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Developing and validating a scoring tool for identifying people who inject drugs at increased risk of hepatitis C virus infection

Handan Wand, Jenny Iversen, David Wilson, Libby Topp and Lisa Maher

The Kirby Institute, Sydney, Australia, University of New South Wales

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Corresponding author:

Handan Wand, PhD

The Kirby Institute, University of New South Wales, Sydney, Australia
Telephone: +61-2-9385 0900
Facsimile: +61-2-9385 0920
email: hwand@nchecr.unsw.edu.au

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Objective: To develop and a validate a scoring tool based on demographic and injecting risk behaviors to identify those who require additional, non-routine serological screening for HCV by assessing their personal risk.

Methods: The analysis included 16,127 participants who attended Needle and Syringe Programs (NSP) in Australia (1998-2008). Univariate and multivariate logistic regression models were used to develop a prediction model by age groups.

Results: Type of drug last injected, frequency and duration of injecting, sharing needles and syringes or other injecting equipments and imprisonment history were associated with HCV infection in all age groups. Strong relationship between an individual's 'HCV score' and their risk of testing HCV antibody positive was observed. An estimated 78% (95% CI: 75%, 81%), 82% (95% CI: 80%, 84%) and 80% (95% CI: 77%, 82%) of HCV infections across the age groups would be avoided if participants who were in the upper four quintiles of HCV scores had reduced risk to be in the lowest quintile of HCV scores.

Conclusion: Knowledge of HCV status has important implications for public health and care and treatment. Risk assessment strategies may assist to alert PWID who are at increased risk of HCV infection to present for testing.

Key words: Hepatitis C infection, injecting drug users, risk assessment

INTRODUCTION

Worldwide, infection with hepatitis C virus (HCV) is common among people who inject drugs (PWID) [1]. Estimates suggest that more than 70% of new cases of HCV infection are associated with injecting drug use [2,3]. Epidemiologic studies have identified independent risk factors for HCV infection, including sharing of contaminated needles and syringes [4-7] and other injecting equipment [8, 9], female gender [10,11], duration of injecting [12] and intravenous cocaine use [13, 14]. Although the risk factors for incident infection are well established, the literature suggests that a number of barriers may prevent PWID presenting for screening and many PWID face the possibility of HCV infection with a sense of inevitability, fostered by structural barriers to risk avoidance [15, 16]. PWID are a priority population in Australia as HCV prevalence remains high in this group. The burden of advanced liver disease (liver failure and hepatocelluar carcinoma) continues to grow among HCV-infected people [17]. It is estimated that 5,300 Australians are living with HCV-related cirrhosis and this figure is expected to double by 2020 without increased therapeutic intervention [18]. Despite the mounting burden of disease and recent advances in antiviral treatments, HCV treatment uptake among PWID remains very low (1-2% of chronic hepatitis C cases) [17]. A major public health challenge is to more effectively identify individuals with HCV before the development of significant clinical consequences.

Our study aimed to develop a scoring tool that can be used by PWID and primary care providers to identify individuals at increased risk of HCV infection. With increasing recognition of the clinical benefits of early diagnosis and treatment uptake [19-21], a simple self-administered tool may provide a way for PWID to identify personal risk and to modify risk behavior and/or seek health care/further assessment.

A large database of serial cross sectional samples of PWID attending Needle and Syringe Programs (NSP) in Australia (1998 -2008) was used to develop a statistical model underpinning the tool. Retrospective validation was carried out on the HCV risk assessment algorithm.

The following characteristics were considered essential in the development of the new prediction algorithm: (1) the use of routinely available and minimally intrusive variables and (2) estimation of the cumulative effect of concurrent risk factors on the likelihood of HCV prevalence. We are unaware of any studies to date that have quantified the cumulative effect of concurrent risk factors on the acquisition of HCV infection among PWID.

STUDY POPULATION

The Australian Needle and Syringe Program Survey (ANSPS) is a serial cross-sectional study conducted annually over a one to two week period since 1995. More than 50 NSP sites participate annually, with sites selected on the basis of geographic coverage, willingness to participate and an ability to recruit a minimum of 20 survey respondents. The survey methods have been described in detail elsewhere [22-25]. In brief, all PWID who attended participating ANSPS sites during the designated survey period were invited to participate. Participation was anonymous and voluntary and there was no financial reimbursement. Participants were asked to complete a brief, self-administered questionnaire on demographic characteristics and injecting and sexual risk behaviors (www.web.med.unsw.edu.au/nchecr), and to provide a capillary blood sample for antibody HIV and HCV testing. The current study used data for the period 1998-2008, involving more than 16,000 individuals.

Capillary blood was obtained by finger prick using single-use, disposable lancets and cotton-fiber blotting paper. Specimens were kept at room temperature at the survey sites, then couriered to a

central collection point before they were forwarded to the laboratory. A modified, third generation enzyme immunoassay (Abbott hepatitis C 3.0, Chicago, IL, USA) was used to test for HCV antibody. A modified cutoff value for optical density was calculated to capture greater than 95% of the seronegative population. Specimens were considered positive for HCV antibody if the optical density to cutoff ratio was greater than or equal to one on initial and subsequent testing.

Ethical approval was obtained from the Human Research Ethics Committee (HREC) at the University of New South Wales, as well as from relevant jurisdictional and site specific HRECs.

STATISTICAL ANALYSES

A split-sample method was used to develop and subsequently validate a risk equation and scoring system. Participants were randomly allocated to either the development (n=10,662; 67%) or internal validation (n=5,331; 33%) sample datasets.

We selected a range of demographic and injecting behavior variables as potential determinants of HCV infection. These included gender, Indigenous status, imprisonment history, country of birth, language spoken at home, drug last injected, frequency and duration of injecting, sharing of needles and syringes and other injecting equipment (e.g. water, filter, spoon, tourniquet), public injecting, and drug treatment history. All analyses were stratified by age groups (<25, 25-29, 30-39 and 40+).

We used descriptive statistics to characterize the groups according to antibody HCV serostatus: mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Logistic regression was used to create a predictive model based on the development data set. We used all non-

missing observations available in the relevant analyses as only a small proportion of observations had any missing data (except for the variable "imprisonment history"). All analyses were conducted using SAS statistical software version 9.2 (SAS Institute Inc. Cary, North Carolina) and STATA 10.0 (College Station, Texas).

Derivation of a screening score:

Using the development data set (n=10,662), we included a comprehensive list of predictors known to be associated with HCV antibody seropositivity in an initial model. Specifically, we included the main effects of all variables listed in Table 1 and their interaction effects. We first analyzed the univariate associations between the independent variables and HCV seropositivity. Backward elimination was used to reach the final multivariate model, in which factors with the largest *P* value were sequentially deleted until only significant predictors remained. We then created a weighted scoring system by rounding all regression coefficients up to the nearest integer (that is, the smallest integer greater than the estimate). This method was based on the β-coefficients (or log of the odds ratios) rather than odds ratios, which can be excessively influenced by only a few factors [26]. Once the final model was defined, we created integer weights for each variable. We calculated these weights by multiplying the model coefficients by 10. Using the rounded weights in the risk function, we estimated the participant-specific probabilities of HCV seropositivity and characterized the degrees of risk based on cut-off points of the probability distribution.

Cross-sectional and prospective validation:

We examined the predictive validity of the scoring system using the internal validation datasets (n=5,331). We also assessed the predictive validity of this scoring system on the subsequent of HCV antibody seroconversion using prospective data collected from individuals who visited ANSPS sites multiple times and tested HCV seronegative at their first visit.

We used the cross-sectional dataset to check the sensitivity and robustness of the new screening score. We computed standard validation measures: the proportion of antibody HCV seropositive specimens, sensitivity, specificity, positive likelihood and negative likelihood ratio and the area under the receiver operating characteristic curve (AUC) as discrimination statistics. We also assessed the diagnostic characteristics of different cut-points based on the total score in the development as well as validation datasets. The purpose of this analysis was to assess whether the combination of risk factors under consideration could predict those at increased risk with acceptable accuracy.

Population attributable risk:

After we calculated and validated the HCV screening score, we estimated population attributable risks, which estimates the percentage of HCV infections that would not have occurred if all the participants had been in the "lowest risk" (first quintile) category of the HCV screening score. We calculated population attributable risks by using a previously described method [29] that was applied to this study design and appropriate for use with multivariate adjusted relative risks.

RESULTS

Our study population comprised 10,662 individuals in the development dataset. Table 1 summarizes participant characteristics by HCV antibody serostatus. The overall prevalence of HCV was 51%. HCV seropositive participants tended to be older and more likely to report a longer duration of injecting, heroin as the drug last injected, a history of imprisonment, daily or more frequent injecting, public injecting and sharing needles and syringes and other injecting equipment.

Table 2 presents the final multivariate logistic regression model derived from the development data set by age groups. History of imprisonment, duration of injecting (5-9, 10+ years), drug last injected (heroin, cocaine, methadone, morphine, buprenorphine and others), needle and syringe sharing and sharing of ancillary equipment were all significantly associated with increased risk of antibody HCV seropositivity across all age groups. Injecting frequency (daily or more) was determined to be a significant risk factor for those aged less than 30 years. Female gender was associated with an increased risk of HCV seroprevalence for those younger than 40 years of age. Indigenous status was a significant predictor for HCV infection among people aged 30-39 years. Drug last injected and duration of injecting each required multiple categories to capture the risk gradient, whereas other risk factors were binary. The risk factors collectively yielded an AUC of 0.73 (95% CI: 0.70, 0.76), 0.72 (95% CI: 0.70, 0.75), 0.73 (95% CI: 0.70, 0.76) and 0.66 (95% CI: 0.64, 0.71) for the age groups <25, 25-29, 30-39 and 40 plus (data not shown). There were no significant interactions between injecting risk behaviors and gender across age groups (data not shown).

Table 3 shows the odds ratios (ORs) from the logistic regression models and population attributable risks of HCV infection for the quintiles of the risk scores by age groups for the development and validation datasets. There was a linear trend towards increasing HCV infection with increasing score regardless of the age groups in both datasets (trend, p-value<0.001). Using the development dataset, we estimated population attributable risks (95% CI) for the upper four quintiles of the scores. Results showed that 78% (75%, 81%), 82% (80%, 84%) and 80% (77%, 82%) of HCV infections across the age groups would be avoided if participants in the upper four quintiles of the HCV scores instead fell into the lowest quintile. Results from the validation dataset were consistent with those from the development dataset (Table 3).

We also assessed the diagnostic characteristics of cut-points (according to first, second, third and the fourth quintiles in overall population) for total score in the development as well as the validation

datasets (Table 4). An increased risk of HCV was clearly associated with increasing scores. For example, a cut-point score of 10 or higher distinguished a 'increased risk' group with a sensitivity of 96% or higher; similarly a cut-point 20 or higher yielded at least 92% sensitivity in all age groups in the development dataset; in cross sectional validation, sensitivity was estimated to be at least 94% across the age groups for the cut-point 10/15 or more and at least 76% for 20 or more.

Figure 1 illustrates the risk of PWID being HCV seropositive as a continuous function of the total score. Across all age groups, increasing scores were clearly associated with increased risk of HCV antibody positivity.

DISCUSSION

In this study, we developed a scoring tool based on data from ~16,000 PWID who attended ANSPS sites between 1998 and 2008. The tool was validated to accurately identify those at increased risk of HCV infection. Current Australian guidelines recommend HCV antibody screening in all individuals with risk factors for infection regardless of patient characteristics and settings [30]. Increasing the rate of HCV diagnosis and, in particular, diagnosis of acute infection and providing access to effective antiviral treatment has the potential to improve individual quality of life and reduce the burden of HCV infection. Being unaware of one's HCV serostatus has been identified as the major barrier to increasing HCV treatment uptake [31]. While a relatively high proportion (64%) of participants in the ANSPS reported recent HCV testing, HCV antibody negative respondents were less likely to do so than antibody positive respondents (60% versus 67%). One in five (20%) HCV antibody negative participants had not been tested for HCV in the last twelve months, and a further 20% had never been tested (www.web.med.unsw.edu.au/nchecr/Publications). This suggests that both uptake and frequency of testing could be improved. The intention of this study was not to identify a unique and specific cut-point of risk above which to target screening, but rather, to assess whether risk factors under consideration

could predict those at increased risk accurately in order to consider the tool's use in facilitating increased screening. With a high background HCV prevalence of ~70% among Australian PWID, all PWID should be screened for HCV. However, identification of only one of our listed risk factors substantially increased the likelihood of infection. Although Australia has screening guidelines for hepatitis C, current guidelines do not specifically target PWID [30]. By focusing on specific high-risk behaviors, tools such as the one developed in this study may allow for more targeted identification of individuals at increased risk of infection. If used as a self-administered questionnaire, it is likely that respondents will answer more accurately [32]. Since the vast majority of new HCV diagnoses in Australia are among people with a history of injecting drug use, this tool provides a valuable resource which could inform the establishment of more focused national screening guidelines.

Further, although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors among PWID can more precisely identify people in need of additional, non-routine screening. This is particularly pertinent in resource-constrained environments (including time-restricted clinical settings). Our methodology made use of a range of coexisting risk factors that were identified by a rigorous statistical approach in order to accurately identify the most relevant factors for HCV infection.

Risk calculation approaches have been extensively used in decision making about public health and clinical care and have even been proposed as an alternative to diagnosis for some diseases [33]. Our risk calculation was based on a statistical method that yielded a systematic scoring system for carefully selected predictors, guided not only by numerical and scientific evidence but also feasibility perspectives. We chose categorized variables which highlighted the important risk factors to motivate

high-risk persons to be screened or to modify behaviors. This combination of factors may explain the enhanced properties of our scoring tool.

Our study has several strengths, including being the first to validate a predictive model through prospective testing in internal cross sectional and prospective data sets. Our prediction equation is based on 11 years of data and more than 16,000 participants. Ideal risk assessment methods or prediction models should be derived from large representative samples. The current study has several limitations. First, the study population is limited to those who participated in the ANSPS, which may result in selection bias. However, the ANSPS has been shown to be broadly representative of PWID attending NSPs [16]. Second, we were not able to differentiate between acute, recent and chronic infections.

Risk factor screening and identification allows for patients to be educated regarding the risks of injection drug use and needle sharing. Appropriate testing and diagnosis of HCV allows for the patient to be evaluated for treatment and receive counseling regarding HCV prevention. In addition to physician education, patient education campaigns must also be developed to increase patient compliance with testing recommendations made by their physicians.

In conclusion**,** we believe the screening tool described here will provide a simple and cost-effective method of identifying and alerting PWID who are in need of additional, non-routine HCV screening with notable predictive validity. A self-assessment method that helps individual PWID understand their relatively increased risk of infection may encourage increased uptake and regularity of screening among this population.

Article Summary

Article focus:

- Although the risk factors for incident infection are well established, the literature suggests that a number of barriers may prevent PWID presenting for screening.
- Study developed a scoring tool based on demographic and injecting risk behaviors to identify those who require additional, non-routine serological screening for HCV by assessing their personal risk.

Key Messages:

- Current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs.
- However, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors among PWID can more precisely identify people in need of additional, non-routine screening.

Strengths and limitations:

- Our prediction equation is based on 11 years of data and more than 16,000 participants. Ideal risk assessment methods or prediction models should be derived from large representative samples.
- The study population is limited to those who participated in the ANSPS, which may result in selection bias.
- We were not able to differentiate between acute, recent and chronic infections.

Competing interest: None.

Ethics approval: Ethical approvals for the survey were obtained from Institutional Ethics Committees associated with the investigators and participating NSP sites.

Contributors: HW implemented the study, analysed the data and wrote the first draft. LM, JI, LT and DW helped interpreting the data and finalizing the manuscript. All authors saw and approved the final, submitted version of the manuscript.

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REFERENCES

[1] McGinn T, O'Connor-Moore N, Alfandre D, Wisnivesky J. Validation of a Hepatitis C Screening Tool in Primary Care. Arch Intern Med **2008**; 168(18):2009-13.

[2] Thorpe LE, Ouellet LJ, Hershow R et al. Risk of Hepatitis C Virus infection among Young Adult Injecting Drug Users Who Share Injecting Equipment. American Journal of Epidemiology **2002**; 155:7:645-653.

[3] Alter MJ, Kruszon-Moran D et al. The prevelance of hepatitis C virus infection in the United States, 1998 through 1994. New England Medical Journal **1999**; 341:556-62.

[4] Villano S. A., Vlahov D., Nelson K. E., Lyles C. M., Cohn S. & Thomas D. L. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. J Clin Microbiol 1997; **35**: 3274–7;

[5] Garfein RS, Doherty MC, Monterroso ER, et al. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. J Acq Immune Defic Synd Hum Retrovirol **1998**; 18:11–19.

[6] Hahn JA, Page-Shafer K, Lum PJ et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis **2002**; 186:1558–64.

[7] Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology **2004**; 15: 543–9.

[8] Hagan H, Thiede H, Weiss NS et al. Sharing of drug preparation equipment as a risk factor for hepatitis C. Am J Public Health **2001**; 91: 42–6.

[9] Falster K, Kaldor J and Maher L. Hepatitis C Virus acquisition among Injecting Drug Users: a cohort analysis of a national repeated cross-sectional survey of needle and syringe program attendees in Australia, 1995-2004. Journal of Urban Health **2008** [doi:10.1007/s11524-008-9330-7].

[10] Hahn JA, Page-Shafer K, Lum PJ et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis **2002**; 186: 1558–64.

[11] Maher L, Jalaludin B, Chant KG et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction **2006**; 101(10): 1499-1508.

[12] Maher L, Li J, Jalaludin B et al. High hepatitis C incidence in new injecting drug users: a policy failure? Aust N Z J Public Health **2007**; 31(1): 30-35.

[13] Patrick DM, Tyndall MW, Cornelisse PG et al. Incidence of hepatitis C virus infection among drug users during an outbreak of HIV infection. Can Med Assoc J **2001**; 165: 889–95.

[14] Miller CL, Johnston C, Spittal PM et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology **2002**; 36: 737–42.

[15] Davis M, Rhodes T. Beyond prevention? International Journal of Drug Policy **2004**; 15:123-31.

[16] National Centre in HIV Epidemiology and Clinical Research. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2009. National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW.

[17] NCHECR. Hepatitis C Virus Projections Working Group, Sydney: NCHECR, **2006**.

[18] Kwiatkowski CF, Fortiun Corsi K, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug user. Addiction **2002**; 97:1289-94.

[19] Gerlach J, Diepolder H, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology **2003**; 125:80-8;

[20] Kamal SM, Fouly AE, Kamel RR et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology **2006**; 130:632-638;

[21] Gregory JD, Hellard M, Matthews GV, et al. Effective Treatment of Injecting Drug Users with recently acquired hepatitis C virus infection. Gastroenterology **2010**; 138:123-135;

[22] Topp L, Iversen, J, Wand H, Day C, Kaldor J, Maher L. Representativeness of injecting drug users who participate in HIV surveillance: results from Australia's Needle and Syringe Program Survey. J Acquir Immune Defic Syndr **2008**; 47(5), 632-638.

[23] MacDonald M, Crofts N, Kaldor J Transmission of hepatitis C virus: rates, routes, and cofactors. Epidemiol Rev **1996**; 18(2), 137-148.

[24] MacDonald M, Wodak AD, Ali R et al. HIV prevalence and risk behavior in needle exchange attenders: a national study. The Collaboration of Australian Needle Exchanges. Med J Aust **1997**; 166(5),237-240.

[25] MacDonald MA, Wodak AD, Dolan KA et al. Hepatitis C virus antibody prevalence among injecting drug users at selected needle and syringe programs in Australia, 1995-1997. Collaboration of Australian NSPs. Med J Aust **2000**; 172(2),57-61.

[26] Schmidt MI, Duncan BB, Bang H et al. Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care **2005**; 28:2013-2018.

[27] Gonen M. Analyzing Receiver Operating Characteristic Curves with SAS **2007**. Cary, NC: SAS Institute;

[28] Sackett D, Straus SE, Richardson WS, Rosenberg W, Haynes B. Evidence- Based Medicine: How to Practice and Teach EBM. 2nd ed. Philadelphia: Churchill Livingstone; **2000**.

[29] Wand H, Spiegelman D, Law M, Kaldor J, Maher Lisa. Estimating population attributable risk for hepatitis C seroconversion in injecting drug users in Australia: implications for prevention policy and planning. Addiction **2009**, 104(12), 2049-2056(8).

[30] Maher L, Iversen J, Kaldor J. Measuring effectiveness of needle and syringe exchange programs for prevention of HIV among injecting drug users: Response to Amundsen. Addiction **2006**; 101(12):1834-6.

[31] Volk M, Tocco R, Saini S, Lok A. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology **2009**;50:1-6

[32] White B, Day C, Maher L. Self reported risk behavior among injecting drug users: Self versus assisted questionnaire completion. AIDS Care **2007**; 19(3): 441-447.

[32] Vickers AJ, Basch E, Kattan MW. Against diagnosis. Ann Intern Med. **2008**; 149:200-3. [PMID: 18678847]

Table 1: Risk factors for Hepatitis C Virus (HCV)

Characteristics	HCV Seronegative N= 5,214 (49%)	HCV Seropositive N= 5,448 (51%)
Mean age at survey (± SD)	29 ± 8	34 ± 9
<25 years, %	35	16
25-29 years, %	24	19
30-39 years, %	29	37
40+ years, %	12	28
Female, %	33	35
Indigenous, %	8	10
Mean age at first injection (± SD)	20 ± 6	19 ± 6
Mean years of injecting (± SD)	9 ± 7	15 ± 9
<5 years, %	26	12
5-9 years , %	28	21
10-16 years, %	23	28
17+ years, %	14	40
Ever been in Prison, %	17	33
Been in prison last year, %	11	22
Drug injecting behaviors (last month)		
Drug injected, %		
Amphetamine/methamphetamine	51	28
Heroin	35	48
Cocaine	3	5
Methadone	4	8
Morphine	7	9
Buprenorphine	1	2
Others[1]	9	8
Injecting daily or more , %	50	58
Receptive sharing needle/syringe, %	15	18
Receptive sharing ancillary equipments[2], %	33	38
Injected by another, %	14	12
New needle syringe in every injection	72	68
Injected in Public	46	52

[1] benzos, anabolic steroids, mixed drugs, other drugs or not reported

[2] water, spoon, filter, tourniquet

Table 2: Multivariate logistic regression: Odds Ratios (OR) and 95% confidence intervals (CI) for HCV infection Scoring by age groups

	<25			25-29			30-39			40+		
	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score
Sex												
Male	1	-	0	1			1			-		
Female	1.4	3.4	3	1.5 (<0.001)	4.1	4	1.4 (0.002)	3.3	3			
Indigenous												
No	-	-	-	-		-	1	-	-			
Yes							1.3 (0.04)	2.8	3	-		
Ever been in Prison?												
No	1	1	0	1			1			1		
Yes	2.2 (<0.001)	7.8	8	2.8 (<0.001)	10.2	10	1.9 (<0.001)	6.4	6	1.4 (0.003)	3.4	3
Years of injecting												
<5 year	1	-	0	1						1		
5-9 years	2.0 (<0.001)	6.8	7	1.7 (<0.001)	5.5	6	1.9 (<0.001)	6.5	7	1.5 (0.149)	3.7	4
10+ years	3.1 (<0.001)	11.1	11	2.4 (<0.001)	8.9	9	3.6 (<0.001)	12.7	13	4.6 (<0.001)	15.3	15
Drug last injected												
Amphetamine/methamphetamine	1	-	0	1			1	-		1		
Morphine	2.3 (<0.001)	8.3	8	1.7 (0.009)	5.5	6	1.9 (<0.001)	6.7	7	1.9 (<0.001)	6.7	7
Others[2]	2.0 (<0.001)	6.7	7	1.6 (0.010)	4.7	5	1.8 (<0.001)	5.9	6	1.5 (0.053)	4.0	4
Heroin	3.0 (<0.001)	11.1	11	2.7 (<0.001)	10.0	10	3.0 (<0.001)	10.7	11	2.5 (<0.001)	9.0	9
Cocaine	6.4 (<0.001)	18.6	19	3.6 (<0.001)	12.7	13	3.0 (<0.001)	10.9	11	3.6 (<0.001)	12.8	13
Methadone	3.3 (<0.001)	11.3	11	3.4 (<0.001)	12.2	12	3.0 (<0.001	11.0	11	3.1 (<0.001)	11.3	11
Buprenorphine	3.2 (0.003)	11.4	11	2.8 (0.004)	10.4	10	2.8 (0.001)	10.2	10	1.9 (0.141)	6.2	6
(Drug injecting behaviors last month)												
Injecting frequency												
Less than daily	1	-	0	1								
Daily or more	1.4 (0.001)	3.1	3	1.5 (<0.001)	4.0	4	-	-	-	-	-	
Receptive sharing needle/syringe												
No	-			1			1	-		-	-	
Yes	-			1.4 (0.005)	3.4	3	1.4 (0.002)	3.3	3			
Receptive sharing ancillary equipment[2]												
No	1	1	0	1						1		
Yes	1.3 (0.006)	2.5	3	1.3 (0.003)	3.0	3	-	-	-	1.5 (0.001)	3.8	4

[1]benzos, anabolic steroids, mixed drugs, other drugs or not reported

[2]water, spoon, filter, tourniquet

Table 3: Odds Ratios (OR) and 95% confidence intervals (CI) & for HCV infection by quintiles of HCV scoring

	Age <25 years		Age 25-29 years		Age 30-39 years		Age 40 plus	
Development Data Set	OR (95% CI)	P [0]	OR (95% CI)	P[0]	OR (95% CI)	P[0]	OR (95% CI)	P[0]
HCV Risk score[1]		<0.001		<0.001		<0.001		<0.001
Fifth 1	1		1		1		1	
Fifth 2	1.90 (1.33,2.69)		2.60 (1.88,3.57)		2.23 (1.72,2.89)		2.63 (1.94,3.58)	
Fifth 3	2.77 (1.92,4.01)		4.12 (3.00, 5.65)		4.07 (3.13,5.28)		4.56 (3.10,6.70)	
Fifth 4	5.40 (3.95,7.38)		4.85 (3.53,6.66)		5.40 (4.16,7.02)		5.86 (4.25,8.08)	
Fifth 5	10.31 (7.44,14.29)		12.40 (9.08,16.91)		9.10 (7.04,11.75)		7.78 (5.61,10.80)	
Population attributable risk for HCV score (%)[2] **(95% CI)**								
lowest v upper four fifth	78% (75%, 81%)		82% (80%, 84%)		80% (78%, 82%)		80% (77%, 82%)	
lower two v upper three fifth	74% (72%, 77%)		76% (74%, 78%		74% (73%, 77%)		72% (69%, 74%)	
Validation Data Set								
HCV Risk score[1]		<0.001		<0.001		<0.001		<0.001
Fifth 1	1		1		1		1	
Fifth 2	1.92 (1.12,3.28)		2.75 (1.73,4.38)		2.73 (1.94,3.85)		1.98 (1.30,3.02)	
Fifth 3	4.70 (2.75,8.04)		4.33 (2.78,6.77)		5.34 (3.74,7.63)		5.03 (2.78,9.10)	
Fifth 4	6.00 (3.76,9.56)		6.13 (3.93,9.56)		7.46 (5.19,10.74)		3.79 (2.44,5.87)	
Fifth 5	11.97 (7.41,19.32)		9.28 (6.07,14.19)		10.68 (7.56,15.10)		5.42 (3.50,8.42)	
Population attributable risk for HCV score (%)[2] **(95% CI)**								
lowest v upper four fifth	82% (79%, 85%)		80% (77%, 83%)		84% (82%, 85%)		73% (68%, 77%)	
lower two v upper three fifth	79% (76%, 81%)		74% (71%, 77%)		78% (76%, 79%)		67% (62%, 71%)	

[0] Test for trend

[1] HCV score **for age <25** was <7 for fifth 1, 7-<14 for fifth 2, 14-<17 for fifth 3, 17-<24 for fifth 4 and 24+ for fifth 5; **for age 25-29** was <12 for fifth 1, 12-<17 for fifth 2, 17-<22 for fifth 3, 22-<26 for fifth 4 and 24+ for fifth 5; **for age 30-39** was <13 for fifth 1, 13-<19 for fifth 2, 19-<24 for fifth 3, 24-<27 for fifth 4 and 27+ for fifth 5; **for age 40 plus** was <15 for fifth 1, 15-<22 for fifth 2, 22-<24 for fifth 3, 24-<27 for fifth 4 and 27+ for fifth 5;

Table 4: Optimal characteristics of HCV Scoring[1]

	Age <25 years		Age 25-29 years		Age 30-39 years		Age 40 plus	
Score cut points[2]	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Development Data Set (n=10,662)								
≥ 10	96%	17%	99%	9%	99%	7%	98%	10%
≥ 15	92%	32%	95%	23%	97%	15%	97%	19%
≥ 20	74%	60%	86%	42%	90%	36%	94%	24%
≥ 25	55%	74%	68%	64%	73%	57%	75%	54%
Validation Data Set (n= 5,465)								
≥ 10	96%	18%	99%	8%	99%	10%	99%	10%
≥ 15	94%	32%	95%	25%	97%	19%	97%	15%
≥ 20	76%	57%	88%	40%	87%	43%	94%	21%
≥ 25	59%	72%	67%	61%	73%	61%	74%	52%

[1]HCV Score :

For age < 25: (female)*3+ (indigenous) *0 + (Injecting 5-9 years)*7 + (Injecting 10+ years) *11+ Morphine*8 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*7 + (heroin)*11 + (cocaine)*19 + (methadone)*11 + (morphine)*8 + (Buprenorphine) *11 + (daily or more)*3 + (shared needle and syringe)*0 + (shared other equipment)*3 + (been in prison)*8

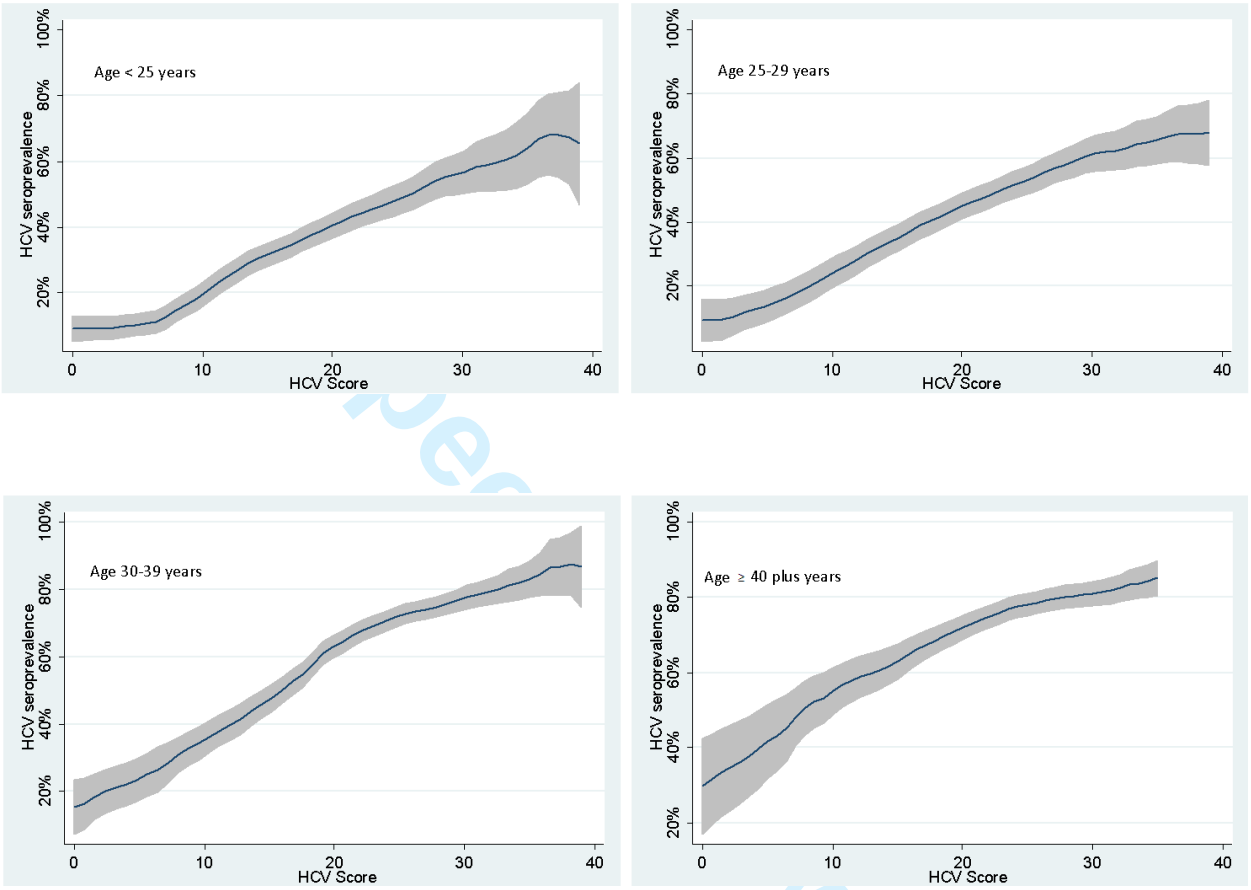
For age 25 -29 year: (female)*4+ (indigenous) *0 + (Injecting 5-9 years)*6 + (Injecting 10+ years) *9+ Morphine*6 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*5 + (heroin)*10 + (cocaine)*13 + (methadone)*12 + (morphine)*5 + (Buprenorphine) *10 + (daily or more)*4 + (shared needle and syringe)*4 + (shared other equipment)*0 + (been in prison)*6

For age 30 -39 year: (female)*3+ (indigenous) *3 + (Injecting 5-9 years)*7 + (Injecting 10+ years) *13+ Morphine*7 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*6 + (heroin)*11 + (cocaine)*11 + (methadone)*11 + (morphine)*7+ (Buprenorphine) *10 + (daily or more)*0 + (shared needle and syringe)*3 + (shared other equipment)*0 + (been in prison)*6

For age 40 + year: (female)*0+ (indigenous) *0 + (Injecting 5-9 years)*4 + (Injecting 10+ years) *15 + Morphine*7 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*4 + (heroin)*9 + (cocaine)*13 + (methadone)*11 + (morphine)*7+ (Buprenorphine) *6 + (daily or more)*0 + (shared needle and syringe)*3 + (shared other equipment)*0 + (been in prison)*6

[2]Approximate cut points for the first, second, third and the fourth quintiles.

Figure 1: Total score versus risk of HCV infection



BMJ open

Developing and validating a scoring tool for identifying people who inject drugs at increased risk of hepatitis C virus infection

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Manuscript ID:	bmjopen-2011-000387.R1
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RESPONSE TO REVIEWER'S COMMENTS: MANUSCRIPT ID BMJOPEN-2011-000387

Reviewer #1: Natasha Martin, University of Bristol, UK. I have no conflicts of interest.

Reviewer comment #1.*1*: *This is an important study which develops and validates a scoring tool to assess HCV risk among PWID, with the aim of facilitating increased screening. The paper is strengthened by the large data set (16,000 PWID), which allowed for the use of development and validation data sets. Given the low rates of testing and treatment in this population, a tool such as this could be of value to identifying those who would benefit from increased testing. As such, I believe this paper should be published in BMJ Open.*

My only minor comment surrounds the use of the tool. In the abstract the authors state that "risk assessment strategies may assist to alert PWID who are at increased risk of HCV infection to present for testing." However the discussion centres more on the use of the tool to "inform the establishment of more focused national screening guidelines." Can the authors please discuss the importance of self-assessment and presentation for testing in the discussion? Additionally, can the authors clarify what they mean by 'more focused national screening guidelines'? Do they feel that screening should be focussed only on 'high-risk' PWID identified by the tool, or if these individuals should be targeted for increased screening-- over and above a comprehensive PWID screening program?

Author's response #1.1: We would like to thank to the reviewer for her positive and constructive comments. We have clarified the potential use of the tool and what we mean by "more focused screening guidelines", as well as discussing the importance of self-assessment and presentation for testing. We revised the relevant section as follows:

(Please also see DISCUSSION, page 9):

"Current Australian guidelines recommend HCV antibody screening in all individuals with risk factors for infection regardless of patient characteristics and settings [30]. Increasing the rate of HCV diagnosis and, in particular, diagnosis of acute infection and providing access to effective antiviral treatment has the potential to improve individual quality of life and reduce the burden of HCV infection. Being unaware of one's HCV serostatus has been identified as a major barrier to increasing HCV treatment uptake, including among PWID [31,32]. While a relatively high proportion (64%) of participants in the ANSPS reported recent HCV testing, HCV antibody negative respondents were less likely to do so than antibody positive respondents (60% versus 67%). One in five (20%) HCV antibody negative participants had not been tested for HCV in the last twelve months, and a further 20% had never been tested (www.web.med.unsw.edu.au/nchecr/Publications). This suggests that both uptake and frequency of testing could be improved.

(Please also see page 10, 2nd and 3rd paragraphs):

"Although Australia has screening guidelines for hepatitis C, current guidelines do not target specific attributes or injecting risk behaviours [30]. By focusing on particular characteristics and specific high-risk behaviours, tools such as the one developed in this study may allow for more targeted identification of individuals at increased risk of infection. If used as a self-administered questionnaire, it is likely that respondents will answer more accurately [33]. Since the vast majority of new HCV diagnoses in Australia are among people with a history of injecting drug use, this tool provides a valuable resource which could inform the establishment of more focused national screening guidelines.

Further, although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors can more precisely identify people in need of additional, non-routine screening. This is particularly pertinent in resource-constrained environments (including time-restricted clinical settings). Our methodology made use of a range of coexisting risk factors that were identified by a rigorous statistical approach in order to accurately identify the most relevant factors for HCV infection.

(Please also see page 12, last paragraph)

"Self-assessment of individual personal level-risk based on a combination of risk factors may prompt a decision to be tested by current injectors, potentially increasing uptake of screening, diagnosis, and antiviral treatment in this population. In summary, the tool described here has the potential to engage current PWID in timely and accurate risk analysis, potentially modifying risk behaviour, and increasing uptake of HCV screening and antiviral treatment in this population."

Reviewer comment #1.2: *In addition, the authors note that "Although Australia has screening guidelines for hepatitis C, current guidelines do not specifically target PWID" but then go on to say "although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs...". Can the authors please clarify whether the screening guidelines do or do not recommend/target PWID for testing?*

Author's response #1.2: We are grateful to the reviewer for spotting this error. The text on page 9 has now been changed to read as follows:

(Please also see DISCUSSION, page 10)

”Although Australia has screening guidelines for hepatitis C, current guidelines do not target specific attributes or injecting risk behaviours [30]. By focusing on particular characteristics and high-risk behaviours, tools such as the one developed in this study may allow for more targeted identification of individuals at increased risk of infection”.

This is now consistent with the text which goes on to say (same page, paragraph 2):

“Further, although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors among PWID can more precisely identify people in need of additional, non-routine screening. This is particularly pertinent in resource constrained environments (including time-restricted clinical settings). Our methodology made use of a range of coexisting risk factors that were identified by a rigorous statistical approach in order to accurately identify the most relevant factors for HCV infection.”

Reviewer # 2: Vana Sypsa
Lecturer of Epidemiology and Preventive Medicine Dept. of Hygiene, Epidemiology and Medical Statistics Athens University Medical School Greece

The sample consisted of injecting drug users participating in a needle exchange program. This limitation is acknowledged by the authors.

This paper proposes a tool - based on demographic and injecting risk behavior- to identify injecting drug users at increased risk for HCV. The analysis was based on a large sample of injecting drug users in Australia and a sub-sample was used to validate the scoring system.

Major comments

Reviewer comment #2.1: *Although the authors have done a lot of work in developing and validating this scoring tool, they fail to provide a clear message that would guide decisions based on the use of this tool. The authors mention in the discussion of their paper that "The tool was validated to accurately identify those at increased risk of HCV" and after a few sentences "The intention of this study was not to identify a unique and specific cut-point of risk above which to target screening, but rather, to assess whether risk factors under consideration could predict those at increased risk accurately in order to consider the tool's use in facilitating increased screening". They also mention that as HCV is highly prevalent among injecting drug users in Australia, they should all be screened and that identification of at least one risk factor increased substantially the likelihood of infection. It seems that the authors conclude that if a person reports at least one of these risk factors, then he/she has to be screened. What is the utility of the score then? The discussion should be re-organized in this*

aspect in order to provide a clearer message on how this screening tool can be used. You mention that the scoring system was also validated using prospective data. Are these results included in the paper?

Author's response #2.1:

We would like to thank to the reviewer for raising this valid point. The most important contribution of this study is in determining the combined impact of the risk factors in relation to risk of HCV. We agree that the use of "tool" was not clearly described. We have now revised the discussion on page 10 as follows:

"The tool was validated to more accurately identify those at increased risk of HCV infection. Current Australian guidelines recommend HCV antibody screening in all individuals with risk factors for infection regardless of patient characteristics and settings [30]. Increasing the rate of HCV diagnosis and, in particular, diagnosis of acute infection and providing access to effective antiviral treatment has the potential to improve individual quality of life and reduce the burden of HCV infection. Being unaware of one's HCV serostatus has been identified as a major barrier to increasing HCV treatment uptake, including among PWID [31,32]. While a relatively high proportion (64%) of participants in the ANSPS reported recent HCV testing, HCV antibody negative respondents were less likely to do so than antibody positive respondents (60% versus 67%). One in five (20%) HCV antibody negative participants had not been tested for HCV in the last twelve months, and a further 20% had never been tested (www.web.med.unsw.edu.au/nchecr/Publications). This suggests that both uptake and frequency of testing could be improved.

The intention of this study was not to identify a unique and specific cut-point of risk above which to target screening, but rather, to assess whether risk factors under consideration could predict those at increased risk accurately in order to consider the tool's use in facilitating increased screening. With a high background HCV prevalence of ~70% among Australian PWID, all PWID should be screened for HCV. However, identification of only one of our listed risk factors substantially increased the likelihood of infection. Although Australia has screening guidelines for hepatitis C, current guidelines do not target specific attributes or injecting risk behaviours [30]. By focusing on particular characteristics and high-risk behaviours, tools such as the one developed in this study may allow for more targeted identification of individuals at increased risk of infection. If used as a self-administered questionnaire, it is likely that respondents will answer more accurately [33]. Since the vast majority of new HCV diagnoses in Australia are among people with a history of injecting drug use, this tool provides a valuable resource which could inform the establishment of more focused national screening guidelines.

Further, although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors can more precisely identify people in need of additional, non-routine screening. This is particularly pertinent in resource constrained environments (including time-restricted clinical settings). Our methodology made use of a range of coexisting risk factors that were identified by a rigorous statistical approach in order to accurately identify the most relevant factors for HCV infection.

(Please also see page 12, last paragraph)

"Self-assessment of individual personal level-risk based on a combination of risk factors may prompt a decision to be tested by current injectors, potentially increasing uptake of screening, diagnosis, and antiviral treatment in this population. In summary, the tool described here has the potential to engage current PWID in timely and accurate risk analysis, potentially modifying risk behaviour, and increasing uptake of HCV screening and antiviral treatment in this population."

Reviewer comment #2.2: *You mention that the scoring system was also validated using prospective data. Are these results included in the paper?*

Author's response #2.2: We have performed this validation using data from a prospective study [3] we did not include these results in the current study. Below, we present these results (Table A and Figure A) for the reviewer. If the editors deem necessary we would also be happy to include these results in the revised manuscript. We have also edited the relevant sentence as follows:

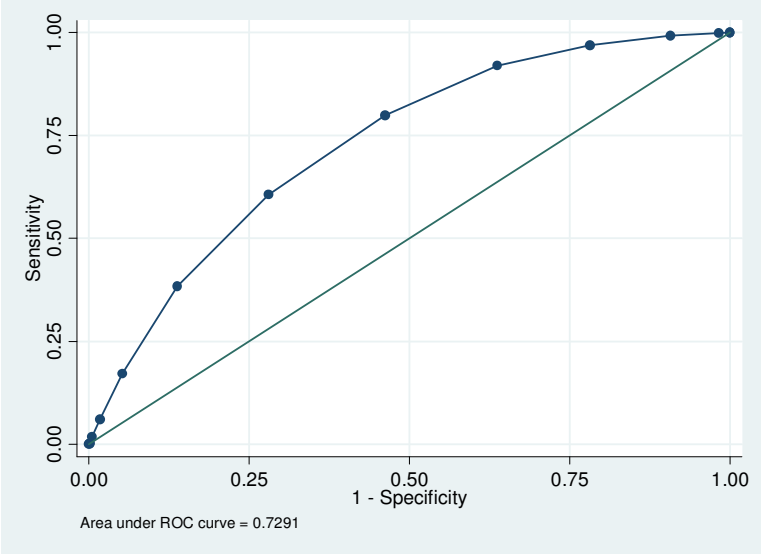
(Please also see on page 11, second paragraph)

"Our study has several strengths, including being the first to validate a predictive model through in internal cross sectional and prospective data sets (data not shown)."

Table A: Results from prospective data

	Validation Data set Prospective	
Risk factors, No.	**HR (95% CI)**	**P Value**
2 or less	Reference	
3	1.10 (0.74,1.60)	0.667
4	1.15 (0.78,1.65)	0.504
5	2.17 (1.45,3.17)	<0.001
6 or more	3.19 (2.30,5.51)	<0.001

Figure A: Sensitivity/Specificity for the prospective validation:



Minor comments

Reviewer comment #2.3: Abstract (objective): "To develop and validate" instead of "To develop and a validate"

Author's response #2.3: Done.

Reviewer comment #2.4: *Abstract (methods): More appropriate terms for "univariate" and "multivariate" are "univariable" and "multivariable" (as you refer to the number of independent variables in your model) (see also Hosmer & Lemeshow, Applied Logistic Regression, Wiley, 2000).*

Author's response # 2.4: Done.

Reviewer comment #2.5: *Abstract (line 4 of results): The age grouping should be added.*

Author's response # 2.5: In response to this reviewer's comments we have included age groups in the abstract as follows:

"An estimated 78% (95% CI: 75%, 81%), 82% (95% CI: 80%, 84%), 80% (95% CI: 78%, 82%) and 80% (95% CI: 77%, 82%) of HCV infections across the age groups (<25, 25-29, 30-39 and 40 or older) would be avoided if participants in the upper four quintiles of HCV scores fell instead into the lowest quintile. "

Reviewer comment #2.6: *Abstract (last line of results): This sentence is not clear. It is more clearly written in the main body of the paper i.e. "fell in the lowest quintile" instead of "had reduced risk to be in the lowest quintile of HCV scores".*

Author's response #2.6: Following the reviewer's comments we edited the relevant sentence as follows:

"An estimated 78% (95% CI: 75%, 81%), 82% (95% CI: 80%, 84%), 80% (95% CI: 78%, 82%) and 80% (95% CI: 77%, 82%) of HCV infections across the age groups (<25, 25-29, 30-39 and 40 or older) would be avoided if participants in the upper four quintiles of HCV scores fell instead into the lowest quintile. "

Reviewer comment #2.7: Abstract (conclusion). The abbreviation PWID should be explained in the abstract.

Author's response #2.7: Done.

Reviewer comment #8: *Page 4, Study population: Is there an estimate of the participation rate? (i.e. on how many consented to complete the questionnaire and provide blood sample). Did you obtain written informed consent? Did the study require ethics approval?*

Author's response #2.8: Due to the illicit behaviour of participants, no identifying information is collected by the study and verbal informed consent is obtained from participants. The response rate ranged from 38% to 50% over the period 1998 to 2008. Ethical approval was obtained from the Human Research Ethics Committee (HREC) at the University of New South Wales, along with relevant jurisdictional and site-specific HRECs.

This was mentioned on page 4 (second paragraph) as follows:

"Following provision of verbal informed consent to participate, respondents were asked to complete a brief,..."

This was mentioned on page 5 (second paragraph) as follows:

"Ethical approval was obtained from the Human Research Ethics Committee (HREC) at the University of New South Wales, as well as from relevant jurisdictional and site specific HRECs."

Reviewer comment #2.9: *Discussion, page 9, ln 41-44. Is this true for injecting drug users too?*

Author's response #2.9: We thank the reviewer for drawing this to our attention. We did not mean to infer that being unaware of one's HCV serostatus was the major barrier to increasing treatment uptake in PWID. While being unaware of one's serostatus is also a barrier to treatment uptake in this group, several studies have identified a number of barriers specific to PWID and we have now included a citation [32] to a review of barriers specific to this group.

We have revised this sentence as follows:

(Please also see DISCUSSION, page 9)

"Being unaware of one's HCV serostatus has been identified as a major barrier to increasing HCV treatment uptake, including among PWID [31,32]."

Reviewer comment #2.10: *Page 18. Last reference is number 33.*

Author's response #2.10: Since we have added another reference ([32] Edlin BR et al.]), last reference number is 34 now.

Reviewer comment #2.11: *Table 2. It would be useful to include an extra line with the number of persons (N=...) under the line with the age-group headings.*

Author's response #2.11: Following the reviewer's comment we added an extra line with the number of persons in each age category in Table 2 (please also see below)

Table 2: Multivariable logistic regression: Odds Ratios (OR) and 95% confidence intervals (CI) for HCV infection scoring by age groups

	<25 N=2,686			25-29 N=2,291			30-39 N=3,563			40+ N=2,122		
	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score

Reviewer comment #2.12: *The authors do not mention whether they obtained a written informed consent or if the study required ethics approval.*

Author's response #2.12: Ethical approval is noted on page 5, second full paragraph (please also see below):

"Ethical approval was obtained from the Human Research Ethics Committee (HREC) at the University of New South Wales, as well as from relevant jurisdictional and site specific HRECs."

Developing and validating a scoring tool for identifying people who inject drugs at increased risk of hepatitis C virus infection

Handan Wand, Jenny Iversen, David Wilson, Libby Topp and Lisa Maher

The Kirby Institute, Sydney, Australia, University of New South Wales

October 11, 2011

Revised

Corresponding author:

Handan Wand, PhD

The Kirby Institute, University of New South Wales, Sydney, Australia
Telephone: +61-2-9385 0900
Facsimile: +61-2-9385 0920
Email: hwand@nchecr.unsw.edu.au

Word counts:

Abstract: 206

Manuscript: 2,693

Objective: To develop and validate a scoring tool based on demographic and injecting risk behaviors to identify those who require additional, non-routine serological screening for HCV by assessing their personal risk.

Methods: The analysis included 16,127 participants who attended Needle and Syringe Programs (NSP) in Australia (1998-2008). Univariable and multivariable logistic regression models were used to develop a prediction model by age groups.

Results: Type of drug last injected, frequency and duration of injecting, sharing needles and syringes or other injecting equipment and imprisonment history were associated with HCV infection in all age groups. Strong relationships between an individual's 'HCV score' and their risk of testing HCV antibody positive were observed. An estimated 78% (95% CI: 75%, 81%), 82% (95% CI: 80%, 84%), 80% (95% CI: 78%, 82%) and 80% (95% CI: 77%, 82%) of HCV infections across the age groups (<25, 25-29, 30-39 and 40 or older) would be avoided if participants in the upper four quintiles of HCV scores fell instead into the lowest quintile.

Conclusion: Knowledge of HCV status has important implications for public health and care and treatment. Risk assessment strategies may assist in alerting people who inject drugs (PWID) who are at increased risk of HCV infection to present for testing.

Key words: Hepatitis C infection, injecting drug users, risk assessment

INTRODUCTION

Worldwide, infection with hepatitis C virus (HCV) is common among people who inject drugs (PWID) [1]. Estimates suggest that more than 70% of new cases of HCV infection are associated with injecting drug use [2,3]. Epidemiologic studies have identified independent risk factors for HCV infection, including sharing of contaminated needles and syringes [4-7] and other injecting equipment [8, 9], female gender [10,11], duration of injecting [12] and intravenous cocaine use [13, 14]. Although the risk factors for incident infection are well established, the literature suggests that a number of barriers may prevent PWID presenting for screening and many PWID face the possibility of HCV infection with a sense of inevitability, fostered by structural barriers to risk avoidance [15, 16]. PWID are a priority population in Australia as HCV prevalence remains high in this group. The burden of advanced liver disease (liver failure and hepatocelluar carcinoma) continues to grow among HCV-infected people [17]. It is estimated that 5,300 Australians are living with HCV-related cirrhosis and this figure is expected to double by 2020 without increased therapeutic intervention [18]. Despite the mounting burden of disease and recent advances in antiviral treatments, HCV treatment uptake among PWID remains very low (1-2% of chronic hepatitis C cases) [17]. A major public health challenge is to more effectively identify individuals with HCV before the development of significant clinical consequences.

Our study aimed to develop a scoring tool that can be used by PWID and primary care providers to identify individuals at increased risk of HCV infection. With increasing recognition of the clinical benefits of early diagnosis and treatment uptake [19-21], a simple self-administered tool may provide a means for PWID to identify personal risk and to modify risk behavior and/or seek health care/further assessment.

A large database of serial cross sectional samples of PWID attending Needle and Syringe Programs (NSP) in Australia (1998-2008) was used to develop a statistical model underpinning the tool. Retrospective validation was carried out on the HCV risk assessment algorithm.

The following characteristics were considered essential in the development of the new prediction algorithm: (1) the use of routinely available and minimally intrusive variables and (2) estimation of the cumulative effect of concurrent risk factors on the likelihood of HCV prevalence. We are unaware of any studies to date that have quantified the cumulative effect of concurrent risk factors on the acquisition of HCV infection among PWID.

STUDY POPULATION

The Australian Needle and Syringe Program Survey (ANSPS) is a serial cross-sectional study conducted annually over a one to two week period since 1995. More than 50 NSP sites participate annually, with sites selected on the basis of geographic coverage, willingness to participate and an ability to recruit a minimum of 20 survey respondents. The survey methods have been described in detail elsewhere [22-25]. In brief, all PWID who attended participating ANSPS sites during the designated survey period were invited to participate. Participation was anonymous and voluntary and there was no financial reimbursement. Following provision of verbal informed consent to participate, respondents were asked to complete a brief, self-administered questionnaire on demographic characteristics and injecting and sexual risk behaviors (www.web.med.unsw.edu.au/nchecr), and to provide a capillary blood sample for antibody HIV and HCV testing. The current study used data for the period 1998-2008, involving more than 16,000 individuals. Response rates ranged from 38%-50% during the study period (cite the 16 year report). Previous research has demonstrated the representativeness of ANSPS samples of the broader population of NSP clients [22].

Capillary blood was obtained by finger prick using single-use, disposable lancets and cotton-fiber blotting paper. Specimens were kept at room temperature at the survey sites, then couriered to a central collection point before they were forwarded to the laboratory. A modified, third generation enzyme immunoassay (Abbott hepatitis C 3.0, Chicago, IL, USA) was used to test for HCV antibody. A modified cutoff value for optical density was calculated to capture greater than 95% of the seronegative population. Specimens were considered positive for HCV antibody if the optical density to cutoff ratio was greater than or equal to one on initial and subsequent testing.

Ethical approval was obtained from the Human Research Ethics Committee (HREC) at the University of New South Wales, as well as from relevant jurisdictional and site specific HRECs.

STATISTICAL ANALYSES

A split-sample method was used to develop and subsequently validate a risk equation and scoring system. Participants were randomly allocated to either the development (n=10,662; 67%) or internal validation (n=5,331; 33%) sample datasets.

We selected a range of demographic and injecting behavior variables as potential determinants of HCV infection. These included gender, Indigenous status, imprisonment history, country of birth, language spoken at home, drug last injected, frequency and duration of injecting, sharing of needles and syringes and other injecting equipment (e.g. water, filter, spoon, tourniquet), public injecting, and drug treatment history. All analyses were stratified by age groups (<25, 25-29, 30-39 and 40+).

We used descriptive statistics to characterize the groups according to antibody HCV serostatus: mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Logistic regression was used to create a predictive model based on the development data set. We

used all non-missing observations available in the relevant analyses as only a small proportion of observations had any missing data (except for the variable "imprisonment history"). All analyses were conducted using SAS statistical software version 9.2 (SAS Institute Inc. Cary, North Carolina) and STATA 10.0 (College Station, Texas).

Derivation of a screening score:

Using the development data set (n=10,662), we included a comprehensive list of predictors known to be associated with HCV antibody seropositivity in an initial model. Specifically, we included the main effects of all variables listed in Table 1 and their interaction effects. We first analyzed the univariate associations between the independent variables and HCV seropositivity. Backward elimination was used to reach the final multivariate model, in which factors with the largest *P* value were sequentially deleted until only significant predictors remained. We then created a weighted scoring system by rounding all regression coefficients up to the nearest integer (that is, the smallest integer greater than the estimate). This method was based on the β-coefficients (or log of the odds ratios) rather than odds ratios, which can be excessively influenced by only a few factors [26]. Once the final model was defined, we created integer weights for each variable. We calculated these weights by multiplying the model coefficients by 10. Using the rounded weights in the risk function, we estimated the participant-specific probabilities of HCV seropositivity and characterized the degrees of risk based on cut-off points of the probability distribution.

Cross-sectional and prospective validation:

We examined the predictive validity of the scoring system using the internal validation datasets (n=5,331). We also assessed the predictive validity of this scoring system on the subsequent risk of

HCV antibody seroconversion using prospective data collected from individuals who visited ANSPS sites multiple times and tested HCV seronegative at their first visit.

We used the cross-sectional dataset to check the sensitivity and robustness of the new screening score. We computed standard validation measures: the proportion of antibody HCV seropositive specimens, sensitivity, specificity, positive likelihood and negative likelihood ratio and the area under the receiver operating characteristic curve (AUC) as discrimination statistics. We also assessed the diagnostic characteristics of different cut-points based on the total score in the development as well as validation datasets. The purpose of this analysis was to assess whether the combination of risk factors under consideration could predict those at increased risk with acceptable accuracy.

Population attributable risk:

After we calculated and validated the HCV screening score, we estimated population attributable risks, which estimates the percentage of HCV infections that would not have occurred if all participants had been assigned the "lowest risk" (first quintile) category of the HCV screening score. We calculated population attributable risks using a previously described method [29] that was applied to this study design and appropriate for use with multivariable adjusted relative risks.

RESULTS

Our study population comprised 10,662 individuals in the development dataset. Table 1 summarizes participant characteristics by HCV antibody serostatus. The overall prevalence of HCV was 51%. HCV seropositive participants tended to be older and more likely to report a longer duration of injecting, heroin as the drug last injected, a history of imprisonment, daily or more frequent injecting, public injecting and sharing needles and syringes and other injecting equipment.

Table 2 presents the final multivariate logistic regression model derived from the development data set by age groups. History of imprisonment, duration of injecting (5-9, 10+ years), drug last injected (heroin, cocaine, methadone, morphine, buprenorphine and others), needle and syringe sharing and sharing of ancillary equipment were all significantly associated with increased risk of antibody HCV seropositivity across all age groups. Injecting frequency (daily or more) was determined to be a significant risk factor for those aged less than 30 years. Female gender was associated with an increased risk of HCV seroprevalence for those younger than 40 years of age. Indigenous status was a significant predictor for HCV infection among people aged 30-39 years. Drug last injected and duration of injecting each required multiple categories to capture the risk gradient, whereas other risk factors were binary. The risk factors collectively yielded an AUC of 0.73 (95% CI: 0.70, 0.76), 0.72 (95% CI: 0.70, 0.75), 0.73 (95% CI: 0.70, 0.76) and 0.66 (95% CI: 0.64, 0.71) for the age groups <25, 25-29, 30-39 and 40 plus (data not shown). There were no significant interactions between injecting risk behaviors and gender across age groups (data not shown).

Table 3 shows the odds ratios (ORs) from the logistic regression models and population attributable risks of HCV infection for the quintiles of the risk scores by age groups for the development and validation datasets. There was a linear trend towards increasing HCV infection with increasing score regardless of the age groups in both datasets (trend, p-value<0.001). Using the development dataset, we estimated population attributable risks (95% CI) for the upper four quintiles of the scores. Results showed that 78% (75%, 81%), 82% (80%, 84%) and 80% (77%, 82%) of HCV infections across the age groups would be avoided if participants in the upper four quintiles of the HCV scores instead fell into the lowest quintile. Results from the validation dataset were consistent with those from the development dataset (Table 3).

We also assessed the diagnostic characteristics of cut-points (according to first, second, third and the fourth quintiles in overall population) for total score in the development as well as the validation datasets (Table 4). An increased risk of HCV was clearly associated with increasing scores. For example, a cut-point score of 10 or higher distinguished a 'increased risk' group with a sensitivity of 96% or higher; similarly a cut-point 20 or higher yielded at least 92% sensitivity in all age groups in the development dataset; in cross sectional validation, sensitivity was estimated to be at least 94% across the age groups for the cut-point 10/15 or more and at least 76% for 20 or more.

Figure 1 illustrates the risk of PWID being HCV seropositive as a continuous function of the total score. Across all age groups, increasing scores were clearly associated with increased risk of HCV antibody positivity.

DISCUSSION

In this study, we developed a scoring tool based on data from ~16,000 PWID who attended ANSPS sites between 1998 and 2008. The tool was validated to more accurately identify those at increased risk of HCV infection. Current Australian guidelines recommend HCV antibody screening in all individuals with risk factors for infection regardless of patient characteristics and settings [30]. Increasing the rate of HCV diagnosis and, in particular, diagnosis of acute infection and providing access to effective antiviral treatment has the potential to improve individual quality of life and reduce the burden of HCV infection. Being unaware of one's HCV serostatus has been identified as a major barrier to increasing HCV treatment uptake, including among PWID [31,32]. While a relatively high proportion (64%) of participants in the ANSPS reported recent HCV testing, HCV antibody negative respondents were less likely to do so than antibody positive respondents (60% versus 67%). One in five (20%) HCV antibody negative participants had not been tested for HCV in the last twelve

months, and a further 20% had never been tested (www.web.med.unsw.edu.au/nchecr/Publications). This suggests that both uptake and frequency of testing could be improved.

The intention of this study was not to identify a unique and specific cut-point of risk above which to target screening, but rather, to assess whether risk factors under consideration could predict those at increased risk accurately in order to consider the tool's use in facilitating increased screening. With a high background HCV prevalence of ~70% among Australian PWID, all PWID should be screened for HCV. However, identification of just one of our listed risk factors substantially increased the likelihood of infection. Although Australia has screening guidelines for hepatitis C, current guidelines do not target specific attributes or injecting risk behaviours [30]. By focusing on particular characteristics and specific high-risk behaviors, tools such as the one developed in this study may allow for more targeted identification of individuals at increased risk of infection. If used as a self-administered questionnaire, it is likely that respondents will answer more accurately [33]. Since the vast majority of new HCV diagnoses in Australia are among people with a history of injecting drug use [16], this tool provides a valuable resource which could inform the establishment of more focused national screening guidelines.

Further, although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors can more precisely identify people in need of additional, non-routine screening. This is particularly pertinent in resource-constrained environments (including time-restricted clinical settings). Our methodology made use of a range of coexisting risk factors that were identified by a rigorous statistical approach in order to accurately identify the most relevant factors for HCV infection.

Risk calculation approaches have been extensively used in decision making about public health and clinical care and have even been proposed as an alternative to diagnosis for some diseases [34]. Our risk calculation was based on a statistical method that yielded a systematic scoring system for carefully selected predictors, guided not only by numerical and scientific evidence but also feasibility perspectives. We chose categorized variables which highlighted the important risk factors to motivate high-risk persons to be screened or to modify behaviors. This combination of factors may explain the enhanced properties of our scoring tool.

Our study has several strengths, including being the first to validate a predictive model through internal cross sectional and prospective data sets (data not shown). Our prediction equation is based on 11 years of data and more than 16,000 participants. Ideal risk assessment methods or prediction models should be derived from large representative samples. The current study has several limitations. First, the study population is limited to those who participated in the ANSPS, which may result in selection bias. However, the ANSPS has been shown to be broadly representative of PWID attending NSPs [16]. Second, we were not able to differentiate between acute, recent and chronic infections.

Risk factor screening and identification allows for patients to be educated regarding the risks of injection drug use and needle sharing. Appropriate testing and diagnosis of HCV allows for the patient to be evaluated for treatment and receive counseling regarding HCV prevention. In addition to physician education, patient education campaigns must also be developed to increase patient compliance with testing recommendations made by their physicians.

In conclusion, we believe the screening tool described here will provide a simple and cost-effective method of identifying and alerting PWID who are in need of additional, non-routine HCV screening with notable predictive validity. A self-assessment method that helps individual PWID understand their relative increased risk of infection provides the basis for increased uptake of screening, diagnosis, and antiviral treatment among this population.

In summary, the tool described here has the potential to engage current PWID in timely and accurate risk analysis, potentially modifying risk behaviour, and increasing uptake of HCV screening and antiviral treatment in this population.

Article Summary

Article focus:

- Although the risk factors for incident infection are well established, the literature suggests that a number of barriers may prevent PWID presenting for screening.
- Study developed a scoring tool based on demographic and injecting risk behaviors to identify those who require additional, non-routine serological screening for HCV by assessing their personal risk.

Key Messages:

- Current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs.
- However, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors among PWID can more precisely identify people in need of additional, non-routine screening.

Strengths and limitations:

- Our prediction equation is based on 11 years of data and more than 16,000 participants. Ideal risk assessment methods or prediction models should be derived from large representative samples.
- The study population is limited to those who participated in the ANSPS, which may result in selection bias.
- We were not able to differentiate between acute, recent and chronic infections.

Competing interest: None.

Ethics approval: Ethical approvals for the survey were obtained from Institutional Ethics Committees associated with the investigators and participating NSP sites.

Contributors: HW implemented the study, analysed the data and wrote the first draft. LM, JI, LT and DW helped drafting, interpreting the data and finalizing the manuscript. All authors saw and approved the final, submitted version of the manuscript.

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REFERENCES

[1] McGinn T, O'Connor-Moore N, Alfandre D, Wisnivesky J. Validation of a Hepatitis C Screening Tool in Primary Care. Arch Intern Med **2008**; 168(18):2009-13.

[2] Thorpe LE, Ouellet LJ, Hershow R et al. Risk of Hepatitis C Virus infection among Young Adult Injecting Drug Users Who Share Injecting Equipment. American Journal of Epidemiology **2002**; 155:7:645-653.

[3] Alter MJ, Kruszon-Moran D et al. The prevelance of hepatitis C virus infection in the United States, 1998 through 1994. New England Medical Journal **1999**; 341:556-62.

[4] Villano S. A., Vlahov D., Nelson K. E., Lyles C. M., Cohn S. & Thomas D. L. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. J Clin Microbiol 1997; **35**: 3274–7;

[5] Garfein RS, Doherty MC, Monterroso ER, et al. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. J Acq Immune Defic Synd Hum Retrovirol **1998**; 18:11–19.

[6] Hahn JA, Page-Shafer K, Lum PJ et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis **2002**; 186:1558–64.

[7] Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology **2004**; 15: 543–9.

[8] Hagan H, Thiede H, Weiss NS et al. Sharing of drug preparation equipment as a risk factor for hepatitis C. Am J Public Health **2001**; 91: 42–6.

[9] Falster K, Kaldor J and Maher L. Hepatitis C Virus acquisition among Injecting Drug Users: a cohort analysis of a national repeated cross-sectional survey of needle and syringe program attendees in Australia, 1995-2004. Journal of Urban Health **2008** [doi:10.1007/s11524-008-9330-7].

[10] Hahn JA, Page-Shafer K, Lum PJ et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis **2002**; 186: 1558–64.

[11] Maher L, Jalaludin B, Chant KG et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction **2006**; 101(10): 1499-1508.

[12] Maher L, Li J, Jalaludin B et al. High hepatitis C incidence in new injecting drug users: a policy failure? Aust N Z J Public Health **2007**; 31(1): 30-35.

[13] Patrick DM, Tyndall MW, Cornelisse PG et al. Incidence of hepatitis C virus infection among drug users during an outbreak of HIV infection. Can Med Assoc J **2001**; 165: 889–95.

[14] Miller CL, Johnston C, Spittal PM et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology **2002**; 36: 737–42.

[15] Davis M, Rhodes T. Beyond prevention? International Journal of Drug Policy **2004**; 15:123-31.

[16] National Centre in HIV Epidemiology and Clinical Research. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2009. National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW.

[17] NCHECR. Hepatitis C Virus Projections Working Group, Sydney: NCHECR, **2006**.

[18] Kwiatkowski CF, Fortiun Corsi K, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug user. Addiction **2002**; 97:1289-94.

[19] Gerlach J, Diepolder H, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology **2003**; 125:80-8;

[20] Kamal SM, Fouly AE, Kamel RR et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology **2006**; 130:632-638;

[21] Gregory JD, Hellard M, Matthews GV, et al. Effective Treatment of Injecting Drug Users with recently acquired hepatitis C virus infection. Gastroenterology **2010**; 138:123-135;

[22] Topp L, Iversen, J, Wand H, Day C, Kaldor J, Maher L. Representativeness of injecting drug users who participate in HIV surveillance: results from Australia's Needle and Syringe Program Survey. J Acquir Immune Defic Syndr **2008**; 47(5), 632-638.

[23] MacDonald M, Crofts N, Kaldor J Transmission of hepatitis C virus: rates, routes, and cofactors. Epidemiol Rev **1996**; 18(2), 137-148.

[24] MacDonald M, Wodak AD, Ali R et al. HIV prevalence and risk behavior in needle exchange attenders: a national study. The Collaboration of Australian Needle Exchanges. Med J Aust **1997**; 166(5),237-240.

[25] MacDonald MA, Wodak AD, Dolan KA et al. Hepatitis C virus antibody prevalence among injecting drug users at selected needle and syringe programs in Australia, 1995-1997. Collaboration of Australian NSPs. Med J Aust **2000**; 172(2),57-61.

[26] Schmidt MI, Duncan BB, Bang H et al. Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care **2005**; 28:2013-2018.

[27] Gonen M. Analyzing Receiver Operating Characteristic Curves with SAS **2007**. Cary, NC: SAS Institute;

[28] Sackett D, Straus SE, Richardson WS et al. Evidence- Based Medicine: How to Practice and Teach EBM. 2nd ed. Philadelphia: Churchill Livingstone; **2000**.

[29] Wand H, Spiegelman D, Law M et al. Estimating population attributable risk for hepatitis C seroconversion in injecting drug users in Australia: implications for prevention policy and planning. Addiction **2009**, 104(12), 2049-2056(8).

[30] Maher L, Iversen J, Kaldor J. Measuring effectiveness of needle and syringe exchange programs for prevention of HIV among injecting drug users: Response to Amundsen. Addiction **2006**; 101(12):1834-6.

[31] Volk M, Tocco R, Saini S, Lok A. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology **2009**;50:1-6

[32] Edlin BR, Kresina TF, Raymond DB et al. Overcoming Barriers to Prevention, Care, and Treatment of Hepatitis C in Illicit Drug Users. CID **2005**; 40 (Suppl 5): S276-S285.

[33] White B, Day C, Maher L. Self reported risk behavior among injecting drug users: Self versus assisted questionnaire completion. AIDS Care **2007**; 19(3): 441-447.

[34] Vickers AJ, Basch E, Kattan MW. Against diagnosis. Ann Intern Med. **2008**; 149:200-3. [PMID: 18678847]

Table 1: Risk factors for Hepatitis C Virus (HCV)

Characteristics	HCV Seronegative N= 5,214 (49%)	HCV Seropositive N= 5,448 (51%)
Mean age at survey (± SD)	29 ± 8	34 ± 9
<25 years, %	35	16
25-29 years, %	24	19
30-39 years, %	29	37
40+ years, %	12	28
Female, %	33	35
Indigenous, %	8	10
Mean age at first injection (± SD)	20 ± 6	19 ± 6
Mean years of injecting (± SD)	9 ± 7	15 ± 9
<5 years, %	26	12
5-9 years , %	28	21
10-16 years, %	23	28
17+ years, %	14	40
Ever been in Prison, %	17	33
Been in prison last year, %	11	22
Drug injecting behaviors (last month)		
Drug injected, %		
Amphetamine/methamphetamine	51	28
Heroin	35	48
Cocaine	3	5
Methadone	4	8
Morphine	7	9
Buprenorphine	1	2
Others[1]	9	8
Injecting daily or more , %	50	58
Receptive sharing needle/syringe, %	15	18
Receptive sharing ancillary equipments[2], %	33	38
Injected by another, %	14	12
New needle syringe in every injection	72	68
Injected in Public	46	52

[1] benzos, anabolic steroids, mixed drugs, other drugs or not reported

[2] water, spoon, filter, tourniquet

Table 2: Multivariable logistic regression: Odds Ratios (OR) and 95% confidence intervals (CI) for HCV infection scoring by age groups

	<25 N=2,686			25-29 N=2,291			30-39 N=3,563			40+ N=2,122		
	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score
Sex												
Male	1	-	0	1			1			-		
Female	1.4	3.4	3	1.5 (<0.001)	4.1	4	1.4 (0.002)	3.3	3			
Indigenous												
No	-	-	-	-		-	1	-	-			
Yes							1.3 (0.04)	2.8	3	-		
Ever been in Prison?												
No	1	1	0	1			1			1		
Yes	2.2 (<0.001)	7.8	8	2.8 (<0.001)	10.2	10	1.9 (<0.001)	6.4	6	1.4 (0.003)	3.4	3
Years of injecting												
<5 year	1	-	0	1						1		
5-9 years	2.0 (<0.001)	6.8	7	1.7 (<0.001)	5.5	6	1.9 (<0.001)	6.5	7	1.5 (0.149)	3.7	4
10+ years	3.1 (<0.001)	11.1	11	2.4 (<0.001)	8.9	9	3.6 (<0.001)	12.7	13	4.6 (<0.001)	15.3	15
Drug last injected												
Amphetamine/methamphetamine	1	-	0	1			1	-		1		
Morphine	2.3 (<0.001)	8.3	8	1.7 (0.009)	5.5	6	1.9 (<0.001)	6.7	7	1.9 (<0.001)	6.7	7
Others[2]	2.0 (<0.001)	6.7	7	1.6 (0.010)	4.7	5	1.8 (<0.001)	5.9	6	1.5 (0.053)	4.0	4
Heroin	3.0 (<0.001)	11.1	11	2.7 (<0.001)	10.0	10	3.0 (<0.001)	10.7	11	2.5 (<0.001)	9.0	9
Cocaine	6.4 (<0.001)	18.6	19	3.6 (<0.001)	12.7	13	3.0 (<0.001)	10.9	11	3.6 (<0.001)	12.8	13
Methadone	3.3 (<0.001)	11.3	11	3.4 (<0.001)	12.2	12	3.0 (<0.001	11.0	11	3.1 (<0.001)	11.3	11
Buprenorphine	3.2 (0.003)	11.4	11	2.8 (0.004)	10.4	10	2.8 (0.001)	10.2	10	1.9 (0.141)	6.2	6
(Drug injecting behaviors last month)												
Injecting frequency												
Less than daily	1	-	0	1								
Daily or more	1.4 (0.001)	3.1	3	1.5 (<0.001)	4.0	4	-	-	-	-	-	
Receptive sharing needle/syringe												
No	-			1			1	-		-	-	
Yes	-			1.4 (0.005)	3.4	3	1.4 (0.002)	3.3	3			
Receptive sharing ancillary equipment[2]												
No	1	1	0	1						1		
Yes	1.3 (0.006)	2.5	3	1.3 (0.003)	3.0	3	-	-	-	1.5 (0.001)	3.8	4

[1]benzos, anabolic steroids, mixed drugs, other drugs or not reported

[2]water, spoon, filter, tourniquet

Table 3: Odds Ratios (OR) and 95% confidence intervals (CI) & for HCV infection by quintiles of HCV scoring

	Age <25 years		Age 25-29 years		Age 30-39 years		Age 40 plus	
Development Data Set	OR (95% CI)	P [0]	OR (95% CI)	P[0]	OR (95% CI)	P[0]	OR (95% CI)	P[0]
HCV Risk score[1]		<0.001		<0.001		<0.001		<0.001
Fifth 1	1		1		1		1	
Fifth 2	1.90 (1.33,2.69)		2.60 (1.88,3.57)		2.23 (1.72,2.89)		2.63 (1.94,3.58)	
Fifth 3	2.77 (1.92,4.01)		4.12 (3.00, 5.65)		4.07 (3.13,5.28)		4.56 (3.10,6.70)	
Fifth 4	5.40 (3.95,7.38)		4.85 (3.53,6.66)		5.40 (4.16,7.02)		5.86 (4.25,8.08)	
Fifth 5	10.31 (7.44,14.29)		12.40 (9.08,16.91)		9.10 (7.04,11.75)		7.78 (5.61,10.80)	
Population attributable risk for HCV score (%)[2] **(95% CI)**								
lowest v upper four fifth	78% (75%, 81%)		82% (80%, 84%)		80% (78%, 82%)		80% (77%, 82%)	
lower two v upper three fifth	74% (72%, 77%)		76% (74%, 78%		74% (73%, 77%)		72% (69%, 74%)	
Validation Data Set								
HCV Risk score[1]		<0.001		<0.001		<0.001		<0.001
Fifth 1	1		1		1		1	
Fifth 2	1.92 (1.12,3.28)		2.75 (1.73,4.38)		2.73 (1.94,3.85)		1.98 (1.30,3.02)	
Fifth 3	4.70 (2.75,8.04)		4.33 (2.78,6.77)		5.34 (3.74,7.63)		5.03 (2.78,9.10)	
Fifth 4	6.00 (3.76,9.56)		6.13 (3.93,9.56)		7.46 (5.19,10.74)		3.79 (2.44,5.87)	
Fifth 5	11.97 (7.41,19.32)		9.28 (6.07,14.19)		10.68 (7.56,15.10)		5.42 (3.50,8.42)	
Population attributable risk for HCV score (%)[2] **(95% CI)**								
lowest v upper four fifth	82% (79%, 85%)		80% (77%, 83%)		84% (82%, 85%)		73% (68%, 77%)	
lower two v upper three fifth	79% (76%, 81%)		74% (71%, 77%)		78% (76%, 79%)		67% (62%, 71%)	

[0] Test for trend

[1] HCV score **for age <25** was <7 for fifth 1, 7-<14 for fifth 2, 14-<17 for fifth 3, 17-<24 for fifth 4 and 24+ for fifth 5; **for age 25-29** was <12 for fifth 1, 12-<17 for fifth 2, 17-<22 for fifth 3, 22-<26 for fifth 4 and 24+ for fifth 5; **for age 30-39** was <13 for fifth 1, 13-<19 for fifth 2, 19-<24 for fifth 3, 24-<27 for fifth 4 and 27+ for fifth 5; **for age 40 plus** was <15 for fifth 1, 15-<22 for fifth 2, 22-<24 for fifth 3, 24-<27 for fifth 4 and 27+ for fifth 5;

Table 4: Optimal characteristics of HCV Scoring[1]

	Age <25 years		Age 25-29 years		Age 30-39 years		Age 40 plus	
Score cut points[2]	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Development Data Set (n=10,662)								
≥ 10	96%	17%	99%	9%	99%	7%	98%	10%
≥ 15	92%	32%	95%	23%	97%	15%	97%	19%
≥ 20	74%	60%	86%	42%	90%	36%	94%	24%
≥ 25	55%	74%	68%	64%	73%	57%	75%	54%
Validation Data Set (n= 5,465)								
≥ 10	96%	18%	99%	8%	99%	10%	99%	10%
≥ 15	94%	32%	95%	25%	97%	19%	97%	15%
≥ 20	76%	57%	88%	40%	87%	43%	94%	21%
≥ 25	59%	72%	67%	61%	73%	61%	74%	52%

[1]HCV Score :

For age < 25: (female)*3+ (indigenous) *0 + (Injecting 5-9 years)*7 + (Injecting 10+ years) *11+ Morphine*8 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*7 + (heroin)*11 + (cocaine)*19 + (methadone)*11 + (morphine)*8 + (Buprenorphine) *11 + (daily or more)*3 + (shared needle and syringe)*0 + (shared other equipment)*3 + (been in prison)*8

For age 25 -29 year: (female)*4+ (indigenous) *0 + (Injecting 5-9 years)*6 + (Injecting 10+ years) *9+ Morphine*6 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*5 + (heroin)*10 + (cocaine)*13 + (methadone)*12 + (morphine)*5 + (Buprenorphine) *10 + (daily or more)*4 + (shared needle and syringe)*4 + (shared other equipment)*0 + (been in prison)*6

For age 30 -39 year: (female)*3+ (indigenous) *3 + (Injecting 5-9 years)*7 + (Injecting 10+ years) *13+ Morphine*7 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*6 + (heroin)*11 + (cocaine)*11 + (methadone)*11 + (morphine)*7+ (Buprenorphine) *10 + (daily or more)*0 + (shared needle and syringe)*3 + (shared other equipment)*0 + (been in prison)*6

For age 40 + year: (female)*0+ (indigenous) *0 + (Injecting 5-9 years)*4 + (Injecting 10+ years) *15 + Morphine*7 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*4 + (heroin)*9 + (cocaine)*13 + (methadone)*11 + (morphine)*7+ (Buprenorphine) *6 + (daily or more)*0 + (shared needle and syringe)*3 + (shared other equipment)*0 + (been in prison)*6

[2]Approximate cut points for the first, second, third and the fourth quintiles.

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Developing and validating a scoring tool for identifying people who inject drugs at increased risk of hepatitis C virus infection

Handan Wand, Jenny Iversen, David Wilson, Libby Topp and Lisa Maher

The Kirby Institute, Sydney, Australia, University of New South Wales

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Corresponding author:

Handan Wand, PhD

The Kirby Institute, University of New South Wales, Sydney, Australia
Telephone: +61-2-9385 0900
Facsimile: +61-2-9385 0920
Email: hwand@nchecr.unsw.edu.au

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Objectives: To develop and validate a scoring tool based on demographic and injecting risk behaviors to identify those who require additional, non-routine serological screening for hepatitis C virus (HCV) by assessing their personal risk.

Design: Cross sectional and prospective cohorts.

Setting: People who inject drugs (PWID) and attended Needle and Syringe Programs (NSP) in Australia during the period of 1998-2008.

Participants: Cross sectional data included 16,127 PWID who attended NSP in Australia. Prospective data included 215 HCV negative PWID who were recruited through street-based outreach, methadone clinics in Australia.

Primary and secondary outcome measures: HCV seroprevalence in the cross sectional and HCV seroconversions in the prospective datasets.

Results: Current study included 16,127 PWID who attended NSP in Australia. Type of drug last injected, frequency and duration of injecting, sharing needles and syringes or other injecting equipment and imprisonment history were associated with HCV infection in all age groups. Strong relationships between an individual's 'HCV score' and their risk of testing HCV antibody positive were observed. An estimated 78% (95% CI: 75%, 81%), 82% (95% CI: 80%, 84%), 80% (95% CI: 78%, 82%) and 80% (95% CI: 77%, 82%) of HCV infections across the age groups (<25, 25-29, 30-39 and 40 or older) would be avoided if participants in the upper four quintiles of HCV scores fell instead into the lowest quintile.

Conclusions: Knowledge of HCV status has important implications for public health and care and treatment. Risk assessment strategies may assist in alerting PWID who are at increased risk of HCV infection to present for testing.

Key words: Hepatitis C infection, injecting drug users, risk assessment

INTRODUCTION

Worldwide, infection with hepatitis C virus (HCV) is common among people who inject drugs (PWID) [1]. Estimates suggest that more than 70% of new cases of HCV infection are associated with injecting drug use [2,3]. Epidemiologic studies have identified independent risk factors for HCV infection, including sharing of contaminated needles and syringes [4-7] and other injecting equipment [8, 9], female gender [10,11], duration of injecting [12] and intravenous cocaine use [13, 14]. Although the risk factors for incident infection are well established, the literature suggests that a number of barriers may prevent PWID presenting for screening and many PWID face the possibility of HCV infection with a sense of inevitability, fostered by structural barriers to risk avoidance [15]. PWID are a priority population in Australia as HCV prevalence remains high in this group. The burden of advanced liver disease (liver failure and hepatocelluar carcinoma) continues to grow among HCV-infected people [16]. It is estimated that 5,300 Australians are living with HCV-related cirrhosis and this figure is expected to double by 2020 without increased therapeutic intervention [17]. Despite the mounting burden of disease and recent advances in antiviral treatments, HCV treatment uptake among PWID remains very low (1-2% of chronic hepatitis C cases) [17]. A major public health challenge is to more effectively identify individuals with HCV before the development of significant clinical consequences.

Our study aimed to develop a scoring tool that can be used by PWID and primary care providers to identify individuals at increased risk of HCV infection. With increasing recognition of the clinical benefits of early diagnosis and treatment uptake [18-20], a simple self-administered tool may provide a means for PWID to identify personal risk and to modify risk behavior and/or seek health care/further assessment.

A large database of serial cross sectional samples of PWID attending Needle and Syringe Programs (NSP) in Australia (1998-2008) was used to develop a statistical model underpinning the tool. Cross-sectional (internal) and prospective (external) validation studies were carried out on the HCV risk assessment algorithm.

The following characteristics were considered essential in the development of the new prediction algorithm: (1) the use of routinely available and minimally intrusive variables and (2) estimation of the cumulative effect of concurrent risk factors on the likelihood of HCV prevalence. We are unaware of any studies to date that have quantified the cumulative effect of concurrent risk factors on the acquisition of HCV infection among PWID.

STUDY POPULATION

The Australian Needle and Syringe Program Survey (ANSPS) is a serial cross-sectional study conducted annually over a one to two week period since 1995. More than 50 NSP sites participate annually, with sites selected on the basis of geographic coverage, willingness to participate and an ability to recruit a minimum of 20 survey respondents. The survey methods have been described in detail elsewhere [21-24]. In brief, all PWID who attended participating ANSPS sites during the designated survey period were invited to participate. Participation was anonymous and voluntary and there was no financial reimbursement. Following provision of verbal informed consent to participate, respondents were asked to complete a brief, self-administered questionnaire on demographic characteristics and injecting and sexual risk behaviors (www.web.med.unsw.edu.au/nchecr), and to provide a capillary blood sample for antibody HIV and HCV testing. The current study used data for the period 1998-2008, involving more than 16,000 individuals. Response rates ranged from 38%-50% during the study

period. Previous research has demonstrated the representativeness of ANSPS samples of the broader population of NSP clients [21].

Capillary blood was obtained by finger prick using single-use, disposable lancets and cotton-fiber blotting paper. Specimens were kept at room temperature at the survey sites, then couriered to a central collection point before they were forwarded to the laboratory. A modified, third generation enzyme immunoassay (Abbott hepatitis C 3.0, Chicago, IL, USA) was used to test for HCV antibody. A modified cutoff value for optical density was calculated to capture greater than 95% of the seronegative population. Specimens were considered positive for HCV antibody if the optical density to cutoff ratio was greater than or equal to one on initial and subsequent testing.

Ethical approval was obtained from the Human Research Ethics Committee (HREC) at the University of New South Wales, as well as from relevant jurisdictional and site specific HRECs.

STATISTICAL ANALYSES

A split-sample method was used to develop and subsequently validate a risk equation and scoring system. Participants were randomly allocated to either the development (n=10,662; 67%) or internal validation (n=5,331; 33%) sample datasets.

We selected a range of demographic and injecting behavior variables as potential determinants of HCV infection. These included gender, Indigenous status, imprisonment history, country of birth, language spoken at home, drug last injected, frequency and duration of injecting, sharing of needles and syringes and other injecting equipment (e.g. water, filter, spoon, tourniquet), public injecting, and drug treatment history. All analyses were stratified by age groups (<25, 25-29, 30-39 and 40+).

We used descriptive statistics to characterize the groups according to antibody HCV serostatus: mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Logistic regression was used to create a predictive model based on the development data set. We used all non-missing observations available in the relevant analyses as only a small proportion of observations had any missing data (except for the variable "imprisonment history"). Cox regression analysis was used to validate the scoring tool for HCV seroconversion in external validation set. All analyses were conducted using SAS statistical software version 9.2 (SAS Institute Inc. Cary, North Carolina) and STATA 10.0 (College Station, Texas).

Derivation of a screening score:

Using the development data set (n=10,662), we included a comprehensive list of predictors known to be associated with HCV antibody seropositivity in an initial model. Specifically, we included the main effects of all variables listed in Table 1 and their interaction effects. We first analyzed the univariate associations between the independent variables and HCV seropositivity. Backward elimination was used to reach the final multivariate model, in which factors with the largest *P* value were sequentially deleted until only significant predictors remained. We then created a weighted scoring system by rounding all regression coefficients up to the nearest integer (that is, the smallest integer greater than the estimate). This method was based on the β-coefficients (or log of the odds ratios) rather than odds ratios, which can be excessively influenced by only a few factors [25-27]. Once the final model was defined, we created integer weights for each variable. We calculated these weights by multiplying the model coefficients by 10. Using the rounded weights in the risk function, we estimated the participant-specific probabilities of HCV seropositivity and characterized the degrees of risk based on cut-off points of the probability distribution.

Cross-sectional internal validation:

We examined the predictive validity of the scoring system using the internal validation datasets (n=5,331). We also assessed the predictive validity of this scoring system on the subsequent risk of HCV antibody seroconversion using prospective data collected from individuals who visited ANSPS sites multiple times and tested HCV seronegative at their first visit.

We used the cross-sectional dataset to check the sensitivity and robustness of the new screening score. We computed standard validation measures: the proportion of antibody HCV seropositive specimens, sensitivity, specificity, positive likelihood and negative likelihood ratio and the area under the receiver operating characteristic curve (AUC) as discrimination statistics. We also assessed the diagnostic characteristics of different cut-points based on the total score in the development as well as validation datasets. The purpose of this analysis was to assess whether the combination of risk factors under consideration could predict those at increased risk with acceptable accuracy.

Prospective external validation:

We have also conducted a prospective external validation study to assess the performance of the scoring system for HCV seroconversion among the new PWID. The details of the study population have been described elsewhere [12]. In brief, as part of a multi-site study between 1999 and 2002, 215 hepatitis C seronegative PWID were recruited through street-based outreach, methadone clinics in South Western Sydney and followed-up at 3–6- monthly intervals. Using the Cox regression coefficients in the risk function, the participant-specific probability of HIV seroconversion was estimated. A rule to characterize different degrees of risk based on cut-off points of the probability distribution was then established. We also assessed the diagnostic features and characterized different degrees of risk based on cut-off points of the probability distribution.

Population attributable risk:

After we calculated and validated the HCV screening score, we estimated population attributable risks, which estimates the percentage of HCV infections that would not have occurred if all participants had been assigned the "lowest risk" (first quintile) category of the HCV screening score. We calculated population attributable risks using a previously described method [28] that was applied to this study design and appropriate for use with multivariable adjusted relative risks.

RESULTS

Our study population comprised 10,662 individuals in the development dataset. Table 1 summarizes participant characteristics by HCV antibody serostatus. The overall prevalence of HCV was 51%. HCV seropositive participants tended to be older and more likely to report a longer duration of injecting, heroin as the drug last injected, a history of imprisonment, daily or more frequent injecting, public injecting and sharing needles and syringes and other injecting equipment.

Table 2 presents the final multivariate logistic regression model derived from the development data set by age groups. History of imprisonment, duration of injecting (5-9, 10+ years), drug last injected (heroin, cocaine, methadone, morphine, buprenorphine and others), needle and syringe sharing and sharing of ancillary equipment were all significantly associated with increased risk of antibody HCV seropositivity across all age groups. Injecting frequency (daily or more) was determined to be a significant risk factor for those aged less than 30 years. Female gender was associated with an increased risk of HCV seroprevalence for those younger than 40 years of age. Indigenous status was a significant predictor for HCV infection among people aged 30-39 years. Drug last injected and

duration of injecting each required multiple categories to capture the risk gradient, whereas other risk factors were binary. The risk factors collectively yielded an AUC of 0.73 (95% CI: 0.70, 0.76), 0.72 (95% CI: 0.70, 0.75), 0.73 (95% CI: 0.70, 0.76) and 0.66 (95% CI: 0.64, 0.71) for the age groups <25, 25-29, 30-39 and 40 plus (data not shown). There were no significant interactions between injecting risk behaviors and gender across age groups (data not shown).

Table 3 shows the odds ratios (ORs) from the logistic regression models and population attributable risks of HCV infection for the quintiles of the risk scores by age groups for the development and validation datasets. There was a linear trend towards increasing HCV infection with increasing score regardless of the age groups in both datasets (trend, p-value<0.001). Using the development dataset, we estimated population attributable risks (95% CI) for the upper four quintiles of the scores. Results showed that 78% (75%, 81%), 82% (80%, 84%) and 80% (77%, 82%) of HCV infections across the age groups would be avoided if participants in the upper four quintiles of the HCV scores instead fell into the lowest quintile. Results from the validation dataset were consistent with those from the development dataset (Table 3). We also assessed the diagnostic characteristics of cut-points (according to first, second, third and the fourth quintiles in overall population) for total score in the development as well as the validation datasets (Table 4). An increased risk of HCV was clearly associated with increasing scores. For example, a cut-point score of 10 or higher distinguished a 'increased risk' group with a sensitivity of 96% or higher; similarly a cut-point 20 or higher yielded at least 92% sensitivity in all age groups in the development dataset; in cross sectional validation, sensitivity was estimated to be at least 94% across the age groups for the cut-point 10/15 or more and at least 76% for 20 or more. Figure 1 illustrates the risk of PWID being HCV seropositive as a

continuous function of the total score. Across all age groups, increasing scores were clearly associated with increased risk of HCV antibody positivity.

A total of 61 HCV seroconversions were observed during follow-up with an overall incidence rate of 45.8 per 100 person-years (95% CI: 35.6, 58.8) in our external prospective validation dataset. Results from our prediction model were consistent with the previous results and had the acceptable validity (Table 5). Higher number of risk factors associated with increased risk of HCV seropositivity compared two or less risk factors (reference) (Hazard ratio (HR):1.10, 95% CI: 0.74,1.60, HR:1.15,95% CI:0.78,1.65, HR:2.17, 95% CI: 1.45,3.17 and HR:3.19, 95% CI: 2.30, 5.51 for 3, 4, 5 and 6 or more risk factors respectively). Overall sensitivity of the scoring tool was 73% sensitivity and 33% specificity (Figure 2);

DISCUSSION

In this study, we developed a scoring tool based on data from ~16,000 PWID who attended ANSPS sites between 1998 and 2008. The tool was validated to more accurately identify those at increased risk of HCV infection. Current Australian guidelines recommend HCV antibody screening in all individuals with risk factors for infection regardless of patient characteristics and settings [29]. Increasing the rate of HCV diagnosis and, in particular, diagnosis of acute infection and providing access to effective antiviral treatment has the potential to improve individual quality of life and reduce the burden of HCV infection. Being unaware of one's HCV serostatus has been identified as a major barrier to increasing HCV treatment uptake, including among PWID [30-31]. While a relatively high proportion (64%) of participants in the ANSPS reported recent HCV testing, HCV antibody

negative respondents were less likely to do so than antibody positive respondents (60% versus 67%). One in five (20%) HCV antibody negative participants had not been tested for HCV in the last twelve months, and a further 20% had never been tested (www.web.med.unsw.edu.au/nchecr/Publications). This suggests that both uptake and frequency of testing could be improved.

Although our scoring tool was developed for the prediction of current HCV diagnoses and not incident HCV in the future, strong consistency in risk factors for the prediction incident events of HCV was shown in prospective validation of the tool. Therefore, we expect that the same set of risk factors in our model plays an important role in the prediction of future HCV seroconversion.

The intention of this study was not to identify a unique and specific cut-point of risk above which to target screening, but rather, to assess whether risk factors under consideration could predict those at increased risk accurately in order to consider the tool's use in facilitating increased screening. With a high background HCV prevalence of ~70% among Australian PWID, all PWID should be screened for HCV. However, identification of just one of our listed risk factors substantially increased the likelihood of infection. Although Australia has screening guidelines for hepatitis C, current guidelines do not target specific attributes or injecting risk behaviours [29]. By focusing on particular characteristics and specific high-risk behaviors, tools such as the one developed in this study may allow for more targeted identification of individuals at increased risk of infection. If used as a self-administered questionnaire, it is likely that respondents will answer more accurately [32]. Since the vast majority of new HCV diagnoses in Australia are among people with a history of injecting drug use [21], this tool provides a valuable resource which could inform the establishment of more focused national screening guidelines.

Further, although current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors can more precisely identify people in need of additional, non-routine screening. This is particularly pertinent in resource-constrained environments (including time-restricted clinical settings). Our methodology made use of a range of coexisting risk factors that were identified by a rigorous statistical approach in order to accurately identify the most relevant factors for HCV infection.

Risk calculation approaches have been extensively used in decision making about public health and clinical care and have even been proposed as an alternative to diagnosis for some diseases [33]. Our risk calculation was based on a statistical method that yielded a systematic scoring system for carefully selected predictors, guided not only by numerical and scientific evidence but also feasibility perspectives. We chose categorized variables which highlighted the important risk factors to motivate high-risk persons to be screened or to modify behaviors. This combination of factors may explain the enhanced properties of our scoring tool.

Our study has several strengths, including being the first to validate a predictive model through internal cross sectional and prospective data sets. Our prediction equation is based on 11 years of data and more than 16,000 participants. Ideal risk assessment methods or prediction models should be derived from large representative samples. The current study has several limitations. First, the study population is limited to those who participated in the ANSPS, which may result in selection bias. However, the ANSPS has been shown to be broadly representative of PWID attending NSPs [21]. Second, we were not able to differentiate between acute, recent and chronic infections.

Risk factor screening and identification allows for patients to be educated regarding the risks of injection drug use and needle sharing. Appropriate testing and diagnosis of HCV allows for the patient to be evaluated for treatment and receive counseling regarding HCV prevention. In addition to physician education, patient education campaigns must also be developed to increase patient compliance with testing recommendations made by their physicians.

In conclusion**,** we believe the screening tool described here will provide a simple and cost-effective method of identifying and alerting PWID who are in need of additional, non-routine HCV screening with notable predictive validity. A self-assessment method that helps individual PWID understand their relative increased risk of infection provides the basis for increased uptake of screening, diagnosis, and antiviral treatment among this population.

In summary, the tool described here has the potential to engage current PWID in timely and accurate risk analysis, potentially modifying risk behaviour, and increasing uptake of HCV screening and antiviral treatment in this population.

Article Summary

Article focus:

- Although the risk factors for incident infection are well established, the literature suggests that a number of barriers may prevent PWID presenting for screening.
- Study developed a scoring tool based on demographic and injecting risk behaviors to identify those who require additional, non-routine serological screening for HCV by assessing their personal risk.

Key Messages:

- Current clinical practice guidelines recommend HCV screening of individuals with a history of injecting drugs.
- However, this recommendation focuses on a single risk factor (i.e. injecting drug use) whereas considering the cumulative effect of multiple risk factors among PWID can more precisely identify people in need of additional, non-routine screening.

Strengths and limitations:

- Our prediction equation is based on 11 years of data and more than 16,000 participants. Ideal risk assessment methods or prediction models should be derived from large representative samples.
- The study population is limited to those who participated in the ANSPS, which may result in selection bias.
- We were not able to differentiate between acute, recent and chronic infections.

Competing interest: None.

Ethics approval: Ethical approvals for the survey were obtained from Institutional Ethics Committees associated with the investigators and participating NSP sites.

Contributors: HW and LM implemented the study, analysed the data and wrote the first draft. LM, JI, LT and DW helped drafting, interpreting the data and finalizing the manuscript. All authors saw and approved the final, submitted version of the manuscript.

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REFERENCES

[1] McGinn T, O'Connor-Moore N, Alfandre D, Wisnivesky J. Validation of a Hepatitis C Screening Tool in Primary Care. Arch Intern Med **2008**; 168(18):2009-13.

[2] Thorpe LE, Ouellet LJ, Hershow R et al. Risk of Hepatitis C Virus infection among Young Adult Injecting Drug Users Who Share Injecting Equipment. American Journal of Epidemiology **2002**; 155:7:645-653.

[3] Alter MJ, Kruszon-Moran D, Nainan OV et al. The prevelance of hepatitis C virus infection in the United States, 1998 through 1994. New England Medical Journal **1999**; 341:556-62.

[4] Villano S A, Vlahov D, Nelson KE et al. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. J Clin Microbiol **1997**; 35: 3274–7;

[5] Garfein RS, Doherty MC, Monterroso ER, et al. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. J Acq Immune Defic Synd Hum Retrovirol **1998**; 18:11–19.

[6] Hahn JA, Page-Shafer K, Lum PJ et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis **2002**; 186:1558–64.

[7] Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology **2004**; 15: 543–9.

[8] Hagan H, Thiede H, Weiss NS et al. Sharing of drug preparation equipment as a risk factor for hepatitis C. Am J Public Health **2001**; 91: 42–6.

[9] Falster K, Kaldor J and Maher L. Hepatitis C Virus acquisition among Injecting Drug Users: a cohort analysis of a national repeated cross-sectional survey of needle and syringe program attendees in Australia, 1995-2004. Journal of Urban Health **2008** [doi:10.1007/s11524-008-9330-7].

[10] Hahn JA, Page-Shafer K, Lum PJ et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis **2002**; 186: 1558–64.

[11] Maher L, Jalaludin B, Chant KG et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction **2006**; 101(10): 1499-1508.

[12] Maher L, Li J, Jalaludin B et al. High hepatitis C incidence in new injecting drug users: a policy failure? Aust N Z J Public Health **2007**; 31(1): 30-35.

[13] Patrick DM, Tyndall MW, Cornelisse PG et al. Incidence of hepatitis C virus infection among drug users during an outbreak of HIV infection. Can Med Assoc J **2001**; 165: 889–95.

[14] Miller CL, Johnston C, Spittal PM et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology **2002**; 36: 737–42.

[15] Davis M, Rhodes T. Beyond prevention? International Journal of Drug Policy **2004**; 15:123-31.

[16] National Centre in HIV Epidemiology and Clinical Research. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2009. National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW.

[17] NCHECR. Hepatitis C Virus Projections Working Group, Sydney: NCHECR, **2006**.

[18] Gerlach J, Diepolder H, Zachoval R et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology **2003**; 125:80-8;

[19] Kamal SM, Fouly AE, Kamel RR et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology **2006**; 130:632-638;

[20] Gregory JD, Hellard M, Matthews GV, et al. Effective Treatment of Injecting Drug Users with recently acquired hepatitis C virus infection. Gastroenterology **2010**; 138:123-135;

[21] Topp L, Iversen, J, Wand H et al. Representativeness of injecting drug users who participate in HIV surveillance: results from Australia's Needle and Syringe Program Survey. J Acquir Immune Defic Syndr **2008**; 47(5), 632-638.

[22] MacDonald M, Crofts N, Kaldor J Transmission of hepatitis C virus: rates, routes, and cofactors. Epidemiol Rev **1996**; 18(2), 137-148.

[23] MacDonald M, Wodak AD, Ali R et al. HIV prevalence and risk behavior in needle exchange attenders: a national study. The Collaboration of Australian Needle Exchanges. Med J Aust **1997**; 166(5),237-240.

[24] MacDonald MA, Wodak AD, Dolan KA et al. Hepatitis C virus antibody prevalence among injecting drug users at selected needle and syringe programs in Australia, 1995-1997. Collaboration of Australian NSPs. Med J Aust **2000**; 172(2),57-61.

[25] Schmidt MI, Duncan BB, Bang H et al. Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care **2005**; 28:2013-2018.

[26] Gonen M. Analyzing Receiver Operating Characteristic Curves with SAS **2007**. Cary, NC: SAS Institute;

[27] Sackett D, Straus SE, Richardson WS et al. Evidence- Based Medicine: How to Practice and Teach EBM. 2nd ed. Philadelphia: Churchill Livingstone; **2000**.

[28] Wand H, Spiegelman D, Law M et al. Estimating population attributable risk for hepatitis C seroconversion in injecting drug users in Australia: implications for prevention policy and planning. Addiction **2009**, 104(12), 2049-2056(8).

[29] Maher L, Iversen J, Kaldor J. Measuring effectiveness of needle and syringe exchange programs for prevention of HIV among injecting drug users: Response to Amundsen. Addiction **2006**; 101(12):1834-6.

[30] Volk M, Tocco R, Saini S, Lok A. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology **2009**;50:1-6

[31] Edlin BR, Kresina TF, Raymond DB et al. Overcoming Barriers to Prevention, Care, and Treatment of Hepatitis C in Illicit Drug Users. CID **2005**; 40 (Suppl 5): S276-S285.

[32] White B, Day C, Maher L. Self reported risk behavior among injecting drug users: Self versus assisted questionnaire completion. AIDS Care **2007**; 19(3): 441-447.

[33] Vickers AJ, Basch E, Kattan MW. Against diagnosis. Ann Intern Med. **2008**; 149:200-3. [PMID: 18678847]

Table 1: Risk factors for Hepatitis C Virus (HCV)

Characteristics	HCV Seronegative N= 5,214 (49%)	HCV Seropositive N= 5,448 (51%)
Mean age at survey (± SD)	29 ± 8	34 ± 9
<25 years, %	35	16
25-29 years, %	24	19
30-39 years, %	29	37
40+ years, %	12	28
Female, %	33	35
Indigenous, %	8	10
Mean age at first injection (± SD)	20 ± 6	19 ± 6
Mean years of injecting (± SD)	9 ± 7	15 ± 9
<5 years, %	26	12
5-9 years , %	28	21
10-16 years, %	23	28
17+ years, %	14	40
Ever been in Prison, %	17	33
Been in prison last year, %	11	22
Drug injecting behaviors (last month)		
Drug injected, %		
Amphetamine/methamphetamine	51	28
Heroin	35	48
Cocaine	3	5
Methadone	4	8
Morphine	7	9
Buprenorphine	1	2
Others[1]	9	8
Injecting daily or more , %	50	58
Receptive sharing needle/syringe, %	15	18
Receptive sharing ancillary equipments[2], %	33	38
Injected by another, %	14	12
New needle syringe in every injection	72	68
Injected in Public	46	52

[1] benzos, anabolic steroids, mixed drugs, other drugs or not reported

[2] water, spoon, filter, tourniquet

Table 2: Multivariable logistic regression: Odds Ratios (OR) and 95% confidence intervals (CI) for HCV infection scoring by age groups

	<25 N=2,686			25-29 N=2,291			30-39 N=3,563			40+ N=2,122		
	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score	OR (P)	β*10	Score
Sex												
Male	1	-	0	1			1			-		
Female	1.4	3.4	3	1.5 (<0.001)	4.1	4	1.4 (0.002)	3.3	3			
Indigenous												
No	-	-	-	-		-	1	-	-			
Yes							1.3 (0.04)	2.8	3	-		
Ever been in Prison?												
No	1	1	0	1			1			1		
Yes	2.2 (<0.001)	7.8	8	2.8 (<0.001)	10.2	10	1.9 (<0.001)	6.4	6	1.4 (0.003)	3.4	3
Years of injecting												
<5 year	1	-	0	1						1		
5-9 years	2.0 (<0.001)	6.8	7	1.7 (<0.001)	5.5	6	1.9 (<0.001)	6.5	7	1.5 (0.149)	3.7	4
10+ years	3.1 (<0.001)	11.1	11	2.4 (<0.001)	8.9	9	3.6 (<0.001)	12.7	13	4.6 (<0.001)	15.3	15
Drug last injected												
Amphetamine/methamphetamine	1	-	0	1			1	-		1		
Morphine	2.3 (<0.001)	8.3	8	1.7 (0.009)	5.5	6	1.9 (<0.001)	6.7	7	1.9 (<0.001)	6.7	7
Others[2]	2.0 (<0.001)	6.7	7	1.6 (0.010)	4.7	5	1.8 (<0.001)	5.9	6	1.5 (0.053)	4.0	4
Heroin	3.0 (<0.001)	11.1	11	2.7 (<0.001)	10.0	10	3.0 (<0.001)	10.7	11	2.5 (<0.001)	9.0	9
Cocaine	6.4 (<0.001)	18.6	19	3.6 (<0.001)	12.7	13	3.0 (<0.001)	10.9	11	3.6 (<0.001)	12.8	13
Methadone	3.3 (<0.001)	11.3	11	3.4 (<0.001)	12.2	12	3.0 (<0.001	11.0	11	3.1 (<0.001)	11.3	11
Buprenorphine	3.2 (0.003)	11.4	11	2.8 (0.004)	10.4	10	2.8 (0.001)	10.2	10	1.9 (0.141)	6.2	6
(Drug injecting behaviors last month)												
Injecting frequency												
Less than daily	1	-	0	1								
Daily or more	1.4 (0.001)	3.1	3	1.5 (<0.001)	4.0	4	-	-	-	-	-	
Receptive sharing needle/syringe												
No	-			1			1	-		-	-	
Yes	-			1.4 (0.005)	3.4	3	1.4 (0.002)	3.3	3			
Receptive sharing ancillary equipment[2]												
No	1	1	0	1						1		
Yes	1.3 (0.006)	2.5	3	1.3 (0.003)	3.0	3	-	-	-	1.5 (0.001)	3.8	4

[1]benzos, anabolic steroids, mixed drugs, other drugs or not reported

[2]water, spoon, filter, tourniquet

Table 3: Odds Ratios (OR) and 95% confidence intervals (CI) & for HCV infection by quintiles of HCV scoring

	Age <25 years		Age 25-29 years		Age 30-39 years		Age 40 plus	
Development Data Set	OR (95% CI)	P [0]	OR (95% CI)	P[0]	OR (95% CI)	P[0]	OR (95% CI)	P[0]
HCV Risk score[1]		<0.001		<0.001		<0.001		<0.001
Fifth 1	1		1		1		1	
Fifth 2	1.90 (1.33,2.69)		2.60 (1.88,3.57)		2.23 (1.72,2.89)		2.63 (1.94,3.58)	
Fifth 3	2.77 (1.92,4.01)		4.12 (3.00, 5.65)		4.07 (3.13,5.28)		4.56 (3.10,6.70)	
Fifth 4	5.40 (3.95,7.38)		4.85 (3.53,6.66)		5.40 (4.16,7.02)		5.86 (4.25,8.08)	
Fifth 5	10.31 (7.44,14.29)		12.40 (9.08,16.91)		9.10 (7.04,11.75)		7.78 (5.61,10.80)	
Population attributable risk for HCV score (%)[2] **(95% CI)**								
lowest v upper four fifth	78% (75%, 81%)		82% (80%, 84%)		80% (78%, 82%)		80% (77%, 82%)	
lower two v upper three fifth	74% (72%, 77%)		76% (74%, 78%		74% (73%, 77%)		72% (69%, 74%)	
Validation Data Set								
HCV Risk score[1]		<0.001		<0.001		<0.001		<0.001
Fifth 1	1		1		1		1	
Fifth 2	1.92 (1.12,3.28)		2.75 (1.73,4.38)		2.73 (1.94,3.85)		1.98 (1.30,3.02)	
Fifth 3	4.70 (2.75,8.04)		4.33 (2.78,6.77)		5.34 (3.74,7.63)		5.03 (2.78,9.10)	
Fifth 4	6.00 (3.76,9.56)		6.13 (3.93,9.56)		7.46 (5.19,10.74)		3.79 (2.44,5.87)	
Fifth 5	11.97 (7.41,19.32)		9.28 (6.07,14.19)		10.68 (7.56,15.10)		5.42 (3.50,8.42)	
Population attributable risk for HCV score (%)[2] **(95% CI)**								
lowest v upper four fifth	82% (79%, 85%)		80% (77%, 83%)		84% (82%, 85%)		73% (68%, 77%)	
lower two v upper three fifth	79% (76%, 81%)		74% (71%, 77%)		78% (76%, 79%)		67% (62%, 71%)	

[0] Test for trend

[1] HCV score **for age <25** was <7 for fifth 1, 7-<14 for fifth 2, 14-<17 for fifth 3, 17-<24 for fifth 4 and 24+ for fifth 5; **for age 25-29** was <12 for fifth 1, 12-<17 for fifth 2, 17-<22 for fifth 3, 22-<26 for fifth 4 and 24+ for fifth 5; **for age 30-39** was <13 for fifth 1, 13-<19 for fifth 2, 19-<24 for fifth 3, 24-<27 for fifth 4 and 27+ for fifth 5; **for age 40 plus** was <15 for fifth 1, 15-<22 for fifth 2, 22-<24 for fifth 3, 24-<27 for fifth 4 and 27+ for fifth 5;

Table 4: Optimal characteristics of HCV Scoring[1]

	Age <25 years		Age 25-29 years		Age 30-39 years		Age 40 plus	
Score cut points[2]	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Development Data Set (n=10,662)								
≥ 10	96%	17%	99%	9%	99%	7%	98%	10%
≥ 15	92%	32%	95%	23%	97%	15%	97%	19%
≥ 20	74%	60%	86%	42%	90%	36%	94%	24%
≥ 25	55%	74%	68%	64%	73%	57%	75%	54%
Validation Data Set-cross sectional (n= 5,465)								
≥ 10	96%	18%	99%	8%	99%	10%	99%	10%
≥ 15	94%	32%	95%	25%	97%	19%	97%	15%
≥ 20	76%	57%	88%	40%	87%	43%	94%	21%
≥ 25	59%	72%	67%	61%	73%	61%	74%	52%

[1]HCV Score :

For age < 25: (female)*3+ (indigenous) *0 + (Injecting 5-9 years)*7 + (Injecting 10+ years) *11+ Morphine*8 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*7 + (heroin)*11 + (cocaine)*19 + (methadone)*11 + (morphine)*8 + (Buprenorphine) *11 + (daily or more)*3 + (shared needle and syringe)*0 + (shared other equipment)*3 + (been in prison)*8

For age 25 -29 year: (female)*4+ (indigenous) *0 + (Injecting 5-9 years)*6 + (Injecting 10+ years) *9+ Morphine*6 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*5 + (heroin)*10 + (cocaine)*13 + (methadone)*12 + (morphine)*5 + (Buprenorphine) *10 + (daily or more)*4 + (shared needle and syringe)*4 + (shared other equipment)*0 + (been in prison)*6

For age 30 -39 year: (female)*3+ (indigenous) *3 + (Injecting 5-9 years)*7 + (Injecting 10+ years) *13+ Morphine*7 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*6 + (heroin)*11 + (cocaine)*11 + (methadone)*11 + (morphine)*7+ (Buprenorphine) *10 + (daily or more)*0 + (shared needle and syringe)*3 + (shared other equipment)*0 + (been in prison)*6

For age 40 + year: (female)*0+ (indigenous) *0 + (Injecting 5-9 years)*4 + (Injecting 10+ years) *15 + Morphine*7 + (other drugs e.g. benzos, anabolic steroids, mixed drugs, other drugs)*4 + (heroin)*9 + (cocaine)*13 + (methadone)*11 + (morphine)*7+ (Buprenorphine) *6 + (daily or more)*0 + (shared needle and syringe)*3 + (shared other equipment)*0 + (been in prison)*6

[2]Approximate cut points for the first, second, third and the fourth quintiles.

Table 5: Optimal characteristics of HCV Scoring using external prospective validation (N = 215)

	Validation with Prospective dataset	
Risk factors, No.	Hazard Ratio (95% CI)	P
Less than 2	Reference	
3	1.10 (0.74,1.60)	0.667
4	1.15 (0.78,1.65)	0.504
5	2.17 (1.45,3.17)	<0.001
6 or more	3.19 (2.30,5.51)	<0.001
Score cutpoints	Sensitivity	Specificity
≥ 10	89%	16%
≥ 15	78%	33%
≥ 20	60%	54%
≥ 25	41%	70%

Figure 1: Total score versus risk of HCV infection in cross-validation data set

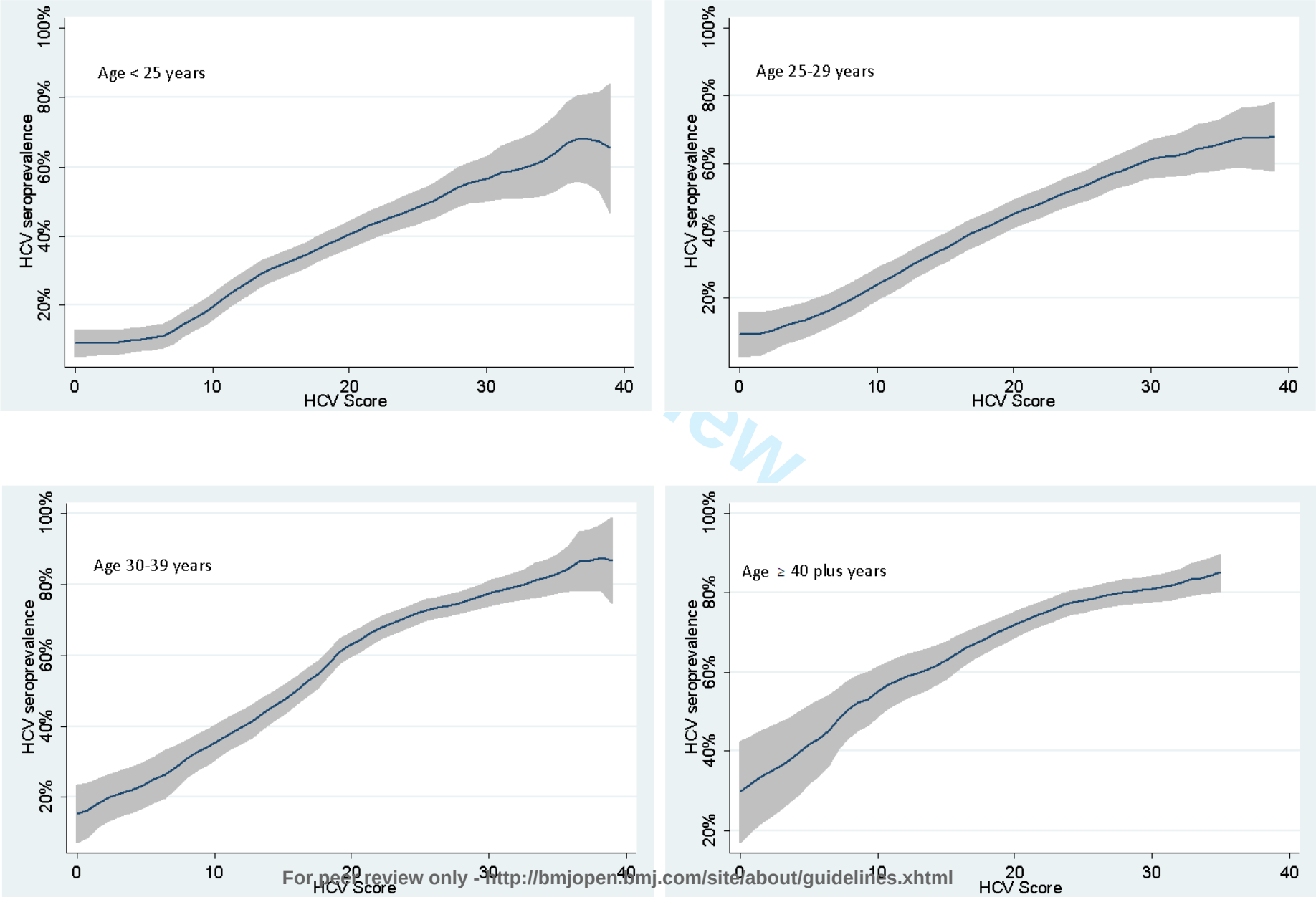

Figure 2: Sensitivity/Specificity for the prospective validation dataset: