

Review Article

A Narrative Review of Natural History, Epidemiology and Risk Factors for Hepatitis C Infection

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ABSTRACT

Hepatitis C infection is a major public health problem that can be dealt with urgent and timely attention. Recently, WHO Global Hepatitis Report showed that 71 million people, equivalent to approximately 1% of the world population, are infected with hepatitis C. The disease incidence, mortality rate and risk factors vary across geographical regions. The virus is transmitted primarily through drug injection and exposure to infected blood products in healthcare and community settings. The common causes of death related to virus infections are decompensated liver cirrhosis and hepatocellular carcinoma. Hepatitis C infection is mainly prevented by identifying and controlling any possible risk factors for virus transmission because treatment is costly and limited in availability. In this review, articles discussing the natural history, epidemiology and risk factors for hepatitis C infection are reviewed.

Keywords: Epidemiology, hepatitis C virus, infection, mortality, risk factors, transmission

ARTICLE INFO

Article history:

Received: 24 April 2018

Accepted: 13 February 2019

Published: 24 July 2019

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INTRODUCTION

Hepatitis C is a blood-borne disease that results from infection with the hepatitis C virus (HCV). World Health Organization (WHO) estimated that 71 million persons would be living with chronic HCV infections by 2015 (WHO, 2017a). According to the Global Hepatitis Report, the global

incidence rate is highest in the WHO Eastern Mediterranean (23.7 per 100,000 population) and European regions (61.8 per 100,000 population) (WHO, 2017a). The global mortality rate from viral hepatitis is 18.3 deaths per 100,000 population. The Western Pacific region has the lowest incidence rate but also showed the highest mortality rate (24.1 deaths per 100,000 population), followed by the Southeast Asian region (21.2 deaths per 100,000 population) (WHO, 2017a). HCV chronically affects the liver, and the global burden attributed to HCV-related liver disease is substantial and expected to increase in the next few years (Razavi et al. 2014).

A vaccine for preventing hepatitis C infection is still unavailable (WHO, 2017b). Thus, the infection is prevented mainly by identifying and controlling any possible risk factors that promote virus transmission. Prevention can be accomplished through the implementation of safety precaution by healthcare workers, introduction of reuse preventive devices, reduction of unnecessary healthcare injection (WHO, 2016), implementation of harm reduction interventions for people who inject drugs (PWIDs) (Csete et al., 2016) and provision of access to treatment and early screening for high-risk groups (WHO, 2017a). Thus, the pathogenesis, disease distribution and infection risk factors for HCV must be understood for the planning of appropriate preventive strategies.

In this review article, the authors conducted a literature search for articles related to the natural history, epidemiology and risk factors of hepatitis C infection through several online databases (e.g. Cumulative Index to Nursing and Allied Health Literature, Cochrane database, PubMed, Medical Literature Analysis and Retrieval System Online, and Science Direct). The search terms included 'hepatitis C', 'pathogenesis', 'epidemiology', 'incidence', 'prevalence', 'mortality' and 'risk factors'. Only articles and abstracts published in English were included in this review. For risk factor section, articles with systematic reviews, cohort or case-control study designs were selected as such high-quality study designs provide stronger evidence that an exposure is associated with hepatitis C infection.

HCV NATURAL HISTORY

Route of Transmission

Humans are the only known natural hosts for HCV (Pawlotsky, 2004). HCV is blood-borne and thus transmitted by contaminated blood mainly via clinical procedures (surgery, blood transfusion and needle stick injuries) and intravenous drug use. As improved testing and screening methods for blood donors become increasingly available, blood transfusion is becoming safer than before, and the principal cohorts of newly infected patients are now PWIDs.

Pathogenesis of HCV

After entering a susceptible host, HCV invades, infects and replicates within the bloodstream, repeating the process in various tissues, as it proceeds to the liver, a principal site for virus replication (Chen & Morgan, 2006). HCV infection causes acute infection in which most patients (70%–80%) do not develop symptoms (Figure 1). In the remaining 20%–30% of patients, acute hepatitis exhibits mild symptoms and is thus infrequently diagnosed (Chen & Morgan, 2006; Omata et al., 2016). Symptoms occur 6–7 weeks after exposure on average, but it can range from 2 weeks to 6 months (Westbrook & Dusheiko, 2014).

The initial features of the acute illness are non-specific flu-like symptoms. Additional specific symptoms of viral hepatitis, such as jaundice, dark urine, anorexia and abdominal discomfort, can be encountered in only a few individuals with acute hepatitis (Westbrook & Dusheiko, 2014). Acute hepatitis is self-resolved in 20%–50% of incidences but chronic in most cases (Pawlotsky, 2004). A patient may remain undiagnosed until they manifest complications of end-stage liver disease.

Chronic HCV infection is marked by the persistence of HCV RNA in the blood for at least 6 months after the onset of acute infection (Gupta et al., 2014). The progression to chronic state is influenced by several factors, such as age, gender, ethnicity, co-infection with the human immunodeficiency virus (HIV) or Hepatitis B virus (HBV), alcohol consumption and other co-morbid conditions, such as cancer, obesity and immunosuppression (Gupta et al., 2014). Twenty to 30 years after initial HCV infection, persistent hepatic inflammation leads to the development of cirrhosis in approximately 10%–20% of patients (Omata et al., 2016; Westbrook & Dusheiko, 2014).

Once cirrhosis is diagnosed, 1%–5% annual risk of developing hepatocellular carcinoma (HCC) and 3%–6% annual risk of hepatic decompensation and eventual death are observed (Modi & Liang, 2008; Omata et al., 2016; Westbrook & Dusheiko, 2014). Patients with decompensated cirrhosis have 15%–20% risk of dying the following year, and liver transplants are the only potential treatment option for such patients. HCV-associated liver disease is the leading reason for liver transplant in the US (Wong et al., 2015).

Figure 1 shows the progression of HCV infection from initial viral exposure until death. The risk percentage for each disease stage is given in parentheses. (Source: Chen & Morgan, 2006; Gupta et al., 2014; Modi & Liang, 2008; Omata et al., 2016; Pawlotsky, 2004; Westbrook & Dusheiko, 2014).

Seventy to 74% of HCV patients experience extrahepatic conditions (Cacoub et al., 2000). Such diseases as sicca syndrome, lichen planus, type 2 diabetes and non-Hodgkin's lymphoma are linked to chronic HCV infection (Westbrook & Dusheiko, 2014). The risk of developing non-Hodgkin's B cell lymphoma is also increased with HCV infection. Patients with HCV infections are prone to developing insulin resistance, hence type 2 diabetes which in turn increases the risk of vascular diseases (Antonelli et al., 2014).

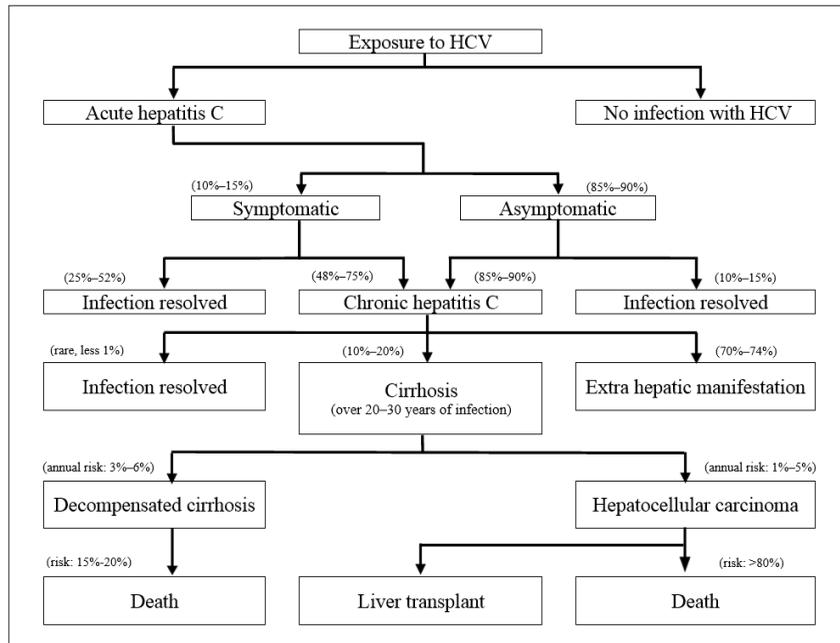


Figure 1. Natural Progression of Hepatitis C Infection

Causes of death among patients with HCV vary with age. The primary cause of death of patients aged 20–39 years is unnatural factors (death from external causes or due to mental and behavioural disorders related to psychoactive substance use) (Omland et al., 2011). Deaths of patients aged 40–59 years are equally caused by liver-related, non-liver-related and unnatural causes. The most common causes of death of the elderly are non-liver-related. In a previous study, the cause of death of HCV-infected patients was explored using data from the death registry of four countries (Australia, Sweden, Scotland and Denmark) (Grebely & Dore, 2011). The results revealed that among HCV patients, the proportion of liver disease-related deaths (including decompensated cirrhosis and HCC) varied from 10% to 24%, and that of drug-related deaths (such as drug overdose and suicide) was from 18% to 27%. The proportion of HIV-related deaths ranged between 0.4% and 7.9%.

HCV EPIDEMIOLOGY

A comprehensive literature review performed by Petruzzello et al. (2016) using data published up to 2015 revealed that total global HCV prevalence (adults) was estimated at 2.5%, which was equalled to 177.5 million. The global time trends of HCV prevalence were described by Hanafiah et al. (2013) in their systematic review article on the global epidemiology of HCV infection. The number of persons found positive for anti-HCV antibody increased from 122 million in 1990 to more than 184 million in 2005. Nineteen

Global Burden of Disease regions (excluding west sub-Saharan Africa and the Middle East) showed an increase in HCV prevalence between 1990 and 2005. In 2005, the HCV prevalence in west sub-Saharan Africa and the Middle East decreased from 4.0% to 2.8% and from 4.2% to 3.7%, respectively.

The same study also mentioned that the prevalence pattern across age groups was similar in all regions. Remarkably low prevalence was seen in the age group below 20 years old. This prevalence increased with age and peaked at 55–64 years (Hanafiah et al., 2013). For gender distribution, a systematic review found that men had higher prevalence than women (Bruggmann et al., 2014). However, women of age over 69 had higher prevalence due to unscreened blood transfusion after childbirth in France and Germany. In Turkey, as more women being hospitalised, nosocomial infection was thought to be the main reason for women becoming more infected than men (Bruggmann et al., 2014).

HCV prevalence also varies across WHO regions. The WHO Eastern Mediterranean and European regions have the most number of affected patients, with prevalence of 2.3% and 1.5%, respectively (WHO, 2017b). The prevalence of HCV infection in other WHO regions varies from 0.5% to 1.0%. The prevalence variation can be related to differences in the proportion of high-risk behaviour across populations. For instance, HCV transmission in most developed countries is primarily through drug injection, whereas exposure to infected blood products in healthcare and community settings is common among patients from developing countries (Averhoff et al., 2012).

The global number of deaths due to viral hepatitis is increasing. The estimated number of deaths gradually increased from 1.2 million in 2000 to 1.4 million in 2010; these deaths were mostly due to hepatitis-related liver cancer and cirrhosis (WHO, 2016). Of these deaths, 48% were due to HCV infection. In another mortality report by CDC, more Americans now die due to HCV infection than those by all other infectious diseases (Ly et al., 2016). The number of deaths in America due to HCV infection increased from 11,051 in 2003 to 19,368 in 2013.

RISK FACTORS OF HCV INFECTION

Through the literature search, various risk factors for HCV infection were found. These factors were grouped into four main categories to ease understanding. The categories were occupational profile, medical history, high-risk behaviour and traditional practices. Summary of reviewed literature for risk factors of HCV infection are presented in Table 1.

Occupational profile

Healthcare Workers. Westermann et al. (2015) conducted a systematic review comparing the prevalence of HCV infection among healthcare workers and the general population. Their meta-analysis indicated that the probability of HCV infection among healthcare

workers was 1.6 times higher than that for the control population. Further analysis by occupational group stratification revealed that medical, dental and laboratory staff had 2.7, 3.5 and 2.2 times higher risk of HCV infection, respectively, in comparison with the control group. Nursing staff had an insignificant risk of contracting HCV infection despite that they handle patients more frequently than do other healthcare groups (Westermann et al., 2015).

Marine-related Work. Individuals with marine-related work, mainly fishermen, have an increased risk of infection (HIV, HCV, HBV) because the nature of their work, which requires them to be away from home for extended periods (West et al., 2014), makes them likely to seek casual partners and engage in drug addiction, which are risk behaviours that promote the above-mentioned infectious diseases. A matched hospital-based case-control study was conducted in the Republic of Korea to examine the risk factors associated with HCV infection (Sohn et al., 2016). Their study analysis was based on information obtained from a sample with 234 participants in each case (patient with positive HCV infection) and patient-control (patient with negative hepatitis C antibody) groups. The research found that 11.1% of patients with HCV infection had marine-related occupations; these individuals were fishery workers, sailors and dockworkers. Multiple logistic regression analysis showed that contact dockworkers had nearly twice as much risk of HCV infection compared with the patient-control group.

Medical History

Blood Transfusion. Various case-control studies have investigated and revealed a strong association between blood transfusion and HCV infection. Rosa et al. (2014) conducted a matched population-based case-control study at a medium-sized town in Catanduva state, Brazil involving 190 participants for each case and control group. The study found that participants with HCV infection were 7 times more likely to have blood transfusion in the past than in the control group (Rosa et al., 2014). Another matched hospital-based case-control study was performed at five blood donation centres in China (Huang et al., 2015). The study findings indicated that donors with previous blood transfusion had nearly 10 times higher risk of HCV infection than those without any previous blood transfusion. However, the findings cannot be generalised to the general population because the study sample consisted merely of blood donors. In Egypt, Kandeel et al. (2012) conducted a hospital-based case-control study among 86 patients and 287 controls. Study analyses revealed that the variable 'receiving blood transfusion' was significant in univariate analysis but not in the multiple regression analysis.

Needle Stick Injury. Needle stick injuries containing blood from infected patients and mucosal exposure to contaminated blood or body fluids are common modes of infection

among healthcare workers (Pozzetto et al., 2014). Gorar et al. (2014) reported that among their study population, those who had needle stick injuries were 6 times more likely to contract hepatitis C than was the control group. Additionally, attempts to recap needles after use was also a risk factor associated with hepatitis C infection, according to multiple logistic regression analysis. Rosa et al. (2014) reported that participants with history of accidents with syringes and/or needles had 11 times higher probability of contracting HCV.

Haemodialysis. Sohn et al. (2016) found that blood dialysis was not a significant risk factor for HCV infection. This result was probably skewed by the involvement of only a small number of patients with history of blood dialysis in the studied population. Sun et al. (2009) conducted a systematic review of HCV infection and related risk factors among haemodialysis patients in China. The review found that haemodialysis patients who had long treatment durations and received blood transfusions during haemodialysis were associated with an increased risk of HCV infection. Additionally, HCV infection rates was significantly higher among patients who had haemodialysis for 1 year or more than individuals who underwent haemodialysis for less than a year (Sun et al., 2009).

Surgical Procedures. Incidents of surgery-related HCV transmission resulted from breaches in injection safety and infection prevention practices have been documented in many previous studies (Kandeel et al., 2012; Karmochkine et al., 2006; Sohn et al., 2016). Karmochkine et al. (2006) conducted a population-based case-control study in France, in which 460 HCV-infected patients and 757 controls participated. Their multiple regression analysis identified digestive endoscopy and abortion as independent risk factors for HCV infection. Other significant medical procedures associated with HCV infection were varicose vein sclerotherapy and ulcer wound care. In another hospital-based case-control study (Kandeel et al., 2012), patients with history of invasive procedures (including minor surgeries) had 4.7 times higher risk of HCV infection than those who had not undergone such procedures. By contrast, Sohn et al. (2016) concluded that gastroscopy and colonoscopy were not risk factors for HCV infection.

HIV Infection. HIV-infected individuals have an increased risk of HCV infection because these infections share several common routes of transmission, namely, parenteral, sexual and vertical exposures (Rotman & Liang, 2009). However, the prevalence rates of HIV–HCV co-infection greatly differ among high-risk groups. The highest co-infection rates were found among PWIDs and were between 65% and 87% (Bollepalli et al., 2007; Cacoub et al., 2015). A retrospective cohort study in Korea identified that HIV-infected injectable drug users had 16 times higher risk of HCV infection than HIV-infected non-users of injectable drugs (Lee et al., 2016). Sexual risk factors were found not associated

with co-infection (Bollepalli et al., 2007). Nevertheless, the prevalence rate of HCV–HIV co-infection among men who have sex with men (MSM) increased from 4% to 6% in a 10-year period (Cacoub et al., 2015).

Vertical Transmission. HCV can be transmitted from infected mothers to their children at all stages of pregnancy, namely, antenatal, intrapartum and postnatal (Arshad et al., 2011; Mok et al., 2005). A meta-analysis by Benova et al. (2014) revealed that more than 1 in 20 babies born to HCV-infected mothers were infected through vertical transmission. This study also identified that maternal HIV co-infection introduced children to 2.6 times higher risk for HCV infection through vertical transmission when compared to HIV-negative mothers (Benova et al., 2014).

High-risk Behaviour

Persons Who Inject Drugs. Several case-control studies have shown an association between PWIDs and risk of HCV infection. Jimenez et al. (2009) designed a matched hospital-based case-control study in Egypt, where 94 HCV-positive patients and 188 controls were enrolled. Multiple logistic regression analysis indicated that injection drug use was independently linked to HCV infection. In another study in Egypt by Kandeel et al. (2012), PWIDs carried 12 times higher risk of HCV infection than the control group. Having sexual contact with PWID also carried 3.5 higher risk for HCV infection (Brandao and Fuchs, 2002). Similarly, Sohn et al. (2016) found that the risk of contracting HCV by Koreans increased by nearly 4 times with the involvement of intravenous drug abuse. However, this association became insignificant after other variables were adjusted in multiple regression analysis. Rosa et al. (2014) investigated the association between PWIDs and risk of HCV infection among Brazilian population. Their study analysis found that 33.2% of HCV carriers had previous or current injectable drug use. However, none of the participants in the control group was reported of injectable drug use. Consequently, the authors could not conduct a comparative analysis.

Intranasal Drug Use. Intranasal drug use is also associated with an increased risk of HCV infection. Sniffing illicit drugs was mentioned by Jimenez et al. (2009) to be related to contracting HCV. In a study in Brazil by Rosa et al. (2014), the risk of HCV infection was found to be 7 times greater among participants who used non-injectable illicit drugs than among those who did not use non-injectable illicit drugs. Karmochkine et al. (2006) also suggested that HCV was significantly associated with intranasal cocaine use.

Tattoos. Jafari et al. (2010) evaluated HCV infection risks related to tattooing by systematically reviewing 124 studies, of which 83 were included in a meta-analysis. The

pooled odds ratio (OR) of the association between tattooing and HCV infection from all studies was 2.74. Kin et al. (2013) conducted a matched hospital-based case-control study among Asian Americans residing in northern California. A total of 384 patients were recruited into each case and control group. For Asian Americans ethnic cases compared with controls, body tattoo was a common risk factor, but it was present in only a small proportion of cases (4.4% vs. 0.5%, $p=0.001$). Nonetheless, in multiple logistic regression, HCV infection was 12 times higher among those with body tattoos than those without such tattoos (Kin et al., 2013). Two other studies also indicated a strong relationship between tattoos and HCV infection. Among the Korean population, persons with tattoos were twice as likely to contract HCV as those in the patients-control (Sohn et al., 2016). Rosa et al. (2014) also confirmed the link between tattoos and HCV infection among Brazilian population.

Imprisonment. The association between imprisonment and risk of HCV infection has been proven in several studies. Kandeel et al. (2012) reported that 7.0% of HCV-positive participants were imprisoned within six months before the study, whereas merely 0.3% of the controls had such history. Imprisonment is also a risk factor for HCV infection in the Republic of Korea. Sohn et al. (2016) revealed that imprisonment could double the risk of contracting HCV. However, no significant association was established via multiple logistic regression analysis in both studies (Kandeel et al., 2012; Sohn et al., 2016). By contrast, a population-based case-control study conducted in Brazil stated that history of imprisonment was an independent risk factor for HCV infection (Brandão & Fuchs, 2002).

Cosmetic Treatment (Including Pedicures and Manicures). Reuse of blood-contaminated instruments that are not adequately cleaned and sterilised is a possible mode of HCV transmission during cosmetic procedures. However, three studies that explored the role of cosmetic treatment as a risk factor for HCV infection gave inconsistent findings. Firstly, in multivariate analysis by Karmochkine et al. (2006), having beauty treatments or pedicures/manicures were independently associated with an increase in HCV risk. However, a study by Sohn et al. (2016), which considered the Korean population, showed that manicures were not a significant risk factor after other variables were adjusted. Similarly, a third study by Jimenez et al. (2009) in Egypt revealed that manicures were not associated with an increased risk of HCV infection.

Contact Sports. In contact sports, such as rugby and boxing, individuals can come into contact with blood through percutaneous injuries and thus have an increased possibility of HCV transmission. Only one study has explored the potential of engagement in contact sports as a risk factor for HCV infection. A study by Karmochkine et al. (2006) showed that participation in contact sports could double the risk of HCV infection.

Sexual Contact with HCV Carriers Among Monogamous Couples. The risk of HCV infection via sexual activity is remarkably low in monogamous heterosexual relationships. El-Ghitany et al. (2015) in their systematic review and meta-analysis found that having HCV infected partner carried 3 times greater risk for HCV infection. Study by Brandao and Fuchs (2002) also found similar result. However, study by Rosa et al. (2014) reported that sexual contact with HCV carriers was not an independent risk factor for HCV infection.

Men Who Have Sex with Men. There is a rise in the incidence of sexually acquired HCV among the MSM community (Chan et al., 2016). Asian countries have a lower incidence rate than do European countries. In South Korea, the incidence rate of HCV infection among HIV-infected MSM patients who deny use of injectable drugs is 1.40/1,000 person-years (Lee et al., 2016). Injectable drug use was the only independent risk factor for the prevalence of HCV infection in this study. In the cross-sectional study by Urbanus et al. (2014) on 777 HIV-positive MSM who visited the STI clinic in Amsterdam, the seroprevalence of HCV escalated from 5.6% in 1995 to 10.3% in 2010, peaking in 2008 (20.9%). Additionally, HCV infection in this population was associated with chlamydia infection, injectable drug use, unprotected anal intercourse and old age (Urbanus et al., 2014). Nevertheless, most studies investigating MSM as a risk factor for HCV infection were conducted in the MSM population itself and did not compare such individuals with the general population.

Sex with Female Sex Workers/Prostitutes. Female sex workers/prostitutes can be a source of HCV infection, but the prevalence of infection contracted from them is relatively small, ranging from 0.8% to 6.6% (Laurent et al., 2001; Wang et al., 2014). Russell et al. (2009) conducted a hospital-based case-control study and found that sexual intercourse with high-risk persons, frequent casual sexual intercourse and exposure to blood during sexual activity were not significant predictors for HCV infection.

Traditional Practices

Acupuncture. Many articles cited acupuncture as a risk factor for HCV infection owing to the presence of HCV genetic material on acupuncture needles used for patients known to be carriers of the virus (Lemos et al., 2014). In France, participants with history of acupuncture have 1.5 times higher risk of HCV infection than individuals without such history (Karmochkine et al., 2006). A study by Brandao and Fuchs (2002) found contradictory results. The researchers concluded that acupuncture was not a significant high-risk practice leading to HCV infection.

Cupping Therapy. Cupping therapy, a traditional method of ventouse blood-letting procedure, is popular in Egypt, Arabic countries and the Asian region (Mehta & Dhapte,

2015). Cupping is commonly performed as an alternative for pain treatment, inflammation reduction, relaxation and well-being improvement (Mehta & Dhapte, 2015). However, the hygiene and sterilisation status of equipment used during the therapy is uncertain because this procedure is performed mostly by non-medical personnel. A meta-analysis concluded that cupping therapy presented a heightened risk of HCV infection, with a pooled OR of 1.40 (El-Ghitany et al. 2015).

Body Piercing. Aside from the common ear and nose piercings, lip, tongue, nipple and genital piercings are becoming popular throughout the world and across all ages (Laumann & Derick, 2006). Yang et al. (2015) conducted a systematic review to establish the association between body piercing and transmission of HCV. The authors performed a data analysis of 30 studies (16 cross sectional studies and 14 case-control studies). The meta-analysis indicated a considerable risk of HCV infection, with a pooled OR of 1.83, among individuals with body piercings.

Male Circumcision by Traditional Practitioners. WHO estimated that one-third of males aged 15 years or older, mostly Muslims, would be circumcised by 2007 (WHO & Joint United Nations Programme on HIV/AIDS, 2007). Circumcision is highly prevalent in Islamic countries but is also commonly practised in parts of African countries mainly as a preventive measure to counter HIV epidemic (Wise, 2006). Findings from a meta-analysis by El-Ghitany et al. (2015) indicated that male circumcision was not a significant risk factor for HCV infection. Another cross-sectional study evaluating the association between male circumcision and HCV infection was conducted in southern Cameroon (Pépin et al., 2010). This study found that male circumcision by traditional practitioners was not a significant risk after other variables were adjusted in multivariate modelling.

Home Birth by Traditional Midwives. Home births facilitated by traditional midwives was commonly practised for several centuries before the advent of modern medicine. Similar to the cleanliness of equipment used in circumcision, that in this mode of birth is questionable; moreover, this practice can transmit HCV because it involves blood and body fluids. Metwally et al. (2014) conducted a hospital-based case-control study among the Egyptian population. Results from this study analysis showed that among Egyptian women, delivery at home with traditional midwives was associated with increased HCV infection risk of 3 and 4 times in comparison with delivery by doctors at the hospital, respectively. However, no multiple logistic regression analysis was conducted in this study.

Table 1

Summary of reviewed literature for risk factors of HCV infection

Authors, year of publication	Study design	Sample size and population setting	Significant risk factors
Benova et al. (2014)	Systematic review and meta-analysis	109 studies of HCV vertical transmission risk included in systematic review and meta-analysis	Maternal HIV co-infection (aOR 2.6).
Brandão and Fuchs (2002)	Hospital-based, case-control study	178 HIV positive blood donors and 356 controls recruited from eight blood centres in southern, Brazil	Been imprisoned (aOR 5.2), blood transfusion (aOR 9.9), tattoo (aOR 4.4), PWID (aOR 105.2), sexual intercourse with HCV positive partner (aOR 3.7), sexual intercourse with partner of PWID (aOR 3.5).
El-Ghitany et al. (2015)	Systematic review and meta-analysis	357 studies on HCV risk factors included in systematic review and meta-analysis.	PWID (pooled OR 9.0), MSM (pooled OR 2.4), HIV co-infection (pooled OR 4.6), tattoo (pooled OR 2.3), been imprisoned (pooled OR 2.3), blood transfusion (pooled OR 2.5), hospitalization (OR 2.5), having HCV positive partner (pooled OR 3.4), haemodialysis (pooled OR 2.9), medical procedures (pooled OR 1.6), acupuncture (pooled OR 1.8), cupping (aOR 1.4), body piercing (pooled OR 1.2).
Gorar et al. (2014)	Population-based, case-control study	81 healthcare workers with HCV positive and 83 controls from rural district of Pakistan	Needle stick injury (aOR 6.0), recap needle after use (aOR 5.7), treated at A&E hospital (aOR 5.5), female gender (aOR 3.4).
Huang et al. (2015)	Hospital-based, matched case-control study	174 HCV positive blood donors and 174 controls from five blood centres in China	Received blood transfusion (OR 9.9), tattoo (OR 2.8), body piercing (OR 1.5), intravenous medicine injection (OR 1.8).*

Table 1 (Continued)

Authors, year of publication	Study design	Sample size and population setting	Significant risk factors
Jafari et al. (2010)	Systematic review and meta-analysis	124 studies include in systematic review and 83 studies in meta-analysis. All studies related to tattooing as risk factor for hepatitis C	Tattoo (pooled OR 2.7).
Kandeel et al. (2012)	Hospital-based, case-control study	86 patients with HCV infection and 287 controls from two hospitals in Cairo and Alexandria, Egypt	PWID (aOR 12.1), invasive medical procedures (aOR 4.7), been admitted to hospital (aOR 7.8).
Karmochkine et al. (2006)	Population-based, case-control study	450 HCV seropositive patients and 757 seronegative controls in Paris	Digestive endoscopy (aOR 1.9), abortion (aOR 1.7), sclerotherapy (aOR 1.6), wound care treatment (aOR 10.1), acupuncture (aOR 1.5), intranasal cocaine use (aOR 4.5), contact sports (aOR 2.3), beauty treatments (aOR 2.0), pedicure/manicure (aOR 1.7).
Kin et al. (2013)	Hospital-based, matched case-control study	384 patients of Asian Americans ethnic with HCV positive and 384 controls recruited from two clinics in Northern California	Acupuncture or exposure to dirty needles (OR 12.9), body tattoo (OR 12.0), blood transfusion (OR 5.7).*
Lee et al. (2016)	Retrospective cohort study	45 HCV positive patients and 745 HCV negative patients from a tertiary care hospital in Korea	PWID (aOR 16.2).
Metwally et al. (2014)	Hospital-based, case-control study	540 HCV patient and 102 controls at six health centres in Egypt	Medical procedures [laparoscopy (OR 2.3), cannula (OR 2.3), wound sutures (OR 1.9), endoscopy (OR 5.0)], delivery by traditional midwives (OR 3.9), home birth (OR 2.9).*

Table 1 (Continued)

Authors, year of publication	Study design	Sample size and population setting	Significant risk factors
Jimenez et al. (2009)	Hospital-based, matched case-control study	94 HCV patients and 188 controls in two hospitals at Greater Cairo, Egypt	PWID (aOR 7.9), illicit drug sniffing (aOR 4.4), medical stiches (aOR 4.2), medical intravenous injection (aOR 5.0).
Rosa et al. (2014)	Population-based, case-control study	190 chronic HCV carriers and 190 controls recruited from Sao Paulo, Brazil	Blood transfusion (aOR 7.33), needle stick injury (aOR 11.0), tattoo (aOR 6.9), use of non-injectable drugs (aOR 7.6).
Russell et al. (2009)	Hospital-based, case-control study	170 HCV positive patients and 345 controls of STD clinic, western New York state	PWID (aOR 20.2), intranasal drug use (aOR 1.8).
Sohn et al. (2016)	Hospital-based, matched case-control study	234 HCV patients and 234 patient controls from three hospitals in Korea	Dockworker (aOR 1.9), tattoo (aOR 2.2).
Sun et al. (2009)	Systematic review and meta-analysis	43 studies on HCV infection among haemodialysis patients in China included in systematic review and meta-analysis.	Haemodialysis with blood transfusion (pooled OR 5.7).
Westermann et al. (2015)	Systematic review and meta-analysis	57 studies included in systematic review and 44 studies in meta-analysis. All studies related to HCV infection among healthcare workers	Medical personnel (pooled OR 2.7), dental staff (pooled OR 3.5), medical laboratory staff (pooled OR 2.2).
Yang et al. (2015)	Systematic review and meta-analysis	30 studies on body piercing as risk factor for HCV infection were included in systematic review and meta-analysis	Body piercing (pooled OR 1.8).

* No multivariable regression analysis, only univariable analysis available.

Note: A&E, accident and emergency; aOR, adjusted odd ratio; OR, odd ratio; HCV, hepatitis C virus; HIV, human immuno-deficiency virus; MSM, men who have sex with men; PWID, person who inject drugs; STD, sexually transmitted disease.

CONCLUSION

The high prevalence, incidence and mortality rate of HCV infection at the global level indicates that the challenge in preventing HCV transmission is far from over. The difficulty in detecting this virus infection at early stages worsens the situation. Thus, the best preventive strategy is through awareness of the risk factors for virus transmission. Individuals belonging to high-risk groups (healthcare workers, PWIDs and prisoners) should take extra precaution to avoid infection. Nevertheless, more study is needed to establish links between HCV infection and several high-risk activities that are commonly practised in the community, such as contact sports, cosmetic treatments and home births.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health, Ministry of Health Malaysia for his permission to publish this review article. Our gratitude to the academic staff of the Department of Community Health, Faculty of Medicine and Health Sciences, UPM, for their valuable comments and input for this article.

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