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Review Article

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Epidemiology of Acute Liver Failure Attributable To Viral Infections in Sub-Saharan Africa: A Systematic Review

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Abstract

Viral hepatitis remains the leading cause of acute liver failure (ALF) in Asia and Africa, Sub-Saharan Africa (SSA) inclusive. Data on viral hepatitis-induced ALF is scarce, and systematic screening for rare viral causes is infrequent. This systematic review aims to determine the epidemiological, clinical, therapeutic, and prognostic profiles of viral hepatitis-induced ALF in SSA in the last four decades. We conducted a systematic review using the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Records were obtained through an electronic search of MEDLINE (PubMed), EMBASE, SCOPUS, and African Journals Online (AJOL) databases for all relevant studies published from database inception to September 21st, 2023. A total of 16,059 articles were identified from our initial search and 11 studies from 6 countries were included in our final analysis. One hundred and fifty-two cases of viral hepatitis-induced ALF were recorded from 1982-2022. The most frequent causes were hepatitis A virus (HAV) with 62 cases (40.8%), hepatitis E virus (HEV) with 54 cases (35.5%), and hepatitis B virus (HBV) with 18 cases (11.8%). HAV was the most frequent cause in children, HEV in pregnant women, and HBV and HEV in adults in general. Treatment was mainly supportive and liver transplantation was only reported in studies from South Africa. In the last four decades, HAV has been the leading cause of viral hepatitis-induced ALF in the pediatric population. HEV and HBV account for cases in adults while HEV is frequently reported in pregnant women. Treatment is mainly supportive; liver transplantation is not readily available, and the case fatality rate remains high. These findings highlight the need for implementing routine HAV immunization in expanded programs on immunization available in SSA, especially for children, and routine screening for HEV in pregnant women in HEV endemic zones.

Keywords: Acute Liver Failure, Viral Hepatitis, Viral Infections, Sub-Saharan Africa, Epidemiology

1. Introduction

Acute liver failure (ALF) is commonly defined as the concomitant presence of a coagulation abnormality evidenced by an international normalized ratio (INR) value ≥1.5 and any degree of mental alteration (encephalopathy) in a patient without cirrhosis or pre-existing liver disease and with an illness of ≤26 week`s duration [1,2]. In paediatric subjects, hepatic encephalopathy is not a mandatory definition criterion [3-5]. Drug-induced and viral hepatitis are the most common causes of ALF worldwide [6]. The main viruses responsible for ALF are Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), and Hepatitis E Virus (HEV) [7,8]. However, hepatitis C virus (HCV), hepatitis D Virus (HDV), cytomegalovirus (CMV), Epstein Barr Virus (EBV), Herpes Simplex Virus (HSV), Parvovirus B19, and adenovirus have also been incriminated [8-11]. Other causes of ALF include vascular disorders, toxins, herbal supplements, pregnancy-related disorders (HELLP syndrome and pregnancy-associated steatosis), immune-mediated disorders, malignancies, and metabolic disorders like Wilson disease [1,4,5,7].

The global annual incidence of ALF ranges from 62.9 per 1000,000 to 1.13 per 100,000 population [12,13]. In the European population, viral hepatitis-induced ALF accounts only for 19% of all ALF cases [8]. This is largely due to the implementation of universal HBV and HAV immunization programs in Europe and the United States [7]. In Asia and South America by contrast, the frequency of viral infections among causes of ALF remains high, with viral infections being the first cause of ALF [14,15].

Population-and/or registry-based studies on the incidence and prevalence of viral hepatitis-induced ALF in sub-Saharan Africa (SSA) are scarce as systematic screening for rare viral causes is infrequent. However, SSA, Asia, and South America remain

epicenters of the most common viral infections responsible for ALF [16-19]. The burden of viral hepatitis-induced ALF in SSA may therefore be at least as high as in Asia and South America. Considering the lack of comprehensive data synthesis on viral hepatitis-induced ALF in SSA, we conducted this systematic review to provide data on the overall frequency, etiology, clinical features, treatment and outcomes of ALF attributable to viral infections in sub-Saharan Africa.

2. Methods

2.1. Design

We conducted this systematic review using the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. This review was registered in The International Prospective Register of Systematic Reviews (PROSPERO, CRD42023399270).

2.2. Data sources and literature search

Records were obtained through an electronic search of MEDLINE (PubMed), EMBASE, SCOPUS, and African Journals Online (AJOL) databases for all relevant studies published from database inception to September 21st, 2023. The search of articles in Google Scholar proved inefficient as previously observed by other authors [21]. The search strategy was initially built for PubMed following recommendations for developing effective search strategies and then adapted to the other databases (supplementary data table I) [21]. Briefly, the core of the search included a combination of acute liver failure, viral hepatitis, and a list of sub-Saharan African countries as key terms and/or Medical Subject Headings (MeSH). No language restrictions were used [22].

#1	PubMed	"acute liver failure"[All Fields] OR "fulminant hepatitis"[All Fields] OR "fulminant hepatic failure"[All Fields] OR "acute hepatic failure"[All Fields] OR "ALF"[All Fields]
	Embase	'acute liver failure' OR 'fulminant hepatitis' OR 'fulminant hepatic failure' OR 'acute hepatic failure' OR alf
	Scopus	“acute liver failure” OR “fulminant hepatitis” OR “fulminant hepatic failure” OR “acute hepatic failure” OR alf
#2	PubMed	"hepatitis"[All Fields] OR "viral hepatitis"[All Fields] OR "hepatitis A"[All Fields] OR “HAV”[All Fields] OR "hepatitis B"[All Fields] OR "HBV"[All Fields] OR "hepatitis C"[All Fields] OR "HCV"[All Fields] OR "hepatitis D"[All Fields] OR "HDV"[All Fields] OR "hepatitis E"[All Fields] OR "HEV"[All Fields] OR "herpes simplex virus"[All Fields] OR "HSV"[All Fields] OR "Epstein-Barr virus"[All Fields] OR ("herpesvirus 4, human"[MeSH Terms] OR "human herpesvirus 4"[All Fields] OR "ebv"[All Fields]) OR "CMV"[All Fields] OR ("cytomegalovirus"[MeSH Terms] OR "cytomegalovirus"[All Fields] OR "cytomegaloviruses"[All Fields]) OR ("adenoviridae"[MeSH Terms] OR "adenoviridae"[All Fields] OR "adenovirus"[All Fields])
	Embase	hepatitis OR 'viral hepatitis' OR 'hepatitis a' OR 'hepatitis b' OR hbv OR 'hepatitis c' OR hcv OR 'hepatitis d' OR hdv OR 'hepatitis e' OR hev OR 'herpes simplex virus' OR hsv OR 'epstein-barr virus' OR ebv OR 'Epstein Barr virus'/exp OR cmv OR cytomegalovirus OR 'Cytomegalovirus'/exp OR adenoviridae OR adenovirus OR 'Adenoviridae'/exp
	Scopus	"hepatitis" OR "viral hepatitis" OR "hepatitis A" OR “HAV” OR "hepatitis B" OR "HBV" OR "hepatitis C" OR "HCV" OR "hepatitis D" OR "HDV" OR "hepatitis E" OR "HEV" OR "herpes simplex virus" OR "HSV" OR "Epstein-Barr virus" OR "human herpesvirus 4" OR "ebv" OR "CMV" OR "cytomegalovirus" OR "adenoviridae" OR "adenovirus"

#3	PubMed	"sub-saharan africa"[All Fields] OR "Sub-saharan african"[All Fields] OR "SSA"[All Fields] OR "subsaharan africa"[All Fields] OR "subsaharan african"[All Fields] OR "africa*"[All Fields] OR "Eastern Africa"[All Fields] OR "east african"[All Fields] OR "east africa"[All Fields] OR "Eastern african"[All Fields] OR "British indian ocean territory"[All Fields] OR "burund*"[All Fields] OR ("comoros"[MeSH Terms] OR "comoros"[All Fields] OR "comoro"[All Fields]) OR "djibout*"[All Fields] OR "eritrea*"[All Fields] OR "ethiopia*"[All Fields] OR "French southern territories"[All Fields] OR "kenya*"[All Fields] OR "madagasca*"[All Fields] OR "malaw*"[All Fields] OR "mauriti*"[All Fields] OR ("comoros"[MeSH Terms] OR "comoros"[All Fields] OR "mayotte"[All Fields]) OR "mozambi*"[All Fields] OR ("reunion"[MeSH Terms] OR "reunion"[All Fields] OR "reunions"[All Fields]) OR "rwanda*"[All Fields] OR ("seychelles"[MeSH Terms] OR "seychelles"[All Fields]) OR "somalia*"[All Fields] OR "south sudan"[All Fields] OR "south sudanese"[All Fields] OR "uganda*"[All Fields] OR "tanzania*"[All Fields] OR "zambia*"[All Fields] OR "zimbabw*"[All Fields] OR "middle africa"[All Fields] OR "Middle african"[All Fields] OR "angola*"[All Fields] OR "cameroon*"[All Fields] OR "Central african republic"[All Fields] OR ("chad"[MeSH Terms] OR "chad"[All Fields]) OR "congo*"[All Fields] OR "equatorial guinea"[All Fields] OR ("gabon"[MeSH Terms] OR "gabon"[All Fields]) OR "sao tome and principe"[All Fields] OR "southern africa"[All Fields] OR "southern african"[All Fields] OR "bostwana"[All Fields] OR ("eswatini"[MeSH Terms] OR "eswatini"[All Fields]) OR ("lesotho"[MeSH Terms] OR "lesotho"[All Fields]) OR "namibia*"[All Fields] OR "south africa"[All Fields] OR "south african"[All Fields] OR "west african"[All Fields] OR "west africa"[All Fields] OR "western africa"[All Fields] OR "western african"[All Fields] OR ("benin"[MeSH Terms] OR "benin"[All Fields] OR "benin s"[All Fields]) OR ("burkina faso"[MeSH Terms] OR ("burkina"[All Fields] AND "faso"[All Fields]) OR "burkina faso"[All Fields]) OR "cabo verde"[All Fields] OR ("cote d ivoire"[MeSH Terms] OR ("cote"[All Fields] AND "d ivoire"[All Fields]) OR "cote d ivoire"[All Fields]) OR "ghana*"[All Fields] OR "guinea*"[All Fields] OR ("guinea bissau"[MeSH Terms] OR "guinea bissau"[All Fields] OR ("guinea"[All Fields] AND "bissau"[All Fields]) OR "guinea bissau"[All Fields]) OR "liberia*"[All Fields] OR "mali*"[All Fields] OR "mauritania*"[All Fields] OR "niger*"[All Fields] OR "Saint helena"[All Fields] OR "senegal*"[All Fields] OR "sierra Leone"[All Fields] OR "togo*"[All Fields]
	Embase	'sub-saharan africa' OR 'sub-saharan african' OR ssa OR 'subsaharan africa' OR 'subsaharan african' OR africa* OR 'eastern africa' OR 'east african' OR 'east africa' OR 'eastern african' OR 'british indian ocean territory' OR burund* OR djibout* OR eritrea* OR ethiopia* OR 'french southern territories' OR kenya* OR madagasca* OR malaw* OR mauriti* OR mozambi* OR rwanda* OR somalia* OR 'south sudan' OR 'south sudanese' OR uganda* OR tanzania* OR zambia* OR zimbabw* OR 'middle africa' OR 'middle african' OR angola* OR cameroon* OR 'central african republic' OR congo* OR 'equatorial guinea' OR 'sao tome and principe' OR 'southern africa' OR 'southern african' OR bostwana OR namibia* OR 'south africa' OR 'south african' OR 'west african' OR 'west africa' OR 'western africa' OR 'western african' OR 'cabo verde' OR ghana* OR guinea* OR liberia* OR mali* OR mauritania* OR niger* OR 'saint helena' OR senegal* OR 'sierra leone' OR togo* OR 'comoros'/exp OR 'mayotte'/exp OR 'reunion'/exp OR 'seychelles'/exp OR 'chad'/exp OR 'gabon'/exp OR 'eswatini'/exp OR 'benin'/exp OR 'cote d`ivoire'/exp OR 'guinea-bissau'/exp OR 'burkina faso'/exp OR 'lesotho'/exp

	Scopus	"sub-saharan africa" OR "sub-saharan african" OR ssa OR "subsaharan africa" OR "subsaharan african" OR africa* OR "eastern africa" OR "east african" OR "east africa" OR "eastern african" OR "british indian ocean territory" OR burund* OR djibout* OR eritrea* OR ethiopia* OR "french southern territories" OR kenya* OR madagasca* OR malaw* OR mauriti* OR mozambi* OR rwanda* OR somalia* OR "south sudan" OR "south sudanese" OR uganda* OR tanzania* OR zambia* OR zimbabw* OR "middle africa" OR "middle african" OR angola* OR cameroon* OR "central african republic" OR congo* OR "equatorial guinea" OR "sao tome and principe" OR "southern africa" OR "southern african" OR bostwana OR namibia* OR "south africa" OR "south african" OR "west african" OR "west africa" OR "western africa" OR "western african" OR "cabo verde" OR ghana* OR guinea* OR liberia* OR mali* OR mauritania* OR niger* OR "saint helena" OR senegal* OR "sierra leone" OR togo* OR "comoros" OR "mayotte" OR "reunion" OR "seychelles" OR "chad" OR "gabon" OR "eswatini" OR "benin" OR "cote d`ivoire" OR "Ivory coast" OR "guinea-bissau" OR "burkina faso" OR "lesotho"
#4	Pubmed, Embase, Scopus	#1 AND #2 AND #3

Supplementary Table 1: Detailed Search Strategy by Database

2.3. Study Selection

Two reviewers (BN and KM) independently performed the study selection using the Rayyan online software by screening titles and abstracts. They then read full-text articles after removing duplicates. Discrepancies were resolved through consensus with the third reviewer (LN). We included peer-reviewed full-text articles of observational studies (cross-sectional, case-control, and cohort) on viral hepatitis-induced ALF in SSA that used either widely accepted criteria for the diagnosis of ALF or had enough information to imply the presence of ALF [1,3]. We excluded abstracts for conferences, editorials, reviews, and studies that did not define ALF diagnostic criteria or whose full texts could not be retrieved. We also excluded studies involving participants with multiple potential causes of ALF and did not consider multinational studies whose data from the SSA region could not be disentangled from those of other regions.

2.4. Data Extraction and Evaluation of the Risk of Bias in Individual Studies

We predesigned Google form to extract the last name of the first author, year of publication, the country where the study was carried out, study design, study period, the timing of data collection, study population, sample size, median or mean age, ALF diagnosis criteria, number of viral-induced ALF cases, causal virus, number of deaths, treatment and other outcomes like delivery. This form was piloted using 4 randomly selected eligible articles. The methodological quality of the included articles was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool for reporting prevalence and incidence data or case-control studies as appropriate [23]. KM and BN independently assessed the quality of the included articles and resolved disagreements with LN. (Supplementary data Tables 2A and 2B).

First Author	1. Was the sample frame appropriate to address the target population?	2. Were study participants recruited in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and setting described in detail?	5. Was data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Was appropriate statistical analysis used?	9. Was the response rate adequate, and if not, was the low response rate managed appropriately
Mudawi	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Solomons	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Goumba	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Bruckmann	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Keles	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Heemelaar	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patterson	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Walabh	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Unclear
Rayis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Supplementary Table 2A: Risk Of Bias Assessment Using The Joanna Briggs Institute (JBI) Critical Appraisal Tool For Studies Reporting Prevalence and Incidence

First Author	1. Were the groups comparable other than presence of disease in cases or absence of disease in controls?	2. Were cases and controls matched appropriately?	3. Were the same criteria used for identification of cases and controls?	4. Was exposure measured in a standard, valid and reliable way?	5. Was exposure measured in the same way for cases and controls?	6. Were confounding factors identified?	7. Were strategies to deal with confounding factors stated?	8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	9. Was the exposure period of interest long enough to be meaningful?	10. Was appropriate statistical analysis used?
Coursaget	No	No	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear
Mackenjee	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Yes	Yes	Yes

Supplementary Table 2B: JBI Critical Appraisal for Case-Control Studies

2.5. Data Synthesis

Data was synthesized narratively.

3. Results

3.1. Study Selection

We identified 16,059 citations from our initial search of databases. We removed duplicates and then screened 15,148 titles and abstracts for inclusion. Finally, 48 full texts were sought for retrieval, and eleven were included in this review. Figure 1 details the study selection process [24-34].

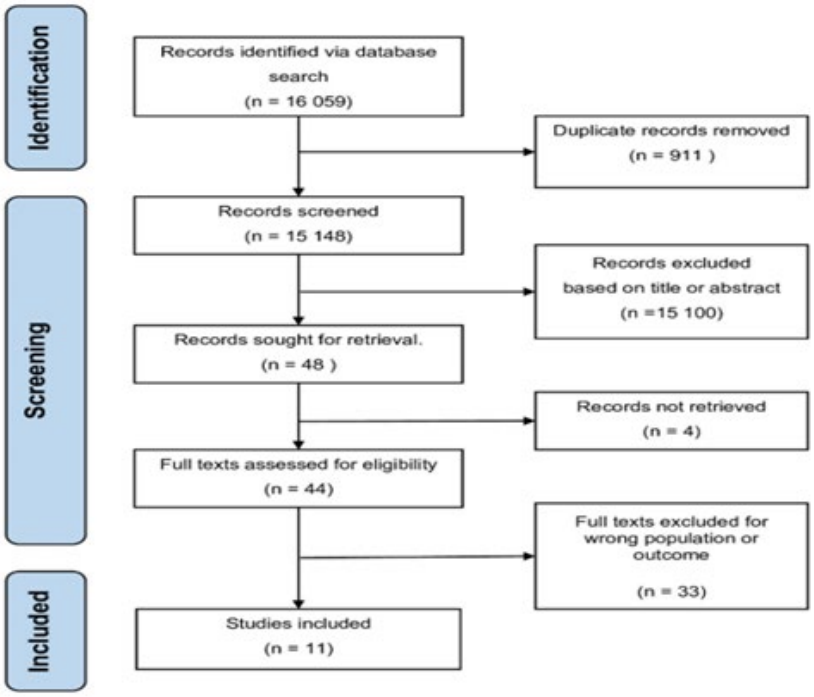

Figure 1: PRISMA flow chart for Study Selection

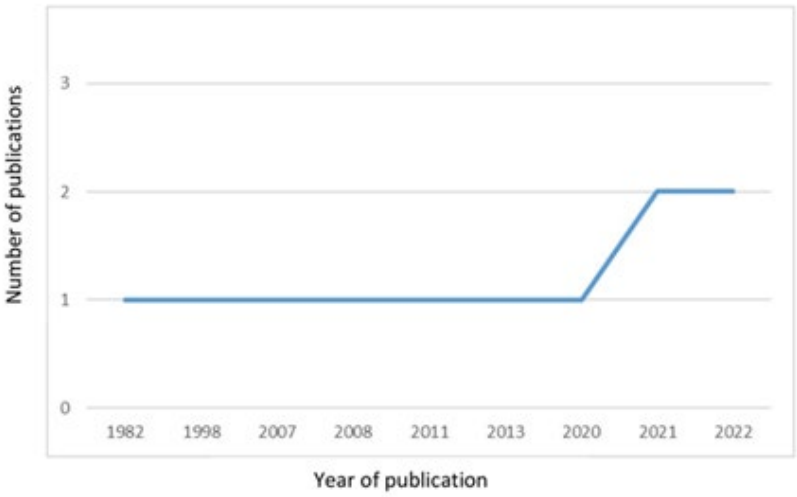

Figure 2: Timeline of publications on ALF in sub-Saharan Africa over the last 40 years

3.2. Characteristics of Included Studies

The studies included in this review were carried out between 1982 and 2022 (Figure II) in South Africa, Chad, Sudan, Central African Republic, Somalia, and Namibia [24-34]. The study population also varied between and within the studies. Five studies focused only on the pediatric age group, one on adults only, two on both pediatric and adult, two on pregnant and/or women within 42 days post-partum, and one on all three [24-28,30,31,33,34]. They were all conducted in urban health facilities using non-random sampling methods. Two of these studies were case-control and the rest were cross-sectional. Data collection was retrospective except for two studies where it was prospective. These characteristics are detailed in Table 1.

							ALF cases				Viral-induced ALF		
Author, Year of publication	**Country**	**Study design**	**Study period**	**Timing of data collection**	**Type of population**	**Sample size**	**Diagnostic criteria**	**n**	**Mean/ Median age in years (range)**		**n (% of ALF cases)**	**Causal virus (n)**	**Deaths (CFR %)**
Mackenjee, 1982	South Africa	Case-control	NR	Retrospective	Pediatric	46	Jaundice, encephalopathy, no previous liver disease, Illness of < 8-weeks	11	NR (3-11)		8 (72.7)	HBV (8)	6 (66.7)
Coursaget, 1998	Chad	Case-control	1/1993-12/1993	Retrospective	Pediatric Adults Pregnant women	127	SGOT > 100 U/L, encephalopathy	14	29.3 (16-64)		12 (85.7)	HEV (8) HBV (2) HCV (2)	12 (100)
Mudawi, 2007	North Sudan	Cross-sectional	7/2003-10/2004	prospective	Adults	37	Jaundice, encephalopathy occurring within 12 weeks of the onset of jaundice	37	38 (19-75)		10 (27.0)	HBV (8) HEV (2)	7 (70.0)

Solomons, 2008	South Africa	Cross-sectional	1/2001-8/2004	Retrospective	Pediatric	184	INR >2 non-responsive to vitamin K, encephalopathy, no previous liver disease, clinical liver disease of < 8 weeks	2	NR (< 13)		2 (100)	HAV (2)	2 (100)
Goumba, 2011	Central African Republic	Cross-sectional	6/2004-9/2005	prospective	Pediatric, Adult	411	NR*	5	NR		5 (100)	HEV (5)	NR
Rayis, 2013	Eastern Sudan	Cross-sectional	11/2010-3/2011	Retrospective	Pregnant women	39	Fulminant hepatitis with encephalopathy	11	NR		11 (100)	HEV (11)	11 (100)
Bruckmann, 2020	South Africa	Cross-sectional	11/2005-9/2019	Retrospective	Pediatric	193	PALFSG criteria	27	3.7 (unclear)		16 (59.3)	HAV (11) Enterovirus (2) Adenovirus (1) Parvovirus (1) EBV (1)	NR
Keles, 2021	Somalia	Cross-sectional	6/2019-12/2019	Retrospective	Pediatric	219	PALFSG criteria	25	6.7 (NR)		25 (100)	HAV (25)	NR
Heemelaar, 2021	Namibia	Cross-sectional	10/2017-5/2019	Retrospective	pregnant women and women within 42days post-partum	70	Acute elevation of serum transaminases, encephalopathy of any grade, INR>1.5	28	NR		28 (100)	HEV (28)	13 (46.4)
Patterson, 2022	South Africa	Cross-sectional	1/2008-3/2018	Retrospective	Pediatric, Adult	451	2005 AASLD criteria	5	NR		5 (100)	HAV (5)	4 (80.0)

Walabh, 2022	South Africa	Cross-sectional	1/2015-10/2020	Retrospective	Pediatric	45	PALFSG criteria	45	3.3 (NR)		30 (66.7)	HAV (19) Adenovirus (5) HSV (3) Enterovirus (2) EBV (1)	NR**

AASLD: American Association for the Study of Liver Disease, ALF: acute liver failure, CFR: case fatality rate, HAV: hepatitis A virus, HBV: hepatitis B virus, HCV: hepatitis C virus, HEV: hepatitis E virus, HSV: Herpes Simplex Virus, INR: International Normalized Ratio, NR: not reported, PALFSG: pediatric acute liver failure study group, SGOT: serum glutamate oxaloacetic transaminase.

*The authors did not formally report ALF in any patient, but we classified the five patients who had a positive anti-HEV IgM serology and encephalopathy (n=5) as ALF cases,
**The authors reported 19 deaths due to ALF but did not specify the etiology of ALF

Table 1: Acute liver failure of viral origin in sub-Saharan Africa: General characteristics of included studies, demographics of affected populations, diagnostic criteria and case fatality rate

3.3. Frequency of Viral-Induced ALF

As shown in Table 2, one hundred and fifty-two of the 210 cases (72.4%) of ALF in sub-Saharan Africa were attributed to viral infections. There is possibly an overlap of patients who underwent LT in the same institution as data were collected over almost the same period [30,34]. Fifty-five percent (84/152) of viral-induced ALF cases were reported in children and twenty-eight percent (42/152) in pregnant women and/or those within the 6-week postpartum period.

	Pediatric n (%)	Adult n (%)	Pregnant women or post-partum n (%)	Total
HAV	58 (69.0)	4(15.4)	0 (0)	62
HBV	9 (10.7)	9(34.6)	0 (0)	18
HCV	0 (0)	2(7.7)	0 (0)	2
HEV	1 (1.2)	11(42.3)	42 (100)	54
Adenovirus	6 (7.1)	0 (0)	0 (0)	6
HSV	3 (3.6)	0 (0)	0 (0)	3
Enterovirus	3 (3.6)	0 (0)	0 (0)	3
EBV	2 (2.4)	0 (0)	0 (0)	2
Parvovirus B19	2 (2.4)	0 (0)	0 (0)	2
Total	84	26	42	152

HAV: Hepatitis A Virus, Hbv: Hepatitis B Virus, Hcv: Hepatitis C Virus,
HSV: Herpes Simplex Virus, Ebv: Epstein-Barr Virus, Alf: Acute Liver Failure

Table 2: Etiology of Viral-Induced ALF by Study Population

3.4. Etiology of Viral-Induced ALF

HAV (40.8%), HEV (35.5%), HBV (11.8%), Adenovirus (3.9%), Enterovirus and Herpes Simplex (2.0%), and Parvovirus virus B19, EBV and HCV (1.3%), were all reported as ALF triggers in SSA. HAV (69.0%) was the most reported virus in paediatric subjects. In adults, HEV (42.3%) and HBV (34.6) were the most reported viruses while HEV infection was the only incriminated cause in pregnant women (Table 2).

3.5. Clinical Features and Diagnostic Criteria

Signs and symptoms of ALF attributable to viral infections in sub-Saharan Africans were not well specified across studies. However, clinical manifestation (encephalopathy) from the ALF diagnostic criteria was reported in all studies. Regarding non-diagnostic ALF manifestations, increased serum bilirubin and liver enzymes were frequently reported in the studies. Though standard diagnostic criteria were used in most of the studies, the study from Chad used only raised serum transaminase values instead of INR alongside encephalopathy for diagnosis and we classified the five patients who had a positive anti-HEV IgM serology and encephalopathy as ALF in the study from Central African Republic [25,28]. The stated duration of manifestation

of clinical symptoms considered to diagnose viral-induced ALF across the studies varied from 8 to 26 weeks as shown in Table 1. Table 3 summarizes the clinical and laboratory features reported across the studies.

Organ/System	Signs and symptoms
Hepatoenteric	Hepatalgia, Hepatomegaly, ascites, nausea, vomiting, epigastric/abdominal pain/tenderness, diarrhea, constipation
Neurological	Headaches, Drowsiness,
Immuno	Bleeding/DIC, splenomegaly, hypovolemic shock, postpartum hemorrhage
Renal	Dark urine, acute kidney injury
Skin	Jaundice, pruritus, unspecified rash
Musculoskeletal	joint pains, myalgia
Respiratory	ARDS
General	Fever, weight loss, limb edema
Abnormal Laboratory findings	
increased	serum bilirubin, Serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alpha-fetoprotein (AFP), alkaline phosphatase (AP), Lactate, NH4+, activated partial thromboplastin time (aPTT), (prothrombin time (PT)
decreased	serum albumin, complements C3, C4, CH50, and Factor B, clotting factor V, serum glycemia

Table 3: Non-ALF Diagnostic Criteria Signs, Symptoms, and Laboratory Findings Associated with Viral-Induced Alf Reported in One or More Studies

3.6. Treatment

The main reported treatment was supportive care [24,31,33,34]. Pregnant women with viable foetuses were offered delivery and dialysis was administered to subjects with associated acute kidney injury [30,34]. No precision was made on the supportive care provided to patients. Liver transplantation was done in two studies from one health facility in South Africa [30,34]. In one of the studies, 27 LTs were carried out between 2005 and 2019 [30]. Fifteen of the patients received the standard living split liver transplant and the remaining subjects received cadaveric grafts.

3.7. Outcomes

The case fatality rate (CFR) of viral hepatitis-induced ALF was not reported in all the studies. For the studies that reported deaths [24-27,29,32-34], the overall CFR was 72/106 (68%). It was higher in adults 17/21 (81.0%). In pregnant women, the CFR was 100% among 11 pregnant women who developed ALF during the 2010-2011 hepatitis E outbreak in Eastern Sudan, and 46.4% among 28 women who developed ALF during the 2017-2019 hepatitis E outbreak in Namibia [29,32]. The reported adverse pregnancy outcomes were post-partum hemorrhage, pregnancy-related arterial hypertension, and miscarriages. In pediatric subjects, CFR was 29/46 (63.0%) when reported. Importantly, all deaths of pediatric subjects also occurred shortly after hospital admission [24]. The one-year post-LT survival rate was 81% (95% CI 61%- 92%) [30]. Five (18.5%) recipients died within one month, due to graft rejection, septic shock, cardiac tamponade, or acute respiratory distress syndrome. However, all five recipients of ABO-incompatible LT were still alive at the end of the study. Non-fatal LT complications included bowel and anastomotic leaks, and biliary or vascular complications.

4. Discussion

In this systematic review, one hundred and fifty-two cases of viral hepatitis-induced ALF were recorded in the 11 included studies. The most frequent causes of ALF were HAV, HEV and HBV. The other reported viruses included Adenovirus, HSV, Enterovirus, EBV, HCV and Parvovirus. The widely accepted diagnostic criteria were used in most of the studies and the most common treatment modality was supportive care. The overall case fatality rate was high (68%).

Viruses account for 7-37% of ALF in the USA, Europe, and the United Kingdom (UK) and up to 68% in Asian-Pacific and South American regions [5,14,15]. In the last four decades, viral hepatitis accounted for close to 75% of ALF cases in SSA. ALF induced by HAV was more common among children (58/62 cases), while HEV was more frequent in pregnant women and HBV(9/26 cases) and HEV(11/26 cases) were the most frequent in adults. In Africa, IgM anti HAV seroprevalence was 7% in children and adolescents and 5% in adults between 2008 and 2018 [35]. Globally, the combined prevalence of HAV-induced ALF in countries without routine vaccination is 27% (95% CI 13% to 43%) as compared to 2% (95% CI 1% to 3%) for countries practicing routine immunisation [8]. Though hepatitis A is a vaccine-preventable virus, as of 2018, no African country has included routine hepatitis A vaccination as part of its expanded program on immunization [36]. Furthermore, WHO does not recommend routine immunization against Hepatitis A in high endemic areas [37].

This could explain the high prevalence of HAV in this population. Hepatitis E virus was the second most frequent virus in this review and was most common in pregnant women and associated with miscarriages and intrauterine death. HEV IgM se-

roprevalence ranged from 0 to 85% in pregnant women during outbreaks between 1990 and 2018 in SSA Routine screening for hepatitis E virus is not a common practice in most countries in SSA and thus could highlight the need for policies on routine screening in HEV endemic areas [38]. For non-vaccine-related viral infections, the pooled prevalence for HCV-induced ALF is 9% (95% CI 1% to 21%) and the combined prevalence rates for HDV, HHV/HSV, CMV, and EBV are respectively 4% (95% CI 0% to 13%), 6% (95% CI 1% to 12%), 13% (95% CI 1% to 35%) and 6% (95% CI 0% to 24%) [12]. The very low point frequencies of ALF induced HSV, EBV, parvovirus, adenovirus, and enterovirus could be attributed to the fact that they require PCR testing which is not readily available in most of our hospital settings in SSA.

In most of the included studies, detailed clinical features were not always reported but the diagnosis of ALF in adults was based on widely accepted criteria [1,3]. The pathogenesis and clinical features of ALF depend on the aetiology and include both direct liver and systemic immune-mediated injury [39]. Hepatotropic viruses trigger innate immunity via pathogen-associated molecular patterns whereas endogenous signals derived from injured cells called damage-associated molecular patterns are more frequent with toxins [39]. Most patients with ALF have consistent clinical features, acute loss of hepatocellular function, systemic inflammatory response, and multi-organ system failure. SIRS reflect the release of pro-inflammatory cytokines which contributes to cerebral oedema by decreasing cerebral vascular tone thus increasing thus causing cerebral hyper-perfusion [40]. Cerebral oedema and multiple organ failure mediated by SIRS are the two main causes of death in patients with ALF [40]. Common para-clinical features associated with ALF included elevated INR>1.5, elevated bilirubin and liver enzymes, anemia, thrombocytopenia, electrolyte imbalance, and features of acute kidney injury [6]. The exact mechanism of coagulopathy in ALF remains unclear. However, several hypotheses have been put forward to explain this. On the one hand, decreased synthesis of procoagulant and anticoagulant factors and on the other hand defective platelets and/or thrombocytopenia and impaired fibrinolytic systems. Though INR values are elevated in ALF, spontaneous bleeding is usually mucosal and of gastrointestinal origin [41].

Globally, the management of ALF includes supportive and preventive care, management of complications, and specific treatment in the case where the aetiology is known [6]. Supportive and preventive care involves maintaining hemodynamic stability with adequate fluid resuscitation, normal electrolytes, normal acid-base equilibrium, workups for fever and eventually starting antibiotics when necessary, and monitoring for bleeding, hepatic encephalopathy, and hypoglycaemia. Prophylactic protein pump inhibitors should be given adequate nutrition (1-1.5g/kg/day of protein) and renal replacement therapy in case of AKI [6]. With regards to specific treatment, viral hepatitis A and E have no specific antiviral agents, and as such patients diagnosed with these viruses should receive supportive treatment [6]. Patients with HBV-induced ALF should receive nucleotide analogues, those with HSV acyclovir (5-10mg/kg every 8 hours intravenously), and those with CMV ganciclovir [6]. Over the last 40 years, the management of ALF in SSA has been mainly unspecified supportive care and no precisions were given with regards to specific antiviral therapies. Furthermore, children who developed severe acute kidney injury were dialysed and pregnant women with viable foetuses had deliveries [30,31,33].

Though no treatment has been shown to improve the outcome of all patients with ALF, liver transplantation (LT) remains the ultimate treatment in patients without spontaneous recovery [42]. Selection criteria for liver transplantation varies from centre to centre. However, some factors such as multiple organ failure, severe sepsis, uncontrolled septic shock, brain death, patients aged above 70 years, and certain malignancies are considered to exclude ALF patients from liver transplantation [43]. Several criteria and prognostic scores exist to ascertain which patients need liver transplantation but they are not universally accepted hence the clinical judgement of clinicians and surgeons coupled with various prognostic indices could be used to determine the timing and appropriateness of LT [6]. In SSA, the suboptimal management of patients with an indication for liver transplantation LT may be accounted for by the fact that LT is mostly performed only in a few countries like South Africa.

In this review, the main outcomes explored were case fatality and the materno-foetal outcomes for pregnant women. Globally, case fatality associated with ALF varies from 60 to 80% depending on the cause and access to care [44]. Several factors could account for this high fatality in SSA from late referral of ALF patients to hospitals to insufficient specialists for appropriate diagnosis and the unavailability of LT when indicated. Furthermore, the lack of routine screening for rare viral causes of ALF makes management difficult and could also account for the high fatality rate.

This review is limited by the fact that only 6 sub-Saharan African countries had data on viral hepatitis-induced ALF with close to 50% being from South Africa. It is thus difficult to conclude that these findings reflect the reality in other countries. The low number of published articles within the last 40 years might be due to underreporting and thus highlight the need for better data collection and reporting methods within the region. Also, we did not include Google Scholar as one of the searched databases due to the lack of stored searches, filters, indexing, and replicability [21].

5. Conclusion

Over the last four decades, only 11 articles from 6 countries reported epidemiological data on viral hepatitis-induced ALF in SSA. HAV remains the leading cause of viral hepatitis-induced ALF in the pediatric population, HEV and HBV account for cases in adults while only HEV has been reported in pregnant women. Treatment is mainly supportive; liver transplantation is not readily available, and the case fatality rate remains high. These findings highlight the need for the implementation of routine HAV immunization in expanded programs on immunization available in SSA and routine screening for HEV in HEV endemic zones especially for pregnant women.

Ethical Approval

This systematic review was registered in PROSPERO and no ethical board was required.

Authors' Contributions

LN: study conception, selection of studies, screening, and extraction of data, writing of manuscript.
KM: Study selection, screening, and review of manuscript.
BN: study search, screening, and extraction of data, reviewing of selected studies, review of the initial draft.

Conflicts of Interests

All authors have read the final manuscript and declare no conflict of interest.

Data Availability

All supplementary tables and search queries used have been made available in the manuscript.

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