Liver diseases among Arab world, current state and unmet needs, a scoping review

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Introduction

A worrisome increase in liver diseases over the recent decades is noticed. Liver diseases are major causes of death and disability in Arab world, present with different patterns in all ages, both genders with variable socioeconomic status and culture.

Liver diseases have a significant burden of disease and costs worldwide, with variable etiologies and presentations, acute liver disease mainly due to viral hepatitis, while chronic liver disease due to alcohol and viral hepatitis. It’s expected that drug induced liver injury (DILI) will be a major cause of acute hepatitis. Metabolic associated fatty liver disease (MAFLD) and alcoholic liver disease (ALD) will be the main causes of chronic liver disease in the world (1).

Deaths per year due to liver disease accounts for approximately 2 million deaths per year worldwide, half of them due to cirrhosis and it’s complications and the second half is due to viral hepatitis and hepatocellular carcinoma (HCC) (2). However, increase in the global burden of both acute and chronic liver diseases is expected (2,3).

Viral hepatitides show a disastrous increase among the last decades, Acute hepatitis A showed a nearly 850% increase in incidence (3.8 in cases per 100,000 population in 2018) in comparison to 2014 (0.4 cases per 100,000 population), Acute hepatitis C showed a nearly 71% increase in incidence (1.2 in cases per 100,000 population in 2018) in comparison to 2014 (0.7 cases per 100,000 population), however acute hepatitis B showed a steady incidence rate in 2014 and 2018 due to vaccination (4,5).
Egypt is one of the top 6 countries in prevalence of chronic hepatitis C infection. Viral hepatitis became 7th leading cause of death in 2013 in comparison to 1990 was 10th leading cause (6).

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MAFLD shows a terrifying increase in incidence reporting. MAFLD prevalence globally estimated 25.2%, with a prevalence above 30% in the Middle East (7,8). It’s expected that MAFLD cases will increase from 83 million (2015) to 101 million (2030), with non-alcoholic steatohepatitis NASH cases increase from 1.5 million to 2.7 million (9).

Assessment of the global burden of compensated cirrhosis vs. decompensated cirrhosis is difficult. Liver cirrhosis related deaths are underestimated and hampered as many regions underestimate liver cirrhosis as the main cause of death (10). Compensated cirrhosis patients have a 5-fold mortality risk and decompensated cirrhosis have a 10-fold increased mortality risk than general population, irrelevant to comorbidity (11). Globally in 2017, 10.6 million cases with decompensated cirrhosis and 112 million with compensated cirrhosis, the highest age-standardized death rate among GBD was in Sub-Saharan Africa (12).

Liver cancer (primarily HCC) is the 6th leading cause of cancer worldwide in 2015. Men are affected more than women (5th leading cancer among men and 8th among women). It’s the 4th most common cause of cancer deaths globally as it causes 810,000 deaths worldwide, also it’s the 2nd leading malignant cause of absolute years of life lost, 2nd leading cause of cancer deaths among men and 6th among women worldwide (13). 5-year survival for liver cancer was only 18% (31% in localized tumors, 11% with regional spread and only 3% with distant metastasis), these data from The Surveillance, Epidemiology, and End Results (SEER) Program (14). Incidence and mortality due to liver cancer is expected to be doubled by 2035 globally and near 3-fold increase in middle east and Mediterranean region specifically (15). The Saudi Cancer Registry (2015) revealed that incidence of liver cancer ranked as the sixth most common cancer among Saudi males and 12th among Saudi women (16).

Liver diseases in Arab World represents a major health problem in morbidity and mortality. Liver cirrhosis is one of four main causes of death in Arabs, Egypt has the highest death rate due to cirrhosis among the world, 2/3rd of the admissions in Iraq are due to chronic liver diseases, by this order hepatitis B, alcohol, hepatitis C, immune hepatitis and metabolic diseases are major causes (17). Egypt has the highest incidence in chronic hepatitis C infection (18). In the Arab world, liver cancer caused a total of 17,638 deaths. 36% of them were due to HBV and 40% with HCV, Alcohol-associated cases was only less than 10% (19).

In Egypt, the total economic burden of HCV is $7.94 billion which is equivalent to 2.7% of Egypt GDP. Nearly $2.6 billion is the direct healthcare costs of HCV in Egypt which consume around 17.4% of the total health expenditure in Egypt (20). By 2025 a small reduction in HCV incidence is expected after 10 years, there will be 4.1 million chronic active HCV patients, 25% of them are cirrhotic, near 25 thousand have HCC, and a high annual number of deaths, about 25 thousand deaths. Unfortunately, the economic burden will be high, the direct costs will be estimated at $23.3 billion, while the total costs will be $48.3 billion between 2015-2025 (21).

In Egypt liver disease library, HCV-related and parasitic liver infestations literature represent the main interest of publications being the most important topics regard the prevalence and burden of the diseases. Publications of hepatocellular carcinoma (HCC) occupies the 3rd interest in Egyptian liver disease mapping. After that comes liver fibrosis/cirrhosis around (16%) of publications, less attention paid to other non-C, non-B viral infections, viral/parasitic co-infections, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and other liver diseases, although they have a major role influencing the outcome of liver disease, necessitating an urgent need for widening the scope of liver disease registry and study (22).

Regarding pediatric and hereditary liver diseases, In Oman, progressive familial intrahepatic cholestasis (PFIC) is the most common, followed by autosomal recessive polycystic disease of the kidney (ARPCDK) with congenital hepatic fibrosis (CHF), those represent (51%) of the presented hereditary liver diseases, followed by autoimmune liver disease, biliary atresia and metabolic liver diseases (23). This distribution is similar to Saudi distribution where PFIC is the most common one (35%) (24), also PFIC is reported in Arabs (25). Congenital hepatic fibrosis (CHF) with autosomal recessive polycystic disease of the kidney (ARPCDK) is the second one, reported in Kingdom of Saudi Arabia (26), and Kuwait (27).

Arab world literature about liver diseases is like a growing child. Viral hepatitides literature has the main interest due to its prevalence and burden in Arabs, liver cirrhosis and...
cancers come then, but wide gaps are there in other liver disease categories. Literature about autoimmune liver disease (ALD) is deficient, continuous efforts needed to be performed for incidence, diagnostic procedures and clinical management beside geographic distribution (28). Liver cirrhosis mortality rate registry has a major uncertainty worldwide and in Africa specifically, therefore, there is a bad need to system registry to fulfill the gaps (29). Better surveillance of liver diseases in MENA can be achieved by improving the infrastructure of health care system including cancer registries and electronic recording of outpatient. Despite expensive treatment, it’s easy and feasible to prevent liver diseases. Strengthening of the health care systems in the region can be performed for prevention and control (30). By studying publications in Arab world about liver diseases will reveal deficient parts and gaps in literature. We aim in this review to demonstrate the gaps in literature about liver diseases in Arabs for the future literature to fulfill the gaps for better registry and medical health.

Subjects and Methods

Methods

We searched PubMed, Scopus, Web of Sciences (WOS), EBSCO, and Wiley databases for relevant articles from 2011 to January 29th, 2021. We used different search terms that cover all liver diseases in addition to names of the Arab countries.

Study selection

All relevant studies that discuss any liver disease in any of the Arab countries were selected irrespective of age, sex, region, publishing year, or publishing language. We excluded review articles, non-human studies and publications study the surgically related liver diseases as liver transplantation and biliary diseases. Study selection was done by two groups from the search team in two steps: title and abstract then full text screening according to the inclusion criteria. Any disagreements were solved by discussion with the whole team.

Classification and Data extraction

After full text screening, all included studies were classified according to the main topic they discuss (acute liver failure, alcoholic liver diseases, viral hepatitis, non-viral hepatitis, non-infectious hepatitis, vascular liver diseases, and so on). Then relevant data was collected (authors, year of publishing, country, study type, and category of liver disease) by the research team.

Data analysis

As this is a scoping review, we aimed to collect the finding and provide an overview of the current state and unmet needs in liver disease research in the Arab countries rather than evaluating detailed or qualitative analysis. The collected data was summarized using data mapping showing the distribution of the studies by the liver disease category with subgroup data whenever possible.

Chart 1: search strategy and review process

RESULTS

Research results found 15055 publications related to our work, in title and abstract screening step, 7037 publications were excluded, 2243 were duplicates. 5775 publications screened in the second step, full text screening, 3030 publications were included in our study, they were classified by topics according to the type of liver diseases, 1583 studies were about viral hepatitis (1284 studies were about hepatitis C virus, 279 studies were about hepatitis B virus and 20 studies were about the other viral). 94 publications studied the non-viral infectious liver diseases. Another 252 publications studied the metabolic liver diseases. The others were about acute liver failure, drug induced liver injury, liver cirrhosis and HCC.

1. Viral hepatitis

A- Hepatitis C virus infection (HCV)

Despite large number of excluded publications as they are abstract only, one thousand, two hundreds and eighty-four (1284) papers about chronic hepatitis C virus (HCV) infection are included in our review.

Included publications from 2011 up till now, stationary course of publications allover these years is noticed, in 2011 there are 89 publications, in 2012 there are 133 publications, in 2013 there are 117 publications, in 2014 there are 118 publications and so on, although, there is a noticed decline in publications in 2021, only 11 publications are included, may be due to decline in infection rate, good preventive measures, eradication of infection by the new direct acting antivirals and due to taking attention to COVID-19 pandemic.

Of the 1284 included publications, 999 papers (77.8%) nearly ¾ of included publications are from Egypt which has the highest rate of publication as Egypt is one of the highest rates of chronic hepatitis C infection among the Arab world. Kingdom
of Saudi Arabia (KSA) occupies the second place in publications about chronic hepatitis C infection, then comes Morocco, Iraq, Tunisia, Qatar, Lebanon, Libya, Kuwait, Jordan, Yemen, Sudan, Oman, Bahrain, Algeria, Palestine, United Arab of Emirates, Syria and Mauritania. Least publication is in Mauritania, only one paper, no publications is found from Djibouti, Somalia and Comoros.

Most of collected data about HCV infection in Arab world are observational studies (97.5%), only 32 papers are randomized controlled trials and clinical trials (2.5%). More than half studies are case control and cross-sectional studies, 368 (28.7%) of these studies are case control studies, 362 (28.2%) are cross sectional studies, 2.5% of publications are case reports and case series.

One fifth of included papers studying the epidemiology of HCV infection, either prevalence in general population, prevalence in specific groups of patients, Co-infections, risk factors of transmission of infection

HCV structure and diagnostic tests and techniques has the least attention in publication, only 8 papers (0.8%) of 1284 included papers are discussing the virus structure and diagnostic techniques (31–35).

In Arab World, HCV genotyping has less attention, studying the prognosis and prognostic factors, fibrosis detection and staging, available treatment and drug safety and efficacy and complications have a greater attention. Only 2.1% of publications asr studying the genotyping of HCV in arab world (36–41).

Available tratment options, efficacy ot treatment and safety have a high publication rate and importance, 241 papers (18.8%) are studying drug safety and efficacy among different populations, variable genotypes and different clinical situations. Regardin available tratment options, up to 2015, studies are about pegylated interferon and ribavirin efficacy (42–44) and side effects (45–47). From 2015 literature started to study new directly acting antiviral agents efficacy (48–62). Recent research about DAAs is discussing a conflict of being a cause of HCC increase or not (63–66).

Prognosis, prognostic factors and complications of chronic HCV infection have the highest attention, they are being studied in more than half of publications, 433 (33.6%) papers are studying prognosis (67–70) and 238 (18.5%) papers are studying complications (71–74), however liver cirrhosis and hepatocellular carcinoma (HCC) are being studied in another part.

Detection of fibrosis and staging of it in chronic HCV patients is also important among arab world patients, 90 papers (7%) are studying this topic (75–81).

**B- Hepatitis B virus infection (HBV)**

Global eradication of both hepatitis B virus (HBV) and hepatitis C virus (HCV) was aimed by the World Health Organization (WHO) by 2030. Several efforts worldwide are implemented to achieve these goals (82).

Reviewing the available literature regarding different HBV research areas in the Arab countries revealed 279 publications arising during the period from 2011 till 2021. The publication rate was almost stationary allover these years except in 2011 that could be attributed to the COVID-19 pandemic that drew the attention of all authors and publishers.

Of the 279 included papers, 95 papers (34.1%) are from Egypt (83,84) which has the highest rate of publication followed by KSA (85), Sudan (86), Tunisia (87), Iraq (88) and Morocco (89).

Most of collected studies about HBV infection in Arab world are observational studies cohort, case control or cross-sectional studies, only 2 papers are randomized controlled trials (90,91).

One third of included studies were focused about studying the epidemiology of HBV infection, either prevalence in general population (85–87), prevalence in specific groups of patients (age groups, specific locality, immunocompromised, transplant patients, hemodialysis (87) or cancer patients) risk factors of transmission of infection.

Viral genotyping and host genomics came second in frequency of publications (92,93). Furthermore, vaccination coverage, efficacy and awareness among healthcare workers, students and general population comprised about 15 % of publications (94,95). This could be justified by the life-long treatment of HBV and the importance of prevention of infection especially with the presence of effective vaccination program that was adopted worldwide and in the Arab countries as well (96).

There is paucity in the studies about different antivirals drugs used in HBV treatment despite its availability in most countries (97). This could be attributed to the long term follow up needed in HBV patients and most of the clinical studies performed were multicentric with international countries.

**C- Hepatic viral infections other than HCV and HBV**

About viral infections affecting the liver other than hepatitis C and hepatitis B , There were twenty original articles , about 50 % of them about hepatitis A virus (HAV) as it is more endemic in the Arab world , four of them were case reports, the other studies were from Egypt, Oman, Morocco, Lebanon, Iraq, Syria, Algeria and Tunisia (98–100).

One of them about epidemiology in Morocco (101), the rest are about treatment and emergent complications.

Other articles are about hepatitis E virus (HEV), cytomegalovirus, dengue fever, measles, herpes simplex virus, coronavirus, SEN virus and Bacillus Calmette Guerin . Most of them are case reports (102–105).

Definitely, there is a great gap in this point of research , especially covering epidemiology in different countries , genotyping , effect of treatment interventions , especially as regard endemic viruses (HAV, HDV and HEV).

**2. Infectious liver disease other than viral hepatitis**

Regarding infectious liver disease other than viral hepatitis, 94 studies were done in Arab world. Most of the studies were case reports (51.1%), followed by case control (13.8%), cross sectional (12.8%), prospective (8.5%),
retrospective (7.4%) and case series (5.3%). Only one study was randomized controlled trial (RCT) (106).

Regarding Countries, most studies were from Morocco (24.5%), Tunisia (19.1%), Egypt (18.1%) and KSA (12.8%) followed by Iraq (5.3%), Lebanon (4.3%), three publications for each of Yemen and United Arab of Emirates (UAE), 2 studies from Sudan, while other countries like Qatar, Jordan, Syria, Libya, Kuwait, Bahrain and Algeria (1 for each).

Most of the studies were related to hydatid cyst in the liver (61.7%) with its rupture at unusual sites as duodenum (107), peritoneum (108,109), cutaneous fistulation to the right Breast (110), abdominal wall and psoas muscle (111), inferior vena cava (112) or serious presentation as anaphylactic shock (113,114) and treatment modalities (115,116).

3. Acute liver failure (ALF) and acute on chronic liver failure (ACLF)

Fifteen studies in Arab world discussed acute liver failure. Out of them, 6 studies were case reports, 4 were cross sectional, 3 were prospective, one was case control, and one was retrospective. Forty percent of studies were from Egypt (117–121), followed by two publications from each KSA, Iraq, Kuwait, Qatar and lastly one study from Yemen.

Three studies highlighted acute on chronic liver failure (ACLF) (118,121,122). A publication in Qatar showed significantly reduced cortical thicknesses in multiple brain sites and significantly increased glutamate/glutamine (GLX) metabolites were observed in ACLF compared to those of controls at baseline study. Follow-up patients showed significant recovery in cortical thickness and GLX level compared to baseline study (122).

Another Egyptian publication demonstrated that HEV viraemia is a common cause of acute on chronic liver failure in Egypt. Hepatitis E virus RNA was detected in the sera of 13 of 100 presented with ACLF patients (13%) (118).

Another one analyzed 52 patients with ACLF and reported that infection was the main precipitating factors (38 cases; 73.1%) followed by variceal bleeding in 9 (17.3%). The 28-day mortality rates were 86.5% which was higher than what reported in the literature (121).

As regard ALF, an Egyptian study reported that Acute HEV infection was detected in 30 out of 300 acute hepatitis patients with unknown etiology (AHUE) (10%). Four out of 30 patients (13%) died due to fulminant hepatic failure within 3–6 weeks of hospitalization (123). A multicenter study in Kuwait showed the effect of N-Acetylcysteine (NAC) on mortality and liver transplantation rate in non-Acetaminophen induced acute liver failure. The NAC group included 85 patients and the control group included 70 patients. Recovery from ALF was reported in 82 (96.4%) patients in the NAC group with no need for liver transplantation. The success rate (transplant-free survival) in the NAC group was 96.4%. The success rate (transplant-free survival) in the control group was 23.3% as only 17 patients survived without liver transplantation. The remaining 53 (76.6%) patients did not recover from ALF, 37 (53.3%) of them had liver transplantation and 16 (23.3%) died (124).

A case control study in Iraq included 175 individuals (125 patients and 50 healthy control who represented the different stages of HBV infection (ALF, AHB, CHB and LC). IL-17A 197 A/G gene polymorphism G allele have a significant association in hepatitis B virus infection (125).

A first case report of fulminant hepatitis after laparoscopic Sleeve Gastrectomy associated with protein calorie malnutrition, multiple nutritional deficiencies in addition to concomitant use of therapeutic doses of acetaminophen (126).

Seven studies (46.7%) were done on pediatric patients (117,119,120,127–130). Four of them were case reports (117,127–129).

An Egyptian study included 126 children: 46 with acute HAV infection (13 out of them with fulminant presentation), 53 with AIH, and 27 healthy controls. Autoantibodies were detected in the majority of HAV (63.1%) and AIH (79.2%) groups. They conclude that Hypergammaglobulinemia and a high occurrence of autoantibodies are encountered in HAV infection. The higher gamma globulins in fulminant HAV, with an insignificant difference from that in AIH, suggest that a more aggressive immunological reaction is related to this presentation (119).

Another Saudi study did a retrospective study on early infantile liver failure (EILF) where 42 cases were identified. The etiology was indeterminate in 14 (33.3%) and established in 27 (64.3%): galactosemia (7 cases, 16.6%), tyrosinemia (5, 12%), neonatal hemochromatosis (NH) and hemophagocytic lymphohistiocytosis (HLH) [4 each, 9.5%], mitochondrial hepatopathy (3, 7%), and miscellaneous (5, 12%). LF resolved in 15 cases (35.7%), either spontaneously or in response to specific therapy, 23 (54.7%) died, and 4 underwent LT (9.5%). Galectosemia and tyrosinemia predicted good outcome (130). Both pediatric chronic liver failure sequential organ failure assessment (pCLIF-SOFA) score (pCLIF-SOFA) and Pediatric End-Stage Liver Disease (PELD) scores at cut-off values > 8 and > 30 respectively on admission could predict death in children with acute liver failure (ALF) with high sensitivity. The pCLIF-SOFA score is better than the PELD score as a predictor of death in PALF and can be used for accurate selection of children with ALF who are in a real need of liver transplantation (LT) (120).

With respect to acute liver failure (ALF) and acute on chronic liver failure (ACLF) in Arab World, we should screen for underestimated viral infection as Hepatitis E and different types of treatable bacterial infections. We are in need for development of guidelines for proper management of acute liver failure and ACLF and urgent assessment for suitability for LT due to high mortality rates. We are in need for urgent application of validated scores that help in selection of candidates with ALF who are in a real need of LT. Randomized controlled trials (RCTs) are missing in Arab World.
4. Metabolic liver diseases
A- Metabolic associated liver disease (MAFLD)

The prevalence of MAFLD is increasing in an epidemic manner parallel to an increase in the prevalence of associated risk factors such as obesity, metabolic syndrome, and type 2 diabetes mellitus. About 20% to 30% of the patents, progress to develop nonalcoholic steatohepatitis (NASH). NASH can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma. Some papers suggest that NASH may soon be the leading cause of cirrhosis, HCC (even without cirrhosis) and liver transplantation (LT) (131).

MAFLD is present in 20 to 40% of the general population in industrialized countries and is the most prevalent chronic liver disease (132). Among all subjects with MAFLD, features of non-alcoholic steatohepatitis (NASH) can be seen in 10-20%. The prevalence of NASH in Western countries is approximately 2-6% (133).

In our Arab world review, we included 228 papers. 145 papers (64%) of included publications are from Egypt. No available research discusses prevalence of MAFLD and NASH in Arab countries. Most of publications is about prevalence of obesity, metabolic syndrome and Diabetes mellitus. Most publications discuss demographics, risk factors and association of MAFLD with other health conditions (diabetes mellitus, obesity, viral hepatitis .... etc.,) (134,135)

Diagnosis:

Ultrasound of the liver has a high sensitivity and specificity (both approaching 90%) for detection of fatty infiltration but does not allow assessment for the presence or degree of inflammation and fibrosis (Davies 1991) (136).

Although, many publications available discuss the diagnosis of NAFLD using ultrasound, there is research gap in the assessment of biochemical markers and Non-invasive predictors of NASH. And no available evidence evaluates non-invasive markers such as HAIR index, BAAT index, BARD score, NFS calculated, APRI and The Enhanced Liver Fibrosis (ELF) score in the Arab world (137).

Mortality and morbidity in hospitalized patients with MAFLD are approximately 5 times higher than what is seen in the general population (138). Probably around 10% of MAFLD patients will progress to NASH over a period of 10 years. Cirrhosis later develops in 5-25% of patients with NASH and 30-50% of these patients die from liver-related causes over a 10-year period (138). Cirrhosis in patients with NASH can also decompensate into subacute liver failure, progress to hepatocellular cancer (HCC), and recur after liver transplantation. Steatosis alone is reported to have a more benign clinical course, with cirrhosis developing in only 1-3% of patients (138).

Patients with NASH and fibrosis also have a significant risk for hepatocellular carcinoma (139).

Research gap is obvious in the pathogenesis of MAFLD. No clear data about the determinants of progression to steatohepatitis, liver fibrosis and hepatocellular carcinoma. Few research available on human genetic factors. No clear data about treatment of MAFLD. Only few publications available about Diet, physical exercise and lifestyle intervention recommendations to treat MAFLD (140).

Also, very few data available on pharmacological treatment of MAFLD (fenofibrate, fish oil, probiotics ...... etc.). Only two studies from Egypt study alterations of the intestinal microbiome and MAFLD. Few studies also observed the effect of laparoscopic sleeve gastrectomy (LSG) and bariatric surgeries on the resolution of MAFLD (141,142).

Important research gaps

- Health education and public health awareness are the essence to stop the increasing prevalence of NAFLD in Arab world. This represents a major research gap. No available publications discuss this important topic.
- NAFLD is found in 8-19% of non-obese people. The PNPLA3 gene polymorphism has a greater effect on liver fat in patients without metabolic syndrome. No available publication discusses non-obese NAFLD.
- Extrahepatic diseases associated with NAFLD/ NASH such as ischemic heart disease, obstructive sleep apnea and colorectal neoplasia. This association not well studied among Arab populations.
- There were no publications from Yemen, Comoros, Djibouti and Somalia.

B- Wilson’s disease, hereditary hemochromatosis, Alpha1 antitrypsin deficiency and Cystic fibrosis

Only few publications, twenty-one publications discuss Wilson’s disease, hereditary hemochromatosis, Alpha1 antitrypsin deficiency and cystic fibrosis in Arab world. Mostly case series and case reports. No available evidence discusses the pathophysiology, diagnosis, treatment, compilations and prognosis among Arab people (143–148).

C- Alcoholic liver disease (ALD)

Unfortunately, only three publications about alcoholic liver disease (ALD) are published among Arab countries, first one was a case report revealed a Moroccan alcoholic cirrhotic patient diagnosed when presented with acanthocytosis (149). Second one was in 2017 about a Lebanese alcoholic cirrhotic patient presented with torsade’s de point during alcohol withdrawal (150). Last publication in 2020 in Iraq revealed that alcohol abuse cause impaired lipid profile which predispose to cardiovascular accidents, also it impairs liver enzymes causing liver dysfunction (151).

The very low reported number of publications about ALD is attributed to religious causes. Even the alcoholics can’t confess their habit not only religiously but also culturally.

Lots of gaps about ALD among Arab world from diagnosis to pathophysiology, classifications, biomarkers, treatment lines, efficacy, prognosis and complications. Many
research points need to be investigated among Arabs.

5. Autoimmune liver diseases

Thirty eight publications among Arab world about autoimmune liver diseases, 26 publications about autoimmune hepatitis (AIH), 5 publications for each primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), one publication about lupus hepatitis (152) which was case series and another about overlap syndrome (153) which was a case report also. Most of publications were from Egypt, Tunisia and KSA. Near half of publications were only in 2011 and 2013. 18 of 38 publications are case reports, the rest were prospective, retrospective, cross-sectional and observational. No randomized controlled trials were reported about autoimmune liver disease among Arab world.

Twenty six publications were about AIH, about one third of them were case reports (154–161). The second one third of publications were reported about the pediatric AIH (162–168). The last one third discuss the characteristics of the disease (169,170), poor prognostic factors and risk factors (171,172), biomarkers for diagnosis (173–175) and lastly complications of AIH (156). No reported publication about the experience of transplantation in AIH hepatitis and long term follow up.

As regard primary biliary cholangitis (PBC), only 5 publications among Arab countries, two publications were from Tunisia, two from Morocco and last one from Qatar. 4 of them were case reports (176–179), the last one was retrospective study detecting prevalence of antiphospholipid antibody level among PBC patients. Unfortunately, no randomized controlled trials, no prospective or observational studies, no studies reported about the diagnosis, biomarkers, disease characteristics, treatment efficacy and safety, complications of the disease and long term follow up. Lots of gaps in PBC publications among Arabs needs to be studied.

Another 5 publications were reported about primary sclerosing cholangitis (PSC) from different Arabian countries (180–184), two of them were case reports and the others were case control and cohort studies. They discussed the characteristics and evaluation of PSC with imaging modalities. No reported publications about complications, transplantation and long term follow up.

6. Toxic and drug induced liver injury

Fifty-three publications were reported about drug induced liver injury (DILI) and toxic liver diseases among Arabs. Around one third of them were from Egypt, then Tunisia, Qatar and Kingdom of Saudi Arabia. From 2011 to 2020, publications per year were nearly stationary but no reported publications in 2021. Near half of publications were case reports (185–189), but the others were variety of randomized controlled trials (190,191), prospective (192,193), retrospective (194,195), cohort (196–198) and observational studies studying the presentation, causes, diagnosis and outcomes of DILI but no studies in liver transplantation in DILI and toxic liver patients.

7. Vascular liver diseases

As regard research work about vascular liver disorders in Arab world, we have sixty-four original articles, twenty-eight of them are about Budd Chiari syndrome. Two publications were about hepatic artery diseases, one about ischemic hepatitis, one about congestive hepatopathy (199), and the rest about portal vein thrombosis and portal hypertension (200–203).

One of the papers about hepatic artery diseases is a case report from Tunisia (204), the other is a retrospective study from Egypt about management of hepatic artery thrombosis post transplantation (204).

The two studies were about congestive hepatopathy and ischemic hepatitis are case reports, one from Qatar and another from Egypt (199,204). Budd Chiari studies are twenty-eight, most of them are from Egypt, especially due to presence of scientific group for Budd Chiari syndrome in Ain Shams University in Cairo. Four of them are case reports, the rest are cross sectional studies, two of them are discussing epidemiology, two about therapeutic interventions, four about diagnostic modalities, two about complications and the rest about associations and risk factors (205–209).

The rest of the studies are about portal vein hypertension and portal vein thrombosis, it may be due to the fact of endemicity of hepatitis C and B, with their complications of portal hypertension and thrombosis especially that associated with malignancy.

Most of studies about portal vein are from Egypt followed by Morocco and Tunisia, the upper hand is for cross sectional studies followed by cohort and case control studies.

Most of them are discussing portal hypertension and its complications, followed by portal vein thrombosis as regard diagnostic tools and therapeutic interventions.

We need more studies about role of anticoagulation in vascular disorders in hepatic patients, development of new markers for early prediction and diagnosis of thrombosis, to assess role of liver transplantation.

Also, we need more about congestive hepatopathy, ischemic hepatitis and their management with cardiology team.

8. Pediatric liver disease

Most of publications from Egypt, have discussed diagnosis and treatment outcomes. No Available data on prevalence, pathophysiology, genetic polymorphism and prognosis of pediatric disease among Arabs. Publications were mentioned each in its category, either metabolic, genetic, acute liver cell failure or chronic liver disease with its complications. The absence of data from population-based studies in Arab world highlights the need for further studies to reliably define the health service needs for this region and plan a cost-effective health care program (210).

9. Granulomatous liver disease

It is considered one of the scarcest subjects as regards Arab publications with only four case reports published. Two from Tunisia, one from Bahrain and the last from Lebanon. Publication years were 2011 (211), 2018 (212), 2020 (213) and 2021 (214) with the rate of one per mentioned year. Two of them mentioned hepatic tuberculosis, either in isolated form
resembling hydatid cyst (213) or in concomitance with hepatocellular carcinoma (214), one about Langerhans’ cell histiocytosis (211) and the last one about Bacillus Calmette-Guerin (BCG) infection after BCG bladder instillation (212).

There was no published data about sarcoidosis which is considered among the commonest causes of hepatic granulomas (215), nevertheless, some entities like primary biliary cholangiopathy and some of drug-induced liver injuries should be classified under the title of granulomatous liver diseases.

Many other less common etiologies were also mentioned in the literature without any Arab publications like talc, barium, and silicone from therapeutic and diagnostic procedures have also been found to be associated with this condition. Other causes include chronic hepatitis B and C infection, brucellosis, leprosy, histoplasmosis, coccidioidomycosis, schistosomiasis, amebic liver abscess, lymphoma, and malignant granuloma or even idiopathic (216).

We think that Arab authors should be encouraged to publish more and more of their case reports, collaborate to collect series of common etiologies and develop a common pool of database that would help to retrieve retrospectively enough information to facilitate further and more advanced forms of research and publications.

10. Liver diseases and pregnancy

Liver disease in pregnancy presents a real challenge for hepatologists. In review of literature in the Arab World, we found forty-seven original articles discussing different liver diseases that occurs during pregnancy, most of them (60%) investigating viral hepatitis among pregnant women either HBV (217–222), HCV (223–228) or HEV (229–231).

Nearly 25% of these papers were just reported cases of unique liver diseases in pregnancy like Fatty liver of pregnancy which was the most reported case in different countries; Tunisia (232), Oman (233), KSA (234), Jordan (235), Lebanon (236) and Morocco (237,238). Tunisia published a retrospective study in this life threatening condition over 10 year period (239). Intrahepatic cholestasis of pregnancy was discussed in two papers from Egypt; one prospective study (240), another case control (241) and reported in one case from Lebanon (242).

Other unique liver diseases in pregnancy like pre-eclampsia and its associated complications and Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome (HELLP syndrome) were also discussed in case series from Morocco, cross sectional study from Sudan (221,243) and finally case control from Egypt (244).

Vascular liver disease in pregnancy like Budd chiari syndrome was discussed and reported in two papers from Egypt (208,245).

Liver cirrhosis is not a contraindication for pregnancy, although cirrhotic women difficult to get pregnancy, only one prospective Egyptian study discussed maternal and fetal outcome in pregnant women with liver cirrhosis (246), and one reported case from Saudi Arabia of acute on top of chronic liver failure complicated by invasive fungal infection (247).

A lot of important topics of pregnancy associated liver diseases needs to be investigated in the Arab world, like Hyperemesis graviderum, pregnancy among cirrhotic patients, and post liver transplant with evaluation of both mother and fetal outcome.

11. Liver cirrhosis and its complications

Two hundred and eighty-one publications were included regarding liver cirrhosis and its complications among Arab world from 2011 to 2021. Most of publications were from Egypt (230, 82.9%), followed by 20 publications from KSA (7.1%). No publications from Jordan, Djibouti, Syria, Somalia, Comoros, Lebanon, Libya, Palestine, Kuwait and Mauritania. Egypt has the highest rate of publication due to increased prevalence of viral hepatitis and posthepatitic cirrhosis. From 2011 to 2021, publication rate was nearly stationary, but least publication was recorded in 2021 (7) and 2019 (9), mostly due to eradication of HCV after the era of direct acting antiviral drugs (DAAs). Most of studies were case control (29.2%) and cross sectional (22.8%) studies, the others were variable between cohort, prospective, retrospective and observational studies. There were (21, 7.5%) RCTs.

Sixty five publications studied the vascular complications of liver cirrhosis, for portal hypertension early detection either by invasive or non-invasive procedures and predictors of bleeding (248–250), invasive management with trans jugular intrahepatic Porto-systemic shunt (251,252) and rectal ozone(253), management of portal hypertensive gastropathy (254), gastric varices diagnosis and different modalities of management and survival (255–259), esophageal varices from early noninvasive prediction and diagnosis (260–267), management (268–273) and risk of rebleeding (274,275), small bowel varices (276), and portal hypertensive colopathy (277). Prediction of risk of portal vein thrombosis (278), diagnosis (201,279,280) and survival (281). Two publications studied portal hypertension and portal vein thrombosis in children (282,283). Another publication studied portal and splanchnic hemodynamics after partial splenic embolization in hypersplenism cirrhotic patients (284). Systemic vascular resistance and affection of carotid intima thickness were studied among Arabs (285,286), also pulmonary hypertension in cirrhotic patients (287).

As regard central nervous system affection, there were seventeen publications, most of them studied hepatic encephalopathy from early detection, diagnosis, management and prognosis (288–293), one article studied minimal hepatic encephalopathy in children (294). Also, sudomotor changes, extrapyramidal manifestations and depression were studied (295–297).

High-rate incidence of infections is recorded in cirrhotic patients. Most common infection recorded is spontaneous bacterial peritonitis (SBP) which is studied in detail from early detection, diagnosis, management and outcomes (298–303). SBP was studied among infants and children (304). Also, septic shock and fungal infection were recorded among cirrhotic Arabs.
The high rate of infections among cirrhotic patients is due to immune dysfunction occurs (308, 309).

Renal affection of cirrhotic patients is common, hepatorenal syndrome (HRS) is the most studied one (310–313). HRS in children is a rare presentation (314, 315). Also, acute kidney injury in cirrhotic patients is a challenging presentation (316–319).

Coagulopathy in cirrhotic patients is a major problem that we face from either coagulation defect or thrombocytopenia and platelet dysfunction (320–323). Facing pediatric cirrhotic patients with coagulopathy is a difficult situation (324).

Liver cirrhosis can cause multisystem affection, cardiopulmonary complications can occur secondary to liver cirrhosis, many publications among Arabs had studied the cardiopulmonary complications, as regard cardiac muscle affection and myocardial perfusion abnormalities (325–328), hepatic hydrothorax (329, 330), affection of respiratory function (331–333) and hepatopulmonary syndrome (334).

While investigating the publications studying liver cirrhosis and its complications among Arabs, sporadic studies about metabolic bone mineral affection (335–337), fasting in Ramadan and liver cirrhosis (338, 339), nutrition and malnutrition among cirrhotic patients (340, 341), sleep pattern and disturbance (342, 343), refractory ascites (344, 345), stem cell transplantation and liver cirrhosis (346–348) and liver cirrhosis and fertility (349). Many studies about hepatocellular detection in cirrhotic patients which will be discussed later.

Liver cirrhosis and its complications is well covered among Arab world, we think that there are no gaps need to be fulfilled.

12. Hepatocellular carcinoma

In this review, 599 original articles and case reports related to HCC were included and published from 2011 to 2021. The publication rate was stationary from 2011 to 2016 and increased from 2017, while the maximum rate of publications is observed in 2020 which had 107 publications, however significant decline was observed during 2021. This decline in publication may be attributed to era of HCV treatment and paying attention to COVID-19 pandemic.

Of 599 reviewed HCC publications, 514 publications were from Egypt (85.80%). KSA was represented as the 2nd Arabian country for HCC publications with 28 publications (4.087%). Tunisia was represented as the 3rd Arab country with 14 HCC publications (2.59%), followed by Morocco (2.11%). There were 6 publications from Lebanon, 5 publications from Qatar, 3 publications from UAE, Algeria and Sudan each, 2 publications were from each Oman and Iraq. Finally, single publication was from each of Jordan, Yemen, Bahrain, Kuwait and Syria. Single shared multi-center study from Morocco, Tunisia and Algeria. There was no publication from Libya, Palestine, Mauritania, Djibouti, Somalia or Comoros.

In Arab world, 39.73% of study design was case control (238 studies), 27.37% was cohort (164 studies), 17.52% was cross sectional (105 studies), 8.01% was case reports (48 publications), 1.83% was randomized controlled trials (11 studies), 1.83% was observational (11 studies), 1.16% was case series (7 publications), 1.13% was retrospective descriptive (7 studies), 0.66% was comparative analysis (4 publications), 0.33% was clinical trial (2 studies), 0.33% was pilot (2 studies), and 0.16% was parallel concurrent interventional (single study).

Case control studies:

Out of 238 published Case control studies, 95.37% were from Egypt (227 studies), 5 publications from Morocco (350–354), Single case control study was published from each of Sudan (355), Jordan (356), KSA (357), Syria (358), Tunisia (359) and single shared multicenter study between Tunisia, Morocco and Algeria (360).

Four studies (0.66%) describe the epidemiological characteristics of HCC in Arab world, 2 studies from Egypt (361, 362), there was single study from Qatar (363) and another single study from KSA (364).

Nineteen studies assessed the different risk factors associated with development, progression and recurrence of HCC. 17 studies were from Egypt and two were from Tunisia.

Another four publications had assessed the incidence of hepatocellular carcinoma (HCC); three publications from Egypt and one from KSA (365).

Only single Arab study assessed the prevalence of HCC among HCV patients in Mid Delta, Egypt (366).

Two Arabian studies discussed the histo-pathological features of HCC, one from Egypt (367) and another from Morocco (367).

There were fourteen studies investigate the role of DNA or RNA in the pathogenesis and gene pathway of HCC. All studies were from Egypt apart of single study from Algeria (368).

There were two studies described the clinical characteristics among patients with HCC. One study from KSA (369), while the second study was from Oman (370).

Three studies evaluate the clinic-pathological features of patients with HCC; 2 studies were from Egypt and one from Tunisia (371).

There were 41 studies reported unusual presentation of hepatocellular carcinoma and metastasis; 36 studies were case reports, single case series from Egypt (372), two cohort studies from Egypt (373), two cross sectional studies; one from Algeria and another from Tunisia.

Twenty eight Arabian publications evaluated biomarkers that predict early the occurrence of HCC in patients with hepatitis C virus (HCV) induced liver cirrhosis. All studies were from Egypt.

Seven Arabian studies assessed the feasibility and effectiveness of protocols as a screening tool for the detection of early HCC in patients with liver cirrhosis. All studies were from Egypt.

Regarding diagnosis of HCC, there were 228 studies (38.06%) investigated and evaluated the diagnostic performance of multiple serum markers and imaging modalities in diagnosis
prediction and monitoring of HCC. Most of them was from Egypt (95.61%), three from KSA, two studies from Morocco and single study from either of Jordan (356), Sudan, Syria, Tunisia and Bahrain (374).

Ninety-nine studies (16.52%) have discussed the effect of different curative and palliative modalities of HCC on objective response, overall survival, local recurrence and tumor free survival. Most of the studies was from Egypt (88.88%), six studies from KSA, two studies from Lebanon and single study from each of Morocco, Qatar and UAE (375).

Hepatocellular carcinoma (HCC) is a major contributor to the worldwide cancer burden. Incidence rates of HCC have increased in many countries in recent decades (376).

HCC is the seventh-most frequently occurring cancer in the world and the second-most common cause of cancer mortality (377).

There is paucity of publications about incidence and prevalence of HCC in different countries of Arab world. Many research studies are required to detect the incidence and prevalence rates of HCC in Arab world.

Among Arab world, early detection of HCC occurrence is of great clinical value from the diagnostic and prognostic points of view. Review of published screening protocols for early detection of HCC resulted in the need for more and more studies in this important point of research, also we need more research to study and evaluate the efficacy and safety of immune therapies and gene therapy among HCC Arabian patients.

![Figure 1: Numbers of publications of each disease title published in Arab world.](image1)

![Figure 2: Percentage of publications of each disease title published in Arab world.](image2)
Figure 3: Numbers of publications of each disease title among countries of Arab world.

Declarations: Nothing to declare

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