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(2018) Screening for hepatitis C at the emergency department: Should babyboomers also be screened in Belgium?. In: LIVER INTERNATIONAL, 39 (4), p. 667-675.

DOI: 10.1111/liv.14016
Handle: http://hdl.handle.net/1942/28108

Screening for hepatitis C at the emergency department: should babyboomers also be screened in Belgium?

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Figures: 3 Tables: 3 Word Count: 5.043

Abbreviations: HCV: hepatitis C virus; WHO: World Health Organization; Ab: antibodies; DAA: direct acting antiviral; ED: emergency department; CDC: Center for Disease Control; qRT-PCR: quantitative real-time polymerase chain reaction; RNA: ribonucleic acid; KCE: knowledge center; PWUD: people who use drugs; PWID: people who inject drugs; HBV: hepatitis B virus; HIV: human immunodeficiency virus; MSM: men who have sex with men; ROC: receiver-operating characteristic

Conflict of interest declaration: R.B. has received travel grants from Abbvie, MSD and Gilead to attend scientific congresses. O.M.K. has received travel grants from Gilead to attend scientific congresses. F.N. has received research grants, consultancy agreements and travel grants from UCB, Ipsen, Roche, Astellas, Ferring, Novartis, Janssen-Cilag, Abbvie, Gilead, CAF, Intercept, Gore, BMS, MSD, Promethera Biosciences, Ono Pharma, Durect. G.R. has received research grants from MSD, AbbVie, Janssen Pharmaceuticals, and has acted as a consultant/advisor and for Gilead Sciences, Abbvie, MSD and BMS. C.K., D.B., D.M.H., P.V. and N.H. report no conflict of interest. No one other than the authors had control over the study design, data, data analysis or interpretation, or wording of conclusions.

Financial support: This work was supported by Gilead Sciences by two unrestricted grants registered as V-1988 and V-1856 at Hasselt University.

Abstract

Introduction

Patients are not screened adequately for hepatitis C virus (HCV) infection in Belgium. In the USA, the CDC recommends screening for patients born in the babyboom period (1945-1965). In Europe, the babyboom cohort was born between 1955-1974, but no screening policy has been targeted to this group. We aimed to study the prevalence of HCV in an emergency department (ED) population in Belgium and the risk factors associated with HCV infection.

Method

We performed a monocentric, cross-sectional seroprevalence study between January and November 2017 in a large Belgian non-university hospital. Patients aged 18-70 years presenting at the ED were eligible. Patients completed a risk assessment questionnaire and were screened for HCV Ab with reflex HCV RNA testing.

Results

Of 2,970 patients, 2,366 (79.7%) agreed to participate. HCV Ab prevalence was 1.31%. Twenty-one (67.7%) HCV Ab positive patients were born between 1955-1974. With a previous treatment uptake of 54.5%, the prevalence of viremia was 0.9% in retrospect; 0.2% were newly diagnosed. The weighted multiple logistic regression model identified males born in the 1955-1974 cohort, intravenous drug use, and high endemic birth country as significant risk factors for HCV infection ($p < .05$).

Conclusion

Although the prevalence of HCV Ab at the ED was higher than previously estimated for the general population in Belgium, the number of newly diagnosed patients with viremia was low. To optimize

screening strategies, screening should be offered to males born in the 1955-1974 cohort, but especially in drug users, the prison population, and immigrants from high-endemic countries.

250 words - keywords: Screening, HCV, birth cohort, emergency department

Lay summary: Improving HCV screening is essential to reach the goals of the WHO. This seroprevalence study at the emergency department investigated who should be screened in Belgium: males born in the 1955-1974 birth cohort, PWID, the prison population and immigrants from high-endemic countries.

INTRODUCTION

Hepatitis C virus (HCV) remains one of the leading causes of chronic liver disease and liver-related deaths worldwide,[1-3] prompting the World Health Organization (WHO) to define targets for eliminating HCV as a public health threat by 2030.[4] In Europe, one of the most important challenges in this endeavour is the lack of reliable estimates of the burden of disease in several countries since this impedes the development of policies to scale-up prevention and treatment.[5] This knowledge gap is also present in Belgium. The seroprevalence of HCV antibodies (Ab) in Belgium is estimated to be low (0.87%) and is based on a trial published in 1997.[6] Since then, few trials have been executed with several limitations regarding the methodology of these studies.[7-10] In addition, highly effective direct acting antiviral (DAA) treatment became available. To develop a realistic disease control strategy for the disease burden of HCV, there is a need for new epidemiological data.[11]

The Center for Disease Control and Prevention (CDC) recommends a one-time screening for HCV infection for all persons born between 1945 and 1965 as they represent the bulk of the HCV

epidemic in the USA, and screening in this group is also cost-effective.[12,13] In Europe, a peak in the prevalence of diagnosed HCV patients was described in the 1955-1974 birth cohort.[14] Recently, a clear birth cohort variation in liver cirrhosis between eight European countries was demonstrated.[15] For Belgium, estimations are that ≥ 50% of all HCV RNA positive patients were born between 1955 and 1974.[16] Screening in this cohort would be cost-effective. However, there remains a lack of sufficiently powered prospective trials to analyse the distribution of HCV by birth cohorts while correcting for confounders such as risk behaviour. Today, the Belgian national hepatitis C plan (2014-2019) aims to develop a nationwide screening strategy, but there is no screening strategy implemented up to now.[17,18]

Higher rates of HCV Ab (2.5-3.5%) have been reported in European emergency departments (ED) compared to the general population.[19-23] In the United States of America (USA), due to the presence of a large number of high-risk patients, prevalence was even higher ranging from 9.5-18.0%.[24-27] According to these studies, screening at the ED would also be cost-effective.

We studied the seroprevalence of HCV infection in patients visiting the ED in a large non-university hospital in Belgium in order to obtain relevant epidemiological data and to identify future target groups for HCV screening in Belgium.

METHODOLOGY

Study design

This study is a monocentric, cross-sectional seroprevalence trial. All patients aged 18-70 years presenting at the ED of Ziekenhuis Oost-Limburg Genk (Belgium) between January-November 2017 were eligible for participation. After informed consent, two blood samples were drawn. Risk assessment questionnaires were performed using face-to-face interviews. Analysis for HCV Ab was performed using a third generation ELISA assay (Abbott HCV 3.0 R, Abbott Diagnostic,

Chicago, IL, USA). If HCV Ab positivity was confirmed, reflex HCV ribonucleic acid (RNA) testing was done using quantitative real-time polymerase chain reaction (qRT-PCR). Positive results of the HCV-RNA tests were communicated by phone to the patients. Negative results were sent to the patient's general practitioner. The study was approved by the medical ethics committees of Hasselt University and Ziekenhuis Oost-Limburg Genk (16-072U) and was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments. Good clinical practice guidelines were followed throughout the study.[28]

Endpoints of study

The primary endpoint was to assess the seroprevalence of HCV infection in an ED population.

The secondary endpoint was an analysis of risk factors (including birth cohorts) associated with HCV prevalence, in order to develop an effective screening strategy.

Definition of risk factors

Possible risk factors were available from screening recommendations of the Belgian health care Knowledge Center (KCE) in 2012 and the Belgium hepatitis C plan of the government. [9,17] Strict definitions of the risk factors as used in our questionnaire were:

- Birth country:
    - high endemic: HCV Ab prevalence > 2.9% as based on the data of Polaris observatory 2016[29] (Egypt, Romania, Georgia, Russia, Mongolia, Gabon, Uzbekistan, Pakistan, and Syria)
    - low endemic: all countries other than Belgium, HCV Ab prevalence ≤ 2.9% as based on the data of Polaris observatory 2016
- Blood transfusion before 1990
- Drug use:
    - People who use drugs (PWUD): ever used any illicit drugs at least once
    - People who inject drugs (PWID): ever injected illicit drugs at least once
- Dialysis: patients who have ever received dialysis

- Health care workers: working in health care, in contact with blood specimens
- Hemophilia: patients with hemophilia
- History of HBV infection: patients with self-reported hepatitis B virus infection
- History of HIV infection: patients with self-reported human immunodeficiency virus infection
- Imprisonment: patients ever imprisoned at least once
- Living together with another person infected with HCV: lived together at least one year with a person infected with HCV
- Multiple unsafe sexual contacts: sexual contacts outside of a long-term relationship with different people without use of condoms
- Sexual preference: men who have sex with men (MSM)
- Surgery:
    - invasive surgical procedures before 1990
    - surgical procedures in non-western countries
- Tattoo:
    - in a Western tattooshop
    - in non-hygienic circumstances (self-made, in prison, in non-Western countries)

Statistical analysis

RStudio version 1.0.136 was used to perform all statistical analyses. The analysis plan is described in detail in Figure 1. Two-sided Fisher's exact tests were used to identify risk factors associated to HCV Ab positivity. Risk factors that were found to be associated with HCV-Ab positivity ($p < .10$) in the Fisher's exact tests were included as covariates in a weighted multiple logistic regression model using Firth's correction for data sparseness. Model selection was done in a stepwise backward manner based on significance ($p < .05$). Since all included samples were linked to the questionnaires, corrections for over- or undersampling of certain age and gender groups was performed. For this purpose, weights were created for the interaction of age and gender, where age was divided into being born in the 1955-1974 birth cohort or outside of this cohort. Population

numbers of the year 2017 for Middle-Limburg (total population of about 165,647) were obtained from www.limburg.incijfers.be.[30]

The final weighted model was used for inference as well as a prediction rule for classifying patients. To evaluate the discriminative power of this prediction rule, a receiver-operating characteristic (ROC) curve was constructed. Finally, in order to assess whether conclusions based on the results obtained by analyzing the observed sample would be valid, a post-hoc power analysis was conducted for the Fisher's exact tests. A sensitivity analysis was conducted to assess how removing all previously diagnosed patients from the analyses would influence the results. Results were considered statistically significant at the .05 level.

RESULTS

Prevalence of hepatitis C

Out of 2,970 eligible patients, 2,366 (79.7%) agreed to participate. Description of the enrolment process and categorization of the prevalence of HCV is presented in Figure 2.

Insert Figure 2.

Out of 2,366 patients tested, 31 (1.3%) were positive for HCV Ab. Twelve (0.5%) patients had a current chronic HCV infection. The characteristics of these patients are described in Table 1. There was one new diagnosis of chronic HCV infection per 473 tested patients. However, none of the twelve patients were linked to care at the time of screening. Thus retesting was necessary to reengage them into care, which lowered the number needed to test to 1 per 197 tested patients. Of the HCV Ab and RNA positive patients, 67.7% and 66.7% were born between 1955 and 1974, respectively.

Insert Table 1.

Linkage to care

Of the current twelve chronically HCV infected patients, nine (75.0%) were linked to care after being informed of their results. Of the three patients not linked to care, one died due to reasons not related to HCV infection, and two were active PWID who could not be reached (incorrect telephone number, no contact information of general physician). Six patients (50%) had genotype 1a, two (16.7%) genotype 1b, two (16.7%) genotype 3 and one (8.3%) genotype 5. One was unknown. Three patients (25.0%) had severe liver fibrosis (≥F3 based on fibroscan). All five (41.7%) patients eligible for therapy (reimbursement criteria in Belgium: ≥F2 based on fibroscan and FIB-4 test)[31] received DAA treatment and reached sustained viral response.

Risk factors for hepatitis C infection

Results of the univariate analyses using Fisher's exact tests are provided in Table 2. Categories not mentioned in this table were used as the reference category for calculating odds ratios. The association with HCV Ab could not be studied in the following risk factors due to small sample sizes: patients on dialysis (n=30, no HCV Ab positives), patients with HIV infection (n=5), HIV-infected men who have sex with men (MSM) (n=3), and patients with haemophilia (n=1). Both birth cohort and gender had an influence on HCV Ab positivity. A higher prevalence of HCV Ab was found especially in males born between 1955 and 1974, Furthermore, being born in a high endemic country, PWUD, more specifically PWID, having a history of HBV infection, having been imprisoned, having lived together with an HCV infected person and having tattoo(s) not placed in a tattoo shop in the Western world, were all significantly associated with HCV infection ($p < .05$).

Insert Table 2.

According to the post-hoc power analyses, enough power (>80%) was obtained to make valid conclusions about the age by gender interaction (0.88), birth country (0.84), drug use (0.99), history of HBV infection (0.82), imprisonment (0.99), and tattoos placed in non-hygienic circumstances (0.97). To correct for over- or under sampling of males or females in- and outside of the 1955-1974 birth cohort, logistic regression analysis was performed with post-stratification weights for the middle Limburg region. The trial resulted in a slight oversampling of individuals belonging to the 1955-1974 birth cohort (ages 43 to 62), and males in general were slightly oversampled as well. None of the weights had a deviation of more than 0.2 (from 1) which indicates that our ED population was not so different from the general population of middle Limburg in terms of age and gender. The results of the logistic regression model are shown in Table 3 and were in accordance to those from a non-weighted model. Age by gender interaction, PWUD, PWID, history of HBV infection, and immigrating from a high endemic birth country remained significant risk factors for HCV Ab positivity.

Insert Table 3.

Stukel's test indicates this model is a good fit for the data (p = .718). McFadden's pseudo-R^2 was also calculated to assess model goodness of fit. This had a value of 0.43, indicating that 43% of the variability is explained by our model. Based on the final weighted model a prediction rule was constructed, shown by the ROC curve in Figure 3. The optimal cutoff value based on the Youden index was 0.022. If a patient's predicted probability is higher than this value, the patient will be classified as being at high risk for HCV-Ab positivity. At this cutoff value, the specificity and sensitivity were 0.97 and 0.74, respectively, indicating good discriminative power of the model, as also shown by the AUC (0.87).

Insert Figure 3.

The results of the sensitivity analysis are shown in Appendix A.

DISCUSSION

This is the first study investigating the prevalence of HCV RNA in Belgium. The prevalence of HCV Ab (1.3%) was slightly higher than expected based on earlier trials in the general Belgian population (0.9%).[6,9] As the spontaneous clearance rate was 29.0%, and 32.3% were cured by previous treatment, only 38.7% had a chronic infection, resulting in a HCV RNA prevalence of 0.5%, with a number of newly diagnosed patients of 0.2%.

We found that males from the birth cohort 1955-1974 were at significantly increased risk of HCV Ab positivity. Persons having a history of HBV infection, (intravenous) drug use, and migrants from a high endemic country were also at increased risk of HCV Ab positivity. A model without the age and gender interaction revealed a significantly higher risk of HCV Ab positivity for patients who have ever been imprisoned.

Compared to other studies in Europe, the prevalence of HCV infection in our ED was low. There are several reasons for this discrepancy. In Picardy, France, testing was only performed after a risk assessment questionnaire, and only patients with at least one risk factor were screened for HCV Ab.[19] In Germany, two large-scale studies were performed in urban areas in Berlin and Frankfurt/Mainz.[20,23] Main risk factors were migration and PWID. The location of these clinics in large cities explained the higher prevalence of these risk factors as compared to the general population in Germany. In England, a smaller anonymous study in London also found an HCV Ab prevalence of 2.6% and an HCV RNA prevalence of 1.2%.[21] The higher prevalence especially in white British males could not be explained due to the anonymous study design. Risk factors were unfortunately not studied. Finally, in Switzerland, another large study in a tertiary hospital in

Bern also revealed a higher prevalence, three times higher than in the general population.[22] Again this was explained by a higher proportion of PWID, patients with no insurance and a primarily urban population. This is in contrast with our present study, where patients originated from a mixed urban and rural area, namely the middle Limburg region.

In Europe, HCV prevalence varies within different birth cohorts between countries. In France, the new complementary screening strategy consists of one-time simultaneous HCV, Hepatitis B virus (HBV) and HIV testing in men aged 18-60 and pregnant women in the first trimester.[32-34] They did not find an effect of a specific birth cohort, but decided a pragmatic approach was necessary to detect the undiagnosed population. As men had a higher risk of HCV infection (and also similar demographics for HBV and HIV), these guidelines were developed.[34,35] In Germany, there was no effect of birth cohorts on the prevalence of HCV infection in a large study conducted in a primary care setting.[36] Also, in the Netherlands, there was no effect of birth cohort on the prevalence of HCV infection when screening was offered to patients born between 1948 and 1978 in a primary care setting, even though the study was performed in two hot-spots for HCV (prevalence >1%).[37] A seroprevalence study in the Czech Republic in 2015 did identify a birth cohort with a higher HCV prevalence, namely patients born between 1971 and 1985.[38] In Spain, seroprevalence was 1.6% in patients born between 1949 and 1974 who visited the hospital for a colonoscopy.[39]

The effect of age and gender found in the present study could have been influenced by higher proportions of PWID and imprisonment in certain groups. In the 1955-1974 cohort, 61.9% (13/21) of the HCV Ab positive patients were PWID versus 20.0% (2/10) in the other age groups, and 71.4% (15/21) were ever imprisoned vs. 20.0% (2/10) outside the cohort. In total, in the 1955-1974 cohort, 1.5% (15/1031) were PWID and 5.7% (59/1031) had ever been in prison, versus 0.7% (9/1335) and 5.1% (68/1335) in the other age groups. Therefore, screening policy should focus on

high-risk groups in Belgium (PWID, prison population and migrants from a high endemic country), instead of on a specific birth cohort. Nevertheless, a risk-based screening policy is difficult to implement based on the challenges faced by clinicians and patients when discussing sensitive personal behaviors, particularly when they are not relevant to the medical care visit.[40,41] To overcome this, screening could be offered to males born in the 1955-1974 cohort in the middle Limburg region, as the underlying risk factors were more prevalent in this cohort.

This study has several limitations. Being a single center trial in a large non-university hospital, it is possible that the sample does not adequately represent the general Belgian population. Nevertheless, since all Belgian hospitals with EDs are general hospitals that are freely accessible for the population, a similar case mix in the EDs of these general hospitals is plausible. The sample does differ from the general population, as this department is reached by patients whom are more engaged in high-risk behavior.[25] However, the relatively high presence of these risk groups made it possible to study the impact of risk factors on HCV prevalence with sufficient power. The stability of our prediction rule should be validated in other cohorts, and other important risk factors could still be implemented such as HIV-infected MSM, patients on dialysis, and patients with a blood transfusion before 1990, who could not be studied with sufficient power due to limited sample size with respect to these risk factors within the study population. Especially a risk-group with ongoing transmission such as HIV-co infected MSM should also be screened.[42,43] McFadden's pseudo-R^2 had a value of 0.43, indicating that 43% of the variability is explained by our model. According to Louviere et al.[44], a pseudo-R^2 value between 0.2 and 0.4 indicates very good model fit. However, this model still leaves 57% of the variability unexplained, indicating that further research might reveal other important risk factors not included in the present study.

Not every eligible participant that visited the emergency department could be informed and asked to participate due to logistical barriers: limited enrolment time per day and limited study staffing which could have led to unintentional selection bias. A small proportion of patients could not be included due to language barriers, which could have led to a lower uptake of migrants from high endemic countries. Finally, although Firth's bias correction for data sparseness was used, the odds ratios for PWID, HBV infection, and high endemic birth country seem to be inflated (due to small sample sizes) and thus should be interpreted with care.

CONCLUSION

In agreement with findings in other countries, the prevalence of HCV Ab at the emergency department was higher than estimated for the general population in Belgium. However, the number of newly diagnosed patients with viremia was low and to link a patient to care 197 HCV Ab tests were needed. We could confirm in our region that screening should be offered to males born in the 1955-1974 cohort, but especially in drug users, the prison population, and immigrants from high-endemic countries.

AUTHOR CONTRIBUTIONS

R.B., O.M.K., P.V. and G.R. conceived and designed the study, R.B. and G.R. obtained funding for the work. R.B. and O.M.K. acquired the data. Analysis was conducted by R.B., C.K., D.M.H and N.H., and all authors (including D.B. and F.N.) assisted with interpretation of the data. R.B. drafted the manuscript, and all authors (including D.B. and F.N.) assisted with revision. R.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

This study is part of the 'Limburg Clinical Research Program' (LCRP), supported by the foundation Limburg Sterk Merk, province of Limburg, Flemish government, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital.

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TABLES

Table 1. Characteristics of the study population.

Characteristics of current HCV RNA +	**Patients (N=12) (n, %)**
Born between 1955-1974	8 (66.7%)
Genotype	
1a	6 (50.0%)
1b	2 (16.7%)
3	2 (16.7%)
5	1 (8.3%)
unknown	1 (8.3%)
Fibrosis stage	
≥ F2	5 (41.7%)
≥ F3	3 (25.0%)
Linked to care due to study	9 (75.0%)

Table 2. Univariate influence (Fisher's exact tests) of risk factors on HCV Ab prevalence.

Risk factor	**HCV Ab+ (total)**	***p*-value**	**OR**	**95% CI**
Birth cohort		.010		
Other	10 (1335)			
°1955-°1974	21 (1031)		2.754	1.235 ; 6.579
Gender		.029		
Female	8 (1075)			
Male	23 (1291)		2.418	1.039 ; 6.280
Age by gender (°1955-°1974 vs. other)		.003		
Other (f)	4 (610)			
Other (m)	6 (725)		1.264	0.355 ; 4.501
1955-1974 (f)	4 (465)		1.315	0.327 ; 5.284
1955-1974 (m)	17 (566)		4.691	1.569 ; 14.027
Birth country		.001		
Belgium	23 (1821)			
High endemic	3 (16)		18.040	4.814 ; 67.602
Low endemic	5 (529)		0.746	0.282 ; 1.972
Blood transfusion before 1990		.4339		
No	28 (2221)			
Yes	3 (145)		1.654	0.318 ; 5.456
Drug use		<.001		
None	10 (2151)			
PWUD	6 (191)		6.944	2.496 ; 19.318
PWID	15 (24)		356.833	126.901 ; 1003.379
Health care worker		.214		
No	29 (1992)			
Yes	2 (374)		0.364	0.049 ; 1.450
History of HBV infection		.002		
No	28 (2348)			
Yes	3 (18)		16.487	2.900 ; 63.150

Imprisonment		<.001		
No	14 (2239)			
Yes	17 (127)		24.453	11.029 ; 55.135
Living together with another person infected with HCV		.010		
No	26 (2263)			
Yes	5 (103)		4.384	1.287 ; 11.944
Multiple unsafe sexual contacts		.140		
No	15 (1455)			
Yes	16 (911)		1.716	0.790 ; 3.746
Surgery		.110		
Never	5 (409)			
Western country	11 (1121)		0.801	0.277 ; 2.319
Before 1990	13 (799)		1.337	0.473 ; 3.775
Non-western country	2 (37)		4.617	0.864 ; 24.667
Tattoo		.005		
No	14 (1644)			
Yes	17 (722)		2.806	1.294 ; 6.186
Tattoo placed in non-hygienic circumstances		<.001		
No	22 (2240)			
Yes	9 (126)		7.741	3.066 ; 17.968

Abbreviation: m = male, f = female, PWUD = people who use drugs, PWID = people who inject drugs, HBV = hepatitis B virus, HCV = hepatitis C virus

Table 3. Final weighted logistic regression model for HCV Ab, with Firth's correction.

	Estimate	**Std. error**	***p*-value**	**Crude OR**	**Adjusted OR (95% CI)**
(Intercept)	-6.053	0.583	<.001		
Male, other	0.200	0.680	.769	1.264	1.222 (0.310 ; 5.831)
Female, 1955-1974 cohort	0.296	0.760	.697	1.315	1.345 (0.260 ; 6.960)
Male, 1955-1974 cohort	1.471	0.619	.018	4.691	4.352 (1.347 ; 20.082)
Drug use, PWUD	1.979	0.534	<.001	6.944	7.235 (2.225 ; 22.231)
Drug use, PWID	5.504	0.563	<.001	356.833	245.763 (85.184 ; 1004.407)
History of HBV infection	1.884	0.955	.049	16.487	6.579 (0.726 ; 39.014)
Birth country, low endemic	0.124	0.553	.823	0.746	1.132 (0.285 ; 3.306)
Birth country, high endemic	3.764	0.749	<.001	18.040	43.124 (8.313 ; 195.623)

FIGURE LEGEND

Figure 1. Statistical analysis plan.

Figure 2. Enrolment process and categorization of HCV infected patients. (ED = emergency department, HCV = hepatitis C virus, Ab =antibody, RNA=ribonucleic acid)

Figure 3. ROC curve for the final weighted logistic regression model. AUC= area under the curve.