A STUDY PROTOCOL ON RISK FACTORS FOR HEPATITIS C INFECTION AMONG ADULT PATIENTS AT TERTIARY HOSPITALS IN KEDAH STATE

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ABSTRACT

Background: Hepatitis C virus is a bloodborne virus and commonly transmitted by contaminated blood mainly via clinical procedures and intravenous drug use. However, quality design study to explore the potential risk factor for hepatitis C infection in general local population is lacking. Thus, the present study is proposed to fill the gap in the body of knowledge of the related issue.

Materials and Methods: A matched hospital-based, case-control study will be conducted to identify the risk factors for hepatitis C infection. Patients with positive anti-HCV antibodies recruited from two participating tertiary hospitals will be in the case group, and controls will be those with negative serology for HCV infection that attending other specialist outpatient clinic of the same hospital where the case will be recruited. All cases and controls will be matched by gender, age (within 5 years) and ethnicity, with a ratio of one case to one control. Information on patient risk exposure will be collected using a standardised questionnaire. This study requires 291 pairs of matched case-control. Conditional logistic regression will be used for data analysis using STATA software.

Expected Outcome: The conduct of proposed study will help to identify common local practice that has an association with the hepatitis C infection. It is anticipated that the study results will inform the local health authorities and policy makers on key areas to formulate cost-effective preventive programs to reduce the incidence and transmission of this virus infection in Kedah state and Malaysia.

Keywords: bloodborne, hepatitis C, infection, matched case-control, risk factors.
1.0 Introduction

1.1 Background of the study

Hepatitis C is a blood-borne disease that results from infection with hepatitis C virus (HCV). World Health Organization (WHO) has estimated that in the year 2015, 71 million persons are living with chronic HCV infection (WHO, 2017a). Malaysia is also facing the burden of HCV infection. According to the Ministry of Health (MOH) Malaysia, the incidence rate of hepatitis C was 2.56 per 100,000 population in year 2010 and increased to 6.91 per 100,000 population for year 2015 (MOH Malaysia, 2010, 2016). National mortality rate for hepatitis C was 0.1 per 100,000 population in year 2010, and the rate was almost doubled (0.19 per 100,000 population) in year 2015 (MOH Malaysia, 2010, 2016).

Furthermore, local prevalence of HCV among specific high-risk population varied as reported in several studies. The highest prevalence was recorded among person who inject drugs (PWID) population (89.9%) (Chawarski, Mazlan, & Schottenfeld, 2006) and the lowest prevalence was seen among local blood donor (0.45%) (Haslina et al., 2012). Since the availability of HCV screening test in Malaysia, PWID was identified as the main risk factor for HCV infection. In a study between 1985 and 1991, Sinniah and Ooi (1993) have screened various risk groups for the anti-HCV antibody. They found that the highest percentage of positive anti-HCV antibody was among PWID (85%), followed by blood recipients (64%) and dialysis patients (54%). Similar finding was found by Tan et al. (2015) in which 77.8% of patients diagnosed with hepatitis C were PWID. Only a small percentage of HCV positive patient reported a history of blood transfusion (4.9%) and having sexual contact with infected partner (3.9%).

1.2 Problem Statements

Identifying disease risk factor in the population is essential to develop a cost-effective prevention programs (Wilson, Blakely, Foster, Hadorn, & Vos, 2012). Failure to identify will result in large increase of health burden to the country. The presence of large gaps in our understanding of the national epidemiology of HCV (McDonald, Mohamed, Dahlui, Naning, & Kamarulzaman, 2014) is the stepping stone to conduct this study.

In Malaysia, most of the published works were carried out in selected high-risk population, such as PWID, haemodialysis patients, fishermen, and blood donors (Choo et al., 2015; Jaafar et al., 2011; Ng et al., 1995; Tan, Yihui & Abu Hassan, 2015; Vicknasingam, Narayanan, & Navaratnam, 2009). Additionally, some common risk factor was not explored for its association with HCV infection. For example, being a healthcare worker was a known occupational risk for HCV transmission (WHO, 2017a), however, this variable was not investigated in local study. Several other traditional/cultural activities (male circumcision, cupping, acupuncture, home birth) that commonly practised in the local population that could transmit the HCV were also not examined in any published article.

For the present study, Kedah state was chosen for several reasons. First, the incidence rate of HCV infection in Kedah was high, ranked as second highest among other states in Malaysia in year 2013 with 260 cases of HCV were registered in Kedah (the incidence rate of 12.91 per
100,000 population) (MOH Malaysia, 2014). Furthermore, since year 2013 till 2015, the Kedah state rate was higher than the national rate (MOH Malaysia, 2014, 2015, 2016). Second, there was an increased number of local adult population involved in the high-risk activities. For instance, numbers of illicit drug users were getting higher in this state. Almost four thousand drug addicts were recorded from Kedah state, representing 12.5% of total drug abusers caught in Malaysia for the year 2016 (Ministry of Home Affairs Malaysia, 2017). This figure was an increase of 4.1% from the year 2014.

Third, as Kedah state is neighbouring with Southern Thailand, a known place for shopping and night entertainment among local population, sexual transmission may also become a major risk factor for HCV transmission for this state. It is estimated that 3 million Malaysian across the border via Bukit Kayu Hitam gate to visit Thailand (Mohd-Noor, 2017), and the number of visitors were escalated during the weekend. With a high prevalence of HCV among Thailand sex workers (Luksamijarulkul & Deangbubpha, 1997), the virus may be transmitted through sexual promiscuity with sex workers there. Suggestion to open the border gate round-the-clock at Bukit Kayu Hitam may increase the rate of HCV infection (‘Kedah agrees with 24-hour operation at Bukit Kayu Hitam border checkpoint’, 2017).

Forth, many traditional/cultural activities that commonly practised in the local population could transmitted the HCV. These activities, namely male circumcision, cupping, acupuncture and home birth, mainly involved the use of unsterile equipment on a person with unknown HCV status and the same tools were repeatedly use on the other person. In an in-depth interview with a traditional practitioner who performed male circumcision, he admits that the same equipment was used for every child without cleaning and he himself was not using any glove during the procedure (Rashid, Teh & Narayan, 2009).

There was also a growing interest of local population for ‘Muay Thai’ sports. ‘Muay Thai’ is a physical sport which utilizes the stand-up striking and various clinching techniques similar to boxing. Hundreds of local trainees, mostly young adults are involved in this sport (‘Khairy to promote Muay Thai as popular sports’, 2014, ‘Sik daerah MuayThai, tinju’, 2014). Interestingly, Karmochkine et al. (2006) have demonstrated that participating in contact sports (such as rugby and boxing) was significantly associated with HCV infection. HCV transmission may occur through contact with blood from percutaneous injuries. Thus, the possibilities of this ‘Muay Thai’ sport to transmit HCV among local population cannot be ruled out without adequate investigation.

In a nutshell, all of these figures and findings are reaffirming that HCV infection is undoubtedly a public health threat in Kedah state and identifying its risk factors is warranted. Using a case-control study design, the present study will be conducted to determine any association between occupational risks, medical-related procedures, patient behaviour, traditional practices, and sexual-related risk with HCV infection. The interest is on which factor contributed the most towards HCV infection among adult patients in Kedah state.

1.3 Significance of the Study

The conduct of this study will be a significant endeavour in extending existing local knowledge on HCV infection and its risk factor. Quality design study to explore the potential risk factor for HCV infection in general local population is lacking. The effort to halt the
disease transmission may be restrained due to the insufficient data on risk factor of the disease. Thus, the present study and its findings are proposed to fill the gap in the body of knowledge of the related issue.

1.4 Research Questions

The research questions of this study are:

i) Is there an association between the occupational profile and HCV infection?
ii) Is there an association between the patients’ medical history and HCV infection?
iii) Is there an association between patients’ high-risk behaviour and HCV infection?
iv) Is there an association between traditional practices and HCV infection?

1.5 Objectives of the Study

1.5.1 General Objective

This study aims to determine the risk factors that associated with HCV infection among adult patients at a tertiary hospital in Kedah state.

1.5.2 Specific Objectives

The specific objectives of this study are:

i. To describe the sociodemographic characteristics, occupational profile, medical history, high-risk behaviour, and traditional practices of adult patients at tertiary hospitals in Kedah state.

ii. To determine the association between HCV infection among adult patients at tertiary hospitals in Kedah state with the following risk factors:
   a. occupational profile (healthcare worker, marine-related work).
   b. medical history (blood transfusion recipient, needle stick injury, had haemodialysis, previous surgical procedures, HIV status, vertical transmission).
   c. high-risk behaviour (involved with injecting illegal drugs, intranasal drug use, had tattoos, being imprisoned, cosmetic treatment, involved in contact sports, sexual contact with HCV-positive spouse, sexual contact with female sex worker, men having sex with men).
   d. traditional practices (acupuncture, cupping therapy, body piercing, male circumcision by traditional practitioner, home birth by traditional midwife)

iii. To determine the independent risk factors for HCV infection among adult patients at tertiary hospitals in Kedah state.

1.6 Hypothesis

The research hypotheses are:

i. There is an association between occupational profile and HCV infection in the studied population.
ii. There is an association between medical history and HCV infection in the studied population.

iii. There is an association between high-risk behaviour and HCV infection in the studied population.

iv. There is an association between traditional practices and HCV infection in the studied population.

2.0 LITERATURE REVIEW

2.1 HCV Epidemiology

2.1.1 Global

Petruzziello et al. (2016) revealed that total global HCV prevalence was estimated at 2.5%, equal to 177.5 million of HCV infected adults. The global time trends of HCV prevalence have been described by Mohd Hanafiah et al. (2013) in their systematic review article on global epidemiology of HCV infection. Using prevalence data from more than 200 articles, age-standardized prevalence for year 1990 and 2005 was estimated for 21 Global Burden of Disease (GBD) regions. The number of persons found positive for anti-HCV antibody has increased from 122 million in year 1990 to more than 184 million in 2005. Except for west sub-Saharan Africa and middle east region, all other 19 GBD regions shown an increased in HCV prevalence between year 1990 and 2005. The HCV prevalence in west sub-Saharan Africa has reduced from 4.0% to 2.8% in year 2005 while prevalence in the middle east reduced from 4.2% to 3.7% for the same time period.

The same study also mentioned that the prevalence pattern across age groups were similar in all regions. Very low prevalence was seen for the age group below 20 years. Subsequently, the prevalence increased with an increasing age and peak at 55-64 years (Mohd Hanafiah et al., 2013). Based on gender distribution, the same review article found that in most countries, men have higher prevalence than women. However, except in France, Germany and Turkey, more women were found infected than men (Bruggmann et al., 2014).

The HCV prevalence also varied across WHO regions. The WHO Eastern Mediterranean and European Regions had the most affected patients, with the prevalence of 2.3% and 1.5% respectively (WHO, 2017b). Prevalence of HCV infection in other WHO regions varies from 0.5% to 1.0%. The variation in HCV prevalence could be related to the differences in the proportion of high-risk behaviour in a different population. On the other hand, global number of deaths due to viral hepatitis showed an increasing trend. In year 2000, estimated death was 1.2 million and gradually increased to 1.4 million deaths in year 2010, mostly due to hepatitis-related liver cancer and cirrhosis (WHO, 2016). Of those deaths, 48% were due to HCV infection.

2.1.2 WHO Western Pacific Region

Among WHO region, Western Pacific showed the lowest incidence of HCV infection, estimated about 6.0 per 100,000 population (WHO, 2017a). The prevalence for Western
Pacific region was 0.7%. It was estimated that 14 million people are living with HCV in this region (WHO, 2017a). The mortality rate from viral hepatitis is highest in the Western Pacific Region (24.1 deaths per 100,000), accounting for 446,000 deaths (WHO, 2017a).

2.1.3 Malaysia and Kedah State

The incidence rate of hepatitis C was 2.56 per 100,000 population in year 2010 and increased to 6.91 per 100,000 population for year 2015 (MOH Malaysia, 2010, 2016). National mortality rate for hepatitis C was 0.1 per 100,000 population in year 2010, and the rate was almost doubled (0.19 per 100,000 population) in year 2015 (MOH Malaysia, 2010, 2016). The mortality rate of HCV infection in Malaysia was lowest in year 2003 and 2004 (0.01 per 100,000 population), and highest in year 2015 at 0.19 per 100,000 population (MOH Malaysia, 2003, 2004, 2016). For Kedah state, the incidence rate of HCV infection in year 2003 was 0.51 per 100,000. Beginning in year 2013 till 2015, the state rate was higher than the national rate. Higher state incidence rate was probably because of better detection and notification of HCV infection cases in relation to the Methadone Replacement Therapy program in Kedah state. As the number of local health facilities providing the therapy increases, more drug addicts were recruited and being screened for HCV. Eventually, more HCV-positive patients (drug addicts) were captured into the state surveillance system. Kedah state mortality rates showed fluctuating trends. The highest number of deaths in the state was in year 2013 with six cases (0.3 per 100,000 population) (MOH Malaysia, 2014).

2.2 Risk Factors

HCV is a bloodborne virus and commonly spread through contact with contaminated blood or blood products (WHO, 2017a). Thus, the risk was greater among person who injects drugs (PWID) (Ho et al., 2012) and healthcare workers (Ahmed, Irving, Anwar, Myles & Neal, 2012; Averhoff, Glass, & Holtzman, 2012). Other known risk factors are haemodialysis, tattooing, body piercing, acupuncture and having sex with infected partner (Ahmed et al., 2012; Sohn et al., 2016). In Europe, Australia and the United States America, it was also found that hepatitis C is commonly found among men who have sex with men (MSM) infected with human immunodeficiency virus (HIV) (Chan, Sun, Wong, Lee, & Hung, 2016). Other uncommon risk factors associated with hepatitis C were cupping therapy, circumcision (Abd El-Wahab, Mikheal, Sidkey, & Shatat, 2014), home birth (Metwally et al., 2014), and contact sport (Karmochkine et al., 2006). Through literature search, various risk factors for HCV infection were found and grouped into four main categories to ease the understanding as illustrated in Figure 1 below.

2.3 Conceptual Framework

A conceptual framework describes the relationship between population characteristics and a health condition such as infection with HCV. Figure 1 shows the conceptual frame of this study. In this study, the independent variables included were occupational profile, medical history, high risk behaviour, and traditional practices. HCV infection will be the dependent variables in this study.
**Occupational Profile**
1. Healthcare worker
2. Marine-related work

**Medical History**
1. Blood transfusion
2. Needle stick injury
3. Haemodialysis
4. Surgical procedures
5. HIV infection
6. Vertical transmission

**High-risk Behaviour**
1. PWID
2. Intranasal drug use
3. Tattoos
4. Being imprisoned
5. Cosmetic treatment
6. Contact sports
7. Sexual contact with HCV-positive partner
8. MSM
9. Sexual contact with female sex worker

**Traditional Practices**
1. Acupuncture
2. Cupping therapy
3. Body piercing
4. Male circumcision
5. Home birth

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**Figure 1.** Conceptual Framework of Independent Variables and Their Relationship with HCV Infection.
3.0 METHODOLOGY

3.1. Study location

This study will be conducted at Hospital Sultanah Bahiyah (HSB), Alor Setar, and Hospital Sultan Abdul Halim (HSAH), Sg Petani, Kedah. Both hospitals are government-funded tertiary specialist centres offering various medical sub-specialities services including gastroenterology specialty. In HSB, this specialty was headed by a senior consultant gastroenterologist, assisted by five gastroenterologists and eight medical officers. The service provided includes investigations, diagnosis, treatment and management for HCV infection. Stable HCV-infected patients were managed at the gastro specialist outpatient clinic. Seven consultation rooms were run simultaneously, three times a week to cater the need of HCV-infected patients. On average, this clinic is managing between 15 to 20 HCV patients per week. This specialist clinic also served as a referral centre from other departments, health clinics, district hospitals, and private centres from other neighbouring states such as Perlis, Penang, and Northern Perak.

In HSAH, Gastro-specialist clinic was run by the visiting specialist from HSB and assisted by 2 other physicians and 3 medical officers. While HSB mostly catered the need for northern Kedah population, gastroenterology service at HSAH were provided for patients from southern part of Kedah. The services provided were similar to that offered by HSB. The gastro-specialist clinic run once a week with 5 to 10 HCV patients received consultation each week. For the above reasons, HSB and HSAH were chosen as the study location. Thus, the findings of the study were considered to be fairly representative of the HCV-infected population in Kedah state.

3.2. Study Design

This is a matched hospital-based, case-control study.

3.3 Study Duration

This study will be conducted approximately for 2 years (2017-2019)

3.4 Sampling

3.4.1 Study population

3.4.1.1 Case population

Patients for case group will be recruited from gastro specialist outpatient clinic of HSB and HSAH.

3.4.1.2 Control population

Patients for control group will be enrolled from other specialist outpatient clinic (e.g. surgery, ophthalmology, orthopaedic clinic) of the same hospital where the case was recruited.
3.4.2 Sampling population

3.4.2.1 Case definition

Cases were defined as patient with positive anti-HCV antibodies detected by anti-HCV test between period of January 2009 and December 2017. Patients for case group will be recruited from both gastro specialist outpatient clinics at HSB and HSAH.

3.4.2.2 Control definition

The control group will consist of patients with negative serology for HCV infection, which will be determine by anti-HCV antibodies test. Patients for control group will be enrolled from those patients that attending other specialist outpatient clinic of the same hospital (HSAH or HSB) where the case was recruited.

3.4.3 Selection criteria

3.4.3.1 Inclusion criteria

a. Adult patient aged 18 years old or older.
b. Able to understand and complete the questionnaires instrument.

3.4.3.2 Exclusion criteria

a. Non-Malaysian citizen
b. Receiving treatment from Obstetrics-specialist outpatient clinic or Paediatric-specialist outpatient clinic
c. Inconclusive HCV antibody test result

3.4.4 Sampling frame

3.4.4.1 Case-patient

Gastro specialist outpatient clinic managed the HCV patient. A list of HCV-infected patient, whether newly diagnosed or on follow up, was available at the clinic registration counter. The list was created since year 2009. Using this list, cases of HCV positive antibody that fulfilled the inclusion and exclusion criteria can be identified and recruited.

3.4.4.2 Control-patient

Controls will be recruited from other specialist outpatient clinic of the same hospital where the case was enrolled. Using the specialist outpatient clinic appointment list of the day, controls were then selected based on matched gender and age (within 5 years) of the case.

3.4.5 Matching

All cases and controls will be matched by gender, age (within 5 years) and ethnicity, with a ratio of one case to one control (1:1). As the information on traditional practices is different
between ethnics, thus patients need to be matched on ethnicity. Gender and age were proven to be a strong confounding factors in the prevalence of HCV infection. The study findings by Mohd Hanafiah et al. (2013) indicates that the HCV infection was more common among male gender in most countries due to large number of males involved in high-risk activities. Similarly, age will be matched as the same study above concluded that the prevalence of HCV infection increased with increasing age.

3.4.6 Sample size estimation

3.4.6.1 Sample size estimation for pair-matched study
The sample size was calculated using formulae for matched case-control by Schlesselman (1982). Based on the study on similar topic conducted by Rosa et al. (2014), data indicate that the proportion of exposure to blood and/or secretion among controls was 0.16 and with odd ratio of 1.96. Given \( \alpha = 0.05 \) (two-sided) and \( \beta = 0.10 \), the total number of pairs (case-control) required for this study is 247. After adjusted for estimated response rate of 85\%, the number of patients needed in each group will be 291 patients.

3.5 Study Variables

3.5.1. Dependent Variable
The dependent variable will be the HCV infection.

3.5.2 Independent Variables
The independent variables were:

a. Occupation profile
   i. Healthcare worker
   ii. Marine-related work

b. Medical history
   i. History of blood transfusion (particularly before year 1992)
   ii. Needle stick injury
   iii. Had haemodialysis
   iv. Previous surgical procedures
   v. HIV status
   vi. Vertical transmission

c. High-risk behaviour
   i. Involved with injecting illegal drugs
   ii. Intranasal drug use
   iii. Had tattoos
   iv. Being imprisoned
   v. Cosmetic treatment
   vi. Involved in contact sports
   vii. Sexual contact with HCV-positive spouse
   viii. Sexual contact with female sex worker
   ix. MSM
3.6 Data Collection

3.6.1 Study instrument

Based on the literature review on risk factors for HCV infection, a set of questionnaires will be developed. The study instrument / questionnaire will be prepared in English language and Bahasa Malaysia (national language). The questionnaire will include questions on participant’s socio-demographic (e.g. gender, ethnicity, level of education, marital status), occupational profile (working as healthcare worker or marine-related work), medical-related information (e.g. past surgical procedure, blood transfusion, needle-stick injury, HIV status, born by HCV-positive mother), involvement in high-risk behaviour (e.g. history of tattooing, intravenous drug usage, imprisonment, cosmetic treatment, and involved in contact sports, sexual intercourse with HCV-spouse or female sex worker, male respondent who have sex with men), and practiced any traditional ritual (acupuncture, cupping therapy, body piercing, male circumcision, home birth). Overall, beside socio-demographic questions, there will be 23 questions (21 questions with categorical answer (yes/no option) and 2 questions on duration of exposure (numerical answer) to be asked in the questionnaire regarding participants exposure to identified risk factors for HCV infection.

3.6.2 Quality control of study instrument

3.6.2.1 Validity

A set of questionnaires for data collection will be developed based on the literature review on risk factors for HCV infection. In addition, two public health specialists and a gastroenterologist will review the questionnaires for content validity. All the expert comments will be taken into consideration and subsequent correction on the questionnaires will be made.

3.6.2.2 Test-retest reliability study

To ensure reliability, the questionnaires will be test and retested among the HCV-positive patients receiving treatment at Hospital Kulim, Kedah state. The instrument will be administered twice at 14 days interval, based on the routine minimum duration given to the patient with non-emergency illness for subsequent follow up. After answering the first test, the patient will be informed that they will be answering another set of questions after 14 days. By not disclosing to them that they will be taking the same questionnaire, recall bias is expected to be minimised.
3.6.2.3 Sample size for test-retest reliability study

The minimum value for the Cohen’s kappa coefficient for every item with categorical answer (Yes or No) is expected to be 0.7 ($K_\text{2} = 0.7$). Expected kappa coefficient value of 0.7 was chosen based on suggestion by Fleiss (1981) that Cohen kappa agreement of 0.7 is consider as a good reliability. Assuming that there are no agreement for the test-retest at the first place ($K_\text{1} = 0$), with the power of 80% and alpha value set at 0.05, a minimum sample of 18 respondents are required for the detection of a minimum value of kappa coefficient of 0.7 (Bujang and Baharum, 2017). With consideration of 20% dropped-out, the test-retest reliability study will require 22 respondents.

3.6.2.4 Statistical analysis for test-retest reliability study

Cohen’s kappa coefficient test will be used to determine the degree of agreement by the same respondent at two different times for items with categorical answer / variable. Fleiss (1981) has developed a guideline to interpret the kappa value in which kappa over 0.75 indicates excellent agreement, 0.40 to 0.75 as fair to good, and below 0.40 as poor. For items with numerical answer / variable, intra-class correlation coefficient (ICC) will be used to measure the extent of agreement. Cicchetti (1994) suggested the following guidelines for interpretation of ICC agreement measures; less than 0.40 indicates poor agreement, 0.40 to 0.59 for fair agreement, 0.60 to 0.74 for good, and 0.75 to 1.00 will be considered an excellent agreement.

3.6.3 Data collection technique

For case-patient, all eligible patients will be identified and approached at the gastro specialist outpatient clinic at the HSB or HSAH. The purpose and method of the study will be explained to the eligible subjects to obtain their informed consent. Self-administered questionnaire will be distributed to the consented patient. The anonymous questionnaires were completed in the private room at the clinic and once completed, the questionnaires will be handed to the investigator for filling.

For control-patient, a list of patients under the specialist out-patient clinics at the HSB or HSAH will be retrieved. Potential control-patients will be matched for age group and gender of the case-patient. Similarly, the questionnaires will be administered to the consented patient. Additionally, for patient in control group, after completing the questionnaires, 5 ml blood will be collected into a plain tube to test for HCV antibody. Serum was separated by centrifugation at 4 °C and stored in labelled sterile tubes at -40 °C within 6 hours of blood collection. Serological testing will be performed at the private laboratory.

3.7 Data Analysis

The analyses will be performed using Stata software (version 14. College Station, TX: StataCorp LP). Descriptive statistics will be utilized for sociodemographic variables. The results will be presented as frequencies and percentage for categorical data (e.g. gender, ethnicity, level of education). Numerical data which is normally distributed will be presented as mean and standard deviation while median and interquartile range will be presented if the data is not normally distributed.
Conditional logistic regression models will be applied to assess the association between several exposure variables and HCV infection status. These models will be used to estimate odd ratios as a measure of association to identify risk factors for HCV infection. Patient’s HCV infection status will be the dependent variable, and all exposure variables significantly related to HCV status will be selected as independent variables in univariate analyses with p value ≤0.25 (Hosmer & Lemeshow, 2000). In the multivariate models, adjusted odd ratios will be estimated and presented with confidence intervals. To identify independent risk factors, the exposure variables will be removed in a stepwise method at several steps, until only those factors significant at a 0.05 level remained in the final model.

3.8 Ethical Approval

This study will be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. No personal information of studied patients will be disclosed and can be identified in any part of the study. All patients will be made aware that participation in this study is voluntary, anonymous and confidential, and that non-participation will not affect the healthcare received in any way. The Medical Research and Ethics Committee, Ministry of Health Malaysia has approved this study (NMRR-17-3322-38795).

3.9 Study limitation

Some limitations need to be noted while conducting this study. First, the best approach to obtain valid estimates of the association between HCV infection and risk factors will be through prospective cohort study. However, owing to asymptomatic acute infection and latent period required before the chronic state become symptomatic, such study design is not feasible and case control study represent the effective methods in evaluating risk factors for HCV infection. Second, in this case control study, the measurement of exposure is established after the patient had HCV infection. Some exposures may occur over long periods of time. As a result, the information regarding exposure provided by the patient may be influenced by recall bias.

4.0 Expected outcome and conclusion

The result from the proposed study will help to identify common local practice that has an association with the HCV infection. The findings will be the basis for other researchers to conduct future research on the same area. It is also anticipated that the study results will inform the local health authorities and policy makers on key areas to formulate cost-effective preventive programs to reduce the incidence and transmission of HCV in Kedah state and Malaysia.
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Declaration

Authors declare that the article is original and has not been previously published. The article represents original work and take full responsibility for the information provided.

Authors contribution

Author 1: Collected and analysed the information from the published articles, drafted the first version of the manuscript, and is responsible for the final version.
Author 2: Conceived the idea for the study, supervised the conduct of study and revised the final draft critically for important intellectual content.
Author 3: Assisted in reviewing the draft manuscript and supervised the conduct of the study.
Author 4: Contributed to the coordination of the study and gave valuable input in the final draft.

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