

## Prevalence of spontaneous bacteria peritonitis (SBP) in hepatitis B (HBV), and hepatitis C (HCV) liver cirrhosis: A systematic review and meta-analysis

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### ABSTRACT

**Background and Aim:** Spontaneous bacterial peritonitis is a common infection in liver cirrhosis. This systematic review and meta-analysis provides detailed information on the prevalence of SBP among HBV and HCV-related liver cirrhosis globally.

**Methods:** A systematic search for articles describing the prevalence of SBP in HBV, and HCV related cirrhosis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Our search returned ten (10) eligible articles involving 1,713 viral cirrhosis cases representing eight (8) countries. A meta-analysis was performed on our eligible studies using the random effect model. A protocol was registered with PROSPERO (CRD42022321790).

**Results:** The pooled prevalence of SBP in HBV associated cirrhosis had the highest estimate [8.0% (95% CI, 2.7 – 21.0%;  $I^2= 96.13\%$ ;  $p < 0.001$ )], followed by SBP in HCV associated liver cirrhosis [4.0% (95% CI, 1.3% – 11.5%;  $I^2 = 88.99\%$ ;  $p < 0.001$ )]. China (61.8%, CI: 57.1 – 66.3%), the USA (50.0%, CI: 34.6 – 65.4%), and Holland (31.1%, CI: 21.6 – 42.5%) had the highest estimate for SBP in HBV associated liver cirrhosis, SBP in HCV associated liver cirrhosis and SBP in HBV+HCV associated liver cirrhosis respectively.

There was a significant difference in the prevalence of SBP in viral hepatitis-associated liver cirrhosis with the year of sampling and method of SBP detection at  $P<0.001$ . There was an increase in SBP incidence at the beginning of 2016 across the liver cirrhosis in this study.

**Conclusion:** The findings of this review revealed an increase in the incidence of SBP in viral hepatitis over the last decade, the latter could be due to the global increase in Bacterial resistance. This indicates a possible future rise in the global prevalence of SBP among HBV, and HCV-related liver cirrhosis.

**Keywords:** Spontaneous bacterial peritonitis, Hepatitis B virus, Hepatitis C virus, liver cirrhosis, prevalence, and cancer.

## **Introduction**

Spontaneous bacterial peritonitis (SBP) is a bacterial infection that occurs in patients with cirrhosis and ascites without any primary intraperitoneal infection, and it accounts for around 10-40% of all hospitalised cases with ascites and liver cirrhosis globally [1]–[3]. Spontaneous bacterial peritonitis has many predisposing factors, including lifestyle and disease conditions [4].

Liver cirrhosis, in a more histological concept, is a fibrosis-characterised diffusion of standard hepatocyte architecture into a structurally abnormal nodule [5] that reduces the functional mass index of the hepatocyte as well as its vascular architecture [6], [7].

There are two aetiological primary evolutionary sources of cirrhosis, alcoholic liver cirrhosis and non-alcoholic liver cirrhosis [4]

Cirrhosis of the liver has been firmly associated with HBV, and HCV or a coinfection of both (HBV+HCV) [8] [9]. The Hepatitis B and Hepatitis C viruses are the most common cause of viral hepatitis, they are the major non-alcoholic cause of liver cirrhosis. In addition, the infection from SBP can spread to other organs, causing more severe multi-organ failure with poor patient prognosis [8], [10].

The incidence of SBP in liver cirrhosis differs with regions globally, chronic Hepatitis B is the most common etiological condition of liver cirrhosis in sub-Saharan Africa and some parts of Asia [4].

The clinical pattern, pathophysiology, and natural history of SBP among viral hepatitis are still unclear. Still, there are theories that SBP in liver cirrhosis is likely due to translocation and overgrowth of intestinal bacteria, which is an integral step in the colonisation and pathogenic stage of SBP infection [11].

The European Association for the Study of Liver (EASL) has established a preventative treatment for SBP in cirrhosis based on therapeutic studies. It is essential to distinguish between the two types of infections (nosocomial and community-acquired) because the source of SBP has a significant impact on the patient's clinical outcomes [8], [12]

Previous treatment guidelines recommended amoxicillin or a third-generation cephalosporin; however, both have been therapeutic failures in recent decades due to bacterial resistance and evolution. [3], [13]

Although the epidemiological burden, outcome, and related morbidity of SBP in viral cirrhosis are increasing, there is still a need for more information on the pooled prevalence analysis of SBP in patients with HBV- and HCV-related cirrhosis. Thus, this systematic literature review and meta-analysis was conducted to determine the pooled prevalence of SBP in patients with viral-related

cirrhosis and to investigate the importance of individual hepatitis cirrhosis-causing viruses. To the best of our knowledge, this study is the first systematic review and meta-analysis reporting the prevalence of SBP in viral cirrhosis, the findings of this study will provide baseline data on the epidemiology, trend, and potential pattern of SBP endemicity globally. It will also help healthcare givers in the diagnosis, treatment and management of SBP in viral-cirrhotic patients worldwide.

## **Methods**

A study protocol was lodged for this study with PROSPERO, an online systematic review database under the ID record number: CRD42022321790.

### **Study design and protocol**

The Preferred Reporting Items for Systematic reviews and Metanalysis protocol guidelines were used as this study's checklist (supplementary file K1) [14].

### **Literature review search strategy**

The PROSPERO and Database of abstracts of review of effects (DARE) were searched to avoid duplication of an ongoing or an already existing review on our study topic: "Spontaneous bacterial peritonitis in HBV, HCV-based liver cirrhosis". We proceeded to search four other international databases (PubMed, Scopus, Google Scholar and ScienceDirect) on the occurrence of SBP in viral hepatitis-based cirrhosis after our preliminary search confirmed that there was neither an ongoing study nor an existing review on the topic of choice. The PubMed database was searched using standard search terms that best represented the study using the search strategy ("Spontaneous bacterial peritonitis" [All Fields] OR "Ascitic fluid infection" [All Fields] OR ("ascites" [All Fields] OR "ascites" [MeSH Terms] OR "ascites" [All Fields] OR "ascitic" [All Fields]) AND ("liver cirrhosis" [All Fields] OR "viral liver cirrhosis" [All Fields]) AND ("hepatitis B virus" [All Fields] AND ("hepatitis C virus" [All Fields] OR "HBV" [All Fields] OR "Hepatitis B" [All Fields]) OR "HCV" [All Fields] OR "Hepatitis C" [All Fields]). Details of the search strategy is found in supplementary file K2.

The keyword search terms used for the comprehensive search in other databases aside from PubMed were "Spontaneous bacterial peritonitis", "cirrhosis", and "hepatitis". The titles and references from the articles that met our inclusion criteria were utilised as an additional search tool. All searches were done without language restriction or year of study, and a final search was

done on 5<sup>th</sup> November 2021. Two authors carried out an independent probe of the literature to reduce the chances of bias. All included literature references were imported into the Mendeley Reference manager to remove duplicates before screening the titles and abstracts.

### **Inclusion and exclusion criteria**

Studies with designs including retrospective cohort, cross-sectional cohort, prospective cohort, and randomised clinical trials were included. Only original research that reported SBP in viral-related cirrhosis were included in this study. We excluded all reviews, short communications, commentaries, editorials, studies that reported SBP in alcoholic cirrhosis, studies that did not report SBP in viral-based cirrhosis, studies that contained duplicated data, studies that reported SBP in viral-based cirrhosis but without clarity of the numbered of the sampled population, all studies with insufficient information and studies whose full text could not be retrieved.

### **Data extraction**

Two authors independently screened the title, abstract and full-text review of the recruited studies to extract all necessary information into a table. A third author reviewed the results, and all discrepancies between the authors were resolved by consensus. All literature were screened in three phases: title, abstract and full text. Information including the first author's name, year of publication, country of publication, sample size, number of cases, type of viral hepatitis-based cirrhosis and detection method were all extracted from each included study. Studies, where viral cirrhosis was not defined based on their aetiological agent were categorised as both Hepatitis B virus and Hepatitis C virus-related cirrhosis.

### **Quality assessment**

The quality of all the studies was assessed using the Joanna Briggs Institute (JBI) prevalence data appraisal checklist (supplementary file K3) [15]

the appraisal set nine (9) parameters that any standard research should meet. A scoring coding system of "zero (0) for NO" and "One (1) for YES" were assigned. The included studies were scored from 0-9 based on Joanna Brigg's Institute critical appraisal for prevalence data. Studies with an overall score of less than seven (7) were considered unsuitable for this study. Studies with a quality score greater than seven were considered to be of good quality for this study. Studies with a quality score greater than seven were considered to be of good quality for the study. The quality score assessment for all the studies is provided in supplementary file **K4**. Two authors

carried out the quality assessment independently. All studies included in this study were recruited based on consensus between the reviewers.

### **Data analysis**

OpenMeta Analyst and Comprehensive Meta-Analysis software were used to analyse the data [3\* Wallace et al., 2012; closing the gap between methodologists and end users], [16]

the pooled prevalence of SBP in viral hepatitis cirrhosis was calculated, and subgroup analyses were done according to the aetiological source of viral cirrhosis, year of sample collection and region of study. Due to high variability in the area of sample collection and the period of sample collection as the variation on the detection method, the randomised effect model best suits the study [17]. The DerSimonian and Laird method was used for the pool prevalence determination in this meta-analysis [18]

A forest plot was constructed to know the estimated weight of each study, its effect sizes, the proportional prevalence, the confidence interval of the estimated prevalence and the degree of heterogeneity[19]. Then, all data were transformed using logit transformation.

### **Heterogeneity analysis and publication bias test**

Publication bias was examined using Egger's regression test and funnel plots. The heterogeneity of the study level estimates was measured using the Inconsistency index Statistics ( $I^2$ ) OF >75%, 50%, and 25%, which is interpreted as high, moderate and low heterogeneity. Cochran Q test was also used to evaluate the heterogeneity [17]. Non-significant heterogeneity will be accepted if the ratio of Q and degree of freedom (df) is less than one (1) [Q: df <1]. A subgroup meta-analysis was carried out to determine the sources of heterogeneity. The overall effect of each study on the pool prevalence and outcomes and in between study source of heterogeneity was examined using the "Leave One Out" meta-analysis sensitivity test.

### **Search results and eligible studies**

Our comprehensive systematic search retrieved an initial 2,389 abstracts from four databases. All duplicates were removed, and 819 articles were discarded based on their titles and abstracts. A total of 283 papers were eligible for full-text evaluation, but 273 studies were rejected as these did not meet our inclusion criteria or had a low JBI assessment score. Figure 1 shows a complete

overview of the selection procedure. This systematic literature review and meta-analysis included ten (10) publications consisting of 1,713 viral cirrhosis cases.

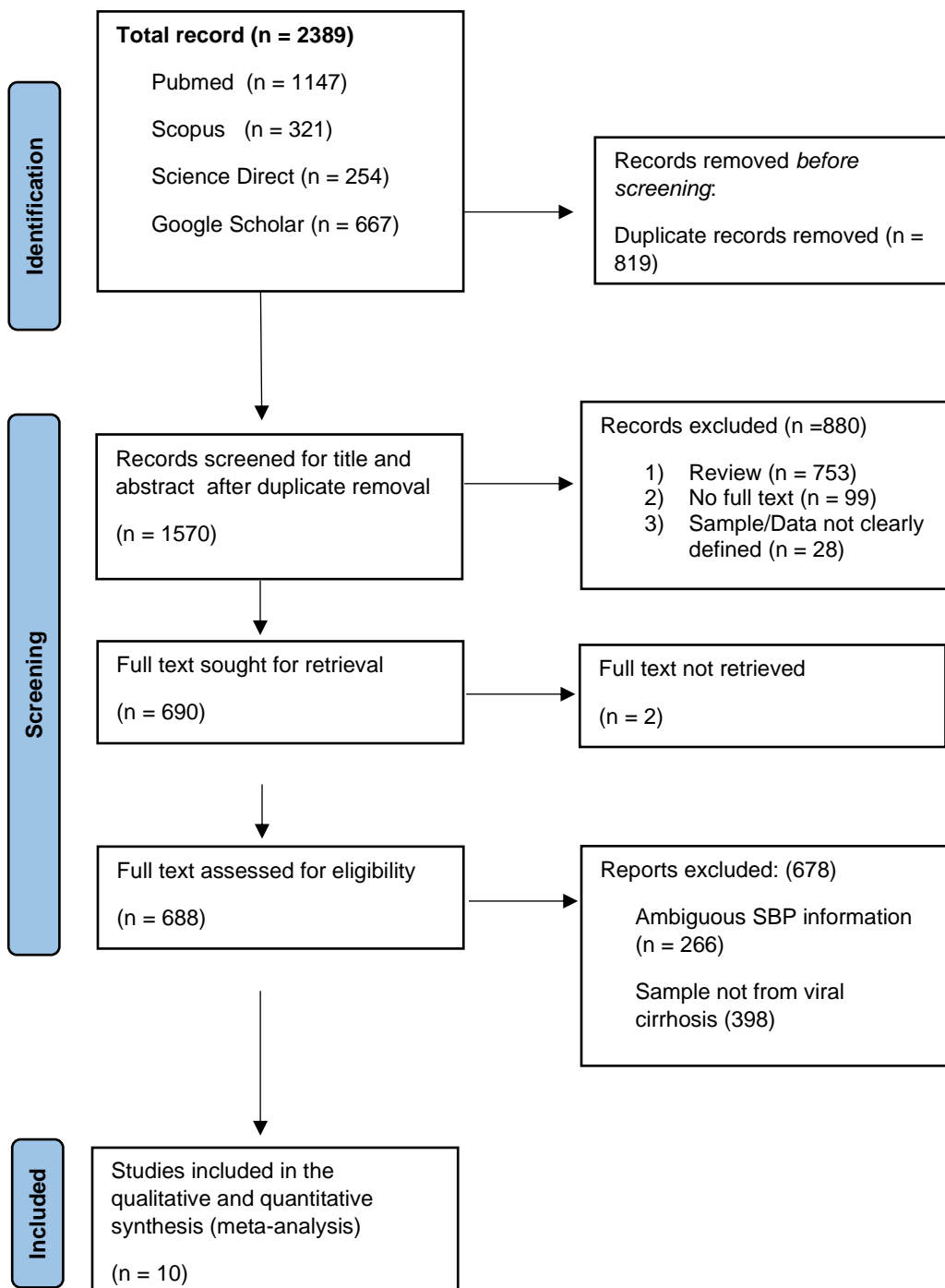


Figure 1. Summary of the article selection process

### Characteristics of the eligible studies

The articles included in this study was conducted across six countries representing four continents. We recovered ten articles that met our inclusion criteria (table 1) in eight countries. The United States of America (USA) and South Korea contributed 40% (n= 4) of the included articles.

A total of 1,713 viral cirrhosis were reported across ten (10) studies ranging from 675 viral cirrhosis (Pakistan) to 38 viral cirrhosis (USA) (Table 1).

Table 1: characteristic of the included studies showing the occurrence of SBP in HBV, and HCV related liver cirrhosis globally.



Three viral cirrhosis conditions with SBP were examined: 1. SBP among HBV cirrhosis, 2. SBP

Author, year	Year	Country	Sampling period	HBV sampled	SBP in HBV	HCV sampled	SBP in HCV	HBV + HCV sampled	SBP in HBV+HCV	Study design	Method of detection
Amelia et al.,[20]	2018	USA	Nov 2011 - March 2016	0	0	32	16	0	0	Case-control	Cell count and culture
Rosalie et al.,[21]	2017	Holland	Jan 2003 - Dec 2005	0	0	0	0	74	23	Retrospective	Culture
Giovambattista et al.,[22]	1983	Italy	Dec 1976 - Dec 1978	40	12	0	0	0	0	Retrospective	Culture
Evangelos et al.,[23]	2006	Greece	June 1999 - June 2001	49	11	27	9	0	0	Retrospective	Culture
Seung et al., (a)[24]	2008	South Korea	Jan 1996 - Dec 2015	203	24	0	0	0	0	Retrospective	Cell count and culture
Seung et al., (b)[25]	2009	South Korea	Jan 1998 - Dec 2007	130	20	0	0	0	0	Retrospective	Culture
Luke et al.,[26]	2003	USA	July 1994 - Dec 2002	0	0	6	3	0	0	Prospective	Culture
Lubna et al.,[27]	2008	Pakistan	Nov 2005 - Dec 2007	0	0	0	0	675	44	Retrospective	Culture
Nhian-Zhi et al., [28]	2018	China	Jan 2012 - Dec 2015	370	265	59	35	0	0	Retrospective	Culture
Trad et al., [29]	2019	Tunisia	Jan 2003 - Dec 2017	0	0	0	0	48	13	Retrospective	Cell count and culture

among HCV cirrhosis, and 3. SBP among HBV and HCV cirrhosis (Table 1).

The most prominent method of SBP detection was culturing. Over 80% of the included were retrospective studies. Studies whose samples were collected from 2006 to 2015 (n=4) and up to 2005 (n=4) were the most dominant. Only 20% of the articles collected their samples from 2016 and above (n=2) (table 1).

A summary of included articles is provided in Table 1. The quality assessment shows that majority of the included articles are of high methodological quality (Supplementary file K4).

### Prevalence of SBP in viral cirrhosis

The pooled prevalence of SBP in viral cirrhosis was diverse relatively to the etiological agent of liver cirrhosis. There was a high significance level of SBP with all the viral categories responsible for liver cirrhosis. The pooled estimates of SBP across the three different viral cirrhosis categories (HBV, HCV, and HBV+HCV) were highly heterogenous, as the heterogeneity index for all the individual categories was greater than 75% (Figure 2)

The pooled prevalence of SBP in HBV liver cirrhosis had the highest estimate [8.0% (95%CI: 2.7 – 21.0%,  $I^2 = 96.13\%$ ,  $p < 0.001$ )] (figure 3), followed by SBP in HCV associated liver cirrhosis,

with an estimate of 4.0% (95%CI: 1.3 – 11.5%,  $I^2 = 88.99%$ ,  $p = <0.001$ ) (figure 5). The pooled estimate of SBP in liver cirrhosis caused by both combination of HBV and HCV had the lowest prevalence in the category of SBP in viral cirrhosis [3.4% (95%CI: 1.2 – 9.4%,  $I^2 = 89.43%$ ,  $p = <0.001$ )] (figure 7).

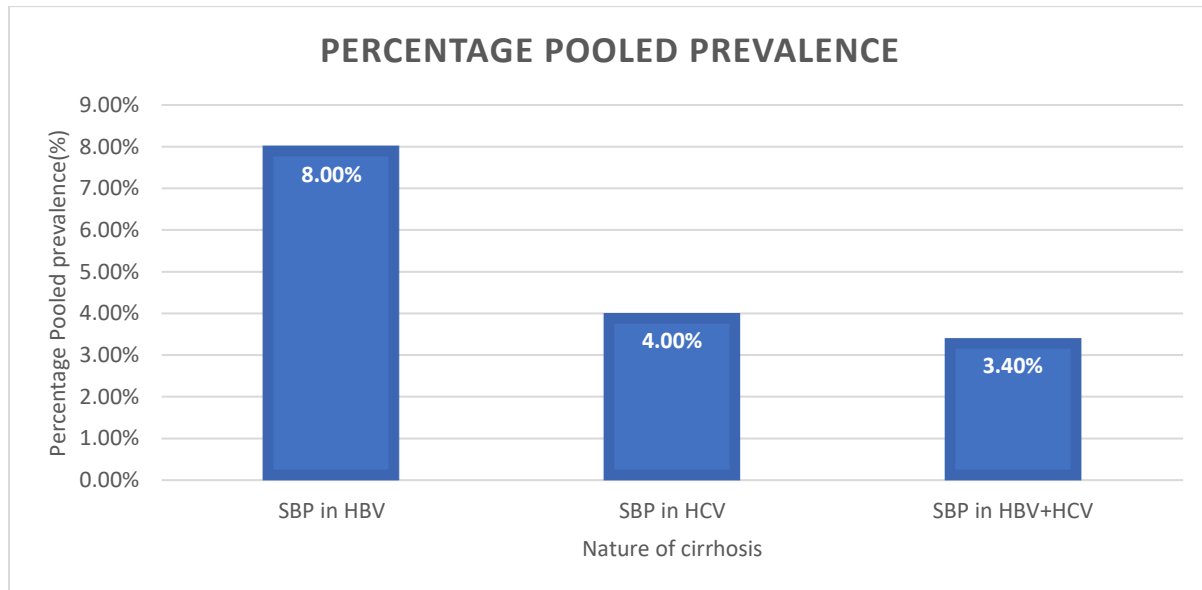


Figure 2: A bar chart showing the pooled prevalence of SBP in HBV, and HCV cirrhosis.

### Publication bias

Despite the diversity in the included studies for this review, there were pieces of evidence of publication bias in the funnel plots for the three categories. The adjusted trim and fill Duval and Tweedie's test for studies reporting SBP in HBV liver cirrhosis revealed four (4) adjusted trimmed studies with a Q-value of 253.55 in the random effect model adapted to the right (Table 2). Kendall's Tau's statistics revealed that the bias in the publication was not significant with and without continuity correction ( $p > 0.001$ ) (Table 2). The prevalence of SBP in HCV liver cirrhosis also revealed evidence of publication bias (Figure 6). After adjusting the included studies with Duval and Tweedie's trim and fill test using the random effect model, it was evident that four (4) studies were trimmed to the right with an adjusted Q value of 119.08. there was no significance in the correlation between the observed and the adjusted values as Kendall's Tau's *p-value* with and without continuity of correction were greater than 0.001 (Table 2).

The pooled estimate of SBP in a combination of both HBV and HCV liver cirrhosis also showed publication bias. After Egger's regression intercept was plotted (Figure 8), there was no significance in SBP pooled prevalence to the source of publication bias (Egger's  $p = 0.247$ ). After Duval and Tweedie's trim and fill test, the adjusted Q value was 111.995. the trim and fill test revealed that four (4) studies were trimmed to the right in the random effect model. The Begg and Mazumdar rank correlation indicated that the Kendal Tau value was not significant with and without continuity of correction ( $p > 0.001$ ) (Table 2).

Table 2: Tau statistic and point estimate

	Random effect model				
	Studies trimmed	Point estimates	Q value	Kendal Tau's $p$	
				Without continuity correction	With continuity correction
SBP in HBV cirrhosis					
Adjusted	4	1.299	253.55	0.180	0.211
Observed	-	2.448	232.86		
SBP in HCV cirrhosis					
Adjusted	4	1.916	119.08	0.788	0.858
Observed	-	3.189	81.73		
SBP in HBV+HCV cirrhosis					
Adjusted	4	2.213	112.00	0.180	0.211
Observed	-	3.342	85.12		

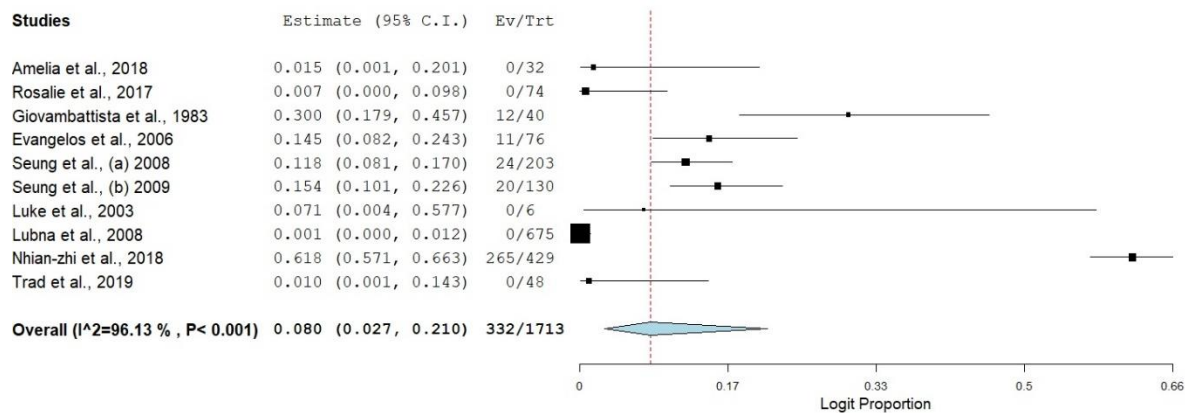


Figure 3: Forest plot showing SBP in HBV cirrhosis

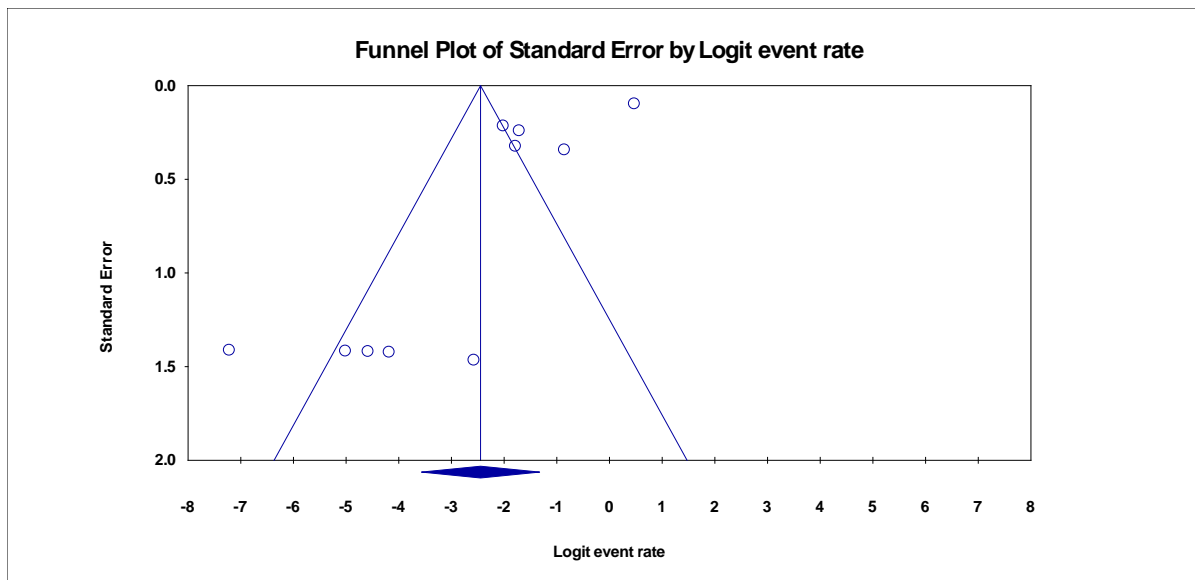


Figure 4: Funnel plot showing publication bias for SBP in HBV cirrhosis (Egger's  $p = 0.01273$ )

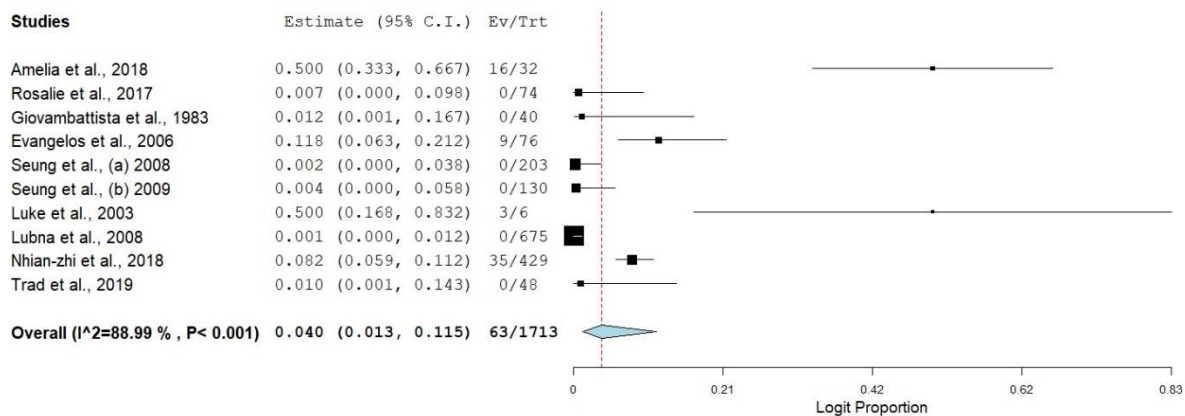


Figure 5: forest plot showing SBP in HCV cirrhosis

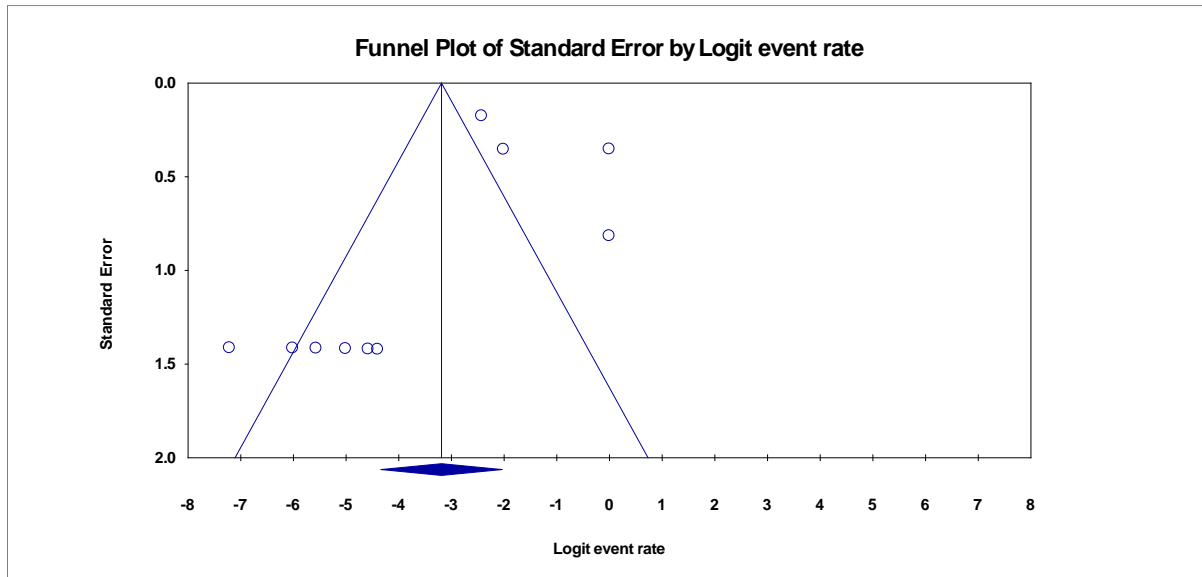


Figure 6: Funnel plot showing publication bias for SBP in HCV cirrhosis (Egger's  $p = 0.28126$ ).

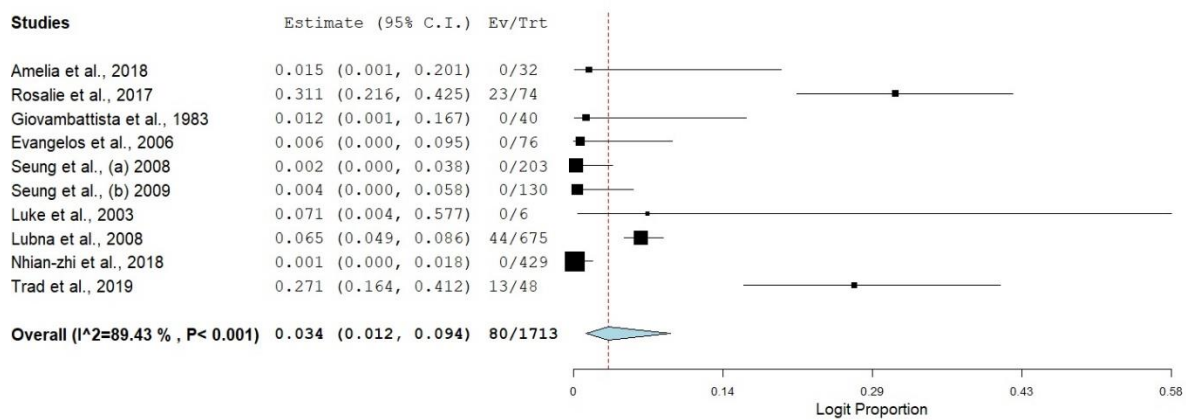


Figure 7: Forest plot showing SBP in HBV and HCV co-infected cirrhosis

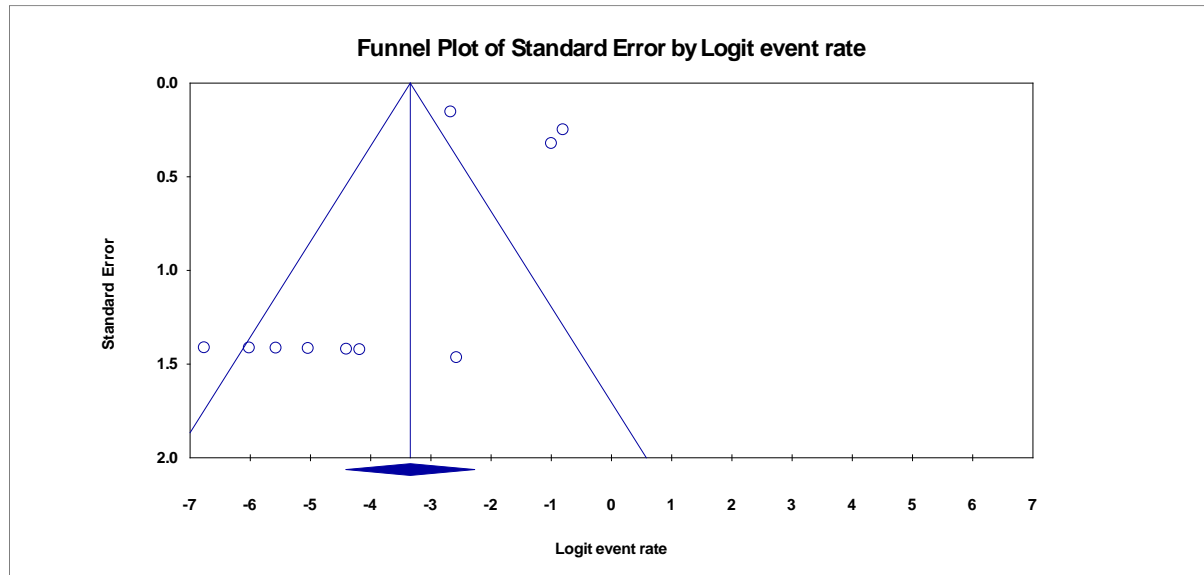


Figure 8: Funnel plot showing publication bias for SBP in HBC cirrhosis (Egger's  $p = 0.24663$ ).

### Subgroup meta-analysis

A subgroup analysis based on country of study, year of study sampling, method of SBP detection and the type of study designs was carried out to determine the sources of heterogeneity from the pooled studies, as substantial heterogeneity was observed. The overall subgroup analysis result based on the study's country revealed a high degree of variability among studies reporting SBP in hepatitis liver cirrhosis. Studies reporting SBP in HBV cirrhosis across the eight countries had the overall Higgin  $I^2$  statistics of 96.13% and a heterogeneity Chi-square (Q) of 232.86 at  $p < 0.001$ . However, most studies were reportedly from the USA and South Korea ( $n=2$  each). Similarly, studies reporting SBP in HCV cirrhosis had no significant Q and Higgin's  $I^2$  index. Despite the latter, the overall pooled estimates revealed a high level of heterogeneity ( $I^2 = 88.99\%$ ) and a significant Chi-square (81.73) at  $p < 0.001$  (Table 3).

In comparison, studies reporting SBP in HBV+HCV liver cirrhosis also had a diverse level of heterogeneity within the countries with the overall Higgin's  $I^2$  statistics of 89.43% and a significant heterogeneity Chi-square value (65.12) at  $p < 0.001$  (Table 3).

The result of subgroup analysis by year of sampling revealed a very high level of heterogeneity among the years of sampling in the studies reporting SBP in hepatitis viral cirrhosis (Table 4). The overall heterogeneity index for studies reporting SBP in HBV cirrhosis was 96.13% with a significant chi-square value (232.86) at  $p < 0.001$ . Studies whose samples were collected between the year 2006 – 2015 and studies whose samples were collected up to the year 2006 had the highest number of studies ( $n = 4$  each) and were diversely heterogenous ( $I^2 = >75\%$ ). Studies whose samples were collected later than the year 2015 revealed no level of heterogeneity ( $I^2 = 0.00\%$ ) and were also not significant ( $p = 0.842$ ) (Table 4).

Studies reporting SBP in HCV liver cirrhosis were highly heterogenous within groups based on their year of sampling ( $I^2 = >75\%$ ). The overall Higgin's  $I^2$  statistic revealed high variability in the studies reporting SBP in HCV liver cirrhosis ( $I^2 = 88.99\%$ ) with a heterogeneity chi-square of 81.73 at  $p < 0.001$ . Studies whose samples were collected later than 2015 revealed the highest variability among the set categories of sampling periods in correlation to SBP in HCV liver cirrhosis ( $I^2 = 89.75\%$ ). The heterogeneity index for studies reporting SBP in both HBV+HCV was diverse within the different years of sampling and was, therefore, highly heterogenous ( $I^2 = >75\%$ ). Studies whose samples were collected between 2006 – 2015 revealed the highest level of heterogeneity ( $I^2 = 82.87\%$ ). Though the studies whose samples were collected later than 2015 were heterogeneous ( $I^2 = 78.93\%$ ), they were not statistically significant ( $p = 0.029$ ) (Table 4).

Table 3: Subgroup analysis of SBP in three different viral hepatitis-related liver cirrhosis across countries.

Country	Number of studies	Prevalence (%)	95% CI	$I^2$ (%)	Q	Heterogeneity test	
						DF	P
<b>SBP in both HBV and HCV cirrhosis</b>							
USA	2	3.3	0.5 – 19.9	0.00	0.619	1	0.431
Holland	1	31.1	21.6 – 42.5	-	-	-	-
Italy	1	1.2	0.1 – 16.7	-	-	-	-
Greece	1	0.6	0.0 – 9.5	-	-	-	-
South Korea	2	0.3	0.0 – 2.1	0.00	0.049	1	0.824
Pakistan	1	0.1	4.9 – 8.6	-	-	-	-
China	1	0.1	0.0 – 1.8	-	-	-	-
Tunisia	1	27.1	16.4 – 32.5	-	-	-	-
<b>Overall</b>	<b>10</b>	<b>3.4</b>	<b>1.2 – 9.4</b>	<b>89.43</b>	<b>65.12</b>	<b>9</b>	<b>&lt;0.001</b>

<b>SBP in HCV cirrhosis</b>							
USA	2	50.0	34.6 – 65.4	0.00	0.00	1	1.000
Holland	1	0.7	0.0 – 9.8	-	-	-	-
Italy	1	1.2	0.1 – 16.7	-	-	-	-
Greece	1	11.8	6.3 – 21.2	-	-	-	-
South Korea	2	0.3	0.0 – 2.1	0.00	0.049	1	0.824
Pakistan	1	0.1	0.0 – 1.2	-	-	-	-
China	1	8.2	5.9 – 11.2	-	-	-	-
Tunisia	1	1.0	0.1 – 14.3	-	-	-	-
<b>Overall</b>	<b>10</b>	<b>4.0</b>	<b>1.3 – 11.5</b>	<b>88.99</b>	<b>81.73</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in HBV cirrhosis</b>							
USA	2	3.3	0.5 – 19.9	0.00	0.619	1	0.431
Holland	1	0.7	0.0 – 9.8	-	-	-	-
Italy	1	30.0	17.9 – 45.7	-	-	-	-
Greece	1	14.5	8.2 – 24.3	-	-	-	-
South Korea	2	13.3	10.1 – 17.4	0.00	0.872	1	0.350
Pakistan	1	0.1	0.0 – 1.2	-	-	-	-
China	1	61.8	57.1 – 66.3	-	-	-	-
Tunisia	1	1.0	0.1 – 14.3	-	-	-	-
<b>Overall</b>	<b>10</b>	<b>8.0</b>	<b>2.7 – 21.0</b>	<b>96.13</b>	<b>232.86</b>	<b>9</b>	<b>&lt;0.001</b>

Table 4: Subgroup analysis of SBP in three different viral hepatitis-related liver cirrhosis with the year of sampling.

Sampling period	Number of studies	Prevalence (%)	95% CI	$I^2$ (%)	Q	Heterogeneity test	
						DF	P
<b>SBP in HBV cirrhosis</b>							
>2016	2	1.2	0.2 – 8.3	0.00	0.040	1	0.842
2006 – 2015	4	11.0	2.1 – 41.9	98.32	178.95	3	<0.001
<2006	4	12.9	4.6 – 31.7	72.48	10.90	3	0.012
<b>Overall</b>	<b>10</b>	<b>8.0</b>	<b>2.7 – 21.0</b>	<b>96.13</b>	<b>232.86</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in HCV cirrhosis</b>							
>2016	2	11.1	0.1 – 91.6	89.75	9.75	1	0.002
2006 – 2015	4	0.6	0.0 – 8.7	86.25	21.81	3	<0.001
<2006	4	7.6	1.3 – 34.1	77.46	13.31	3	0.004
<b>Overall</b>	<b>10</b>	<b>4.0</b>	<b>11.5 – 58.8</b>	<b>88.99</b>	<b>81.73</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in both HBV and HCV cirrhosis</b>							
>2016	2	9.3	0.5 – 68.6	78.93	4.75	1	0.029
2006 – 2015	4	0.7	0.1 – 7.3	82.87	17.52	3	<0.001
<2006	4	4.9	0.5 – 36.0	80.61	15.48	3	0.001



<b>Overall</b>	<b>10</b>	<b>3.4</b>	<b>1.2 – 9.4</b>	<b>89.43</b>	<b>85.12</b>	<b>9</b>	<b>&lt;0.001</b>
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Most of the studies included in this review were retrospective study designs (80% of the included studies). Retrospective study designs were statistically significant in all the categories. Study designs with SBP in only HBV cirrhosis revealed that retrospective studies had the highest estimate (9.2%) compared to case-control (1.5%) (Table 5). The overall pool heterogeneity index was greater than 75% for SBP in HBV cirrhosis. Retrospective studies were highly heterogeneous in distribution (96.87%) with a Q statistic of 223.41. Prospective and case-control designs had the highest estimate (50.0% each) for SBP in HCV cirrhosis. Prospective study designs had the highest estimate of SBP in both HBV and HCV cirrhosis (Table 5).

The two methods of detection were diversely heterogeneous across the three different categories. Culture detection had the highest estimate for SBP in HCV cirrhosis. The heterogeneity index for cell count and culture was moderate (62.7%) at a Q statistic of 5.32 and was not statistically significant. There was a high level of diversity in the studies reporting SBP in both HBV and HCV and studies reporting SBP in HCV ( $I^2 = >80\%$ ) (Table 6).

Table 5: Subgroup analysis of SBP in three different viral hepatitis-related liver cirrhosis with the study design

Study design	Number of studies	Prevalence (%)	95% CI	$I^2$ (%)	Q	Heterogeneity test	
						DF	P
<b>SBP in HBV cirrhosis</b>							
Case-control	1	1.5	0.1 – 20.1	-	-	-	-
Retrospective	8	9.2	3.0 – 25.3	96.87	223.41	7	<0.001
Prospective	1	7.1	0.4 – 57.7	-	-	-	-
<b>Overall</b>	<b>10</b>	<b>8.0</b>	<b>2.7 – 21.0</b>	<b>96.13</b>	<b>232.86</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in HCV cirrhosis</b>							
Case-control	1	50.0	33.3 – 66.7	-	-	-	-
Retrospective	8	1.7	0.6 – 5.0	77.35	30.91	7	<0.001
Prospective	1	50.0	16.8 – 83.2	-	-	-	-
<b>Overall</b>	<b>10</b>	<b>4.0</b>	<b>1.3 – 11.5</b>	<b>88.99</b>	<b>81.73</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in both HBV and HCV cirrhosis</b>							
Case-control	1	1.5	0.1 – 20.1	-	-	-	-

Retrospective	8	3.4	1.1 – 10.2	91.56	82.94	7	<0.001
Prospective	1	7.1	0.4 – 57.7	-	-	-	-
<b>Overall</b>	<b>10</b>	<b>3.4</b>	<b>1.2 – 9.4</b>	<b>89.43</b>	<b>85.12</b>	<b>9</b>	<b>&lt;0.001</b>

Table 6: Subgroup analysis of SBP in three different viral hepatitis-related liver cirrhosis with the method of detection

Method of detection	Number of studies	Prevalence (%)	95% CI	I <sup>2</sup> (%)	Q	Heterogeneity test	
						DF	P
<b>SBP in HBV cirrhosis</b>							
Cell count and culture	3	4.1	0.6 – 21.7	62.4	5.32	2	0.007
Only culture	7	10.7	3.2 – 30.3	95.97	148.75	6	<0.001
<b>Overall</b>	<b>8.0</b>	<b>2.7</b>	<b>2.7 – 57.2</b>	<b>96.13</b>	<b>232.86</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in HCV cirrhosis</b>							
Cell count and culture	3	3.3	0.0 – 70.8	92.09	25.29	2	<0.001
Only culture	7	4.1	1.4 – 11.6	81.1	31.75	6	<0.001
<b>Overall</b>	<b>8.0</b>	<b>4.0</b>	<b>1.3 – 11.5</b>	<b>88.99</b>	<b>81.73</b>	<b>9</b>	<b>&lt;0.001</b>
<b>SBP in both HBV and HCV cirrhosis</b>							
Cell count and culture	3	2.9	0.1 – 46.4	87.48	15.97	2	<0.001
Only culture	7	2.9	0.8 – 10.2	90.37	62.28	6	<0.001
<b>Overall</b>	<b>8.0</b>	<b>3.4</b>	<b>1.2 – 9.4</b>	<b>89.43</b>	<b>85.12</b>	<b>9</b>	<b>&lt;0.001</b>

## Discussion

Spontaneous bacteria peritonitis (SBP) is a common complication of liver cirrhosis. The global burden of SBP on liver cirrhosis was reported by several researchers in reviews and regular research literature. There are several causes of liver cirrhosis, HBV and HCV are the major cause of viral based cirrhosis [30]. Treatment and management of liver cirrhosis highly depend on the aetiology [31]; therefore, an understanding of the prevalence of SBP in viral-based cirrhosis will provide baseline data on the global distribution pattern and epidemiology of SBP in HBV, and HCV related cirrhosis, helpful insight in future epidemiological forecast on the edemicity of the disease globally, the findings of this review will provide a good insight for effective SBP treatment and management worldwide.

This systematic review and meta-analysis aimed to determine the global prevalence of SBP in HBV, and HCV liver cirrhosis. The findings of this review were based on the data collected from three categories of viral hepatitis cirrhosis (liver cirrhosis caused by HBV, liver cirrhosis caused by HCV, and liver cirrhosis caused by both HBV and HCV) globally. In addition, the occurrence

of SBP in viral cirrhosis from different countries, the method of SBP detection, and the sampling period were considered.

The review included ten studies across three continents that met our inclusion criteria. Most of the studies were from the USA and South Korea, accounting for 40% of the included studies. The incidence of SBP in viral cirrhosis was significant in the USA and South Korea, despite the commendable hepatitis surveillance, prevention, and treatment schemes available in both nations.

SBP in HBV liver cirrhosis had the highest prevalence (8.0%). The latter could be due to the relative immunological and epidemiological significance of HBV infection among patients [32]. Our findings are consistent with other reports [33].

SBP coinfecting HBV+HCV-based cirrhosis had the lowest estimate, and the latter could be attributed to several factors; the occurrence of HBV+HCV coinfection incidence is relatively typical compared to other prevailing disease conditions associated with hepatitis and its progression into liver cirrhosis [34], the immunological imprints and cell memories triggers during the viral clearance stage of hepatitis progression into liver cirrhosis is adequate to neutralise SBP infection [35].

Country subgroup analysis revealed that China (61.8%) had the highest estimate of SBP in HBV liver cirrhosis. This could be due to the country's high nosocomial and community-based SBP infection [36]. The findings of this study complement other reports [37].

Italy also had a significant SBP in HBV cirrhosis (30.0%). The probable reason for the high prevalence is unclear. Still, it could be due to the high HBV prevalence in Italy despite the preventive measures already in place to curb the disease's endemicity. The findings of this report agree with the description of [38], who reported a significant HBV occurrence in an Italian city despite the implementation of the HBV vaccination scheme.

USA had a relatively low estimate of SBP in HBV cirrhosis in this study (3.3%). It can be attributed to the evolutionary shift of the HBV infection, as the overall prevalence of HBV infection in the USA has reduced drastically over the past two decades [39].

Despite the variation in the estimate of SBP in HBV cirrhosis in Asia (South Korea [13.3%], China [61.8%]), Pakistan had the lowest estimate (0.1%) in our study, and this could be associated with

the low morbidity of SBP in liver cirrhosis patients in Pakistan, it can also be attributed to the low level of SBP reporting and documentation [40].

Tunisia had a low SBP in HBV cirrhosis estimate (1.0%). This could be due to the low estimate of SBP in North Africa and underreporting [41]. The burden of SBP in HCV liver cirrhosis had the highest estimate in the USA (50.0%). This could be due to the distribution of HCV infection in the USA and high-risk behaviours [42]. Our findings are consistent with the report of others [43], [44].

The trend of SBP infection in HCV liver cirrhosis in Europe was diverse in our study, Greece had the highest estimate (11.8%), and Holland had the lowest estimate (0.7%). The latter could be due to the distribution pattern of SBP and HCV across Europe. This finding compliments the report of [45], [46], who reported a variation in the distribution pattern of HCV in European countries.

Despite the high prevalence of SBP in HCV liver cirrhosis in China (8.2%), the trend of SBP prevalence in HCV cirrhosis in Pakistan (0.1%) and South Korea (0.3%) was relatively low. This could be attributed to the heavy epidemiological burden of HCV in China and the variation in the geographical distribution of HCV in Asia [47], [48].

The prevalence of SBP in both HBV and HCV cirrhosis had the highest estimate in Holland (31.3%). The high estimate is not apparent, but it could be due to the immunological significance of HBV and HVC coinfection. The findings of this study correspond with other reports[34], [49].

Most studies included in this systematic review and meta-analysis were carried out between the year >2006 to 2015, accounting for 80% of the study in this review. Studies whose samples were collected in years <2006 had the highest estimate of SBP in HBV liver cirrhosis (12.9%), followed by studies whose samples were collected between the years 2006 – 2015 (11.0%). The burden of SBP in HBV liver cirrhosis reduced drastically towards the start of the year 2016 (1.2%). The probable reason for the sudden fall in the prevalence of SBP in HBV cirrhosis could be attributed to the improvement in the global health and care system and the impact of HBV vaccination/prevention programs globally [48].

The burden of SBP in HCV cirrhosis is not like the SBP in HBV cirrhosis, as there was a spike in the estimate of SBP in HCV cirrhosis at the start of the year 2016 (11.1%), despite the reduction in the morbidity of SBP burden in HCV cirrhosis from year <2006 (7.6%) to duration between

2015 – 2015 (0.6%) there was a sudden high trend of SBP prevalence among HCV cirrhosis at the start of the year 2016. The reason for the sudden surge in the prevalence of SBP in HCV cirrhosis is not apparent, but it could be attributed to several factors; lack of preventive vaccines for HCV, changes in the epidemiological spectra of the disease and the high level of degeneracy and diversification of the HCV progeny [44], [50], [51].

The prevalence of SBP in both HBV and HCV liver cirrhosis reduced in the year 2006 – 2015 (0.7%) after the initial high prevalence in year < 2006 (4.9), this could be attributed to the effectiveness of the HBV preventive vaccine and adequate awareness of the disease by the appropriate agencies [52].

Despite the drop in overall SBP incidence in both HBV and HCV cases between 2006 – 2015, there was a rise in the overall prevalence of SBP in HBV+HCV cirrhosis in year > 2016 (9.3%). The probable reason for the spike in SBP cases in HBV+HCV could be due to the low immunity of patients due to the dual infection of both HBV and HCV [34].

There were three study designs for our study; case-control, retrospective and prospective study design. Eighty per cent (80%) of the included research were retrospective studies. This could be due to the overall burden of SBP in liver cirrhosis over a long period [53]. In comparison, the retrospective study design had the highest estimate of SBP in HBV cirrhosis (9.2%), while case-control studies had the highest estimate of SBP in HCV liver cirrhosis (50.0%). Studies reporting prospective design had the highest estimate of SBP in both HBV and HCV cirrhosis (7.1%). The variation in the estimate of SBP in the three different Hepatitis cirrhosis cases in our review could be due to other study designs. These findings disagree with the report of [54], who reported that differences in study designs do not significantly impact the prevalence of a disease.

A subgroup meta-analysis was carried out on the method of SBP detection in viral hepatitis liver cirrhosis. Our findings revealed that most of our studies (70%) reported only the cultural method as the mean of SBP detection. In comparison, others reported cell counting and culturing (30%) as their means of SBP detection. The burden of SBP in studies reporting only culturing was high across different groups. Comparatively, SBP in HBV cirrhosis and SBP in HCV cirrhosis had their highest estimate in studies reporting only culturing as means of SBP detection (HBV cirrhosis 10.7% and HCV cirrhosis 4.1%). There was an equivocal estimate of SBP in HBV+HCV cirrhosis (2.9%), and there was no significant change in the prevalence of SBP in the examined detection

method. This could be due to the preference for culturing over other methods in SBP detection [55].

## **Conclusion**

This is the first systematic review and meta-analysis of SBP in viral hepatitis-associated liver cirrhosis. It reveals an uprise in the occurrence of SBP in viral hepatitis over the last decade. This indicates a possible hike in the global prevalence of SBP among viral hepatitis-associated liver cirrhosis. This review will help governments and governmental agencies to set policies towards curbing the morbidity of SBP in viral hepatitis liver cirrhosis globally.

## **Supporting documents**

K1: PRISMA 2009 checklist.

K2: Search strategy.

K3: Joanna Briggs Institute (JBI) critical appraisal checklist for prevalence data.

K4: Quality assessment of the included studies

## **Authors contributions**

Conceptualisation: BKE and NM. Conceived and designed the study.

Methodology: BKE, AAI, NM, APE and RHS select and assess the quality of studies. BKE, SBA, OMO, and RHS extracted and analysed data.

Analysis and writing: BKE interpreted the results and drafted the manuscript.

Writing- review and editing: BKE, AAI, RHS, NM, SBA, APE, and OMO reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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