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Acute Hemorrhagic Fever: Clinical, Epidemiological and Laboratory Aspects in São Tomé and Príncipe

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Abstract

Background: In the last 6 months, cases of acute hemorrhagic fever (AHF) have been recorded in Sao Tome and Principe (STP). **Objective:** To identify the clinical, epidemiological and laboratory parameters associated with AHF cases found in patients hospitalized in STP. **Methods:** Descriptive and quantitative analysis of AHF cases hospitalized in STP in the period December 2021 to May 19, 2022 through the variables: demographic data; clinical data; laboratory data and clinical outcome. **Results:** Analyzed 18 of 22 AHF cases, 50% of them male, mean age 33.7 years, 85.7% residing in the 2 largest districts of the country, 66.7% rural workers, administrative near maritime areas, sailors and domestics. 66.7% were healthy individuals. ≥50% had a fever, asthenia/weakness, myalgia, headache, lethargy, nausea, vomiting, and diarrhea. 22.2% to 33.3% had retro-orbital pain, abdominal pain, decreased consciousness, dyspnea/hypoxia, and cough. In a smaller register (5.6% - 11.1%), exanthema, convulsion, arthralgia, low back pain, chills, and chest pain. Bleeding from the digestive tract was found in 72.2%, followed by vaginal (33.3%), urethral (27.8%), nasal (22.2%), and oral (16.7%). 50% had laboratory confirmation for dengue, and another 50% with suspected clinical diagnosis without laboratory confirmation of the etiologic agent. Despite hemorrhage, 66.7% of confirmed cases were hemodynamically non-severe, and 88.9% of suspected cases were severe. Coinfection with malaria is evidenced in 11.1% of cases. 72.2% recovered and 27.8% died (deaths in 55.5% of suspected cases). Case deaths were male (100%), resident foreigners (40%), tool store employees, sailors and students, healthy (80%), and residing in the larg-

est district in the country (60%). All deaths were hospitalized in serious condition, 80% were hospitalized for hemorrhage and shock, with bleeding arising between day 4 - 5 of illness in 60% and hospitalization on day 5 of illness. 60% died within ≤24 hours of hospitalization. 80% died from shock and multi-organ dysfunction and 20% from respiratory failure. Deaths had thrombocytopenia (100%), renal dysfunction (100%) and significantly increased transaminases (100%), anemia (75%) and leukocytosis (66.7%). 20% had a radiological change of pulmonary infiltrates. **Conclusion:** Our data reveal the complexity of the pathogens causing AHF and suggest the possible presence of other human pathogens usually unknown in the Santomean geographical territory.

Keywords

Acute Hemorrhagic Fever, Viral Hemorrhagic Fever, Dengue, São Tomé and Príncipe, Hospitalization, Epidemic, Dr. Ayres de Menezes Hospital

1. Introduction

Considered a rare and highly lethal disease, acute hemorrhagic fever (AHF) [1] [2] has emerged in São Tomé and Príncipe (STP) with a frequent record of cases in the last 6 months and with increasing character in terms of case numbers [3] [4].

Hemorrhagic fevers are usually caused by viruses, as well as bacteria and Plasmodium, and are a group of diseases of zoonotic origin, characterized by fever and hemorrhagic manifestations that can present extreme severity and high lethality [1] [2]. Depending on the type of agent, these infections can be transmitted through contact with the skin or body fluids of an infected person, by the droppings or urine of infected rodents, by insect bites, or by consuming contaminated food [5].

Indeed, STP is an archipelago located in the tropical region, with 219,078 inhabitants [6], known endemic for malaria in terms of acute febrile illnesses [7], but without any official and usual prior notification of AHF cases. But, in December 2021, STP health authority suspected 2 cases of AHF, without confirmation of the etiological agent. Again in January and February 2022, cases of acute hemorrhagic fever were recorded, just at the time of the fourth wave of covid-19 in the country. And, since April 2022, the country has recorded several cases of hemorrhagic fever, and the investigation done specifically for dengue has confirmed the evidence of circulation of this agent in the country [3] [4].

Several groups of viruses can cause fever and other symptoms that are accompanied by heavy bleeding (hemorrhagic fever). The 6 families: Flaviviridae (Omsk hemorrhagic fever, Kyasanur forest fever, dengue hemorrhagic fever/dengue shock syndrome and yellow fever), Nairoviridae (Congo and Crimean hemorrhagic fever), Phenuiviridae (Rift Valley fever), Hantaviridae (hemorrhagic fever with hantavirus renal syndrome and hantavirus pulmonary and car-

diovascular syndrome), Arenaviridae (hemorrhagic fevers from Junin, Machupo, Guanarito and Sabiá viruses in South America and Lassa virus in Africa) and Filoviridae (hemorrhagic fevers from Marburg and Ebola viruses) [2] [3]. Rickettsiales bacteria can also cause HF [8] [9] [10] [11] [12], as well as leptospirosis and malaria [13].

However, clinical manifestations and severity vary significantly, from extremely high mortality rates in Ebola hemorrhagic fever to asymptomatic in many dengue viral infections [3], and severe fever and coagulopathy are also present in diseases such as leptospirosis and malaria [2].

Taking into account that several viral infections cited are similar, it becomes necessary to describe the profile of the cases of AHF evidenced in STP in order to make the conclusion whether it would be important to investigate other causes of AHF, besides dengue fever, because, the hypothesis is that there is a possibility that there are other emerging infectious diseases causing acute hemorrhagic fever circulating in STP, as well as the possibility of there being hemorrhagic dengue fever with differentiated particularity.

The objective of this work was to identify the clinical, epidemiological and laboratory parameters of acute hemorrhagic fever cases of patients hospitalized in STP.

2. Materials and Methods

This is a descriptive and quantitative analysis of AHF cases hospitalized in STP, in the period from early December 2021 to May 19, 2022.

The patients in this study were all patients who were hospitalized with fever and acute hemorrhage from the emergency department of the central hospital. Data were obtained from the central hospital emergency service record book.

The information was complemented through the database of the epidemiological surveillance service, patient charts including the results of complementary exams.

The variables studied were: demographic data; clinical data; occurrence of comorbidities; warning signs identified in the initial care; time interval between onset and end of fever, time interval between bleeding and end of fever, time interval between onset of disease and bleeding; reason for hospitalization; laboratory data; co-infections or disease associations and the clinical outcome and profile of cases that died and those recovered.

Remarks on the definitions for the job:

- The case definition of AHF included any person of any age admitted to the health service with a history of acute fever (>37.8˚C) and acute bleeding manifestations.
- Considered bleeding, the existence of visible active bleeding. Cases of bleeding based merely on thrombocytopenia were not included.
- Hospitalization: were considered regardless of the period, even if it was for only a few minutes of observation.
- Confirmed cases: all those hospitalized with fever and acute hemorrhage associated with laboratory confirmation of dengue virus were considered.

Continued

- Suspected cases: all those hospitalized with fever and acute hemorrhage with negative laboratory confirmation for dengue, and/or those not submitted to any laboratory investigation for dengue, were considered.
- Hemoconcentration: considered values starting at 50% for men, 44% for women and 38% for children.
- Leukopenia: considered to be values below 3500 total leukocyte cells.
- Thrombocytopenia: considered values below 150 thousand platelets.
- Severe: considered cases with clinical instability.
- Non-severe: considered are the cases without clinical instability.

Statistical analysis: The data were analyzed using Excel and Epi Info software to obtain absolute and relative frequencies, measures of central tendency and dispersion.

Ethical Statement: This study was reviewed by the Hospital Dr Ayres de Menezes team and authorized by the Clinical Directorate of Hospital Dr Ayres de Menezes in São Tomé and Príncipe. No indicative data or sample collection from patients was necessary, so no written consent was required from participants.

3. Results

Demographic characteristics and clinical epidemiology:

22 cases of AHF were found from December 2021 to May 19, 2022. Of which 2 (9.1%) occurred in December/2022, 1 (4.5%) in January/2022, 1 (4.5%) in February/2022, 5 (22.7%) in April/2022 and 13 (59.1%) in May/2022 up to day 19 (Graph 1(a)). In March/2022, no AHF cases were reported in the country. Among the AHF cases, those that tested positive for dengue occurred in April and May 2022, with a higher frequency of cases in women (3 women/1 man and 3 women/2 men, respectively in April and May 2022 (Graph 1(b) and Graph 1(c)).

For analysis, 4 (18.1%) cases were excluded for lack of all variables referred in the study (the 2 cases from January and February/2022 and 2 cases from May 2022), and 18 patients were included for analysis.

We analyzed 18 cases of AHF, of which 9 (50%) had a record of laboratory confirmation of dengue by rapid testing, and 9 (50%) remained with clinical diagnosis with epidemiological link (suspicious) (Table 1).

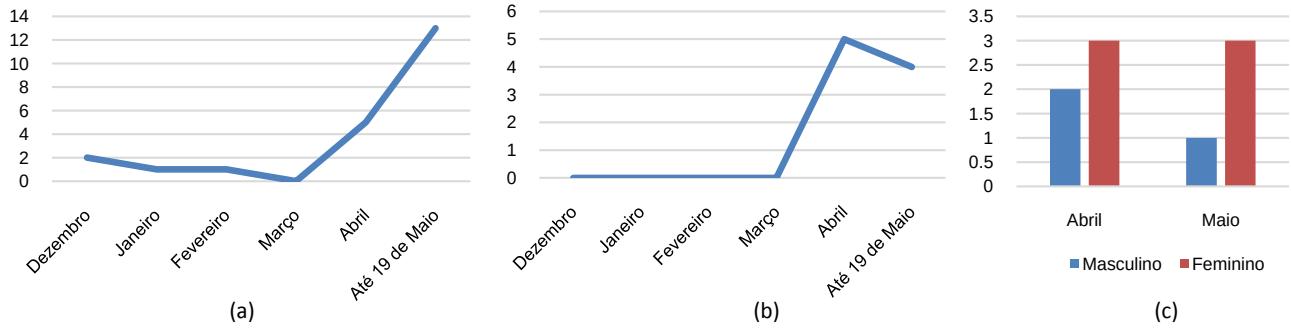
Among the confirmed cases, despite hemorrhage, 6 (66.7%) were hemodynamically non-severe. On the other hand, 8 (88.9%) of suspected cases were severe cases (Table 1).

Overall, it was characterized by preferential involvement of adults aged 20 - 49 years. All cases of AHF had a mean age of 33.7 years, ranging from 2 - 59 years. Confirmed dengue cases had a mean age of 35.2 years, 31.9 years for suspects (Table 1).

The distribution of cases by sex was equal, 9 (50%) male and another 9 (50%) female. Among the confirmed cases for dengue, 6 (66.7%) were female, and for the suspected cases, 6 (66.7%) were male.

Table 1. Distribution of cases by demographic data.

Description		Laboratory confirmed		Suspects		Total	
Total	Total	9	50%	9	50%	18	100%
Severity despite of hemorrhage	Severe	3	16.7%	8	44.4%	11	61.1%
	Non-Severe	6	33.3%	1	5.6%	7	38.9%
Gender	Female	6	33.3%	3	16.7%	9	50%
	Male	3	16.7%	6	33.3%	9	50%
Age group (years old)	under 10	1	5.6%	0	-	1	5.6%
	11 - 19	1	5.6%	1	5.6%	2	11.1%
	20 - 30	0	-	4	22.2%	4	22.2%
	30 - 39	2	11.1%	2	11.1%	4	22.2%
	40 - 49	4	22.2%	2	11.1%	6	33.3%
	50 a 59	1	5.6%	0	-	1	5.6%
	Older than or equal to 60	0	-	0	-	0	-
Residence district	Água Grande	6	33.3%	2	11.1%	8	44.4%
	Mézochi	1	5.6%	3	16.7%	4	22.2%
	RAP	1	5.6%	1	5.6%	2	11.1%
	Caué	0	-	2	11.1%	2	11.1%
	Lobata	1	5.6%	0	-	1	5.6%
	Cantagalo	0	-	1	5.6%	1	5.6%
Profession	Rural worker	1	5.6%	3	16.7%	4	22.2%
	Domestic	4	22.2%	0	-	4	22.2%
	Adminitrative in institutions near maritime offshore	3	16.7%	0	-	3	16.7%
	Tool Warehouse Employees	0	-	2	11.1%	2	11.1%
	Students	1	5.6%	1	5.6%	2	11.1%
	Unknown	0	-	1	5.6%	2	11.1%
	Seaman/fisherman	0	-	1	5.6%	1	5.6%
Age (years old)	Mean	35.2		31.9		33.7	
	Median (min-max)	39.5 (2 - 59)		32 (14 - 45)		38 (2 - 59)	
Comorbidities and lifestyle	Pregnancy-Puerperium	1	5.6%	1	5.6%	2	11.1%
	Epilepsia	0	-	1	5.6%	1	5.6%
	Gastritis	0	-	1	5.6%	1	5.6%
	Obesity	1	5.6%	0	-	1	5.6%
	Drepanocitose	1	5.6%	0	-	1	5.6%
	Covid more than 30 days	0	-	1	5.6%	1	5.6%
	Alcoholism	0	-	1	5.6%	1	5.6%
	Smoker	0	-	1	5.6%	1	5.6%
	Healthy	7	38.9%	5	27.8%	12	66.7%



Graph 1. Acute hemorrhagic fever cases (from December 2021 to May 19, 2022). (a) No. of cases of Acute Hemorrhagic Fever - Dec/2021 to May/2022; (b) Number of cases of AHF: Months of the years (from December/2021 to May/2022) in relation to confirmed dengue cases; (c) Dengue hemorrhagic fever cases: months of the year in relation to the gender of confirmed cases.

The patients were residents of 6 (85.7%) of the districts in the country, with 61.1% of the patients residing in the 2 largest districts in the country (Agua Grande and Mézochi). However, confirmed dengue cases were more found in people residing in Agua Grande district with 6 (66.7%) of cases, on the other hand, suspected cases were more evident in Mézochi with 3 (33.3%) and Caué with 2 (22.2%). 66.7% were rural workers, administrative near the sea area/mariners and domestic workers (Table 1).

7 (77.8%) and 5 (55.6%) among confirmed and suspected cases, respectively, were healthy individuals. However, pregnancy (11.1%), obesity (11.1%) and drepanocytosis (11.1%) were the most frequent comorbidities among the confirmed cases. Pregnancy-puerperium (11.1%), epilepsy (11.1%) and history of covid (11.1%), smoking (11.1%) was the associations found in suspected cases.

The analysis of symptoms among confirmed and suspected cases showed that the first symptom/sign was fever in 16 (88.9%) of the patients and convulsion in 2 (11.1%). All presented with fever. Besides fever, among the confirmed dengue cases, the most frequent symptoms were asthenia/weakness 8 (88.9%), headache 6 (66.7%), myalgia 6 (66.7%), nausea 6 (66.7%), diarrhea 6 (66.7%), vomiting 5 (55.5%), retroorbital pain 4 (44.4%), cough 3 (33.3%), hypoxia/dyspnea 2 (22.2%), and abdominal pain 2 (22.2%). The most frequent clinic among the suspected cases were lethargy 8 (88.9%), myalgia 7 (77.8%), asthenia/weakness 6 (66.7%), headache 6 (66.7%), nausea 4 (44.4%), vomiting 4 (44.4%), abdominal pain 4 (44.4%), decreased consciousness 4 (44.4%), diarrhea 3(33.3%), retroorbital pain 2 (22.2%), and hypoxia/dyspnea 2 (22.2%) (Table 2).

Regarding bleeding, the digestive tract was the most frequent in 13 (72.2%) of the people. Among the confirmed cases, the most common bleeding was from the digestive tract 5 (55.6%), vaginal 5 (55.6%), and urethral 3 (33.3%). There was also, nasal 1 (11.1%) and oral cavity 1 (11.1%). Among the suspects, the most common bleeding was from the digestive tract 8 (88.9%), nasal 4 (44.4%), urethral 2 (22.2%), vaginal 2 (22.2%) and oral mucosa 2 (22.2%). 7 (77.8%) of the confirmed cases and 4 (44.4%) of the suspected cases had bleeding in one topography, but there was bleeding in seven topographies in the same patient.

Table 2. Proportion of signs and symptoms found in the confirmed and suspected cases.

Signs and symptoms	Laboratory confirmed		Suspects		Total	
	n	%	n	%	n	%
Fever	9	50%	9	50%	18	100%
Asthenia/weakness	8	44.4%	6	33.3%	14	77.8%
Myalgia	6	33.3%	7	38.9%	13	72.2%
Headache	6	33.3%	6	33.3%	12	66.7%
Lethargy	3	16.7%	8	44.4%	11	61.1%
Náusea	6	33.3%	4	22.2%	10	55.6%
Vomiting	5	27.8%	4	22.2%	9	50%
Diarrhea	6	33.3%	3	16.7%	9	50%
Retroorbital pain	4	22.2%	2	11.1%	6	33.3%
Abdominal pain	2	11.1%	4	22.2%	6	33.3%
Consciousness reduction	1	5.6%	4	22.2%	5	27.8%
Hypoxia or dyspnea	2	11.1%	2	11.1%	4	22.2%
Dry/productive cough	3	16.7%	1	5.6%	4	22.2%
Exanthema	1	5.6%	1	5.6%	2	11.1%
Seizure	1	5.6%	1	5.6%	2	11.1%
Arthralgia	1	5.6%	1	5.6%	2	11.1%
Lumbar pain	1	5.6%	1	5.6%	2	11.1%
Chills	1	5.6%	0	-	1	5.6%
Chest pain	0	-	1	5.6%	1	5.6%

The time interval between onset and termination of fever was evaluated for the cases. For both groups, the average time interval between onset and termination of fever was 4.9 days and 5.1 days, respectively, with a range of 2 to 8 days for confirmed and 3 to 7 days for suspected cases.

The analysis of the date of occurrence of hemorrhage in relation to the date of the end of fever revealed that among the confirmed cases, 3 (33.3%) developed hemorrhagic symptoms on the date of the end of fever, 2 (22.2%) with an interval of 1 - 2 days after the end of fever. Another 4 (44.4%) developed hemorrhagic symptoms days before the end of the fever. Among the suspected cases, 5 (55.5%) developed hemorrhagic symptoms on the date the fever broke, 2 (22.2%) with an interval of 1 to 2 days after the fever. Another 2 (22.2%) developed hemorrhagic symptoms days before the end of the fever.

Regarding the day of illness on which the hemorrhage occurred, in general, it was observed that in 9 (50%) of the cases the hemorrhage occurred between the 4th and 6th day of illness. 3 (16.7%) of the cases, hemorrhage occurred after 7 days, and correlated with laboratory diagnosis of malaria (2 cases = 11.1%) and respiratory infection (1 case = 5.6%). Overall, the median time from onset of illness to bleeding was 4 days. For suspected cases the median was 5 days, and for

confirmed cases the median was 4 days.

The time interval between symptom onset and hospitalization was calculated and it was observed that overall the median was 4 days. For those confirmed, the median 3.5 days. For those suspected, the median 4 days. Overall range 0 to 7 days. However, 4 (22.2%), *i.e.*, 2 (22.2%) of the suspected and 2 (22.2%) of the confirmed had previously sought health care assistance before the bleeding.

The analysis of the reasons for hospitalization revealed that the main reason exactly were hemorrhage in 4 (44.4%) in the confirmed cases and 3 (33.3%) in the suspected cases. Overall, hypovolemic shock in 3 (16.7%), convulsions in 2 (11.1%), respiratory failure in 2 (11.1%) were also present. Less frequent are the other categories encompassing: diarrhea and vomiting (5.6%), alarm signs of abdominal pain (5.6%) and malaria with bleeding (5.6%).

Regarding the alarm signs, in addition to hemorrhage, it was observed that platelet drop appeared in 66.7% of the confirmed cases and in 100% of the suspected cases, followed by hematocrit increase (14.3%) in the confirmed cases and in 11.1% of the suspected cases. Severe abdominal pain was found in 11.1% of suspected cases and irritability in 5.6% of suspected cases.

Laboratory diagnostics and clinical diagnostics:

In the approach of laboratory confirmed cases of dengue, according to the days of collection of samples for analysis, 5 (55.6%) patients collected sample in 5 days and had NS1 positive, 2 (22.2%) of cases with IgM and IgG collected between 3rd and 6th day. 2 (22.2%) cases of IgM and IgG collected between 6th and 7th day of the disease (Figure 1).

Among the suspects, 4 (44.4%) were tested for dengue with negative result, but by the clinic including fever and hemorrhagic manifestations, the suspected diagnosis of dengue was maintained. All cases were laboratory ruled out covid-19. All patients were submitted to plasmodia investigation, with 2 (11.1%) positive cases for plasmodium falciparum (F4/600 mm^3), 1 (5.6%) being a confirmed dengue case and 1 (5.6%) a suspected case. Both were diagnosed after the 7th day of the disease.

In hematological alterations, hemoconcentration was found in only 2 cases (11.1%), 1 confirmed case and 1 (5.6%) of suspected case, with values of 44.8% for women and 56% for men (Graph 2(a) and Graph 2(b)). In 16 (88.9%) of the cases hemoconcentration was not observed, despite the severity of the cases. More signs of hypochromic and microcytic anemia were observed.

16 (88.9%) of the cases presented thrombocytopenia. The platelet count showed a significant drop from the third day of the onset of symptoms, with a median of 52 thousand platelets between the third and sixth day of the disease Graph 2(c) and Graph 2(d). From day 7 on, the platelet count was over 50,000, a median of 68,000, ranging from 60,000 to 76,000. The drop that was observed in a late period, that is, after day 6 at a value of 12,000, is related to 1 patient (5.6%) who had coinfection with falciparum malaria (Graph 2(e)).

In the WBC curve of Acute Hemorrhagic Fever of the confirmed cases, it was

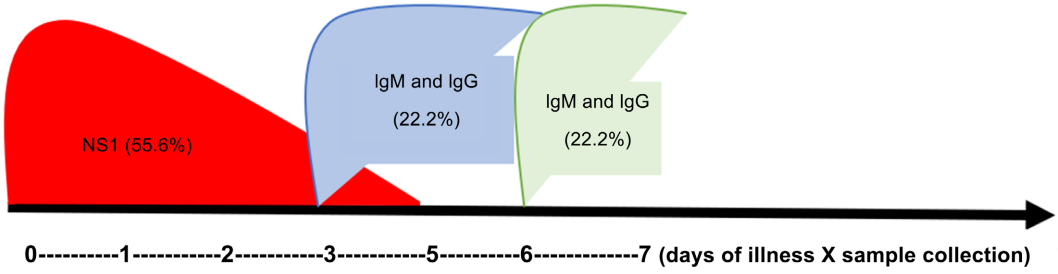
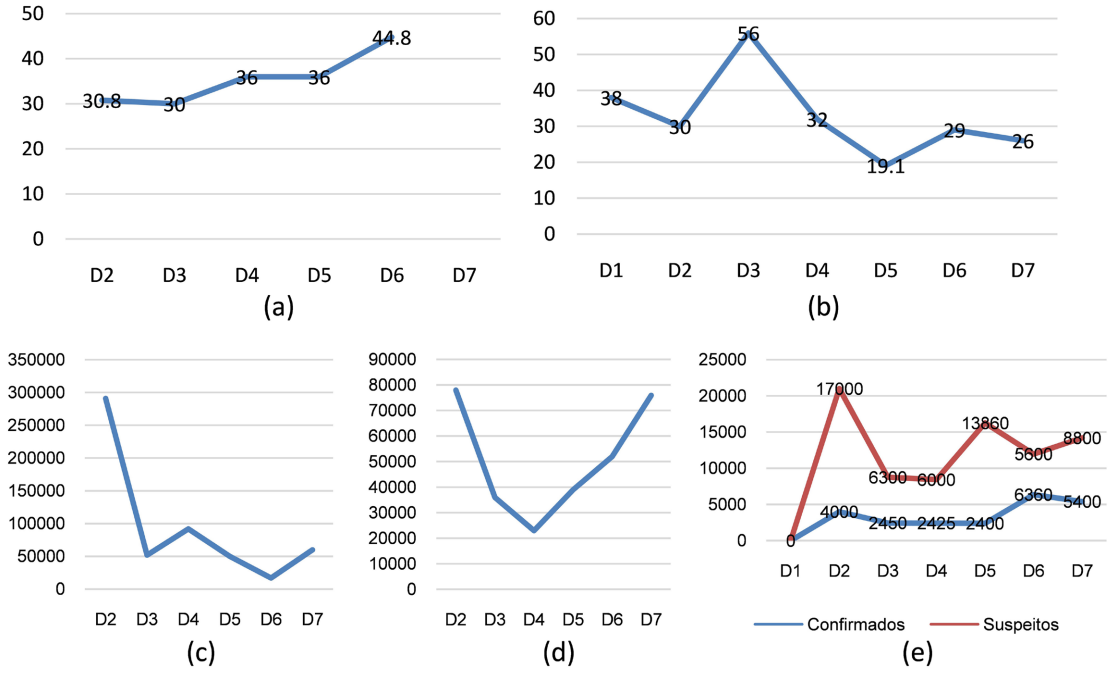


Figure 1. Results of dengue tests in relation to the examination period.



Graph 2. (a) Average hematocrit values in confirmed dengue cases in relation to the day of illness; (b) Average hematocrit values in suspected and confirmed dengue cases in relation to the day of illness; (c) Cases confirmed-evolution of platelets; (d) Suspected cases-evolution of platelets; (e) Median curve of WBCs in suspected and confirmed dengue cases.

observed that between the third and fourth day of illness the median WBC values remained equal to below 2450 cells, at the cutoff point defined for leukopenia. On the other hand, in the suspected cases, a median with normal WBCs was evidenced. Others with WBCs above normal, were post-body injury-vaginal delivery and use of invasive devices (Graph 2(e)).

Transaminases were increased from 5 to more than 10 times of normal values in critically ill patients undergoing these tests. The coagulogram profile as well as liver function including albumin were not analyzed because of reduced recording, however, there was prolongation of bleeding time in the case of coinfection of dengue and malaria. The renal functions were altered in all extremely severe cases.

Regarding imaging examinations, about 16.7% of cases of AHF (33.3% of the suspects) presented hypoxia/dyspnea associated with radiological changes of bi-

lateral alveolar infiltrates associated with hypertrophy of bilateral pulmonary hili, that is, 75% of those who presented hypoxia/dyspnea associated with febrile hemorrhagic picture (Figure 2).

According to the therapeutic conduct, all received volume replacement with crystalloid associated with symptomatic and supportive medications (analgesia, antihistamines, and 3 cases (16.7%) required oxygen therapy by cannula or face mask. 2 (11.1%) of the confirmed cases as well as the other 2 (11.1%) of the suspected cases received empirical antimicrobial (ceftriaxone, ciprofloxacin) for more than 72 hours. A considerable number of cases, *i.e.* 12 (66.7%) did not use antimicrobials or did so for less than 24 hours, being 6 (66.7%) confirmed and 6 (66.7%) suspected cases.

As for the outcomes of the cases, of the 18 cases with AHF, 13 (72.2%) were recovered (all confirmed dengue cases and 22.2% of the suspected cases) and 5 (27.8%) evolved to death (55.6% of the suspected cases).

Regarding the profile of the deaths, all the deaths were male (100%), and 83.3% were male suspects in the study. 2 (40%) were foreign residents. They were cargo-warehouse employees building construction (40%), sailor-fishermen (20%) and students (20%). It was not possible to identify the profession of 1 (20%) of the cases that died. 4 (80%) were healthy people, with epilepsy as the only comorbidity in 1 (20%) of the cases. 60% were of reproductive age between 20 and 39 years. 60% lived in the largest district (Água Grande). There was one case resident in the other island, *i.e.* the RAP (20%) and the 2nd most populous district, Mézochi (20%) (Figure 3(a)). All cases that died came to the hospital through a third party and were admitted in a very severe state of the disease, with hemorrhage and shock as the reasons for hospitalization for 4 (80%). Majority (3 = 60%) presented bleeding on day 4 to day 5 of the disease, another 1 (20%) on day 6 to day 7 of the disease and 1 (20%) on day 3 of the disease, and hospitalization occurred on day 5 of the disease in 80% of the cases. Three (60%) of the cases died in less than or equal to 24 hours and another two (40%) in 48 hours of hospitalization, being shock-multiorgan dysfunction the cause of death in four (80%) of the cases and respiratory failure in one (20%) (Figure 3(a) and Figure 3(b)).

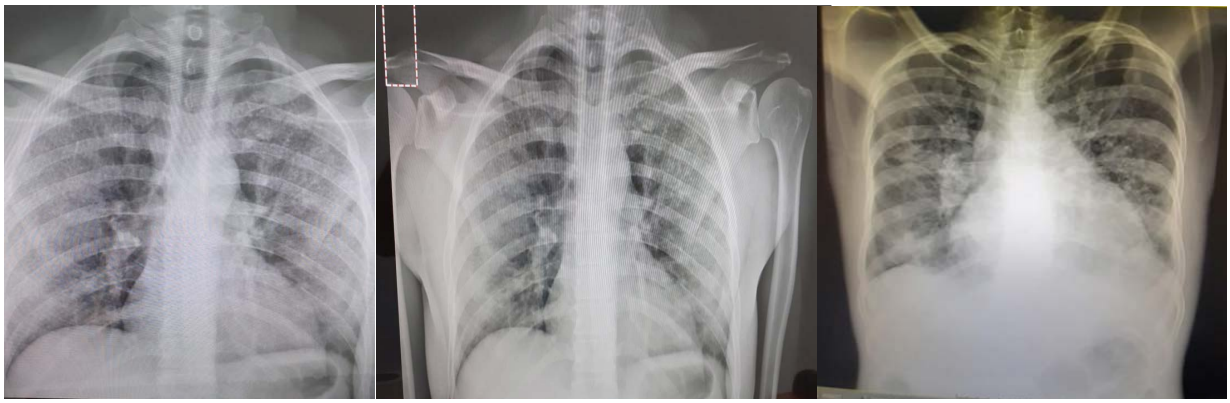
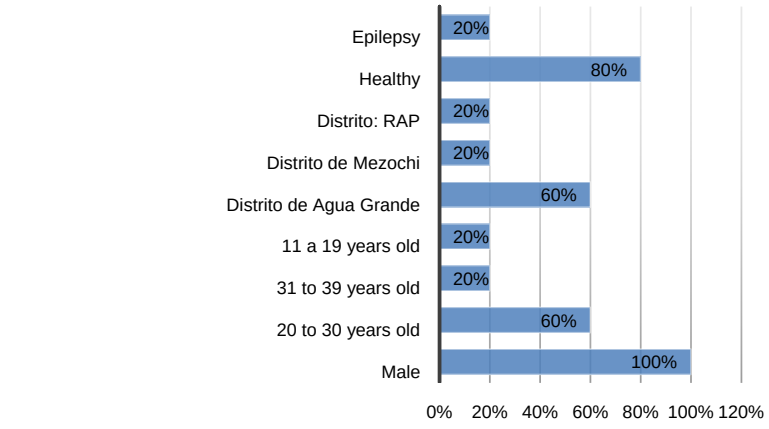
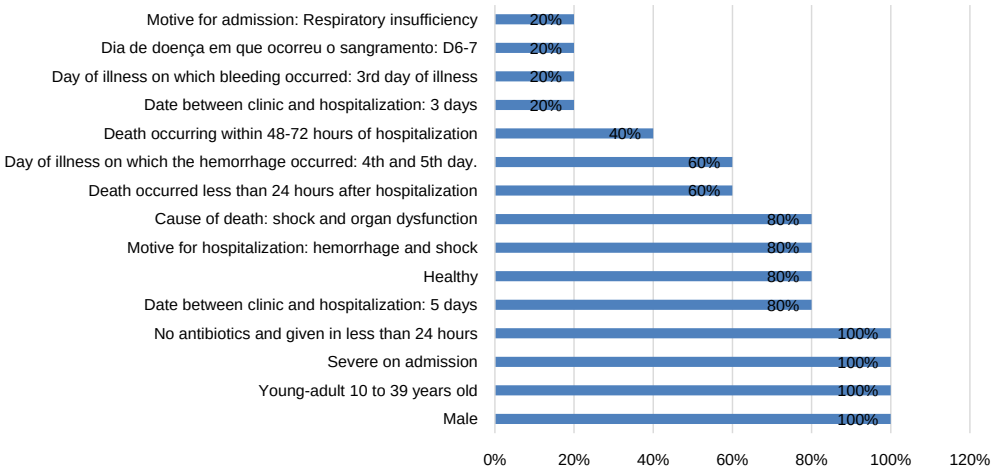


Figure 2. Chest X-ray of AHF patients who had hypoxia/dyspnea.



(a)



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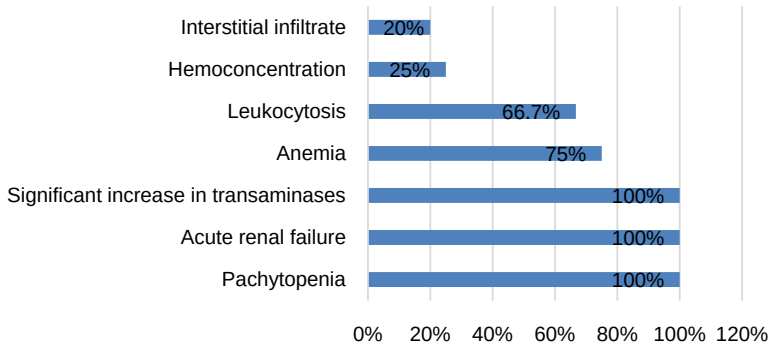

(c)

Figure 3. (a) Demographic information on deaths; (b) Profile of deaths-clinical information; (c) Profile of deaths-Radiological and laboratory changes.

Of radiological and laboratory changes, all (100%) had thrombocytopenia, acute renal failure and significantly increased transaminases, 75% had anemia, and 66.7% with leukocytosis. Hemoconcentration was found in 25% of people. In fewer cases, interstitial pulmonary infiltrate was found in 20% of cases (**Figure 3(c)** and **Figure 4**). 4 of the 5 cases were investigated for HIV with negative serology.

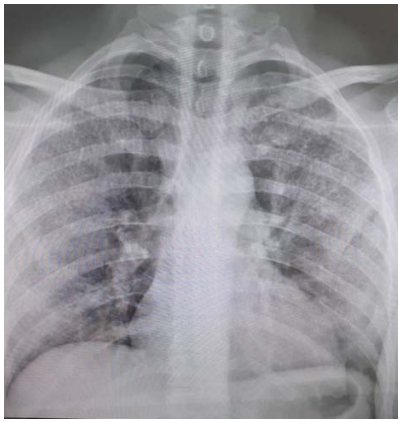

Figure 4. Radiological alteration.

The cases that died, 100% did not receive any antibiotics or the antibiotics were done within 24 hours of death.

On the other hand, regarding the profile of the 13 (72.2%) recovered, the age group with the highest proportion of recovered were those aged 30 - 49 years (61.6%), 9 (69.2%) were non-severe cases and 7 (53.8%) were apparently healthy. In 9 (69.3%) bleeding occurred between the third and fifth day of illness. Hemorrhage and monitoring-prostration and volume replacement were the main reasons for hospitalization in 11 (84.6%) of the cases, with record of hospitalization of majority, *i.e.*, 30.8% at the fourth day of illness. Of the laboratory alterations, 7 (77.8%) presented thrombocytopenia, 4 (30.8%) anemia. A considerable number of cases did not use antimicrobial agents; most of the cases were confirmed dengue cases, and 2 (11.1%) of the cases received antimalarial drugs.

The mean length of hospital stay was 5.1 days (range 3 to 8 days) for the confirmed cases and 4.7 days (range 0 to 12 days) for the suspected cases. 2 (22%) of the cases had a length of stay greater than 7 days and 3 (33.3%) of the suspected cases stayed more than 7 days.

4. Discussion

Hemorrhagic fevers are a diverse group of diseases caused by RNA viruses and a variety of bacteria, such as Rickettsiae, and plasmodia [1] [2] [5] [14] [15] [16]. In the 6-month period, In Sao Tome and Principe, had 18 cases of AHF from December to May 19, 2022, with 50% of cases with laboratory confirmation for dengue and another 50% suspected dengue cases, and 2 (11.1%) coinfected with malaria.

In the country, acute hemorrhagic fever (AHF) was characterized by fever and hemorrhagic manifestations with variable severity presentation and considered of high lethality (27.8%). Although there were no cases of dengue deaths in the period, overall, if we consider all other suspected cases as dengue, our lethality rate would be higher than AHF for dengue cases in the literature, which is 0.3% - 4% (2.5%) [17] [18], lassa fever (1% - 15%) and rift valley fever (1%) [16] [19]. These agents usually have a mortality rate of approximately 1% [20]. However,

our data is closely equivalent to yellow fever (20% - 50%), hantavirus (up to 46%), rickettsiosis, leptospirosis (10% - 50%), malaria (4% - 26%) and crime-congo fever, etiologic agents that can cause a severe form of AHF, with a mortality rate greater than or equal to 15% [20] [21].

In the literature, the main cause of AHF is hemorrhagic dengue fever [18] [22] [23]. But, depending on the context and the epidemiologic course, several other groups of viruses and other agents can cause fever and other symptoms that are accompanied by heavy bleeding. In this study we observed dengue virus infections in 9 (50%) of the cases. However, the etiologic agent could not be identified in another 9 (50%) of AHF patients, although coinfection with malaria was identified in 2 patients (11.1%). Thus, these data may reveal the complexity of the pathogens causing AHF and suggest the possible presence of other commonly unknown human pathogens in the geographical territory of São Tomé and Príncipe. Therefore, it is clear that additional studies and laboratory investigation are needed to establish appropriate diagnostic tests.

However, at the present time, according to the mode of transmission and incubation period and background, it is possible to rule out Ebola/Marburg [24]. Because, to date, according to information from the STP surveillance service, no similar cases of transmission have been recorded during the 3-week margin of follow-up of case contacts in December/2021, and there is no evidence of a picture in a similar "outbreak" of possible transmission during care in hospital units when managing suspected cases with barrier deficit protection.

We analyzed the epidemiological characteristics, our AHF cases occurred in the last month of the year (11.1%) and in the first 5 months of the years (88.9%), being the study month, with an increase of cases in April and May, concurrent with the rainy season in the country. These data suggest that human behavior in rainy seasons and season with risk of increased rodent infestations in households. In addition, the period concurred with the proliferation of ticks/ticks in the country, and the country's climate interspersed with heat and humidity, may justify the increased risk of exposure to ticks and mosquitoes. Thus, the seasonality of the disease may provide some useful indications for diagnosis [25] [26] [27]. Due to favorable ecological conditions and low socioeconomic status throughout STP, the population often becomes the main victims of zoonoses, including hantavirosis, leptospirosis, malaria, in addition to dengue. Thus, our data strongly reinforces the need for surveillance coupled with specific laboratory strengthening to prevent the spread of cases.

It is noted that dengue cases were reported in April and increase in May/2022, a period similar to the literature, because sozanality for dengue involves the first 5 months [28] [29] [30] [31]. It is expected that a decrease in cases from June onwards will occur coinciding with the dry season. Tsai-YingYen, and collators, in 2004, confirmed the prevalence of dengue in the country through an immunofluorescence assay that 31 samples (39.74%) were found positive for dengue virus antibodies, and presence of active cases by IgM and NS1, including secondary dengue infection. The assay showed that 53 samples (67.95%) were posi-

tive for dengue IgG, and 38 samples (48.72%) were positive for NS1 and IgG. A prevalence of 35.9% was thus determined for dengue IgG, and, one sample was positive for dengue IgM. In addition, cross-reactions with other flaviviruses showed stronger absorbance against Japanese encephalitis virus and West Nile virus. These results demonstrated exposure to DENV [32].

Overall, although there was no difference between genders, but among the confirmed cases of dengue, females were the most affected (66.7%), the same was identified in other studies in the literature, probably explained by the fact that women seek health services more often [33] [34]. In the suspected cases, the predominance was for males. This can be explained by the low regular demand of men to the services, attending only in acute-severe cases and accompanied by a third party [33] [34]. However, both sexes are susceptible to developing AHF regardless of the cause, and no cause can be ruled out based on sex.

We noticed a higher frequency of cases in adulthood (83.3%), followed by adolescence (11.1%), and with a lower frequency in childhood (5.6%). The age of individuals ranged from 2 - 59 years overall, with an average of 35.2 years in confirmed cases and 31.9 years for suspected cases. In case of dengue, we identified the similarity in several studies by Mendonça et al, which shows us that the age group most affected by dengue was adults 30 years and older followed by adolescent-youth [35] [36].

Most (61.1%) of the cases come from both the most populous districts of the country (Agua Grande and Mezóchi). This may be related to the population increase and tendency to urbanization, in an underdeveloped country, adding the agglomeration of houses, often with poor sanitation, conditioning the proliferation and dissemination of vectors and reservoirs of different diseases causing AHF [37] [38].

In the literature, chronic comorbidities related to cardiovascular disorders, diabetes, chronic lung diseases are associated with higher severity. But in our study, most (66.7%) of the subjects were healthy, similar to the study of with comorbidities found in only about 9.7% of cases [39] [40] [41] [42] [43]. Pregnancy-puerperium, obesity, epilepsy, drepanocytosis were associated with the main factors, but in small numbers of cases. Information making it difficult to exclude the main causes of AHF mentioned.

Majority of AHF were considered severe (61.1%), however, keeping as suspected case, without conclusion of diagnosis. Suspected cases were the most severe (88.9%) compared to confirmed cases for dengue (33.3%). Severity for AHF is variable depending on the etiologic agents involved [44]. However, our proportion of severity is shown to be higher than literature data in AHF cases from dengue, where severity is 3.45% (2.6% - 5.2%), leptospirosis (5% - 10%), Rift fever (2%), and proximately equivalent to yellow fever (15% - 25%), lassa fever, hantavirus, rickettsiosis, malaria (4-26%), and crime-congo fever [17] [18] [19] [20] [21] [44]. Clearly, more effort is needed to prevent severe AHF in STP.

It was observed that fever and convulsion, with 88.9% and 11.1% respectively, were the first symptoms that appeared, and more than 50% had high fever, as-

thenia, myalgia, headache, lethargy, nausea, vomiting, and diarrhea. To a lesser extent, exanthema, convulsion, arthralgia, low back pain, chills, and chest pain were present. Therefore, these are all often nonspecific symptoms found in the initial phase of different forms of AHF [44] [45] [46], and it is impossible to rule out the causes cited by clinical information alone. Having Ebola/Marburg, already ruled out, however, by clinical information, one could "rule out" also, Ricksetsiosis considering the limited presence of one of the triads (exanthema) which is usually frequent in 88% to 90% of cases [8] [9] [11] [12]. But, important to keep it as one of the differential diagnoses of AHF for laboratory discard. However, dengue, malaria, yellow fever, lassa fever, hantavirus, leptospirosis, rift valley fever, and Crimean-Congo fever should strongly prevail in the diagnostic suspicion of the existence of more than one circulating agent in the country causing AHF. Although STP has yellow fever vaccination coverage above 90%, the 3 cases (16.7%) of severe AHF involved foreigners with unknown vaccination history.

The duration of fever on average of 4.9 days for confirmed and 5.1 days for suspected, with a range of 2 to 8 days are similar in all other diseases causing AHF [3] [44] [45] [46] [47], where the duration usually follows around 7 days, making us maintain the suspicion of the need to investigate other causes of AHF besides dengue. The report of fever longer than 7 days involved a case of coinfection with malaria with defervescence after antimalarial, a typical evolution of plasmodium infection [13].

The digestive tract, vaginal and urethral tracts were the topographies most affected by spontaneous visible bleeding in this study. The frequency of bleeding site varied according to severity, which in more severe cases presented more than one bleeding site, which may relate to higher platelet consumption due to disseminated vascular coagulations, increased incidence of antiplatelet antibodies or thrombolysis by complement often found in all viral and some bacterial AHF [48] [49] [50]. Majority *i.e.* 12(66.7%) presented bleeding between same day or up to 2 days after the end of fever, a picture similar to that reported in other AHF diseases, and viral causes cannot be ruled out. However, another 6 (33.3%) presented 2 to 6 days before the end of fever, so the need to investigate other situations, such as hantavirosis and leptospirosis [44] [51], even malaria [52].

Regarding the day of illness on which the bleeding occurred, it was observed that most cases of bleeding occurred between the 4th and 5th day of illness for both suspected and confirmed cases of dengue fever. The text would look like this: "The occurrence of hemorrhage between the 4th and 5th day of illness onset is notable in various causes of hemorrhagic fever." The bleeding after 7 days in those coinfected by malaria (11.1%) and by respiratory conditions (5.6%) is an alert for a considered number of cases. This situation is not naturally found in cases of malaria, but may be present in clinical events of leptospirosis and hantavirosis [44] [51] [52].

Overall, the average time between onset of illness and bleeding was 4.2 days.

For suspected cases the average was 4.6 days, and for confirmed cases, the average was 3.4 days. And, the time interval between the onset of symptoms and hospitalization was a median of 4 days, ranging from 0 to 7 days. In addition, 22.2% had previously sought health care assistance before the bleeding. The main reasons for hospitalization were bleeding (33.3%) and shock (16.7%). Platelet drop was the main alarm sign. Thrombocytopenia was the most frequent alarm sign, found in 80% of cases.

Taking into account that the probability of worsening occurs around the 4th day, this information shows us the need to reinforce risk communication actions as prevention measures for the main causes of AHF, as well as community engagement actions regarding the prevention of the severities according to the evolutionary time of the disease, in addition to regular training of professionals regarding the early recognition of alarm signs and preventive and control measures.

We can consider that 55.6% of the patients who collected sample within 5 days and had positive NS1, had primary dengue. Another 44.4% had IgM and IgG (22.2% of cases collected between day 3 and 6 and 22.2% of cases collected between day 6 and 7 of the disease). Normally, AHF caused by dengue virus occurs in secondary dengue. No association of IgG and NS1 positives was found simultaneously to warrant possible secondary dengue. IgM and IgG found after the third day of the disease does not guarantee secondary dengue, or only evolution of primary dengue. Therefore, it is necessary to investigate other causes of AHF in the laboratory. However, Tsai-YingYen, and colleagues, in 2004, confirmed the prevalence of dengue in the country by an immunofluorescence assay that found 31 samples (39.74%) positive for dengue virus antibodies, and the presence of active cases by IgM and NS1, including secondary dengue infection. The assay showed that 53 samples (67.95%) were positive for dengue IgG, and 38 samples (48.72%) were positive for NS1 and IgG. A prevalence of 35.90% was thus determined for dengue IgG, and, one sample was positive for dengue IgM. In addition, cross-reactions with other flaviviruses showed stronger absorbance against Japanese encephalitis virus and West Nile virus. These results demonstrated previous dengue exposure to the country [32].

The existence of 4(44.4%) suspected cases with negative diagnosis for dengue, reinforces us to suspect the existence of other causes of circulating AHF.

There are no commercial kits for the diagnosis of various causes of AHF, and the specific diagnoses are only available in specialized laboratories abroad, because, in the country they lack the specific reagents for the diagnosis of various causes of AHF, except dengue by rapid test, which clearly contributes to the high rate of suspicious diagnoses observed here. In addition, the absence of distinctive clinical signs and symptoms in the early phase of the disease increases the suspicious diagnoses. Also, milder or asymptomatic cases may exist that would not be detected by surveillance. Thus, the actual numbers of AHF cases may be several times higher than those reported. Thus, our data highlight the urgent need for

diagnostic reagents, while a better understanding of the clinical features of each AHF disease is also likely to improve its diagnosis.

It was observed that because of the recent dengue notification in the country, the case of co-infection with malaria was investigated late after clinical improvement. Having the country with the endemic record of malaria, the covid-19 pandemic and the current emerging dengue epidemic, important, create strengthen the diagnostic strategy for the 3 diseases simultaneously in order to avoid delays in diagnosis [53] [54] [55] [56].

Focusing for severe dengue in all cases, our data show that in 88.9% of cases hemoconcentration was not observed, despite the severity of the cases, similar to the study conducted at Fiocruz-Brazil in which only 23% of AHA patients had hemoconcentration, the standard percentage adopted by the WHO. If we were to use only this test to denominate whether or not a patient might have hemorrhagic dengue, we would underestimate the number of cases [57]. However, severe dengue usually happens by plasma extravasation with representation of increased hematocrit [52]. The difficulty in classifying patients as dengue hemorrhagic fever (DHF) using this criterion is great even in severe forms of the disease [57]. On the other hand, more signs of hypochromic and microcytic anemia were observed, compatible with those found in malaria cases [53] [56] [58] [59], with the need to raise the diagnosis more robustly and "genotyping" for plasmodium, given that plasmodium malaria was negative in 88.9%. Usually, falciparum malaria is the most severe. Although not usual in STP, but severe forms of malaria can also occur in P. vivax malaria [53] [56] [59]. In some regions of the world, P.vivax infection shows high prevalences of severe anemia (19% - 89%), which is often attributed to repeated frequent relapses or chronic infections. Some series showed high frequency of other severe manifestations (in 4-26% of severe cases), renal failure (4% - 45%), shock - (0% - 54%), significant jaundice (0% - 59%), abnormal bleeding (0% - 11%); often with severe thrombocytopenia, and, in one series, frequent hypoglycemia (13%).

88.9% presented thrombocytopenia, and the platelet count showed a significant drop from the third day of the onset of symptoms, with minimum values of 12 thousand and maximum of 75 mim, with a median of 52 thousand platelets between the third and sixth day of the disease. From day 7 on, the platelet count was over 50,000, median 68,000, ranging from 60,000 to 76,000. The drop that was observed in a late period, that is, after day 6 at a value of 12,000, is related to patients who had coinfection with falciparum malaria. Of course, thrombocytopenia can be present in all the mentioned diseases and correlates with the presence of increased antiplatelet antibodies [52]. In this study, no patient with thrombocytopenia received platelet transfusion. Given the data analyzed, thrombocytopenia is showing us as a biomarker of severity, especially, in the period between the 3rd and 6th day of the disease. This shows us, on one hand, the need for the training of health professionals to reinforce the role of prevention, early diagnosis, and treatment, according to the classification of severity and se-

verity markers. And, on the other hand, the need for accessibility of platelets for the necessary cases through the ideal recommendation, taking into account that platelet transfusion may be indicated to favor tamponade at the site of bleeding and not to increase the platelet blood count, because these suffer destruction in the short term [60].

In the leukocyte curve of AHF of the confirmed cases, it was observed that between the third and fourth day of illness the median of leukocyte values remained below 2050 cells, the cutoff point defined for leukopenia. On the other hand, in the suspected cases, a median with normal leukocytes was evidenced. Others with leukocytosis, were in patients in post-body injury and use of invasive devices, and may be associated with bacterial infection. It is noticed that leukocytosis, a laboratory finding suggestive of bacterial infection, can be found with relative frequency in patients who evolve severely, and that the suspicion of dengue or other viral infections susceptible to hemorrhage should not be ruled out, and other therapy installed, if there are concomitantly other clinical signs of the disease. It is a parameter that should be further observed and studied, in order to provide better understanding of the pathophysiology of the disease and enable appropriate therapeutic interventions with better prognosis for the patient.

Transaminases were increased between 5 to more than 10 times of normal values in patients undergoing these tests. It makes us reinforce the suspicion of the previously mentioned infections for investigation and not merely dengue [60] [61] [62] [63] [64].

According to the result, about 16.7% of the cases of AHF had hypoxia/dyspnea associated with radiological changes of bilateral alveolar infiltrates. Of those who had hypoxia/dyspnea associated with febrile hemorrhagic picture, 75% of these, had radiological changes of bilateral interstitial and alveolar infiltrates. Making it a challenge to diagnose, considering that these are lesions that lead us to think of a leptospirosis or hantavirosis that usually the pulmonary involvement is characterized by pulmonary hemorrhage, or malaria by the characteristic of pulmonary edema/interstitial infiltrates. In yellow fever it is not common to cause respiratory picture with visible radiological lesion, and it is necessary to challenge the laboratory investigation [62] [65] [66]. All of these suspected cases with respiratory picture had negative dengue test, and the clinic is not favored by common dengue, because in dengue pleural effusion or ground-glass opacity or consolidation is more frequent [62]. However, even if they tested positive for dengue, dengue viral genotyping would be important for the purpose of clarification, adjustment of clinical management, and strengthening surveillance.

Most cases recovered (72.2%), however, 27.8% progressed to death. That is, 55.6% of suspected cases, and no deaths were recorded among the confirmed cases of dengue fever. If we take into consideration that these are cases of dengue hemorrhagic fever, our proportion of lethality is very high, because data in the literature on dengue lethality range from 0.3% to 4%, and the World Health Or-

ganization considers acceptable a lethality for DHF of up to 1%.

However, the lethality proportion fits with literature reports for yellow fever (20% - 50%), leptospirosis (10% - 50%), hantavirus (up to 46%), congo-crimea (20% - 50%) and lassa fever. No cases of malaria-associated AHF lethality have been found, but one study has shown AHF from vivax malaria to be between 0% - 26%. This shows that AHF in STP is not only due to dengue, and STP has reservoirs and sanitary conditions favorable for the transmission of dengue (aeds spp and cases), malaria (anopheles sp and cases), leptospirosis and hantavirosis (rodent droppings and possible cases). Although yellow fever is preventable and the country has high coverage for it, the evidence of cases, including death in 2 of 3 foreign individuals with unknown vaccine esquema, makes it difficult for us to eliminate the yellow fever hypothesis.

It alerts us because all the deaths were male (100%), 80% of the suspected male cases, majority in the adult-youth age, including 1 teenager, majority residing in the largest and most populated capital city, and majority healthy (80%). Being male and in the young age is justified by the low demand of these age groups to health services. Need of an awareness strategy in the preventive approach in relation to the male gender.

All were admitted in the severe stage of the disease and late to the 5th day of the disease (80%), where the bleeding appeared between the 4th and 5th day of the disease with shock and another important alarm sign. 80% were hospitalized for bleeding and shock, 20% for respiratory failure.

Of these, 2 (40%) died on the same day of hospitalization and shock, 1 (20%) had a 1 day interval between hospitalization and shock, 1 (20%) died 2 days after hospitalization and shock, and 1 (20%) died 2 days after hospitalization and respiratory failure. It is important to further analyze the association of non-use of antimicrobial or use after severity of cases.

Our data predominated in males. In hemorrhagic dengue, lethality is higher in women (70%) and adult age (96.7%) [57]. It hypothesizes to us that we may be facing AHF by: Any viral or rodent-borne disease.

4 (80%) of the deaths were hospitalized by day 5 of the disease and the time between hospitalization and death occurred in less than 24 hours for 60% of the cases consequent to shock and multiorgan damage, and in 48 hours in 40% of the cases as a consequence of shock (20%) and respiratory failure (20%). Alert us by: All admitted in serious condition, late, on the 4th or 5th day of the disease, in shock or other important alarm sign. It hypothesizes that we may be facing AHF from any viral or rodent-borne disease, and shows us the need for communication to raise awareness of the alarm signs.

All deaths had thrombocytopenia (100%), acute renal dysfunction (100%), and significantly increased transaminases (100%), and most had anemia (75%) and leukocytosis (66.7%). According to the analysis of published articles, 68.5% to 82% of hemorrhagic cases had thrombocytopenia. Thrombocytopenia may be present in all viral diseases cited and correlates with the pathophysiology of viral

diseases, demonstrating the presence of disseminated vascular coagulations, increased incidence of antiplatelet antibodies, or thrombolysis by complement. The evolving clinical course demonstrates multiorgan dysfunction, especially affecting the liver and kidneys, in addition to the associated neurological picture. Thrombocytopenia, changes in transaminases, renal dysfunction and anemia demonstrate us as biomarkers of severity for death in STP by AHF.

The treatment of AHF involved the use of general supportive measures and the viral ones, the use of specific antivirals [62]. In this study, all patients confirmed for dengue and suspected (100% of cases) received supportive therapy when needed, and no patient was treated with any antiviral. In addition, antibiotics including ceftriaxone and ciprofloxacin were used empirically. Despite these measures, five (27.8%) patients with suspected AHF died.

The absence of specific tests to investigate other causes of Acute Hemorrhagic Fever, besides tests for dengue and malaria, was the main limitation of this study.

5. Conclusions

Clearly, a better understanding of the clinical features of Acute Hemorrhagic Fever (AHF) diseases is central to better diagnosis and treatment.

It is concluded that dengue is equivalently predominant in causing 50% of the cases of AHF in STP, and malaria was also found, presumably in the coinfection mode. But besides dengue, there are possibly other causes of AHF in STP, as it is important to note that the etiologic agents could not be determined in 50% of AHF cases. The clinic is nonspecific for many AHF infections. These data therefore highlight the complexity of the pathogens that cause human HF. The lethality is considered high (27.8%) in general terms, but fits with respect to dengue cases at 3%.

It is possible to rule out diseases transmitted by direct contact with biological material. However, it indicates that the country faces a significant number of cases of diseases transmitted by arboviroses or contact with rodent excrement. Emphasis is placed on the need to extend the suspicion and laboratory diagnostic investigation to other infections that cause AHF in addition to dengue, especially leptospirosis and hantavirus. In addition, due to the varied severity, it is important to rule out by viral panel, Congo-Creole hemorrhagic fever, Rift Valley fever, and Lassa virus, as a way to better outline the case management and surveillance system of AHF in the country. It is necessary to promote health education by making the community an active part in the process of combating and preventing vectors and, consequently, AHF.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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