

Determining the true prevalence rate of Hepatitis-C in Pakistan

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RESEARCH

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ABSTRACT

Background

Hepatitis-C is a serious public health concern in Pakistan, with an average prevalence rate of 8.7 per cent, has been reported.

Aims

The objectives of this study are multifold: to comprehensively review the published reports, determine positive predictive value (PPV) of Hepatitis-C using Bayes' Theorem and to perform meta-analysis using both raw prevalence rates and PPV rates.

Methods

Using available search engines and databases, a comprehensive literature search was performed on Hepatitis-C in Pakistan. Positive predictive values for the reported prevalence rates were calculated using Bayes' Theorem.

Results

Average PPV value found to be 33 per cent of the prevalence rate indicating that even after high prevalence reports, the chance of actual disease is still low to moderate, necessitating further confirmatory diagnosis. This discrepancy may be attributed to several factors, including the highly varying rates of prevalence; and test sensitivity and test specificity.

Conclusion

Random samples from various geographical locations and population segments are required to determine a realistic Hepatitis-C prevalence in Pakistan; in the absence of such representative samples, novel analytical and modeling approaches may offer a viable alternative to determine the actual prevalence rate and help devise better public health policy to combat the disease.

Key Words

Hepatitis-C, positive predictive value, meta-analysis, true prevalence rate

What this study adds:

1. What is known about this subject?

Hepatitis-C is a debilitating condition affecting millions. In Pakistan it is clustered in crowded urban areas with cost prohibiting treatments for the masses.

2. What new information is offered in this study?

The true prevalence rate of Hepatitis-C may not be as high as reported in the literature due to lack of representative samples and poor diagnostic techniques.

3. What are the implications for research, policy, or practice?

This research should help revise the actual prevalence rates of Hepatitis-C and related health policy in the absence of country wide representative samples.

Background

The World Health Organization (WHO) estimates that about 180 million people (3 per cent of the world's population) are infected with hepatitis-C virus (HCV), 130–150 million of whom are chronic carriers of the risk of developing liver cirrhosis. HCV in this context refers to the clinically tested positive cases. HCV is responsible for 60–70 per cent of all liver cancer cases and two thirds of all liver transplants in the developed countries¹. Three to four million people are newly infected each year, 70 per cent of whom develop chronic hepatitis and more than 350,000 people die every year from hepatitis-C related liver diseases.² World Health Statistics (2008) lists cirrhosis of the liver as the 18th most common cause of mortality in the world, and it is estimated that by 2030, liver cancer will become the 13th most common cause. The epidemiological estimates by WHO show that the prevalence of hepatitis-C is low (<1 per cent) in Australia, Canada and Northern Europe (In 2014, 35,321 cases of hepatitis C were reported from 28 EU/EEA Member States with a crude rate of 8.8 cases per 100,000 population) and about 1 per cent in countries of medium endemicity, such as USA and Europe. It is high (>2 per cent) in many countries of Africa, Latin America, Central and South-East Asia. In these countries, overall prevalence ranges between 5–10 per cent.² However, studies have previously showed that the total number of HCV infections reported is lower than previous estimates.³

Prevalence of Hepatitis-C in Pakistan

Pakistan is a large country of approximately 173 million people covering 800,000 sq. km and with world's highest fertility rates.⁴⁻⁶ The country is divided into five provinces of Punjab, Sindh, Khyber Pakhton Khuwa (KPK), Balochistan and Gilgit Baltistan, as well as federally administered tribal areas including the Islamabad, and the western third of Azad Jammu and Kashmir.^{6,7} The World Health Organization has rated Pakistan as the second highest country in the world in chronic infections. About 8.6 million Pakistanis are affected with Hepatitis-C. Although public health authorities in Pakistan are running awareness campaigns about Hepatitis through print and electronic media but given the enormity of the situation along with political instability, tremendous efforts are required to achieve any significant reduction in Hepatitis prevalence, particularly Hepatitis-C. One of the major impediments in this regard is also the availability of credible and representative data, particularly from the general Pakistani population, instead of exposed populations, which tend to skew the prevalence estimates. Therefore, collecting representative data from various parts of the country to determine the Hepatitis-C prevalence rate is of paramount importance to develop any viable and

effective public health policy to manage this crippling disease in resource scarce Pakistan. Until such representative data cohorts are attained, alternative methodologies must be adopted to determine the accurate prevalence rates of Hepatitis-C in Pakistan.

Justification

There are several epidemiological studies, on Hepatitis-C in Pakistan, available in the scientific literature; however, majority of those studies have been conducted using exposed populations and none of them, to our knowledge, have been conducted using an adequate random sample from general populations. Most of the studies were hospital based and/or clinical cases addressing the already exposed populations and thus are skewed in their prevalence rates. A few studies covered the wider range of age groups and most studies focused only on male populations. The sample size in most of the studies was small, generally in hundreds rather in thousands, considering the population size of the country. Thus the reported Hepatitis-C prevalence rates in Pakistan, in such studies, were found to be much higher (8.7 per cent on average) compared to other related countries of the region, such as India (0.9 per cent), Indonesia (2.1 per cent) and China (3.2 per cent).⁸ Until a country wide, randomized, multi-tier and broad based samples are not collected and analysed, a reliable Hep-C prevalence estimates cannot be determined. Under the given Pakistan's security situation, collecting such data is a monumental task, even under no financial constraints. Therefore, in the absence of such estimations, we believe the proposed methodology in this paper may offer a viable alternative to correctly estimate the Hep-C prevalence rates and judiciously steer country's beleaguered financial resources.

Objectives

Based on the above justifications, Our objectives are to: 1) identify, compile and categorize relevant studies for Hepatitis-C prevalence rates, 2) Determine positive predictive values (PPV) of the prevalence rates using Bayes' Theorem, 3) Perform meta-analysis for study effect size using fixed and random effect models and create forest plots for actual prevalence rates as well as PPV rates, and, 4) draw conclusions on actual prevalence rate of Hepatitis-C in Pakistan in the absence of representative random sample.

Method

Articles, on Hepatitis-C prevalence in Pakistan, were searched in PubMed, Google scholar and PakMediNet (for non-indexed Pakistani journals) and other databases, using key words: HCV in Pakistan, prevalence of HCV in Pakistan, epidemiological patterns of HCV in Pakistan, HCV in multi-

transfused Pakistani population, and HCV in general Pakistani population. Inclusion criteria entailed the studies demonstrating the prevalence rates and risk factors of HCV in the Pakistani populations. The studies of interest were selected from 2000–2013. Additional articles, through searches of specific authors working in this field, were also explored along with cited references of relevant articles. A total of 70 full length and 150 abstracts were reviewed/evaluated to identify the disease prevalence and diagnostics tests along with their test sensitivity and test specificity.⁹⁻¹³ However, only those articles (27 in total) that carried the required relevant data information were used, first to document and categorize the studies, determine the PPV of Hepatitis-C in Pakistan using Bayes' Theorem, develop Q statistics for meta-analysis, using fixed and random effect models and finally draw conclusions for actual Hepatitis-C prevalence in the absence of representative random sample. The retrieved data were categorized based upon the use of diagnostic techniques and are given in Tables 1-3, respectively for the Immunohistochemistry, ICT⁺ (study 1-18), ELISA (study 1-5) and reverse transcriptase PCR (study 1-4).

Based upon the available values of prevalence rates from the 27 studies along with test sensitivity and test specificity,⁹⁻¹³ the PPV using Bayes' Theorem were determined and are presented in Tables 1-3, respectively for the three diagnostic techniques.

Bayes' Theorem

Bayes' Theorem¹⁴ is a classical mathematical model used for determining conditional probabilities and outcomes.

$$P(D|S) = \frac{P(S|D) \cdot P(D)}{P(S|D) \cdot P(D) + P(S|\bar{D}) \cdot P(\bar{D})}$$

Where,

$P(D|S)$ = Probability of disease given symptom (Positive Predictive Value)

$P(D)$ = Probability of disease

$P(S|D)$ = Probability of symptom given disease (Test Sensitivity)

$P(\bar{D})$ = probability of no disease

$P(S|\bar{D})$ = Probability of symptoms given no disease (1-Test Specificity)

Bayes' Theorem in the form of $P(D|S)$ was applied to determine the PPV using Hepatitis-C prevalence rates along with the test sensitivity and test specificity of the 27 selected studies. For example, if the prevalence rate is 7 per cent, test sensitivity is 95 per cent and test specificity is 97 per cent, then $PPV = \frac{0.07 \times 0.95}{(0.07 \times 0.95) + (0.93 \times 1 - 0.97)} = 0.704$ or 70 per cent. It means that despite the

positive diagnosis of the disease, the actual chance of the disease is only 70 per cent and there still exists 30 per cent chance of no disease for a person who otherwise is diagnosed with the disease using a specific diagnostic test of 95 per cent and 97 per cent test sensitivity and test specificity, respectively. Bayes' PPV is a function of prevalence rate, test sensitivity and test specificity (Table 4) and thus fluctuates based on those three parameters.

Positive predictive values of all 27 selected studies were determined using Excel improvised formula for the above mentioned Bayes' Theorem with respective probability of disease, test sensitivity and test specificity and final values are given in Table 1-3. Study 1-18 (ICT⁺), given in Table 1, were the only studies used for meta-analysis and for further comparisons as they varied the most among 27, from 1.4 to 33.7 per cent in prevalence rates, and had low sensitivity value of 45 per cent. Those 18 PPV were compared with corresponding Hepatitis-C rates and were used to develop fixed and random effect models of the Q statistics for meta-analysis, following Excel based step-by-step procedure of Neyeloff et al.¹⁵ Forest plots, using meta-analysis data of effect size and confidence limits, were developed for ICT⁺ Hepatitis-C rates and PPV rates of study 1-18 and are given in Figure 3 and 4, respectively.

Results

Hepatitis-C in General Populations

Hepatitis-C prevalence rates in study 1-18 varied from 1.4 to 33.7 per cent with an average value of 8.7 ± 0.007 (95 per cent lower and upper confidence limits of 7.22 and 10.14, respectively). Positive predictive values of study 1-18 varied from 8.4 to 76.5 per cent with an average value of 32.5 ± 0.007 . In other words, on an average, the actual prevalence rate of those study 1-18 was 2.83 per cent (8.7×0.325) using the PPV of Bayes' Theorem. The comparative graph is given in Figure 1. Figure 2 compared the ICT⁺ prevalence rates with that of Bayes' PPV rates and may give a realistic picture of underlying disease prevalence.

Meta Analysis

Meta-analysis of the study 1-18 prevalence rates revealed significant ($p < 0.0005$) Q values for the fixed and random effect models indicating high variations among the 18 studies. The average rate was 8.68 per cent with 95 per cent lower and upper confidence limits of 7.22 and 10.14, respectively. Detailed spreadsheet models using step-by-step procedure for various parameters' calculations are available upon request for the interested readers, but are

not given here for brevity. Forest plot of the study effect size is given in Figure 3.

Meta-analysis of the study 1-18 PPV rates revealed significant ($p < 0.0005$) Q values for the fixed and random effect models; however, compared to the ICT⁺ rates, these variations were lot lower indicating that model efficiency can be improved when data were analyzed using Bayes' PPV instead of raw prevalence data. The average PPV rate was 3.09 per cent with 95 per cent lower and upper confidence limits of 2.11 and 4.08, respectively. Detailed spreadsheet model using step-by-step procedure for various parameters' calculations are available upon request for the interested readers, but are not given here for brevity. Forest plot of the study PPV effect size is given in Figure 4. A comparative graph of ICT⁺ Hepatitis rates and PPV rates, developed using spreadsheet models is given in Figure 2.

Discussion

The purpose of the present study was to analyze and understand the existing data of Hepatitis-C studies mostly on exposed and varied populations for their wide variations in prevalence rates; determine the positive predictive values (using Bayes' Theorem, a classical mathematical model for conditional probabilities) of reported prevalence rates of clinically tested HCV; and finally compare the reported prevalence rates vs. PPV rates using the fixed and random effect models of meta-analysis to draw valid conclusions on actual prevalence rate of HCV in Pakistan. Our results revealed that PPV based determination of the prevalence rate, instead of raw ICT⁺ cases may reflect a better picture of the prevailing situation (3.09 per cent vs. 8.68 per cent, average rates for the two, respectively; comparative graph is given in Figure 2). PPV in a way absorbed much of the of the data noise due to fluctuations in reported prevalence rates, test sensitivity and test specificity and thus reflect a better picture of the underlying disease prevalence rate.

These results are in accordance with Khan et al.³⁵ who coupled the ICT⁺ and ELISA with RT-PCR based HCV RNA detection to accurately determine the prevalence of active HCV infection among the blood donors from KPK and FATA region. The scope of ICT⁺ screening against anti-HCV seems to be limited in terms of sensitivity and thus skewed the rates as indicated in the current research. In Pakistan, ICT⁺ is the main tool of determining the HCV prevalence and results are usually based upon the detection of circulating antibodies without any further insights. Majority of studies (1-18 out of 27 reported) relied on ICT⁺ and false positivity is a common problem in such determinations, which does not investigate the active infection.³⁸⁻⁴⁰ Cheaper commercial

available kits for ICT⁺ tests claimed for high sensitivity and specificity ranging from 97–100 per cent, which in reality is significantly lower. Under such scenarios, PPV offers a better and logical alternative for measuring the performance of diagnostic test, besides determining the clear picture of prevalence rates.

Ideal approach, to determine the true Hepatitis-C prevalence, would be through carefully designed randomized study of general populations across various geographical regions of Pakistan using precise test procedures with high test sensitivity and test specificity. This will be a monumental task requiring substantial funding; and under the current security and political conditions, such undertaking seems improbable. In the absence of such comprehensive randomized sampling study and prevailing use of low sensitivity tests, we propose to employ alternative analytical and modeling tools to better determine the Hepatitis-C prevalence rates. Bayes' PPV offers a viable alternative as indicated in this research; and the revised estimate of 3.06 per cent down from 8.68 per cent seems to be more rational estimate of the Hepatitis-C prevalence rates in Pakistan. Such adjustment in turn will save significant resources of the beleaguered country and offer policy makers a fresh look into the situation from a different perspective.

Conclusion

In this study positive predictive values were determined to assess HCV prevalence rates. The main findings of PPV suggested that although different studies showed high prevalence rates, were not reflecting true picture of HCV prevalence and may not be generalized for the overall Pakistani populations. PPV determined a critical measure of the performance of diagnostic methods used in different studies for prevalence of HCV. Random samples from various geographical regions and population segments are required to determine a realistic Hepatitis-C prevalence in Pakistan. Positive predictive value determination using Bayes' Theorem offers a rational alternative and a different perspective in devising public health policy for Hepatitis-C in Pakistan to optimize beleaguered resources.

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ETHICS COMMITTEE APPROVAL

NA

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Figure 1: Comparison of ICT⁺ Hepatitis-C rate and % PPV of Bayes' Theorem

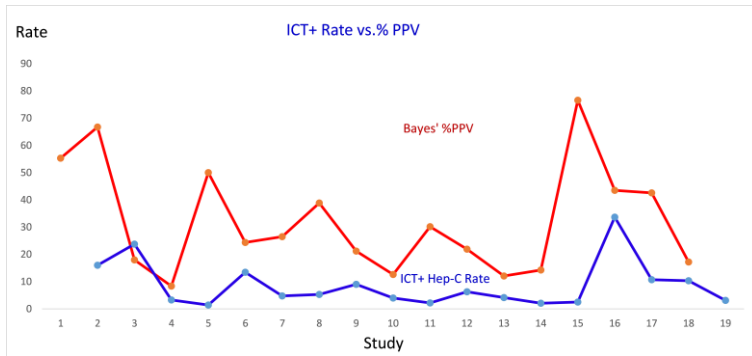


Figure 2: Comparison of ICT⁺ Hepatitis-C rate and Bayes' PPV rate

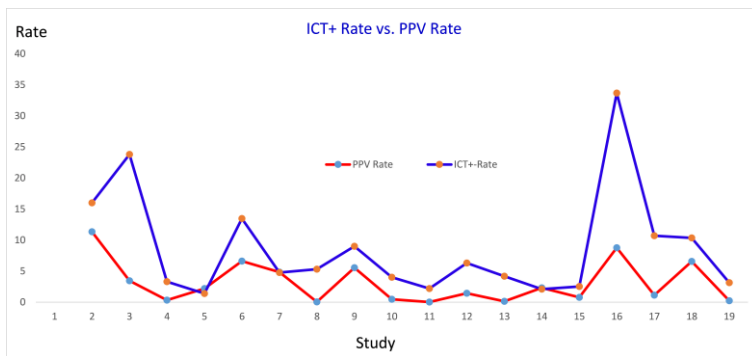


Figure 3: Forest plot of ICT⁺ Hepatitis-C study effect size in Pakistan

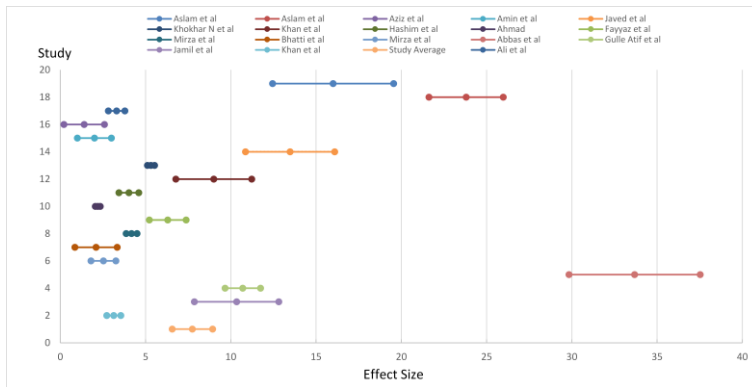


Figure 4: Forest plot of Bayes' PPV effect size

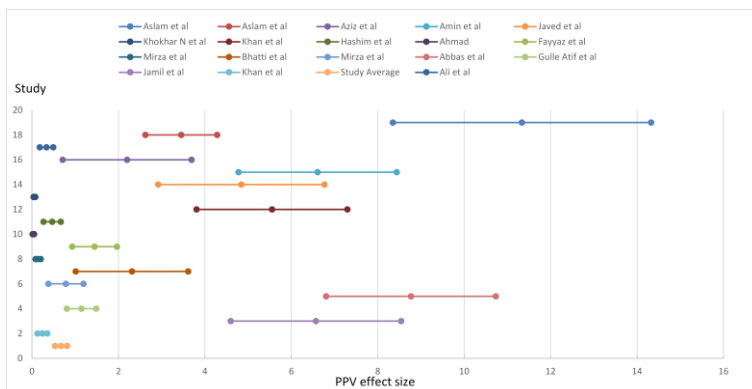


Table 1: ICT⁺ based Hepatitis-C studies in Pakistan

#	Author	Place	Target Population	Year	Age group	SS	ICT	P. disease	Sen	Spe	PPV	Ref
1	Aslam et al.	Lahore	Volunteer screening	2001	28	488	78.08	0.161	45	93	55.32	16
2	Aslam et al.	Gujranwala	Volunteer screening	2001	28	1933	460.05	0.238	45	93	66.75	16
3	Ali et al.	Rawalpindi	Pre-employment	2002	16-20	5,370	177.21	0.033	45	93	17.99	17
4	Aziz et al.	Karachi	Children	2002	5-15	380	5.32	0.014	45	93	8.36	18
5	Amin et al.	Shalimar hospital LHR	Screening camp	2004	15-25	757	102.00	0.135	45	93	24.36	19
6	Javaid et al.	Shifa Int, ISB,	Pregnant women	2004	27-32	503	24.00	0.048	45	93	50.03	20
7	Khokhar N et al.	Shifa Int, ISB,	Pre-employment	2005	34-44	47538	2528.00	0.053	45	93	26.53	21
8	Khan et al.	DHQ Mardan	Hospital based	2004	13-32	700	63.00	0.090	45	93	38.87	22
9	Hashim et al.	CMH, Attock	Pre-employment	2005	17-21	4552	183.00	0.040	45	93	21.21	24
10	Ahmad	Swat	Hospital based	2006	18-55	41613	915.49	0.022	45	93	12.63	25
11	Fayyaz et al.	Bahawalpur	Screening camp	2006	18-90	2086	131.42	0.063	45	93	30.18	26
12	Mirza et al.	CMH Bahawalpur	Pre-employment	2006	16-20	15550	650.00	0.042	45	93	21.90	27
13	Bhatti et al.	Lahore Dental college	Student	2007	17-26	524	11.00	0.021	45	93	12.11	29
14	Mirza et al.	Bahawalpur CMH	Pre-employment	2007	17-23	1840	46.00	0.025	45	93	76.55	30
15	Abbas et al.	Jarwar (Sindh)	Male and Children	2008	2.2-80	873	294.00	0.337	45	93	10.01	31
16	Gulle Atif et al.	Rawalpindi	Screening camp	2009	0.00-60	3800	406.60	0.107	45	93	43.51	33
17	Jamil et al.	Three UC Mansahra	Screening camp	2010	22-50	648	67.00	0.103	45	93	42.57	34
18	Khan al	KPK & FATA	Blood donor	2011	.	7148	224.00	0.031	45	93	17.22	35

ICT (Immunohistochemistry); SS (Sample Size); P. disease probability of disease; Sen (test sensitivity); Spe (test specificity); PPV (positive predictive value): Determined using the Bayes’ Theorem and prevalence data from various referenced sources along with respective test sensitivity and test specificity.

Table 2: ELISA (Enzyme Linked Immunosorbent Assay)

#	Author	Place	Target Population	Year	Age group	SS	ELISA	P. disease	Sen	Spe	PPV	Ref
1	Muhammad N et al.	DHQ, Buner, NWFP	Hospital based	2005	15-65	16400	751	0.046	78.9	100	100	23
2	Mirza et al.	CMH Bahawalpur	Pre-employment	2006	16-20	15550	574	0.037	78.9	100	100	27
3	Mirza et al.	Bahawalpur CMH	Pre-employment	2007	17-23	1821	46	0.025	78.9	100	100	30
4	Butt and Amin	CMH DI Khan	Pre-requisite	2008	17-22		97.019	0.017	78.9	100	11.07	32
5	Khan et al.	KPK & FATA	Blood donor	2011			135	0.019	78.9	100	100	35

ELISA (Enzyme Linked Immunosorbent Assay); RT (Reverse Transcriptase); SS (Sample Size); P. disease probability of disease; Sen (test sensitivity); Spe (test specificity); PPV (positive predictive value): Determined using the Bayes’ Theorem and prevalence data from various referenced sources along with respective test sensitivity and test specificity.

Table 3: Reverse Transcriptase (RT) PCR

#	Author	Place	Target Population	Year	Age group	SS	RT PCR	P. disease	Sen	Spe	PPV	Ref
1	Ahmad et al.	Faisalabad NIBGE	Screening camp	2007	10.2-60	300	48.00	0.160	98	100	100	28
2	Idrees et al.	Lahore	Screening camp	2008	0.00-60		494.00	0.072	98	100	100	36
3	Khan et al.	KPK & FATA	Blood donor	2011			118.00	0.017	98	100	100	35
4	Satti et al.	Rawalpindi & Islamabad	Random sampling	2012	0.00-50	503	59.86	0.119	100	100	100	37

RT (Reverse Transcriptase); SS Sample Size; P. disease probability of disease; Sen test sensitivity; Spe test specificity; PPV (positive predictive value): Determined using the Bayes' Theorem and prevalence data from various referenced sources along with respective test sensitivity and test specificity.

Table 4: Diagnostic power of ICT, ELISA-3 and RT-nested PCR [9-13]

Test	Test sensitivity	Test specificity
ICT	45	93
ELISA	78.9	100
RT-Nested-PCR	98	100
ELISA+ RT-NESTED PCR	100	100

The test sensitivity and test specificity of different diagnostic tests; ICT Immunohistochemistry; ELISA Enzyme Linked Immunosorbent Assay; RT Reverse Transcriptase.