)	1.00 [0.19 - 5.40]	1.000
	≤35	3 (50)	27 (50)	1	
ASAT, IU/L	>36	3 (50)	26 (48.1)	1.08 [0.20 - 5.82]	0.931
	≤36	3 (50)	28 (51.9)	1	
Hep B Viral load, IU/mL	>2000	2 (33.3)	24 (45.3)	0.60 [0.10 - 3.59]	0.579
	≤2000	4 (66.7)	29 (54.7)	1	

ACEI = angiotensin converting enzyme inhibitor, ALAT = alanine aminotransferase, ARB = angiotensin receptor blocker, ASAT = aspartate aminotransferase, BMI = body mass index, NSAIDS = non-steroidal anti-inflammatory drugs, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, TFV = tenofovir.

4.9. Factors Associated with Albuminuria

While factors associated with albuminuria were TDF prodrug use in contrast with TAF prodrug use (OR 8.8 [1.8 - 43.1], p = 0.009), and duration of TFV ≥ 36 months (OR 11.7 [1.3 - 104.5], p = 0.009) (Table 4). Sex, medications (ARB use, ACEI use, Metformin use, NSAIDS use, and diuretics use), comorbidities (hypertension, diabetes mellitus, HDV coinfection), and baseline biological characteristics (ASAT, ALAT, and HVB viral load) was not associated with albuminuria

Table 4. Factors associated with albuminuria (bivariate analysis) (n = 60).

Variable	Categories	Albuminuria		OR (95% CI)	p-value
		Yes (n = 24)	No (n = 36)		
		n (%)	n (%)		
Age (Years)	<60	8 (33.3)	5 (13.9)	1	0.081
	≥60	16 (66.7)	31 (86.1)	3.10 [0.87 - 11.04]	
Sex	Male	14 (58.3)	27 (75)	0.47 [0.15 - 1.41]	0.320
	Female	10 (41.7)	9 (25)	1	
Medication	ARB use			1.00 [0.15 - 6.48]	1.000
	ACEI use	5 (20.8)	3 (8.3)	2.90 [0.62 - 13.48]	0.176
	Metformin use	2 (8.3)	5 (13.9)	0.56 [0.10 - 3.17]	0.516
	NSAIDS use	2 (8.3)	2 (5.6)	1.56 [0.23 - 11.79]	0.326
	Diuretics use	3 (12.5)	2 (5.6)	2.43 [0.37 - 15.58]	0.352
	Herbal med use	8 (33.3)	5 (13.9)	3.10 [0.87 - 11.04]	0.081
TFV prodrug	**TDF**	**22 (91.7)**	**20 (55.6)**	**8.80 [1.80 - 43.15]**	**0.007**
	TAF	2 (8.3)	16 (44.4)	1	
Comorbidities	Hypertension	7 (29.2)	5 (13.9)	2.55 [0.70 - 9.29]	0.155
	Diabetes	2 (8.3)	5 (13.9)	0.56 [0.10 - 3.17]	0.516
	HDV	7 (29.2)	13 (36.1)	0.73 [0.24 - 2.22]	0.577
BMI (kg/m^2)	<18	2 (8.3)	1 (2.8)	3.18 [0.27 - 37.94]	0.356
	≥18	22 (91.7)	35 (97.2)	1	
Duration of TFV therapy	**<36**	**6 (25)**	**1 (2.8)**	**1**	**0.028**
	≥36	**18 (75)**	**35 (97.2)**	**11.7 [1.30 - 104.53]**	
ALAT, IU/L	>36	8 (83.3)	5 (13.9)	1.32 [0.49 - 3.72]	0.598
	≤36	11 (45.8)	19 (58.2)	1	
ASAT, IU/L	>35	12 (50)	17 (47.2)	1.18 [0.40 - 3.12]	0.833
	≤35	12 (50)	19 (52.8)	1	
Hep B Viral load, IU/mL	>2000	12 (50)	14 (40)	1.50 [0.54 - 4.27]	0.448
	≤2000	12 (50)	21 (60)	1	

ACEI = angiotensin converting enzyme inhibitor, ALAT = alanine aminotransferase, ARB = angiotensin receptor blocker, ASAT = aspartate aminotransferase, BMI = body mass index, HDV = hepatitis D virus, NSAIDS = non-steroidal anti-inflammatory drugs, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, TFV = tenofovir.

(Table 4). Age ≥ 60 years (p = 0.081) and herbal medication use (p = 0.081) were marginally associated with albuminuria (Table 4). After controlling for co-founders (age ≥ 60 years, herbal medication use, TDF prodrug, TFV duration), only the TDF prodrug use was independently associated with albuminuria (aOR 9.3, p = 0.024). Therefore, this factor increased the risk to have an albuminuria.

5. Discussion

We included 60 patients receiving TFV for CHB since at least 6 months. We observed a male predominance with a median age of 44 years. This male majority has also been described in Cameroon by Halle et al in 2019 [13]. The explanation is probably due to higher risk of HBV and onset of a hepatocellular carcinoma much elevated in men than in women [18]. For this reason, men could be more often on antiviral treatment than women. Our population was relatively young. Jung *et al*. in 2018 in Seoul (South Korea) observed a mean age of 51.3 ± 11.3 years [12]. African patients seem to develop hepatocellular carcinoma younger than those in Asia and West countries [19]. For this reason, in South Saharan Africa we like to prescribe antiviral treatment against HBV early than in Asia and West.

5.1. Mean Changes in Creatinine

At the time of the study, we registered 6 patients (10%) with an elevated serum creatinine in contrast with only one patient before the treatment. This will induce a poor eGFR which is estimated through the serum creatinine. The changes show that the kidney injury is probably due to the antiviral treatment and not due the HBV itself. This results in inferior to 25.4% observed by Yazie *et al*. in 2018 in Ethiopia [10]. This last study was conducted in a population of HIV-patients receiving TFV in combination with other antiretroviral therapy. For this reason, the poly medication could increase the risk of renal injuries.

5.2. Renal Impairment

We observed 6 participants (10%) who had an eGFR < 60 mL/min/1.73m^2. The ranges were between 45 - 59 mL/min/1.73m^2. This value corresponds to a mild kidney injury but which could become severe later if nothing is done [3]. Also, a hypophosphatemia was observed in 6 participants (10%). This could be associated with a proximal tubular dysfunction leading to excessive urinary excretion of phosphate. This abnormality could reveal a Fanconi syndrome [11]. Concerning albuminuria, it was observed in 24 participants (40%) including 5 with a nephrotic range albuminuria (more than 300 mg/dL)! This abnormality is result in glomerular lesions due to the TFV treatment [8]. Without the diagnosis and treatment, this could induce an irreversible chronic kidney disease.

5.3. Factors Associated with Renal Impairment

Duration of TFV therapy ≥ 36 months were associated with a reduced eGFR OR =

34.00 [4.34 - 266.3], p = 0.001; with a hypophosphatemia OR = 12.50 [1.88 - 83.31], p = 0.009 and with a albuminuria OR = 11.7 [1.30 - 104.53], p = 0.028. Diuretics use was associated with a reduced eGFR OR = 8.50 [1.09 - 6.58], p = 0.024; and TDF prodrug use was associated with an albuminuria OR = 8.80 [1.80 - 43.15], p = 0.007. These kidney injuries in patients receiving TDF pro drug and patients receiving the TFV during more than 36 months have also been demonstrated in other studies. TAF compared to TDF demonstrated superiority in the drug effects on several markers of renal (both glomerular and tubular) function and bone turnover [1]. In contrary with some studies, age ≥ 60 years, hypertension and diabetes mellitus were not associated with kidney injuries in our population [12]. The low size of our sample could explain this observation.

6. Limitations of Current Study

Despite our important results, our study has some limitations. We wish to increase the size of the sample with a multicentric analysis and few loss of view. The baseline parameters should be available for everyone. Moreover, our patients had a different duration of treatment. We wish to realize study where all patients are assessed at the same duration of treatment.

7. Conclusion

Kidney function was impaired in some patients receiving TFV for CHB. It should be monitored, particularly after 36 months and for those receiving TDF prodrug.

Acknowledgements

Our study contributes to describing renal impairments observed in patients receiving the Tenofovir for CHB in sub-Saharan country. We analyzed associated factors with these kidney injuries. And we identified the duration of treatment superior to 36 months and the TDF prodrug use as factor increasing risks of these renal dysfunctions.

Declarations Ethics Approval

Ethical clearance number 2023/0779H/UBa/IRB was obtained from the Institutional Review Board of the University of Bamenda (Bamenda, Cameroon). After clear explanation of the study, risk and benefits, only participants who gave their consent were included in the study.

Administrative Authorization

Before the recruitment, we obtained the administrative authorization from the Centre Regional Delegation of Public Health, the general director of the Yaoundé General Hospital and the director of the Centre Médical la Cathédrale.

Consent to Participate

We approached all the patients of our target population and explained the aim

and procedure of the study to them. We further explained the risk and benefits of the study to them. We then requested their consent to participate in the study. Those who accepted to participate gave their consent either verbally or signed the consent form.

Author Contributions

NDJITOYAP NDAM Antonin Wilson, designed the study protocol, wrote the manuscript;

SHU Sonia Charlsia Ewuo, investigator, collected data, wrote the manuscript;

MAIMOUNA Mahamat, analyzed data;

BEKOLO NGA Winnie, reviewed;

DANG BABAGNA Isabelle, collected data;

TALLA Paul, collected data;

KOWO Mathurin, analyzed data;

ANKOUANE ANDOULO Firmin, worked as supervisor;

ASHUNTANTANG Gloria Enow, worked as supervisor.

Competing Interests

Authors state that there are no conflicts of interest.

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