Epidemiology and Prognostic Factors for Viral Hepatitis C in Western Algeria

Lakhdar ZEMOUR[1], Amina BELGHITRI[2], Nassima AMANI[3], Nori MIDOUN[1]

1 Faculty of medicine of ORAN, epidemiology department of the hospital-university establishment, Oran, Algeria
2 Faculty of medicine of ORAN, Pneumology department of the hospital-university establishment, Oran, Algeria
3 Faculty of medicine of ORAN, gastroenterology department of Oran University Hospital Center, Algeria

Abstract

Background: *Viral hepatitis C is a major public health problem worldwide. Their magnitude stems from their frequency and their short- and long-term health impact due to their evolutionary potential and therefore their complications.*
The objective of our work is to establish the epidemiological profile of viral hepatitis C in western Algeria and to identify the main prognostic factors associated with the progression of liver fibrosis.
Methods: *A cross-sectional descriptive study was carried out in Western Algeria. Information on patients with viral hepatitis C (VHC) was collected prospectively from January 2013 to December 2016. Cox's model was used to model the instant risk logarithm based on a set of predictors predicting the progression of fibrosis over time. The student's t-test and Analysis of variance (ANOVA) were used for the comparison of continuous variables*
Results: *A population of 594 patients was collected. The sex ratio was 0.65.*
Metabolic syndrome was found in 16.5%. Severe fibrosis (F3-F4) accounts for 30.3% of VHB cases.
82.1% of patients are divided into G1 and G2 with almost equivalent frequencies of 41.9% and 40.2% respectively. The discovery of viral infection was systematic in 42.6% of cases.
The patterns of contamination reported in our study population are represented mainly by care (60.6%) and the use of traditional practices (14.8%) such as hijama, scarification and tattooing.
Cirrhosis is found in 30.3% of VHC cases with an average age of 56.3 years. 28.3% of cirrhotics are diabetic.
According to Cox's modelling, Hepatocellular Carcinoma and diabetes are prognostic factors of mortality in viral hepatitis C.
Conclusion: *The most documented mode of contamination in our population, after that related to care, is the use of traditional practices; which could direct us to a population that should not be overlooked in terms of screening and awareness. The predictive factors for cirrhosis were inflammatory activity (A2-A3), age >40 years, diabetes mellitus and use of traditional practices*

Keywords: *Hepatitis C Virus, Fibrosis, Cirrhosis, Hepatocellular Carcinoma, Mortality, Cox model*

Introduction:

The viral hepatitis pandemic is weighing heavily on human lives, populations and health systems.
The magnitude of the problem of viral hepatitis C is not only due to its frequency, but also to its short- and long-term health impact due to its potential for progression and thus its complications. It is a so-called silent disease because most carriers do not know they have it. In many cases, the infection evolves slowly, sometimes over several decades. It then leads to chronic and sometimes incurable diseases such as cancer and cirrhosis of the liver.
Worldwide, 130 to 150 million people are living with chronic hepatitis C. The number of people with hepatitis C is currently increasing, despite the availability of an effective cure [1].
Globally, an estimated 58 million people are chronically infected with the hepatitis C virus, with approximately 1.5 million new infections occurring each year. An estimated 3.2 million adolescents and children are chronically infected with the hepatitis C virus.
The WHO estimates that in 2019, approximately 290,000 people died from hepatitis C, mostly from cirrhosis or hepatocellular carcinoma (primary liver cancer) [2].
The extent of the problem of viral hepatitis C stems not only from its frequency, but also from its short- and long-term health impact due to their evolutionary potential and therefore their complications.

A better understanding of the analytical epidemiology of viral hepatitis C will help to better elucidate the profile of a target population for screening specific to our western Algerian region.
objective: Identify and estimate the effect of the main prognostic factors associated with the progression of liver fibrosis by the Cox model.

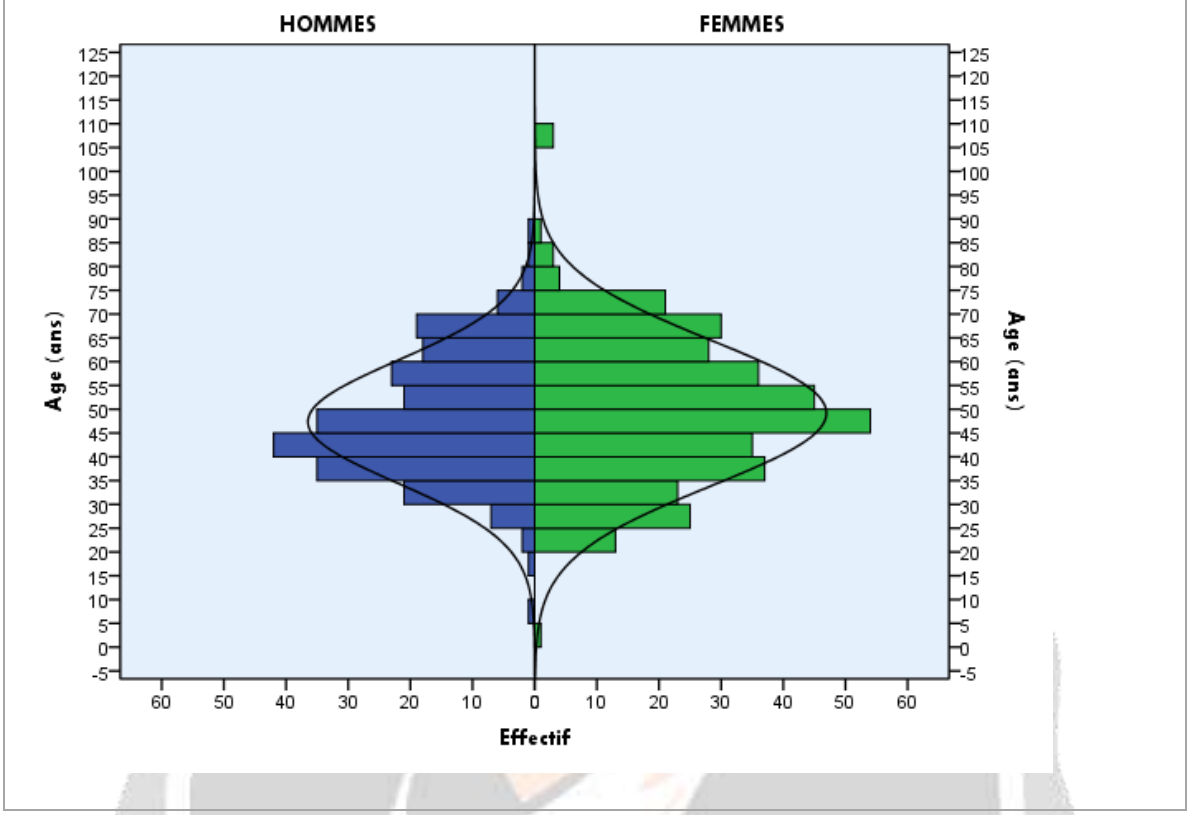
Materials and methods:

This is a descriptive and analytical cross-sectional study. The study population was comprehensively collected at the gastroenterology departments of the Oran University Hospital and the Sidi-bel-Abbes University Hospital. Information on patients with viral hepatitis C was collected prospectively from 2013 to 2016.
Were included in our study, all patients with:
— Chronic hepatitis C virus infection (positive hepatitis C antibody on serology) with the presence of hepatitis C RNA on real-time PCR (threshold < 15 IU/ml)
— With or without histological damage to the liver.
Were excluded from the study population, with subjects presenting:
— Co-infections with HIV and/or HBV-HCV co-infections
— Non-viral hepatitis
— Other viral hepatitis A, C, D or E
NCEP ATP III was used to define metabolic syndrome.
Statistical analysis: Data are collected on standardized sheets compiled from a questionnaire and then entered on standardized sheets with information on the different variables of the study, and used as a support for the processing and subsequent exploitation of the results.
Descriptive and analytical analysis of the data was done using SPSS20 software.
The tests used are: the Pearson 2 test for statistical association research between two qualitative variables, the Sudent's test for two independent samples and the variance analysis (ANOVA) were used for the comparison of continuous variables. A relationship is considered significant if the threshold was $p < 0.05$.
Cox regression predictive modeling is the model for estimating from our observations the effect of a variable on the occurrence of complications such as cirrhosis, hepatocellular carcinoma or death, after adjusting to other explanatory variables.
This is a multiplicative risk model, the presence of an identified factor increases the risk of complication occurrence according to an estimated regression coefficient (Hazard ratio).

Results:

The viral hepatitis C study involved 594 patients during the study period (2013-2016) with a female predominance (Sex-Ratio of 0.65, which corresponds to 2 men for 3 women). (Table 1)
At the professional level, more than half of hepatitic subjects C are active with a frequency of 79.5%. Alcoholism is noted in 1.6% of cases.
Among all patients with viral hepatitis C, 20 subjects in occupations at risk of viral infection C are reported at 7.5%. Two thirds of these high-risk cases are represented by the paramedics.
27.9% of the population is young between the ages of 20 and 39 (Figure 1) with an average age of 48.5±14.4 years with no statistically significant difference between the two sexes ($p=0.2$) and a median of 47.0 years.
The age distribution of hepatitic patients C shows a modal class between 40 and 49 years (27.9%)

Figure 1: Distribution of Viral Hepatitis C Cases by Age and Sex



At the time of virological diagnosis, 82.1% of patients are divided into G1 and G2 with almost equivalent frequencies of 41.9% and 40.2% respectively.
Two-thirds of G2 cases are women (65.7%), whereas for G1, there is no statistical difference in the distribution of this genotype according to sex.

Figure 2 *: Distribution of VHC cases by genotype*

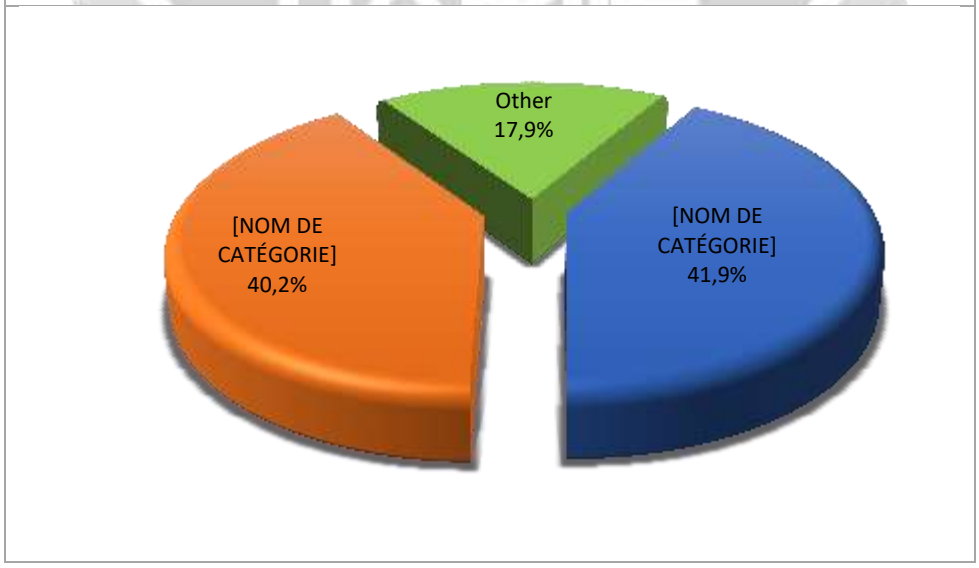
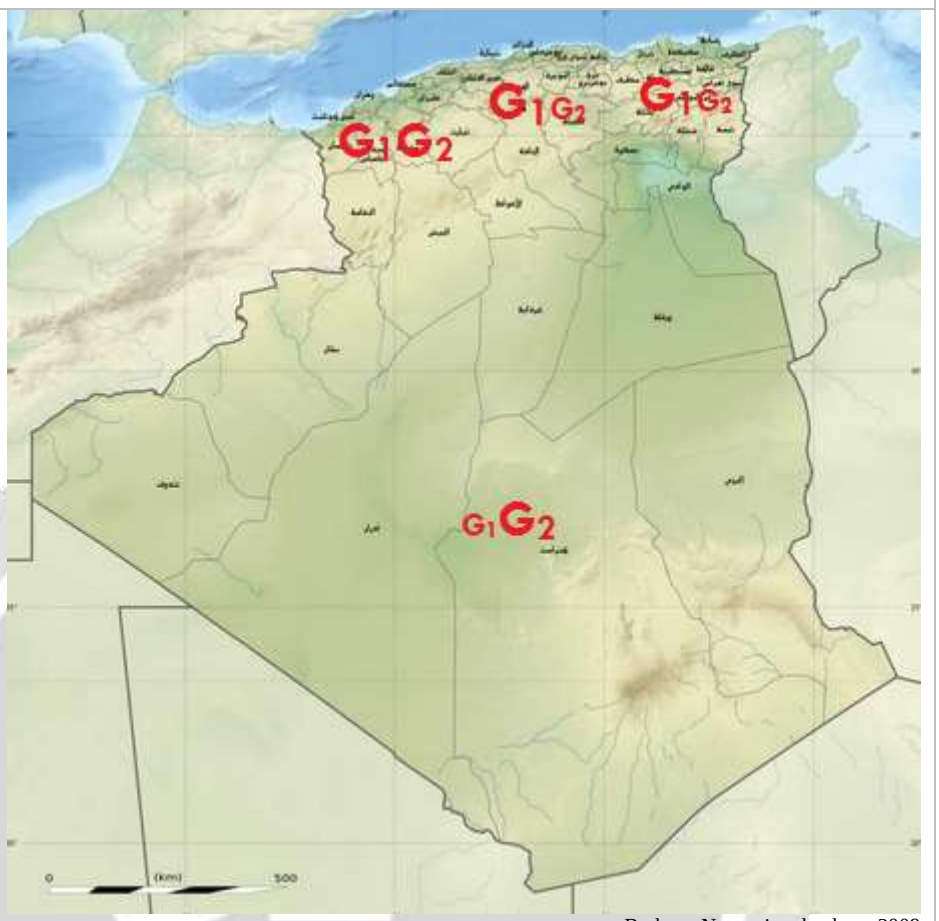


Figure 3 *: Genotype distribution of VHC cases in Algeria*

Our study



Berkane N. ; national cohort, 2009

Table 1: Characteristics of Viral Hepatitis C Cases

Parameter	***Number***	***%***
Men	235	39.6
Wives	359	60.4
Sex ratio	0.65	
Married Subjects	533	89.7
Average age± SD (years)*	48.5±14.4	
Median age (years)	47.0	
Average BMI± SD (kg/m2)*	25.9±4.2	
Overweight (BMI>25 kg/m2)	328	55.2
ALAT (average UI/L)	61.1	
Diabetes (type 1 or type 2)	117	19.7
Metabolic syndrome	98	16.5
Activity score		
A0 : absent	55	9.3
A1 : minimal	97	16.3
A2 : moderate	61	10.3
A3 : severe	29	4.9
Fibrosis score		
F0-F1 : minimal fibrosis	169	28.5
F2 : moderate fibrosis	160	26.9

F3-F4 : Severe fibrosis	180	30.3
Not done	85	14.3
Treated cases	563	94.8
Viral load (log10 IU/ml)	5.7 ± 1.1	
Serological viral response (SVR)	405	68.2
How to discover		
Systematic	253	42.6
Preoperative	46	7.7
Blood donation	35	5.9
Professional	19	3.4
Family	17	2.9
Prenuptial review	12	2.0
Pregnancy	4	1.2
Cytolysis	9	1.5
Asthenia	60	10.1
Jaundice	6	1.0
Likely mode of contamination		
Related to care (incriminated by patients)	360	60.6
Dental (incriminated by patients)	303	51.0
Surgeries (incriminated by patients)	108	18.2
Transfusions (incriminated by patients)	42	7.1
Care abroad	3	0.5
Traditional practices and piercing	88	14.8
Scarification	78	13.1
Hijama	75	12.6
Tattoo	13	2.2
Piercing	9	1.5
Exposed occupation	45	7.5

** SD: Standard deviation*

In our study population, cirrhosis is diagnosed in 30.3% of cases of which 50% are over 56.0 years old with a clear female predominance (sex ratio=0.78).

A quarter of cirrhotics are diabetic. Metabolic factors are found in 23.9% of cirrhotic cases. Care-related contamination (incriminated by patients) is the most common mode found in cirrhotic subjects in 65.6%. Traditional practices such as scarification, hijama and tattooing were reported in a quarter (25.0%) of subjects with advanced fibrosis F4. (Table 2)

Table 2: Characteristics of VHC Cirrhotics

Parameter	***Number***	*%*
Cirrhosis	180	30.3
Sex ratio	0.78	
Average age± SD (years)*	56.3±12.4	
Median age (years)	56.0	
Diabetes	51	28.3
Metabolic syndrome	43	23.9
Treated cases	157	87.2
SVR	95	52.8
Likely mode of contamination		
Care-related contamination	118	65.6
Traditional practices and piercing	45	25.0

Hepatocellular carcinoma (HCC) developed in 13 subjects of CVH or 2.2% with a sex ratio of 0.86. All cases were in the advanced fibrosis stage F3-F4 (Table 3)
G1 and G2 represent 77% of HCC cases. There were 10 deaths in our CVH population of which half (5 deaths) were in G2.

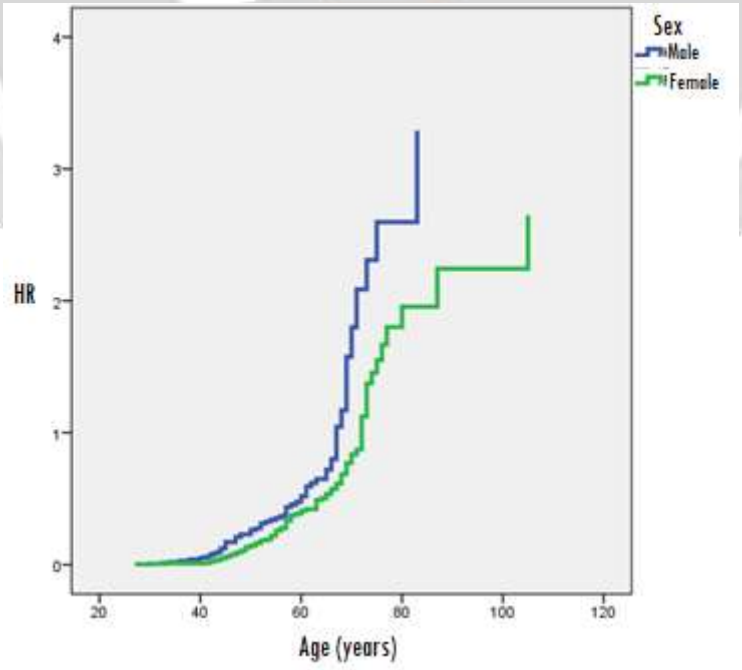
Table 3: VHC Patient Characteristics by Morbi-mortality

Complication	*HCC (n=13)*		*death (n=15)*	
Parameter	Nbre	%	Nbre	%
Sex				
Men	6	46.2	3	30.0
Women	7	53.8	7	70.0
Fibrosis stage				
F3-F4	13	100.0	10	100.0

Metabolic syndrome was found in 38.5% of carcinoma patients. There is a statistical relationship between metabolic syndrome and HCC ($p<0.05$). Patients with metabolic syndrome have a 3.3-fold risk of developing hepatocellular carcinoma (RR 3.3[1.05-10.3]).
There is a statistical relationship between metabolic syndrome and mortality in HVC patients ($p<0.03$) whose risk of death in the presence of metabolic syndrome is increased by 4.8 times.

Risk of cirrhosis in HVC cases by sex:
According to the Cox regression, the probability of progression from fibrosis stages to advanced stages (cirrhosis) is very high in men, reaching a hazard ratio (HR) of 1.5 at around 70 years of age, with a very rapid progression from 65 years of age. (Figure 4)

Figure 4: Risk of cirrhosis in HVC cases by sex



Predictive modelling of the occurrence of cirrhosis in HVC cases by the Cox model:

Table 4: Covariables included in Cox's Model: Stepwise Procedure

Co-variables	b	SE	Wald	*p*	HR	95%CI HR
Age (years)	0.03869	0.006413	36.3914	<0.0001	1.04	[1.03 – 1.05]
Age>40 years old	0,7919	0.3525	5.0453	0.0247	2.2	[1.1 – 4.4]
Arterial hypertension	0.6996	0.2185	10.2515	0.0014	2.0	[1.3 – 3.1]
Metabolic syndrome	0.4095	0.1972	4.3124	0.0378	1.5	[1.03 – 2.2]
HOMA≥3	0.8535	0.2395	12.7031	0.0004	2.3	[1.5 – 3.7]
A2-A3	0.4954	0.1738	8.1263	0.0044	1.6	[1.17 – 2.3]

It is estimated from the analysis of this table (Cox's model) that the necrotic-inflammatory activity "A2 - A3" multiplies the instantaneous risk of developing cirrhosis by 1.6. Similarly, this risk is multiplied by :
- 2.2 in subjects over 40 years of age
- 2.3 in the case of a HOMA score≥3
- 1.5 in the presence of a metabolic syndrome
- 2 if the patient is hypertensive.

The HR of age, which represents the progressive increase in risk per unit increase in age, is equal to 1.04: the instantaneous risk of cirrhosis increases by 4% for a one-year increase.

For a subject i, if we introduce all 6 variables into the model, the instantaneous risk function is such that :

$$H_i(t) = h_0(t)\exp(0{,}5_{A_2A_3}Z_{1i} + 0{,}8_{AGE>40}Z_{2i} + 0{,}9_{HOMA\geq 3}Z_{3i} + 0{,}4_{METABOLI\ SYNDROME}Z_{4i} + 0{,}04_{AGE}Z_{5i} + 0{,}7_{HTA}Z_{6i})$$

Figure 5: Probability curve of cirrhosis in VHC cases using Cox's model

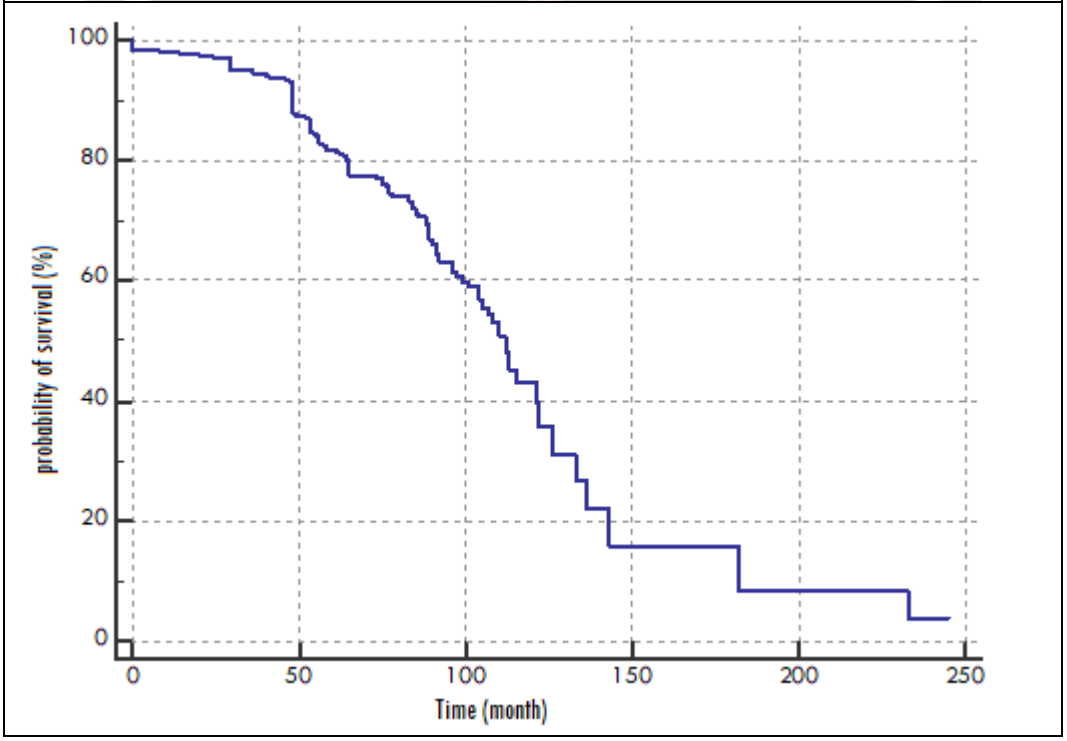
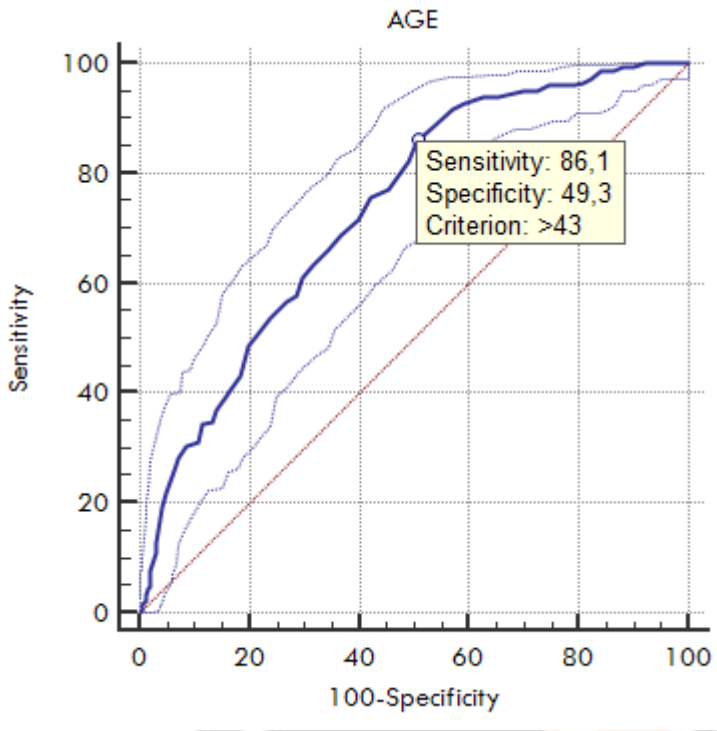


Figure 6: Age and Cirrhosis ROC Curve in VHC patients



Classification variable	Cirrhosis
Population size	594
Cirrhosis +	180
Cirrhosis -	414
Area under the ROC curve	0,74
95%CI	0.70 – 0.77
Z test	11.06
Meaning threshold p (area=0.5)	<0.0001
Index Youden J	0.3539
Threshold	>43ans
Sensitivity	86.11
Specificity	49.28
LR +	1.70
LR -	0.28

The threshold (inflection point) of the values of the age variable, determined in the ROC curve (figure 6), is estimated to be 43 years of age and above which the risk of cirrhosis is at its maximum. This conclusion is illustrated in the dot plot which shows that from this age (43 years) onwards the risk of cirrhosis is increased.
The test shows a statically significant ROC curve with a p<0.0001.
An age above 43 years is still of interest in the monitoring and management of VHC patients for the risk of cirrhosis, since the negative likelihood ratio is still low at 0.28

Predictive modelling of the occurrence of HCC in VHC cases by the Cox model:

For the predictive modelling study of HCC occurrence in patients with viral hepatitis C and among the variables that could be included in the model by the stepwise procedure, two variables were included that were very strongly associated with the occurrence of HCC for hepatitis C patients:
- Age progressively increases the risk of HCC occurrence by 8% per unit increase (one year).
- Diabetes increases the instantaneous risk of HCC by 9 times.
Antiviral treatment would play a role in reducing the instantaneous risk of HCC quantified as follows 1-0,2=0,8. Thus this reduction is estimated at 80%.

Covariable	b	SE	Wald	*p*	HR	95%CI HR
Age (years)	0.07788	0.01564	24.7922	<0.0001	1.08	[1.05 – 1.11]
Diabetes	2.2287	0.6679	11.1368	0.0008	9.3	[2.5 – 34.2]
Treatment (+)	-1.5350	0.5999	6.5483	0.0105	0.2	[0.07 – 0.7]

For a subject i, if we introduce both variables into the model, the instantaneous risk function is such that :

$$H_i(t) = h_0(t)\ \exp(0{,}08_{AGE}Z_{1i} + 2{,}2_{DIABETES}Z_{2i})$$

Figure 7: HCC Probability Curve in VHC Cases under Cox Model

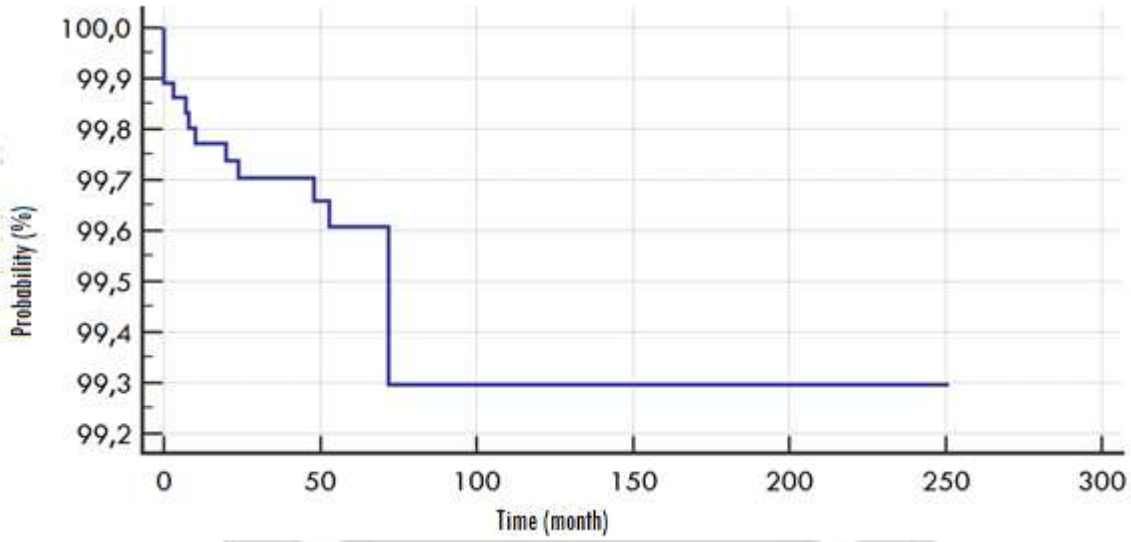
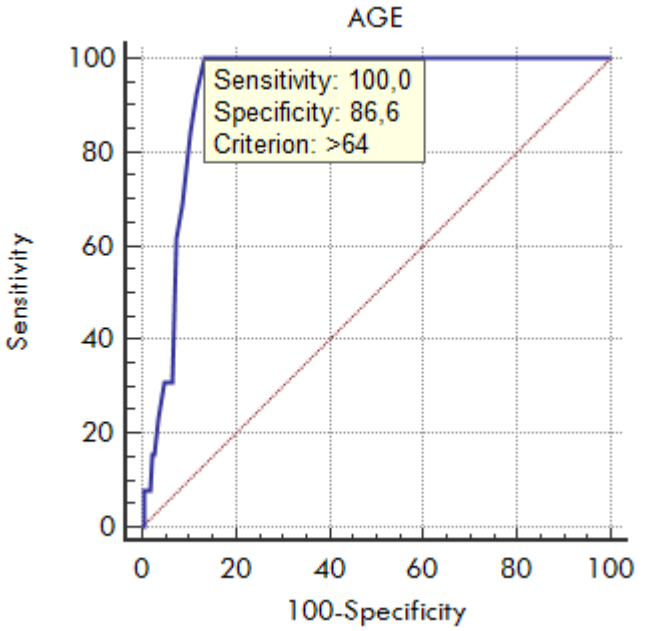


Figure 8: Age and HCC ROC Curve in VHC patients



Classification variable	HCC
Population size	594
HCC (+)	13 (2.2%)
HCC (-)	581 (97.8%)
Area under the ROC curve	0.93
95%CI	0.91 – 0.95
Z test	32.45
Meaning threshold p (area=0.5)	<0.0001
Index Youden J	0.87
Threshold	>64ans
Sensitivity :	100.0
Specificity :	86.57
LR+	7.45
LR -	0.00

The inflection point of the ROC curve is estimated to be 64 years, at which point the risk of HCC is at its highest. This result is illustrated in the dot plot which shows that all HCC cases are over 64 years of age.
The test shows a statically significant ROC curve with a $p<0.0001$.
The negative likelihood ratio is zero since the risk of HCC in our population of patients with CVH occurs from the age of 64 years.

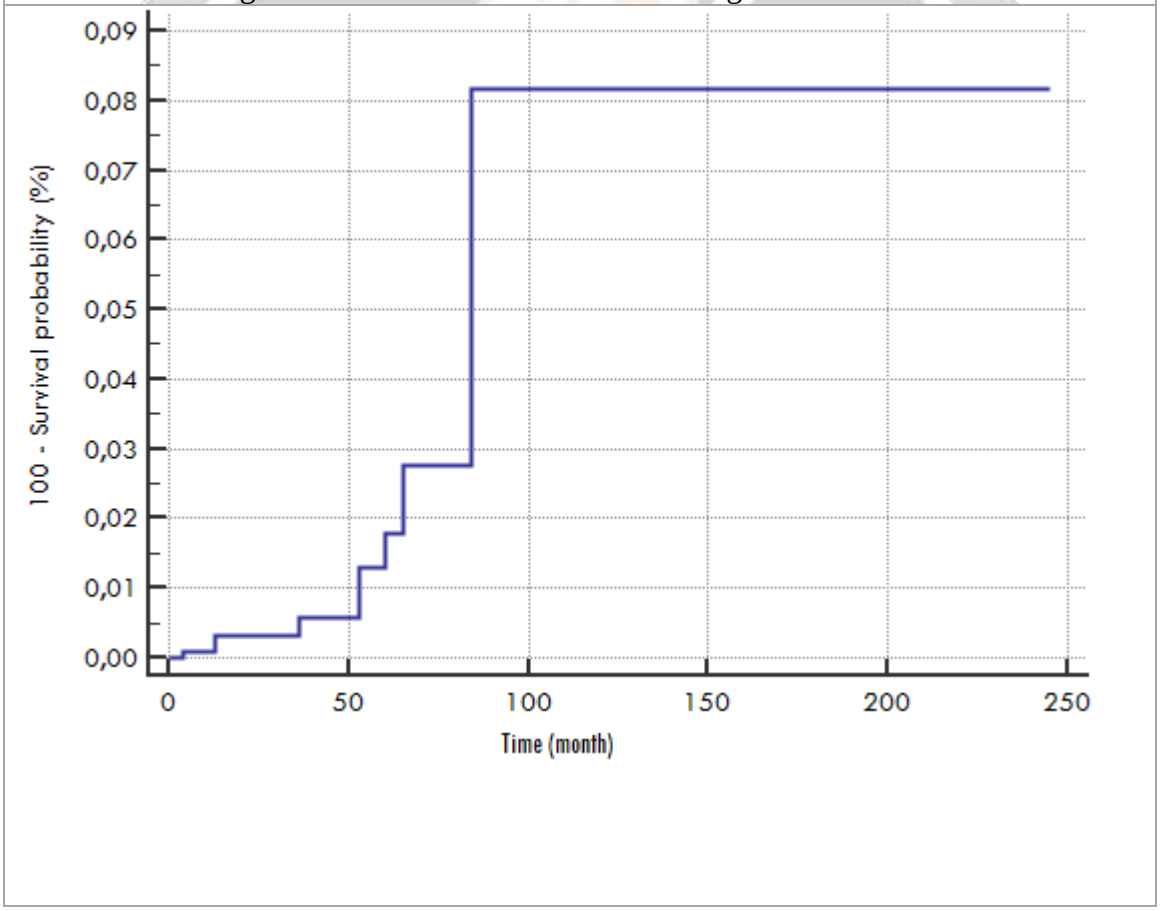
Predictive modelling of mortality in VHC cases by the Cox model:

For the mortality predictive modelling study and among the variables that could be included in the model by the stepwise procedure, 3 variables were included that were very strongly associated with the occurrence of death for hepatitis C patients.
Death is certain if "hepatocellular carcinoma" develops. The two other prognostic factors are diabetes, which multiplies this instantaneous risk by 6, and age, which increases it by 11% for a one-year increase.

Covariable	b	SE	Wald	*p*	HR	95%CI HR
Age (Years)	0.09869	0.01483	44.3171	<0.0001	1.11	[1.07 – 1.13]
Hepatocellular carcinoma	6.26	0.83	52.39	<0.0001	424.0	[83.1 – 2163.8]
Diabetes	1.7223	0.6594	6.8215	0.0090	5.6	[1.6 – 20.3]

$$H_i(t) = h_0(t)\exp(0{,}1_{AGE}Z_{1i} + 6{,}2_{HCC}Z_{2i} + 1{,}7_{DIABETES}Z_{3i})$$

Figure 9: VHC Survival Curve according to Cox's Model



Discussion:

In our study, we note a female predominance with a sex ratio of 0.65, contrary to what has been found in some studies such as that of : AMANI carried out in Oran in 2015[3], MAAMERI in Eastern Algeria, EL FEYDI in Morocco and the HEPATYS study[4].

There is a significant acceleration in the progression of fibrosis after the age of 45 in men and 55 in women, which corroborates the study by POYNARD who found a threshold of 50 years[5].
From this, HCV genotypes are distributed differently according to geographical areas with notably a balanced distribution of the two genotypes G1 (41.9%) and G2 (40.2%) in our patients residing in the west of the country, which corroborates the rates reported (45.8%) by the results of the AMANI study and (50%) of the national cohort of BERKANE.
In our series, G2 predominates in women ($p<0.05$) whereas there is no statistically significant difference between G1 and sex.
On the other hand, the distribution of genotypes in the centre and east of the country shows a clear predominance of genotype 1 with respective rates of 72.5 and 71.6%, which is in line with the majority of studies in European and American countries.
The distribution of genotypes in the Maghreb shows a predominance of genotype 2 in Morocco with a rate of 43.4% close to the rates found in our study in the west of the country, whereas genotype 1 is found in the Tunisian population at a higher rate of 75% close to the rates found in Annaba and Algiers respectively in the east and centre of the country.
In our series, the use of traditional practices was more reported in G2s than in G1s, which could constitute a targeted screening group.
The frequency of diabetes is low in our study population (19.7%) with a predominance of type 2 diabetes (11.3%) joining the national cohort (DEBZI, 2012) with 13%. There was a slight predominance of diabetes in the G1 group than in the G2 ($p=0.06$).
Cohort studies indicate a prevalence of diabetes of 20 to 50% depending on the series [6].
Other national and international studies such as that of MAMMERI in the east of the country (Annaba, 2012), BIZID (Tunisia, 2009) and MOUCARI (AFEF, 2007) find prevalences of type 2 diabetes of 7.8%, 23.0% and 7.0% respectively.
In multivariate analysis, the predictive factors for cirrhosis were inflammatory activity (A2-A3), age >40 years, diabetes mellitus and use of traditional practices; these 4 variables were identified as risk factors that act independently and best explain and predict the occurrence of cirrhosis, thus acting as prognostic factors.
Our results are consistent with the study conducted at the Beaujon Hospital in Clichy (France) on 348 patients hospitalised between 2006 and 2008 in which age and diabetes were identified as prognostic factors for post-HCV cirrhosis[7].

Indeed, our work seems to be the first of its kind in Western Algeria, falling into two categories.
The first is cognitive, with an approach to predictive modelling of the risk factors for the progression of fibrosis and the occurrence of complications, which is currently in full swing throughout the world, and its application to viral hepatitis C, the natural history of which is the subject of several research projects.
The second is to assist in public health decisions in the absence of observable data.

Conclusion:

Viral hepatitis C is therefore a public health problem in our country.
The epidemiology of this condition appears to be different in this country, and our results could lead us to think about new approaches to screening in our population that would have a very cost-effective economic impact given the very high cost of treatment.
Our study showed that the target population for screening can be made up of the subjects: Female sex, Married, 4rd decade of life, Use of traditional practices, Care (dental, transfusion, surgery, ...).
Our results confirm the extent of the epidemic of these viral hepatitis and the threat that the burden of its complications in terms of morbidity and mortality may pose to our health system in the short, medium and long term.

Conflict of interest: None declared.

Bibliographiques references:

[1] WHO Regional Committee for the Eastern Mediterranean , Morocco 2009

[2] M. LAHCENE ; 12° JFMC - Palais de la culture - Alger : 03 juin 2010

[3] Amani N. Evolution des patients porteurs d'une infection chroniquepost-hépatitique virale C sous traitement par bithérapie pégylée. Thèse de doctorat en médecine, Oran, 2015

[4] Bourliere Marc, Traitement De L'hépatite Chronique C Par PegInterferon Alfa-2a Et Rébavirine En Milieu Hospitalier Et Libéral : Résultats Des 2101 Malades Inclus Dans L'étude HEPATYS Communication Orale AFEF 2007

[5] Debzi N Et Al, Résultats Thérapeutiques Par Bithérapie Pegylée De La Cohorte Nationale Algerienne – Vhc – 2012

[6] Serfaty L, Capeau J. Hepatitis C, Insulin Resistance, And Diabetes: Clinical And Pathogenic Data. Liver Intern 2009

[7] Wilson LE et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. hepatology 2006;43:788-95

[8] Fartoux L et al. Impact of steatosis on fibrosis progression in patients with mild hepatitis C. hepatology 2005;41:82-7

[9] Mammeri A, Aspects Epidémiologiques, Cliniques Et Evolutifs Des Hépatites Virales C. Dans La Région D'ANNABA. Thèse Soutenue Publiquemente Le 23-12-2012

[10] Poynard.T : Epidémiologie Et Histoire Naturelle De L'hépatite Virale C. DU 2014 .Groupe Hospitalier Pitié Salpêtrière

[11] Serfaty L, Capeau J. Hepatitis C, Insulin Resistance, And Diabetes: Clinical And Pathogenic Data. Liver Intern 2009

[12] Hepato-gastro & oncologie digestive, SNFGE, AFEF et FFCD, Vol 23, N°1, Janvier 2016

[13] Easl Online Recommendations On Treatment Of Hepatitis C 2014. London : 49th Meeting Of Easl: April 2014

[14] Revue médicale suisse 2015;11(471):896–901

[15] Gower E et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014; 61(1Suppl) :S45-57

[16] Stratégie mondiale du secteur de la sante contre l'hépatite virale, 2016-2021. référence électronique: who.int/hepatitis/strategy2016-2021/ghss-hep/fr/

[17] Guessab, Epidémiologie Des Hépatites Virales Au Maghreb (ABCDE), Xxviiième Journées Nationales D' Hépato- Gastroentérologie Et d'Endoscopie Digestive et Xviiième Journées De Gastroentérologie d'Afrique Francophone, Alger 15/16/17 Décembre 2016

[18] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes : updated criteria and genotype assignment web resource. Hepatology 2014 ; 59 :318-27

[19] Berkane S. et al.; Hépatite C en Algérie : Caractéristique Epidémiologique, Etude rétrospective multicentrique d'une cohorte nationale avec infection VHC chronique , de 2007 à 2013.