Seroprevalence of Hepatitis E Virus Infection in Middle Eastern Countries: A Systematic Review and Meta-Analysis

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Abstract: Hepatitis E virus (HEV) is a hepatotropic virus that is a major public health concern worldwide. Autochthonous HEV is spread through oral feces in unsanitary environments, as well as vertical and, occasionally, blood transfusion. HEV is more common in developing countries, but it has recently become more widespread in developed countries as well. The Middle East (ME) has long been an endemic location for HEV infection. Therefore, the aim of this systematic review and meta-analysis was to assess the seroprevalence of anti-HEV antibodies in ME countries. The author systematically searched five databases, namely ScienceDirect, EMBASE, Scopus, PubMed, and Google Scholar, to identify English-language articles published on or before 25 April 2022. Comprehensive meta-analysis software was used for all statistical analyses (CMA, version 3, BioStat, Englewood, CO, USA). After quality control and exclusion of irrelevant studies, 80 studies were included in the qualitative synthesis and meta-analysis. A forest plot showed that the overall pooled seroprevalence of HEV infection in ME countries in the fixed-effect and random-effect models were 21.3% (95% CI: 0.209–0.216) and 11.8% (95% CI: 0.099–0.144), respectively. Furthermore, the findings showed a high level of heterogeneity (I² = 98.733%) among the included studies. In both fixed-effect and random-effect models, the seroprevalence of HEV infection by country was high in Egypt as compared to other regions, at 35.0% (95% CI: 0.342–0.359), and 34.7% (95% CI: 0.153–0.611), respectively. The seroprevalence of HEV infection by country was high among pregnant women, at 47.9% (95% CI: 0.459–0.499) in the fixed-effect model, and in renal transplant recipients, at 30.8% (95% CI: 0.222–0.410) in the random-effect model. The seroprevalence of HEV infection varies by country and study population in the Middle East. More research is needed to determine the disease’s incidence, morbidity, and mortality in the region, where it is prevalent.

Keywords: hepatitis E virus; prevalence; Middle Eastern countries; systematic review; meta-analysis

1. Introduction

The World Health Organization (WHO) launched a global strategy to stop viral hepatitis transmission in 2016, recommending that persons with viral hepatitis have access to safe, accessible, and effective prevention, care, and treatment services [1]. By 2030, the goals are to reduce the number of new instances of hepatitis by 90 percent, treat 80 percent of eligible patients infected with viral hepatitis, and reduce the number of hepatitis-related fatalities by 65 percent [1]. Globally, nearly 1.34 million deaths were attributed to viral hepatitis in 2015, with 95 percent of those deaths attributed to chronic hepatitis B and C infections and the remainder to hepatitis A and E infections [1,2].

Global estimates suggest that more than 20 million new instances of hepatitis E virus (HEV) infections occur each year, with 3.3 million of those becoming symptomatic [3]. In 2015, the WHO reported 44,000 fatal HEV infections, accounting for about 3.3 percent of all viral hepatitis-related deaths [3].

HEV is a water- and food-borne illness that can cause severe epidemics in areas where sanitation is lacking [1,3]. However, there has been evidence of zoonotic and transfusion-related transmission [4,5]. Because there is no specific treatment for HEV infection, it is
managed mostly through supportive care [1,3]. Prevention, on the other hand, focuses on limiting exposure through improved sanitation, clean food and drinking water, and vaccination [1]. In comparison to hepatitis B and C, HEV infection is less likely to cause chronic liver damage, and the development of fulminant hepatitis, albeit rare, is mostly influenced by host-specific rather than virus-specific variables [6].

Clinical signs and symptoms such as myalgia, arthralgia, anorexia, hepatomegaly, fever, weakness, vomiting, and jaundice emerge two to nine weeks after HEV exposure. In rare and severe cases, HEV can cause abrupt liver failure. Chronic instances are uncommon; however, they can occur in immunocompromised persons [7,8]. There is a variety of laboratory tests for HEV infection diagnosis, which can be divided into direct (detection of HEV or viral protein via polymerase chain reaction or enzyme immunoassay) and indirect (detection of anti-HEV antibodies) approaches [9,10]. Recent HEV infection is linked to the existence of IgM anti-HEV antibodies. Furthermore, the presence of anti-HEV IgG antibodies is indicative of recent or distant HEV exposure. Both antibodies are critical for HEV infection diagnosis and can be linked to long-term infection [9,10].

The majority of people in Middle Eastern (ME) countries live in middle-income countries, where viral hepatitis is a major health concern [11]. Furthermore, HEV infection is highly endemic in most of the countries in this region [12,13]. Given these countries’ changing socioeconomic conditions, identifying the epidemiological pattern of HEV infection will assist healthcare policymakers in making better decisions regarding future strategies for controlling this virus, as well as selecting and implementing cost-effective preventative methods [14,15].

Furthermore, to the very best of our knowledge, there remains a dearth of knowledge with respect to the prevalence of HEV-infected people with anti-HEV antibodies (IgG) in ME countries. Therefore, this systematic review and meta-analysis is the first attempt to provide a summarized and up-to-date estimation of the seroprevalence of HEV infection in ME countries.

2. Materials and Methods
2.1. Data Sources and Literature Search Strategy

The author systematically searched five databases, namely ScienceDirect, EMBASE, Scopus, PubMed, and Google Scholar, to identify English-language articles published on or before 25 April 2022 that originally reported data on the prevalence of HEV infection in ME countries. The following keywords were used: “Hepatitis E virus”, “HEV”, and “Prevalence”, combined with the names of ME countries, namely Akrotiri and Dhekelia, Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, and Yemen.

The current systematic review and meta-analysis was conducted according to the PRISMA recommendations (Supplementary Material S1) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration No. CRD42022330216).

2.2. Eligibility Criteria

The author included all observational studies conducted in ME countries that had, at least, an English abstract and reported on the prevalence of HEV-infected people with anti-HEV antibodies (IgG) among the general population, blood donors, hemodialysis patients, children, acute viral hepatitis patients, pregnant women, male blood donors, drug addicts, HIV positive individuals, thalassemia patients, soldiers, hemophiliac patients, renal transplant recipients, non-A-C hepatitis patients, and solid organ recipients. The systematic review and meta-analysis were designed to include people of all ages. Case reports, case series, letters, commentaries, editorials, non-human studies, symposia, correspondences, and citations without full text were all excluded from the study.
2.3. Study Screening and Data Extraction

The article screening process and removal of duplicates were managed using EndNote V.X8 software. Furthermore, two researchers (F.Q. and S.K.) meticulously and manually treated the data to reduce the chance of duplication. The following details were extracted from the included articles using a standardized data collection form: first-author name, publication year, study sample, study country, sampling year, study population, type of study, participants’ age (range), study city, percentage of male participants, percentage of female participants, and prevalence of HEV-infected people with anti-HEV antibodies (IgG).

2.4. Quality Assessment

The quality of the included articles was assessed using the National Institute of Health quality assessment technique [16,17]. This assessment tool was used because it allows for a thorough evaluation of the quality of the research included. Furthermore, the general quality of the studies was graded as good, fair, or poor, and these ratings were incorporated into the meta-analytic results. The two researchers (F.Q. and R.A.) compared their evaluations for each study, and any disagreements were handled through a joint discussion.

2.5. Data Synthesis and Statistical Analysis

Comprehensive meta-analysis software was used for all statistical analyses (CMA, version 3, BioStat, USA). To reset the effect size value obtained from the meta-analysis, the fail-safe N approach was used to determine the number of studies that should be added to the meta-analysis. The average effect size of the meta-analysis studies was computed. The seroprevalence of HEV infection in ME countries was pooled and investigated using a random-effect model, with the results displayed in forest plots. Using the extracted data, the rate of events, their 95 percent confidence intervals, and their p-values were determined. The \( I^2 \) statistic was used to assess the degree of heterogeneity among the included studies, with \( I^2 \) values of 0–40%, 25–50%, 50–75%, and >75% indicating trivial, low, moderate, and high heterogeneity, respectively [18]. A non-significant degree of statistical heterogeneity was assumed when \( p < 0.1 \) or \( I^2 < 50 \) percent [19]. Because of the considerable heterogeneity, a random-effects model was adopted. A funnel plot was used to discover potential signs of publication bias between included papers, as detected by Begg’s and Mazumdar’s rank correlation tests.

3. Results
3.1. Search Outcomes

The search yielded a total of 14,497 articles from five databases: ScienceDirect (n = 1816), EMBASE (n = 2326), Scopus (n = 2354), PubMed (n = 3328), and Google Scholar (n = 4673). After duplicates were excluded, 6539 articles remained. A further 3257 articles were excluded due to the studies being conducted in non-ME countries, in addition to 1965 studies deemed irrelevant after screening the titles and abstracts. Then, we reviewed the full text of the remaining 1317 articles and excluded 1237 studies for not fulfilling our inclusion criteria. Ultimately, 80 studies were included in the qualitative synthesis and meta-analysis. The PRISMA flow chart for the process of article screening and selection is presented in Figure 1.
3.2. Characteristics of the Included Studies

Of the 80 included studies, 41 were conducted in Iran, 14 in Turkey, 8 in Egypt, 4 in Israel, 3 in Saudi Arabia, 3 in Iraq, 2 in Qatar, 1 in Kuwait, 1 in Syria, 1 in Yemen, 1 in the United Arab Emirates, 1 in Lebanon, 1 in Palestine, and 1 in Jordan. The prevalence of HEV IgG antibodies in the included studies ranged from 0.8% to 84.3% (range = 14.9). The targeted populations in the included studies were the general population (15 studies), blood donors (12 studies), hemodialysis patients (12 studies), children (11 studies), acute viral hepatitis patients (8 studies), pregnant women (7 studies), male blood donors (3 studies), drug addicts (3 studies), HIV-positive individuals (3 studies), thalassemia patients (2 studies), soldiers (1 study), hemophilia patients (1 study), renal transplant recipients (1 study), non-A-C hepatitis patients (1 study), and solid organ recipients (1 study). The sample size of the included articles ranged from 43 to 11,604 (average = 844) (Table 1).
Table 1. Characteristics of the included studies in the systematic review and meta-analysis.

| First-Author Name | Publication Year | Study Sample | Study Country | Sampling Year | Study Population | Type of Study | Participant Age (Range) | Study City | Male (%) | Female (%) | Prevalence (%) | Ref. |
|-------------------|------------------|--------------|---------------|---------------|------------------|--------------|------------------------|------------|----------|------------|----------------|-----|
| Thomas David      | 1993             | 1350         | Turkey        | 1990–1992     | General population | Cross-sectional | 18–65 years | Istanbul, Ayvalik, Aydin, Trabzon region, and Adana | 50.2       | 49.8     | 5.9        | [20]         |
| Abraham Koshy     | 1994             | 57           | Kuwait        | 1992          | Acute viral hepatitis patients | Cross-sectional | 19–46 years | Kuwait | 88       | 12         | 4              | [21]|
| Asher Barzilai    | 1995             | 188          | Israel        | NM            | Hemophiliac patients | Cross-sectional | 2–75 years | Tel Aviv | 98.9     | 1.1        | 9              | [22]|
| Yuory Karetny     | 1995             | 1416         | Israel        | 1988–1993     | General population | Cross-sectional | 1–66 years | West Bank and central region of Israel | NM         | NM       | 2.6        | [23]         |
| Abdelaal Zawawi   | 1998             | 593          | Saudi Arabia  | 1995          | Male blood donors | Cross-sectional | 15–60 years | Jeddah | 100      | 0          | 16.9           | [24]|
| SI Abdel Hady     | 1998             | 95           | Egypt         | NM            | Blood donors      | Cross-sectional | NM          | NM      | NM       | NM         | 45.2           | [25]|
| SI Abdel Hady     | 1998             | 96           | Egypt         | NM            | Hemodialysis patients | Cross-sectional | NM          | NM      | NM       | NM         | 39.6           | [25]|
| Al-Azmeh J        | 1999             | 193          | Syria         | 1995–1998     | Acute hepatitis patients | Hospital-based | 12–70 years | Damascus | 52.4     | 47.6       | 31.9           | [26]|
| Sidal M           | 2001             | 909          | Turkey        | 1997–1998     | Children          | Cross-sectional | Six months–15 years | Istanbul | NM       | NM         | 2.1           | [27]|
| Colak D           | 2002             | 338          | Turkey        | 1996–1997     | Pediatric age groups | Cross-sectional | 1–11 years | Antalya | NM       | NM         | 0.89           | [28]|
| Cesur Salih       | 2002             | 1046         | Turkey        | 2000–2001     | Adults            | Cross-sectional | 15–75 years | Ankara   | NM       | NM         | 3.8            | [29]|
| Arif Serhan Cevrioglu | 2004       | 76           | Turkey        | 2000–2002     | Pregnant women    | Cross-sectional | 19–42 years | Afyon     | 0        | 100        | 12.6           | [30]|
Table 1. Cont.

| First-Author Name | Publication Year | Study Sample | Study Country | Sampling Year | Study Population | Type of Study | Participant Age (Range) | Study City | Male (%) | Female (%) | Prevalence (%) | Ref. |
|-------------------|------------------|--------------|---------------|---------------|------------------|---------------|-------------------------|------------|----------|------------|---------------|------|
| Irfan Sencan      | 2004             | 383          | Turkey        | 1999          | Children         | Cross-sectional | 2–15 years             | Düzce      | 51.7     | 48.3       | 4.7           | [31] |
| Atabek Emre       | 2004             | 210          | Turkey        | 2001–2002     | Children         | Cross-sectional | 1–18 years             | Konya      | 49       | 51         | 5.5           | [32] |
| Aminiafshar S     | 2004             | 90           | Iran          | 2003–2004     | Blood donors     | Cross-sectional | 40–49 years            | Tehran     | 80.2     | 19.8       | 7.8           | [33] |
| Irfan Sencan      | 2004             | 93           | Turkey        | 1999          | Children         | Cross-sectional | 2–15 years             | Golyaka    | 37.6     | 62.4       | 17.2          | [31] |
| Serkan Oncu       | 2005             | 386          | Turkey        | NM            | Pregnant women   | Cross-sectional | 18–32 years            | Aydin      | 0        | 100        | 7             | [34] |
| Alaa A Aboulata   | 2005             | 100          | Egypt         | 2004–2005     | Children         | Cross-sectional | 1–10 years             | Cairo      | NM       | NM         | 26            | [35] |
| Mahnaz Taremi     | 2005             | 324          | Iran          | 2004          | Hemodialysis patients | Cross-sectional | 18–80 years            | Tabriz     | 59       | 41         | 7.4           | [36] |
| Sonia Stoszek     | 2006             | 2428         | Egypt         | 1997–2003     | Pregnant women   | Cross-sectional | 18–40 years            | Nile Delta | NM       | NM         | 84.3          | [37] |
| M. Taremi         | 2007             | 399          | Iran          | 2004          | Male blood donors| Cross-sectional | 20–60 years            | Tabriz     | 100      | 0          | 7.8           | [38] |
| Gholam Ali Ghorbani| 2007            | 800          | Iran          | 2006          | Soldiers         | Cross-sectional | 17–23 years            | Tehran     | 100      | 0          | 1.1           | [39] |
| Seyed Mohammad Alavi| 2008           | 224          | Iran          | 2005–2006     | Drug addicts     | Cross-sectional | 18–54 years            | Ahvaz      | 100      | 0          | 13.5          | [40] |
| Mohammad Ali Assarehzadeh | 2008 | 400 | Iran | 2005 | Blood donors | Cross-sectional | 18–60 years | Khuzestan | 65 | 35 | 11.5 | [41] |
| M. Taremi         | 2008             | 1824         | Iran          | 2003          | General population| Cross-sectional | 6–80 years            | Nahavand   | NM       | NM         | 9.3           | [42] |
| First-Author Name          | Publication Year | Study Sample | Study Country | Sampling Year | Study Population                      | Type of Study       | Participant Age (Range) | Study City         | Male (%) | Female (%) | Prevalence (%) | Ref. |
|---------------------------|------------------|--------------|---------------|---------------|---------------------------------------|---------------------|------------------------|---------------------|----------|------------|----------------|------|
| Uçar Edip                 | 2009             | 92           | Turkey        | NM            | Hemodialysis patients                 | Cross-sectional    | 22–71 years            | Hatay               | 58.7     | 41.3       | 20.6           | [43] |
| Shamsizadeh Ahmad         | 2009             | 566          | Iran          | 2006–2007     | Children                              | Cross-sectional    | 6–15 years             | Southwestern Iran   | 45.4     | 54.6       | 8.5            | [44] |
| Behrooz Ataei             | 2009             | 816          | Iran          | 2005          | General population                    | Cross-sectional    | 6–60 years             | Isfahan             | 47.5     | 52.5       | 3.8            | [45] |
| Pourahmad Morteza         | 2009             | 43           | Iran          | 2007          | Hemodialysis patients                 | Cross-sectional    | NM                     | Jahrom              | 67.4     | 32.6       | 7              | [46] |
| Maral I                   | 2010             | 515          | Turkey        | 2003–2005     | Primary school children               | Cross-sectional    | 6–13 years             | Ankara              | 52.7     | 47.3       | 1.9            | [47] |
| Amen Ahmed Bawazir        | 2010             | 538          | Yemen         | 2005          | General population                    | Cross-sectional    | one month–79 years     | Aden                | 52       | 48         | 16             | [48] |
| Rachana Kumar             | 2010             | 469          | United Arab Emirates | NM | Pregnant women                          | Cohort              | NM                     | Al Ain               | 0        | 100        | 20             | [49] |
| SG Sepanlou               | 2010             | 1423         | Iran          | 2009          | General population                    | Cross-sectional    | NM                     | Tehran and Golestan | NM       | NM         | 7.4            | [50] |
| Turky Ataallah            | 2011             | 9610         | Iraq          | 2005–2006     | Acute viral hepatitis                 | Cross-sectional    | 1–60 years             | Baghdad             | 49.5     | 50.5       | 19.4           | [51] |
| Turky Ataallah            | 2011             | 6972         | Iraq          | 2005–2006     | General population                    | Cross-sectional    | 1–60 years             | Baghdad             | 48.8     | 51.2       | 20.3           | [51] |
| Zakieh Rostamzadeh Khameneh| 2011             | 91           | Iran          | NM            | Renal transplant recipients          | Cross-sectional    | 6–65 years             | Urmia               | 67       | 33         | 30.8           | [52] |
| Seyed Reza Mohebbi        | 2012             | 551          | Iran          | 2006–2007     | General population                    | Cross-sectional    | 1–83 years             | Tehran              | 36.3     | 63.7       | 9.4            | [53] |
| Seyed Reza Mohebbi        | 2012             | 551          | Iran          | 2006–2007     | General population                    | Cross-sectional    | 1–83 years             | Tehran              | 50       | 50         | 9.3            | [53] |
| First-Author Name                  | Publication Year | Study Sample | Study Country   | Sampling Year | Study Population        | Type of Study                  | Participant Age (Range) | Study City     | Male (%) | Female (%) | Prevalence (%) | Ref. |
|-----------------------------------|------------------|--------------|----------------|---------------|------------------------|-------------------------------|----------------------------|-----------------|-----------|-------------|----------------|------|
| Abdolreza Sotoodeh Jahromi        | 2013             | 477          | Iran           | 2009          | Blood donors           | Cross-sectional              | 17–59 years              | Jahrom         | 447       | 30          | 5.4           | [54] |
| Sanaz Ahmadi Ghezeldasht          | 2013             | 1582         | Iran           | 2012          | General population     | Cross-sectional              | 1–90 years                | Mashhad        | 45.4      | 54.6        | 14.2          | [55] |
| Nural Cevahir                     | 2013             | 185          | Turkey         | NM            | Primary school children| Cross-sectional              | 7–14 years                | Denizli         | 50.3      | 49.7        | 12.4          | [56] |
| Hassan Ehteram                    | 2013             | 530          | Iran           | 2012          | Blood donors           | Cross-sectional              | 31–50 years              | Central province | 91.9      | 8.1         | 14.3          | [57] |
| Omid Zekavat                      | 2013             | 80           | Iran           | 2010          | Patients with chronic  | Cross-sectional              | 26–80 years              | Southwestern Iran | 63.7      | 63.3        | 6.3           | [58] |
|                                   |                  |              |                |               | maintenance hemodialysis|                              |                           |                 |           |             |                |      |
| A.R. Mobaien                      | 2013             | 93           | Iran           | 2011          | Hemodialysis patients  | Cross-sectional              | 16–88 years              | Tehran         | 52.7      | 47.3        | 26.9          | [59] |
| Ayman Khalid Johargy              | 2013             | 900          | Saudi Arabia   | 2009          | Male blood donors      | Cross-sectional              | 18–66 years              | Makkah         | 100       | 0          | 18.7          | [60] |
| Nawal Utba                        | 2013             | 270          | Iraq           | NM            | Blood donors and cleaning workers | Cross-sectional              | 18–60 years              | Baghdad        | 67        | 33          | 21.5          | [61] |
| Amitis Ramezani                   | 2013             | 100          | Iran           | 2012          | HIV-positive individuals| Cross-sectional              | 34–43 years              | Tehran         | 71        | 29         | 10           | [62] |
| Fariba Keramat                    | 2014             | 131          | Iran           | 2011–2012     | Injection drug users   | Cross-sectional              | 22–70 years              | Hamadan        | 99.2      | 0.8         | 6.1           | [63] |
| Fariba Keramat                    | 2014             | 131          | Iran           | 2011–2012     | Non-injection drug users| Cross-sectional              | 20–45 years              | Hamadan        | 99.2      | 0.8         | 1.5           | [63] |
| Seyed Seifollah Beladi Mousavi    | 2014             | 47           | Iran           | NM            | Hemodialysis patients  | Cross-sectional              | 20–80 years              | Ahvaz          | 57.4      | 42.6        | 10.6          | [64] |
| Peyman Eini                       | 2015             | 153          | Iran           | 2010          | Hemodialysis patients  | Cross-sectional              | 10–70 years              | Hamadan        | 54.2      | 45.8        | 19.2          | [65] |
| First-Author Name         | Publication Year | Study Sample | Study Country | Sampling Year | Study Population     | Type of Study                           | Participant Age (Range) | Study City       | Male (%) | Female (%) | Prevalence (%) | Ref. |
|--------------------------|------------------|--------------|---------------|---------------|----------------------|-----------------------------------------|-------------------------|-----------------|-----------|------------|----------------|------|
| Orna Mor                 | 2015             | 729          | Israel        | 2009–2010     | General population   | Cross-sectional                        | 10–75 years             | Tel-Aviv        | 54        | 46         | 10.6           | [66] |
| Mojgan Mamani            | 2015             | 1050         | Iran          | 2010–2012     | Pregnant women       | Prospective cross-sectional             | 14–49 years             | Hamadan         | 0         | 100        | 7.4            | [67] |
| Seyed Moayed Alavian     | 2015             | 274          | Iran          | 2012          | Hemodialysis patients| Cross-sectional                        | 21–80 years             | Isfahan         | 52.9      | 47.1       | 9.9            | [68] |
| Hassan Joulaieni         | 2015             | 158          | Iran          | 2012–2013     | HIV-positive individuals| Cross-sectional                        | 1–60 years              | Shiraz          | 76.9      | 23.1       | 16.4           | [69] |
| Behrouz Naeimi           | 2015             | 628          | Iran          | 2013          | Blood donors         | Cross-sectional                        | 19–65 years             | Bushehr         | 95.2      | 4.8        | 16.7           | [70] |
| Daniela Ram              | 2016             | 49           | Israel        | 2013–2015     | Acute hepatitis patients| Cross-sectional                        | NM                      | Haifa, Tel Aviv, Beer Sheva | NM     | NM         | 6.1            | [71] |
| Hossein Keyvani          | 2016             | 200          | Iran          | NM            | Blood donors         | Cross-sectional                        | 20–61 years             | Tehran          | 58.2      | 41.8       | 4.5            | [72] |
| Hossein Keyvani          | 2016             | 100          | Iran          | NM            | Patients with hepatitis C| Cross-sectional                        | 20–61 years             | Tehran          | 58.2      | 41.8       | 7              | [72] |
| Hossein Keyvani          | 2016             | 150          | Iran          | NM            | Patients with hepatitis B| Cross-sectional                        | 20–61 years             | Tehran          | 58.2      | 41.8       | 11.3           | [72] |
| Hajiahmadi Nazila        | 2016             | 149          | Iran          | NM            | Hemodialysis patients| Cross-sectional                        | 15–90 years             | Golestan        | 49        | 51         | 4              | [73] |
| Hajiahmadi Nazila        | 2016             | 102          | Iran          | NM            | HIV-infected patients| Cross-sectional                        | 17–54 years             | Golestan        | 68.6      | 31.4       | 33.3           | [73] |
| Khashayar Hesamizadeh    | 2016             | 559          | Iran          | 2014          | Blood donors         | Cross-sectional                        | 18–37 years             | Tehran          | 95.9      | 4.1        | 8.1            | [74] |
| Zohreh Azarkar           | 2016             | 340          | Iran          | 2013–2014     | Blood donors         | Cross-sectional                        | 20–40 years             | Birjand         | 93.8      | 2.2        | 14.7           | [75] |
| Gamal Hasan              | 2016             | 123          | Egypt         | 2007–2008     | Children             | Multicenter prospective              | 2–18 years             | Assiut          | 59.3      | 40.7       | 26.8           | [76] |
| First-Author Name            | Publication Year | Study Sample | Study Country | Sampling Year | Study Population          | Type of Study | Participant Age (Range) | Study City       | Male (%) | Female (%) | Prevalence (%) | Ref. |
|-----------------------------|------------------|--------------|---------------|---------------|---------------------------|---------------|------------------------|-----------------|----------|------------|-----------------|-----|
| Gülsüm İclal Bayhan         | 2016             | 408          | Turkey        | 2014          | Children                 | Cross-sectional | 2 months-18 years      | Van             | 43.9     | 56.1       | 4.2             | [77]|
| Gheyath Nasrallah           | 2017             | 5854         | Qatar         | 2013–2016     | Blood donors             | Cross-sectional | 15–80 years           | Al Doha         | 97.4     | 2.6        | 20.7            | [78]|
| Mohammad Obaidata           | 2018             | 450          | Jordan        | 2015–2016     | Patients who visit healthcare clinics for routine care | Cross-sectional | 20–80 years           | Eight governorates | 45.1     | 54.9       | 30.9            | [79]|
| Fatemeh Farshadpour         | 2018             | 1331         | Iran          | 2016–2017     | Pregnant women           | Cross-sectional | 14–45 years           | Bushehr         | 0        | 100        | 6.3             | [80]|
| Mehdī Parsa Nahad           | 2018             | 241          | Iran          | 2013–2016     | Acute viral hepatitis patients | Cross-sectional | 10–80 years           | Ahvaz           | 51.9     | 48.1       | 27.4            | [81]|
| Najmeh Dalvand              | 2019             | 120          | Iran          | 2019          | Thalassemia-positive patients | Cross-sectional | 17–45 years           | Tehran          | 35       | 65         | 1.67            | [82]|
| Mohammad Amin Behzadi       | 2019             | 562          | Iran          | 2016–2017     | Healthy individuals      | Cross-sectional | 1–86 years            | Hormozgan       | 29.2     | 70.8       | 15.8            | [83]|
| Doaa Abdelmawla             | 2019             | 140          | Egypt         | 2016          | Children with transfusion-dependent thalassemia | Cross-sectional | 2–6 years             | Mansoura        | 47.1     | 52.9       | 27.15           | [84]|
| Mohamad Bachar Ismail       | 2020             | 171          | Lebanon       | 2016          | Hemodialysis patients    | Cross-sectional | 23–82 years           | Tripoli         | 43.8     | 56.2       | 21.63           | [85]|
| Azza Masoud Abdelbaky Ahmed | 2020             | 11,604       | Egypt         | 2013–2014     | Blood donors             | Cross-sectional | 18–60 years           | Qena            | 88.2     | 11.8       | 28.8            | [86]|
| Mahbube Ouji                | 2021             | 226          | Iran          | NM            | Hemodialysis patients    | Cross-sectional | 23–87 years           | Bushehr, Borazjan, and Genaveh | 56.2     | 43.8       | 68.6            | [87]|
| Farzin Sadeghi              | 2021             | 247          | Iran          | 2020          | Pregnant women           | Cross-sectional | 17–42 years           | Northern Iran    | 0        | 100        | 0.8             | [88]|
| First-Author Name          | Publication Year | Study Sample | Study Country | Sampling Year | Study Population    | Type of Study       | Participant Age (Range) | Study City       | Male (%) | Female (%) | Prevalence (%) | Ref. |
|---------------------------|------------------|--------------|---------------|---------------|---------------------|---------------------|------------------------|-----------------|----------|------------|----------------|------|
| Reem A Al Dossary         | 2021             | 806          | Saudi Arabia  | 2020          | Blood donors        | Cross-sectional     | 18–85 years            | Eastern province     | 94.9     | 5.1        | 3.2            | [89]   |
| Sayed El-Mokhtar          | 2021             | 300          | Egypt         | 2016–2018     | Non-A-C hepatitis patients | Cross-sectional     | 40–60 years            | Assiut           | 53       | 47         | 10             | [90]   |
| Enas Al Absi              | 2021             | 259          | Qatar         | 2017–2019     | Non-A-C hepatitis patients | Cross-sectional     | 6–98 years             | Al Doha           | 61.4     | 83.6       | 32.1           | [91]   |
| Kamal Dumaidi             | 2022             | 432          | Palestine     | 2015–2017     | General population  | Cross-sectional     | 1–86 years             | West Bank and Jerusalem | 49.3     | 50.7       | 3.7            | [92]   |
| Seval Öğüt                | 2022             | 485          | Turkey        | NM            | Solid organ recipients | Cross-sectional     | 1–80 years             | Izmir            | 64.7     | 35.3       | 17.3           | [93]   |

NM denotes “not mentioned”.

Table 1. Cont.
3.3. Overall Pooled Seroprevalence of Hepatitis E Virus Infection in Middle Eastern Countries

All eighty included studies were pooled for meta-analysis; the forest plot showed that the overall pooled seroprevalence of HEV infection in ME countries in the fixed-effect and random-effect models was 21.3% (95% CI: 0.209–0.216), and 11.8% (95% CI: 0.099–0.144), respectively. Furthermore, the findings showed a high level of heterogeneity ($I^2 = 98.733\%$) among the included studies. Furthermore, the overall pooled seroprevalence of HEV infection in ME countries was statistically significant (pooled $p$-value < 0.001) in both fixed-effect and random-effect models (Figure 2). Table 2 shows the mean effect size and confidence intervals based on the random effect analysis of the studies in the meta-analysis.

![Figure 2. Forest plot meta-analysis of seroprevalence of hepatitis E virus infection in Middle Eastern countries.](image-url)
Table 2. Meta-analysis and effect analysis values of included studies, homogeneous distribution value, average effect size, and confidence intervals.

| Model   | Effect Size and 95% Confidence Interval | Test of Null (2-Tail) | Heterogeneity | Tau-Squared |
|---------|-----------------------------------------|-----------------------|---------------|-------------|
|         | Number of Studies | Point of Estimate | Lower Limit | Upper Limit | Z-Value | p-Value | Q-Value | df (Q) | p-Value | I Squared | Tau Squared | Standard Error | Variance | Tau |
| Fixed   | 80 | 0.213 | 0.216 | 0.293 | −124.850 | 0.000 | 6154.911 | 79 | 0.000 | 98.733 | 0.763 | 0.372 | 0.138 | 0.874 |
| Random  | 80 | 0.118 | 0.141 | 0.253 | −19.651 | 0.000 |           |    |        |         |        |        |        |        |
3.4. **Subgroup Analysis**

In both fixed-effect and random-effect models, the seroprevalence of HEV infection by country was highest in Egypt as compared to other countries, at 35.0% (95% CI: 0.342–0.359) and 34.7% (95% CI: 0.153–0.611), respectively (Figure 3).

![Figure 3. Forest plot meta-analysis of seroprevalence of hepatitis E virus infection by country.](image)

The seroprevalence of HEV infection by the study population was highest in pregnant women 47.9% (95% CI: 0.459–0.499) in the fixed-effect model and in renal transplant recipients, 30.8% (95% CI: 0.222–0.410) in the random-effect model, as compared to other populations (Figure 4).
3.5. Publication Bias

The results of Begg’s and Mazumdar’s rank correlation tests revealed a dispersed distribution, implying publication bias. The $p$-values for Kendall’s tau without continuity and Kendall’s tau with continuity were both 0.001 (Table 3). Figure 5 depicts a funnel plot of the seroprevalence of HEV infection in ME countries with publication bias.

**Figure 4.** Forest plot meta-analysis of seroprevalence of hepatitis E virus infection by study population [20–93].
Table 3. Begg’s and Mazumdar’s rank correlation.

|                      | Kendall’s S Statistic (P-Q) | Kendall’s tau without continuity correction |
|----------------------|-----------------------------|--------------------------------------------|
|                      | 6154.911                    | Tau                                         |
|                      |                             | 0.7633                                      |
|                      |                             | z-value for tau                            |
|                      |                             | −124.850                                    |
|                      |                             | p-value (1-tailed)                         |
|                      |                             | 0.001                                       |
|                      |                             | p-value (2-tailed)                         |
|                      |                             | 0.001                                       |
|                      |                             | Kendall’s tau with continuity correction   |
|                      |                             | Tau                                         |
|                      |                             | 0.8737                                      |
|                      |                             | z-value for tau                            |
|                      |                             | −19.65                                      |
|                      |                             | p-value (1-tailed)                         |
|                      |                             | 0.001                                       |
|                      |                             | p-value (2-tailed)                         |
|                      |                             | 0.001                                       |

Figure 5. Publication bias of the seroprevalence of hepatitis E virus infection in Middle Eastern countries.

4. Discussion

Worldwide, seroprevalence-based studies have received increased attention in recent years. However, due to incorrect diagnosis, underestimation, and a lack of awareness among clinicians about HEV, the published literature contains considerable gaps [94,95]. As a result, the goal of this study was to determine the seroprevalence of HEV infection in ME countries. Researchers and policymakers may benefit from the information in this systematic review and meta-analysis in order to better understand disease spread and develop effective control and prevention methods, particularly in ME countries.

Our findings showed that the seroprevalence of HEV infection in ME countries ranged from 0.8% among Iranian pregnant women [88] to 84.3% among Egyptian pregnant women [37]. Different test methodologies and geographic locations, research sample size, surveillance year, and other factors could explain these observed differences in HEV seroprevalence. However, in our study, in the fixed-effect and random-effect models, the overall pooled seroprevalence of HEV infection in ME countries was 21.3% and 11.8%, respectively. According to a recent systematic review and meta-analysis, the overall pooled prevalence of HEV infection in pregnant women around the world was 16.51% [95].
systematic review of HEV seroprevalence in thirteen African nations found that it ranged from zero to eighty-four percent, with pregnant women and rural areas having higher immunoglobulin levels than other areas [96]. The estimated pooled seroprevalence of HEV in Chinese blood donors was 30%. In European countries, the estimated seroprevalence of HEV ranged from 0.6% to 52.5% [97]. Another comprehensive evaluation of the Brazilian population found a 6.0% overall seroprevalence of HEV infection [98]. Furthermore, the pooled prevalence in our study is higher than in certain primary studies conducted among pregnant women in different countries, such as Serbian blood donors (15.0%) [99], as well as in Mexico (5.7%) [100], Pakistan (8.86%) [101], and Sudan (10.3%) [102].

Our analysis showed that Egypt has the highest seroprevalence of HEV infections compared to other countries. In Egypt, HEV infection is a neglected disease. In Egyptian hospitals, HEV testing is not frequently used for the diagnosis of suspected hepatitis patients [90]. Anti-HEV IgG seroprevalence in Egyptians is among the highest in the world, at up to 84 percent [37,103]. Furthermore, an HEV outbreak was previously observed in Assiut governorate rural villages [104].

Despite the fact that the incidence of HEV has declined significantly in recent years as a result of improved hygiene conditions [105], our analysis revealed that the seroprevalence of HEV infection was higher in pregnant women when compared to other populations. There is a considerable chance of vertical transmission of these viruses from the mother to the fetus, which can result in maternal and fetal problems, such as abortion, neonatal mortality, and early labor [106]. To avoid any negative consequences, it is critical to diagnose HEV infections in pregnant women.

An increasing number scientists and researchers are becoming aware of the repercussions of HEV infection, which include severe liver impairment and a high rate of morbidity and mortality, particularly in pregnant women. As a result, the pathophysiology and immunology of HEV interaction during pregnancy have received increased attention. However, especially in HEV endemic areas, it is critical to investigate genetic and environmental causes. To control and stop the disease in the near future, immunological research and prevention, as well as treatment measures, must be enhanced. In addition, in countries where the disease is endemic, cost-effective immunization efforts are required.

Despite the fact that the current meta-analysis has a large sample size and includes all ME countries and populations previously researched, it is subject to numerous limitations. The majority of the studies reviewed used distinct anti-HIV IgG ELISA kits with varying specificity and sensitivity, which could impair the reliability and accuracy of the tests. Only the anti-HEV IgG antibody level, which appears mainly after infection, was used to determine seroprevalence. Furthermore, the studies included in this systematic review and meta-analysis were observational, with a wide range of baseline characteristics, sample sizes, and sampling years.

5. Conclusions

The seroprevalence of HEV infection varies by country and study population in the ME and is highest in Egypt as compared to other countries and is highest in pregnant women and in renal transplant recipients as compared to other populations. More research is needed to determine the disease’s incidence, morbidity, and mortality in the region, where it is prevalent. In addition, essential steps should be taken to control and prevent HEV infection in general and in pregnant women in particular. Visiting endemic areas requires extra attention, especially when it comes to drinking water and food safety.

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