IDENTIFICATION OF EPIDEMIOLOGICAL RISK FACTORS FOR HEPATITIS C IN PUNJAB, PAKISTAN

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Background & Objectives: Hepatitis C virus (HCV) is one of the major health issues in Punjab, Pakistan. About 3% of the world population have been infected by hepatitis C virus. The objective of this study was to find out significantly associated factors with Hepatitis C in the region. Demographic, socio-economic and clinical factors were taken in consideration to determine the predictive strength of these associated factors by the logistic regression model approach. **Methods:** This was a hospital based case-control study of 400 patients; out of which 119 were controlled patients (HCV negative) while 281 were cases (HCV positive). Patients admitted in gastroenterology wards of Jinnah, Shaikh Zayed, and Mayo hospitals in Lahore city were interviewed to gather risk factors information. Data was collected in six months starting from April 2006 to September 2006. **Results:** results from multiple linear logistic regression model for overall data showed that age (OR=1.035, p=0.001), history of blood transfusion (OR=9.204, p=0.004), history of hospitalization (OR=2.979, p=0.043), Tattooing (OR=27.484, p=0.013), family history of hepatitis (OR=4.069, p=0.000), surgical operation (OR=4.290, p=0.030) were found to have significant and positively association with Hepatitis C. **Conclusion:** Hence our estimated logit model can be used to predict the chance of hepatitis C under the presence or absence of certain significant factors.

Keywords: Hepatitis C, Risk factors, Logistic regression, Odds Ratio, Pakistan

INTRODUCTION

Up till now about 8 strains of viral hepatitis have been discovered: A, B, C, D, E, F, G, and H. Hepatitis C is the commonest among these caused by the Hepatitis C Virus (HCV). It is a slowly developing blood born disease which severely affects the liver cells and create a lot of medical complications. It is common all over the world, particularly so in Pakistan. It was estimated that about 3% of the world's population has been infected by HCV and about 170 million are chronic carriers of this disease.[1,2] The prevalence of HCV in Pakistan is 4–6%[3] while a community based study in Hafizabad; Punjab revealed the figure to be 6.5%[4]. In another study seroprevalence of Hepatitis C was found to be 5–8%.[5] Four million carriers in Europe alone were reported.[6] Hepatitis C may be acute or chronic in nature. About 80% patients who develop acute hepatitis have no symptoms.[7] There are about 70% of cases of chronic hepatitis and 20% of acute hepatitis.[2] In about 70–90% of acute Hepatitis C patients chronic carrier states develop[8], and 10–15% lead to cirrhosis and other complications[9]. In Pakistan about 8% among Hepatitis C patients have Hepatocellular Carcinoma (HCC).[10]

There are numerous studies conducted by different researchers to evaluate the significant risk factors associated with Hepatitis C. A study determined the prevalence of transmission of HVC to household members in Hafizabad, Pakistan and showed that household members who have received 4 injections have 9–11 times more chances to develop HCV.[11] Another study investigated the Hepatitis C prevalence and risk factors in the North Alberta Dialysis Population that showed the prevalence of Hepatitis C to be 65% with risk of the disease to be greater in age group 18–55 years.[12] Bari *et al* found that therapeutic injections and barber shaves are significant factors.[13] Farid *et al* showed that blood transfusion, surgery, injections by quacks, tooth extraction, and shaving from barber are also the risk factors of Hepatitis C.[14] Fiaz *et al* investigated that doctors in surgical practice are at high risk of HCV.[15] Drug injection and sexual contact have 31.6 and 3.0 times more chances of Hepatitis C respectively. Champion *et al* showed that patients having shared needles/syringes have 9% more chances of having caught HCV disease.[16] Akhtar *et al* found that patients with history of hospitalization or those who have received multiple injections are at high risk.[17] Maria *et al* found that use of intravenous drugs, sexual partner with history of liver disease, blood transfusion and sexual partner with history of intravenous drug use are the associated factors with Hepatitis C.[18] The Lock *et al* study suggested that chronic Hepatitis C patients should not share tooth brushes, razors, nail clippers and scissors etc.[19]

The objective of this study was to find out significantly associated factors with Hepatitis C in the region.

MATERIALS AND METHODS

This was a hospital based case-control study of 400 observations, for which a questionnaire was designed in consultation with a physician. For questionnaire's reliability analysis, we used Cronbach's alpha test. Its value was found to be 0.736, which indicated that our questionnaire was reliable for data collection. Data

was collected in different visits from different indoors admitted patients of the Mayo, Sheikh Zayed, and Jinnah Hospitals of Lahore City from patients of all ages & sex admitted in gastroenterology wards during the period April to September 2006. During data collection help of the doctors and other paramedics was also taken to reach relevant patients directly. Moreover, to identify the cases and controls, information from medical reports of the concerned patients was obtained. Respondents were interviewed personally by the researcher in face to face interviewing process and questionnaires were filled properly. For cases, only confirmed HCV positive patients (by ELISA method) were included while for controls, confirmed HCV negative patients (by ELISA method) were interviewed.

Data was entered into the SPSS (Statistical Package for Social Sciences) version 13.0 for analyzed descriptively & analysis. Besides describing data, bivariate and multivariate analysis of the data was carried out. To check the degree or strength of association, the values of Phi and Cramer's V[20] statistics were computed. Among the significant factors, those which had the highest value of Phi and Cramer's V were declared as highly associated factors with Hepatitis C.

In multivariate analysis, multiple linear logistic regression model was applied to find the significantly associated factors with hepatitis C. Some diagnostics for logistic regression model to find out any outlying observations in the data i.e. leverage & influential values were also used. They included the graphical representation of residuals and predicted probabilities of the fitted model by the index plot [21]. Cox & Snell R-Square, and Nagelkerke R-Square were used to find out how much variation was explained by the model. Hosmer and Lemeshow test was used to find the overall significance of the fitted model[22]. Forward LR (likelihood ratio) criterion was used to obtain significantly associated factors with Hepatitis C. Later on Wald test was used to check the significance of multiple logistic regressions' coefficients individually. Wald test was used to test the null hypothesis, i.e., the particular logit effect assumed to be zero. Odds ratios of the significant factors were calculated with 95% confidence intervals (CI).

RESULTS

Multiple linear logistic regression model approach is a model building criteria in which a logit model based on significant factors is developed for overall data. The data of 400 observations was taken into account to build an overall logistic regression model. The variable 'HEPC' was taken as dependent variable which was a binary response variable. And all other factors were assumed to be independent variables. Among these variables only three were quantitative, i.e., patient's age, house hold income, and family size, while others were categorical in nature. Forward LR (likelihood ratio) criteria were used to obtain significant factors associated with Hepatitis C.

Our initially collected data was based on 406 observations including 124 controls and 282 cases. Some useful diagnostics for binary response variable were used. These included the graphical representation of residuals and predicted probabilities of the fitted model. The graphs of diagnostics via index plots to eliminate influential & leverage values in the data showed that some observations that were far away from most of other observations in the fitted logistic model were the points that needed particular attention. Deviance residuals were plotted against every case to find the outlying observations. Cases showing abnormally large residuals were taken as outliers [21]. For example, the observations in Fgure-1(a) with case number 125, 215, 221, and 287 have relatively high Deviance residuals. Similarly from Figure-2(a) case numbers 164, 323, and 333 were found as leverage. Hence these were discarded from the data and again the same graphs were repeated to see the removal effect of these values (Figure-1(b) and 2(b)). From Table-1 overall fitted model showed 6 factors significantly associated with Hepatitis C, i.e., patient age, blood transfusion, history of hospitalization, tattooing, family history of hepatitis and surgical operations. The estimated regression coefficients in logistic regression model gives the estimated change in the log-odds corresponding to a unit change in the corresponding explanatory variable conditional on the other explanatory variables remaining constant.

The first risk factor in the fitted model was patient's age. Its coefficient contained positive value and odds ratio 1.035 (1.013–1.057). This indicated that with the increase of one year in the patient's age the risk of Hepatitis C will be increased 1.035 times provided that all other factors are assumed to be constant. As one year increase does not give any significant change, therefore we examined the change after 20 years. This was calculated as $\exp^{(10*0.034)}$=2.0. This suggested that with an increase of 20 years in age the risk of Hepatitis C disease becomes double.

The second factor was BLTRNS (history of blood transfusion). For reference group, patients having no history of transfusion were included. The logistic regression coefficient for patient history of blood transfusion had a positive value of 2.220 and odds ratio (OR) 9.204, which is greater than 1 with a 95% CI of 2.027 to 41.803 and doesn't include one the null value. This suggested that patients with history of blood transfusion have 9 times greater chances to develop Hepatitis C than those with no history of transfusion.

Figure-1: Index Plots to find influential

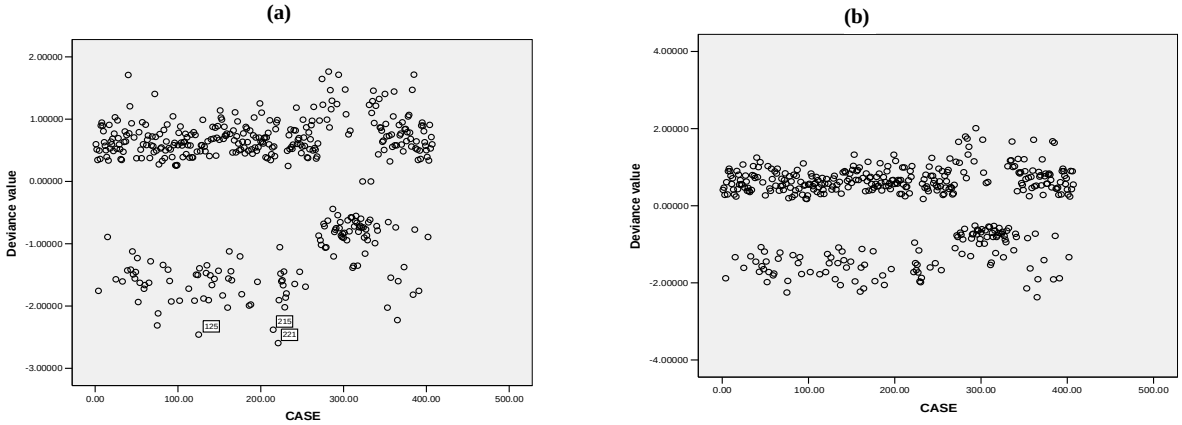

Figure-2: Plots to Eliminate Leverage values

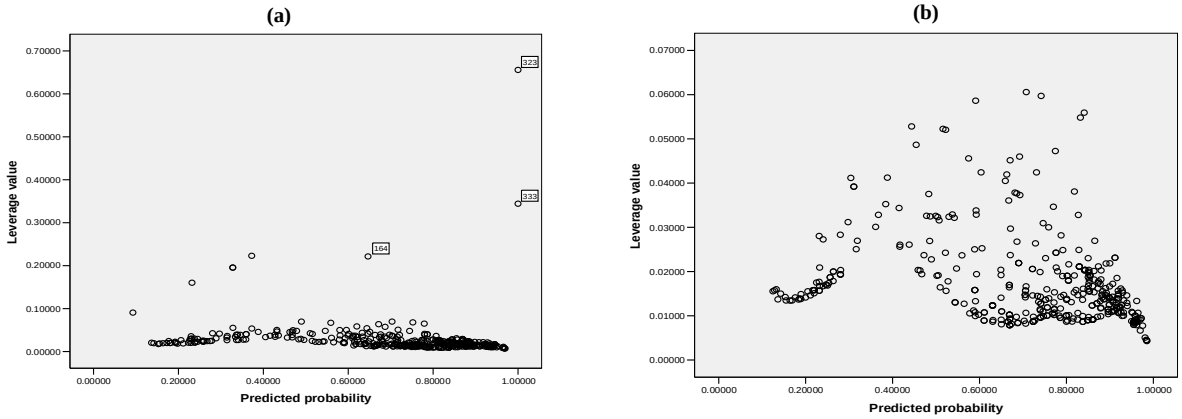

Table-1: Logistic Regression with Coefficients, Their Odds Ratio and 95% CI

Variables	β	Wald test	P-Value	Odds Ratio	95.0% CI for Odds Ratio	
					Lower	Upper
AGE	0.034	10.197	0.001	1.035	1.013	1.057
BLTRNS	2.220	8.265	0.004	9.204	2.027	41.803
HOSADM	1.092	4.103	0.043	2.979	1.036	8.569
TATOO	3.314	6.198	0.013	27.484	2.024	37.25
FAHOFH	1.403	14.292	0.000	4.069	1.966	8.422
OPER	0.593	4.691	0.030	1.810	1.058	3.096
Constant	-1.549	11.228	0.001	0.212		

The third factor was HOHOSP (history of hospitalization). It was found that chances were about three times greater to develop Hepatitis C with history of hospitalization.

The fourth factor was TATTOO (history of tattooing). Odds ratio was 27.484 (95% CI, 2.204 to 373.252). Tattooing had positive association with Hepatitis C and patients with history of tattooing have about 28 times more chances to develop Hepatitis C.

The fifth factor was FAHOFH (family history of hepatitis). Results suggested that family history of hepatitis also had positive association with hepatitis C and there are about 4 times more chances to develop Hepatitis C than others.

The sixth significant factor while running multiple logistic regressions was OPER (patients with history of operation). This showed that patients with history of surgical operations had twice more chances to have Hepatitis C.

For significance of overall fitted model Hosmer and Lemeshow test showed that the overall fitted model was significant with a $p>0.05$.[22] The value of Cox & Snell R-Square was 0.217, which indicated that 21.7% proportion of variance could be explained by this fitted model. Similarly Nagelkerke R-Square showed that 30.8% variation could be explained by this model.

Table-2: Percentage Comparison of Demographic & Socio-economic factors in Controls and Cases

Variable		HEPATITIS C (Controls=119)(%)	HEPATITIS C (Cases=281)(%)
Pt. Age in years	10–20	23 (19.3)	11 (3.9)
	21–30	38 (31.9)	33 (11.7)
	31–40	23 (19.3)	66 (23.5)
	41–50	20 (16.8)	69 (36.3)
	51>=	15 (12.6)	102(36.3)
Gender	Male	83 (69.7)	184 (65.5)
	Female	36 (30.3)	97 (34.5)
Marital status	Ever married	68 (57.1)	253 (90.0)
	Never married	51 (42.9)	28 (10.0)
Occupational status	Unemployed	23 (19.3)	19 (6.8)
	Professionals	23 (19.3)	36 (12.81)
	Business Man	12 (10.1)	25 (8.9)
	House wives	15 (12.6)	87 (30.96)
	Labour	23 (19.3)	61 (21.71)
	Others	23 (19.3)	53 (18.86)
Patient living	Single family	73 (61.3)	180 (61.1)
	Joint family	46 (38.7)	101 (35.9)
Patient location	Urban	60 (50.4)	125 (44.5)
	Rural	59 (49.6)	156 (55.5)
Household income	2000–5000	59 (49.6)	144 (51.2)
	5001–8000	27 (22.7)	67 (23.8)
	8001–12000	15 (12.6)	38 (13.5)
	12001-16000	6 (5.0)	9 (3.2)
	16001>=	12 (10.1)	23 (8.2)
Family size	1–5	34 (28.6)	80 (28.5)
	6–10	68 (57.1)	165 (58.7)
	11–15	13 (10.9)	33 (11.7)
	16>=	4 (3.4)	3 (1.1)
Father education	No	78 (65.5)	202 (71.9)
	Yes	41 (34.5)	79 (28.1)
Mother education	No	95 (79.8)	228 (81.1)
	Yes	24 (20.2)	53 (18.9)
Patient's education	No education	50 (40.0)	148 (52.7)
	Matriculation	46 (38.7)	102 (36.3)
	Graduation	20 (16.8)	29 (10.3)
	Postgraduation	3 (2.5)	4 (1.2)

Overall Logit Model

Y= –1.549+0.034×AGE+1.305×BLTRNS+0.085×HOHOSP+1.882×TATOO+1.403×FAHOFH+0.593×OPER

We can use this model to predict chances of Hepatitis C in presence or absence of these significant risk factors, for example

AGE=50, BLTRNS=1, HOHOSP=1, TATOO=1, FAHOFH=0, OPER (1)=0

Thus the calculated value is Y=3.423 and the predicted probability is f(y)= prop (HepC)= $1/ (1+e^{-y})$= 0.968.

Hence the chance of developing Hepatitis C is 96.8% under presence of these factors, which is >50%. Similarly we can predict different probabilities from this model for different situations. Table-4 gives bivariate analysis in which association of every risk factor was tested individually with Hepatitis C. For this purpose Pearson's Chi-square test was applied and significant factors among all factors were separated. The significance level was taken as 5%. Moreover, to check the degree or strength of association, the values of Phi and Cramer's V were computed. It was found that marital status of the patient had the highest association with Hepatitis C.

Table-3: Percentage Comparison of Clinical Risk Factors in Controls and Cases

Variable		Hepatitis C Controls=119 (%)	Hepatitis C Cases=281 (%)
Patient history of jaundice	No	105 (88.2)	206 (73.3)
	Yes	14 (11.8)	75 (26.7)
Family history of hepatitis	No	105 (88.24)	214 (76.16)
	Yes	14 (11.76)	67 (23.84)
History of blood transfusion	No	95 (79.83)	192 (68.33)
	Yes	24 (20.17)	89 (31.67)
History of Dental surgery	No	91 (76.47)	183 (65.12)
	Yes	28 (23.53)	98 (34.88)
Kidney dialysis	No	117 (98.3)	272 (96.8)
	Yes	2 (1.7)	9 (3.2)
Tattooing	No	106 (89.1)	249 (88.6)
	Yes	13 (10.9)	32 (11.4)
Body piercing	No	83 (69.7)	186 (66.2)
	Yes	36 (30.3)	95 (33.8)
More than one marriages	No	117 (98.3)	268 (95.4)
	Yes	2 (1.7)	13 (4.6)
History of Injected drugs	No	113 (95.0)	277 (98.6)
	Yes	6 (5.0)	4 (1.4)
Contact with blood and needle	No	106 (89.1)	250 (89.0)
	Yes	13 (10.9)	31 (11.0)
Sharing syringes	No	114 (95.8)	270 (98.2)
	Yes	5 (4.2)	11 (1.8)
Sharing tooth brush	No	118 (99.2)	276 (98.2)
	Yes	1 (0.8)	5 (1.8)
Sharing razor	No	114 (95.8)	263 (93.6)
	Yes	5 (4.2)	18 (6.4)
Barber shaves	No	39 (32.8)	102 (36.3)
	Yes	80 (67.23)	179 (63.7)
Surgical operation	No	90 (75.6)	155 (55.2)
	Yes	29 (24.4)	126 (44.8)
Loss of blood due to accident	No	96 (80.7)	205 (73.0)
	Yes	23 (19.3)	76 (27.0)
History of cuts	No	43 (36.1)	86 (30.6)
	Yes	76 (63.9)	195 (69.4)
Ever admitted in hospitals	No	68 (57.1)	110 (39.1)
	Yes	51 (42.0)	171 (60.9)
Organ's transplantation	No	119 (100.0)	280 (99.5)
	Yes	0 (0.00)	1 (0.5)
Family history of liver disease	No	106 (89.1)	219 (77.9)
	Yes	13 (10.9)	62 (22.1)
History of injections	Yes	119 (100.0)	281 (100.0)
Ever imprisoned in past	No	110 (92.4)	253 (90.0)
	Yes	9 (7.6)	28 (10.0)
History of mass vaccination	No	108 (90.8)	243 (86.5)
	YES	11 (9.2)	38 (13.5)

Table-4:Chi-Square Tests of Association with Phi & Cramer's V Statistics

Factors	Pearson χ^2	df	*p*	Phi & Cramer's V
Pt. age in years	61.512	4	0.000	0.392
Marital status	57.066	1	0.001	0.783
Pt. history of jaundice	10.765	1	0.016	0.164
Family history of hepatitis	7.552	1	0.000	0.137
History of Blood transfusion	5.495	1	0.005	0.117
Dental surgery	4.987	1	0.001	0.112
surgical operation	14.759	1	0.043	0.192
Ever admitted in hospitals	10.963	1	0.001	0.166
family history of liver disease	6.809	1	0.000	0.130
Pt. with injected drugs	4.491	1	0.012	0.106

DISCUSSION

Hepatitis C is a worldwide epidemic, particularly in Punjab, Pakistan. Tariq *et al* found high prevalence rate of anti-HCV in Northern Areas of Pakistan.[23] It is generally an infection of liver and most common cause of cirrhosis and HCC all over the world.[24,25] The main

objective of this study was to find out factors which were significantly associated with Hepatitis C and to construct predictive model for the disease on the basis of these significant factors. This study includes almost all possible demographic, socio-economic and clinical factors. Various studies were conducted to determine the risk factors associated with Hepatitis C but most of them have applied weak statistical tools. Although some authors have applied binary response logistic regression to build up a prediction model based on significant factors but none of them have applied diagnostic checks before the construction of model. So in this way results may be unreliable. We have applied some useful diagnostics for binary response logistic regression model to eliminate the outlying observations in the data. After discarding these observations we have done all the analysis. So the results were statistically more reliable.

In our descriptive analysis we divided the patients' age into 5 different age groups to see the significant age group among these. These age groups are 10–20, 21–30, 31–40, 41–50 and above 51 years. Results indicate that, as one moves from lower age group to higher age group the number and percentages for cases increases rapidly. And maximum cases were found in the last age group, i.e., 36.3%. In a study the patients' ages ranged between 13–90 years with a mean of 43± 8.5 years.[16] Mean age for cases and controls were recorded as 47.34 and 34.61 years respectively. Moreover, after the 20 years of age the chances for disease become almost double. It was found that there were 267 (66.8%) males and 133 (33.2%) females in our study. Out of 267 males, 67% were cases. Similarly out of 133 females, 72% were cases. This indicated that females were more likely to have the risk of disease. About marital status it was found that 80.3% patients were married at some point and only 19.8% were never married. About 90.0% cases were from married patients' category. Among the housewives 25.5% were the cases. 51.2% of the cases were found associated with the lowest income group and majorities have shown Rs. 3000 income per month. Hence majority of the cases belonged to low socio-economic status. About 55.5% cases were from rural areas. It was observed that most of the cases were un-educated or less educated. About 52.7% cases had no education while 36.3% were under matriculation or less.[27] Among the cases, 71.9% had un-educated father and 81.1% illiterate mothers. In the overall multivariate and bivariate analysis, it was found that patients' age, blood transfusion, history of hospitalization[17], tattooing, family history of hepatitis, and surgical operations were significantly and positively associated with hepatitis C[27–29]. While in a bivariate analysis chi-square test results showed that marital status, patient history of jaundice, dental surgery, and history of injected drugs were positively associated with hepatitis C. Among the socio-economic factors, marital status and family size were also found positively associated indicating that as family size increases the risk of disease also increases. Tattooing showed highest value of odds ratio among all the significant factors. An international study showed that the risk of hepatitis C via blood transfusion had been reduced to zero[30] but in our study this factor is still found significant in our society. Doctors must always ensure a screened blood for the patients to minimize the risk through blood transfusion. Interestingly, all the patients had history of injections in both cases and controls and among these 42.7% had taken injections from quacks. About 69.4% cases were found with history of cuts and this history of cuts was mainly observed in housewives and farmers (working on land). In some studies history of contact with multiple sex partners was also found significant but we couldn't include this factor in this study because of social limitations. During the pre-testing stage this question was included in our study but none of the respondents responded to this question and had to be eliminated.

CONCLUSION

It was very surprising for us that some factors which were found significant like surgical operation, blood transfusion, dental surgery and history of hospitalization are mainly concerned with doctors and the hospitals as well though they are supposed to know better about this dangerous disease. But still people are getting this disease due to these factors. That may be due to the carelessness of the doctors and other paramedical staff. Researcher personally observed during data collection that at some places, there was no proper disposal system of used syringes and other blood related items in government hospitals. Un-educated people come from the rural areas and they never know about the spread of this disease. Most of the visitors, who come for their patient's hospitality, return back to their homes with the virus of Hepatitis C. Hence, the hospital management should strictly make sure that properly sterilised instruments are used by doctors during the surgical or dental operations. People must be guided about the harmfulness of tattooing and body piercing. Government should take supporting steps to guide and spread awareness about the risk factors and severity of this disease. One principle of cleanliness saves the society from a hundred thousand problems including the risk of Hepatitis.

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