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Cardiovascular risk stratification in patients with hepatitis C undergoing pharmacotherapy follow-up at the specialized services: A cross-sectional study

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Abstract

Objective: To evaluate the risk for the occurrence of possible coronary events in a period of up to 10 years in patients with hepatitis C undergoing pharmacotherapy follow-up and treated with direct-acting antivirals. In this way, to verify if there is a correlation between the possible intervening variables with the Framingham Risk Score (FRS) and whether the variables can predict Cardiovascular Risk (CVR) in patients**. Methods**: This is a cross-sectional and observational study, conducted in the municipality of Uruguaiana, southern Brazil. The data were collected from 71 medical records of patients with hepatitis C, who were being followed-up at the Viral Hepatitis Outpatient Clinic. CVR was evaluated from the FRS. The statistical analyses involved Student's t test for comparison between means, Pearson's chi-square for the association of CVR with categorical variables, and Pearson's or Spearman's correlation to assess correlations with intervening continuous variables, according to distribution. A multiple linear regression model was also used. For all cases, the significance level was considered when $p<0.05$. **Results:** CVR considered moderate/high was present in most patients. The use of antihypertensive drugs and the self-reported diagnosis of diabetes were markedly associated with the FRS result. Except for the time since diagnosis of hepatitis C, the other continuous variables evaluated were correlated with moderate/high CVR. The linear regression model was able to predict up to 62% of the CVR in patients with hepatitis C. **Conclusion**: The FRS has proved to be effective in the stratification of CVR in patients with hepatitis C. It's a simple tool and easily available to pharmacists who carry out the care of these patients. Thus, it is possible to prevent cardiovascular comorbidities that may be associated with hepatitis C.

Keywords: hepatitis c; cardiovascular risk; pharmaceutical services; diabetes mellitus; hypertension.

Estratificação de risco cardiovascular em pacientes com hepatite C em acompanhamento farmacoterapêutico no serviço especializado: um estudo transversal

Resumo

Objetivo: Avaliar o risco da ocorrência de possíveis eventos coronarianos em um período de até 10 anos em pacientes com hepatite C em acompanhamento farmacoterapêutico, tratados com antivirais de ação direta. Verificar se há correlação entre as possíveis variáveis intervenientes com o *Escore de Risco de Framingham* (ERF), e se estas variáveis são capazes de prever o Risco Cardiovascular (RCV) nos pacientes. **Métodos:** Trata-se de um estudo observacional transversal, realizado no município de Uruguaiana, no sul do Brasil. Os dados foram coletados a partir de 71 prontuários de pacientes com hepatite C, que estiveram em acompanhamento no Ambulatório de Hepatites Virais. O RCV foi avaliado a partir do ERF. A análise estatística envolveu o teste t de *Student* para comparação entre médias, Qui-quadrado de *Pearson* para associação do RCV com as variáveis categóricas e correlação de *Pearson* ou *Spearman* para avaliar correlações com variáveis contínuas intervenientes, de acordo com a distribuição. Também foi utilizado um modelo de regressão linear múltipla. Em todos os casos, o nível de significância foi considerado quando $p<0,05$. **Resultados:** O RCV considerado moderado/alto esteve presente na maioria dos pacientes. O uso de anti-hipertensivo e o diagnóstico autorreferido de diabetes foi marcadamente associado ao resultado do ERF. Com exceção do tempo de diagnóstico da hepatite C, as outras variáveis contínuas avaliadas foram correlacionadas ao RCV moderado/alto. O modelo de regressão linear foi capaz de prever em até 62% o RCV em pacientes com hepatite C. **Conclusão:** O ERF demonstrou ser eficaz na estratificação de RCV dos pacientes com hepatite C. É uma ferramenta simples e facilmente disponível aos farmacêuticos que realizam o cuidado desses pacientes. Assim, é possível prevenir comorbidades cardiovasculares que possam estar associadas à hepatite C.

Palavras-chaves: hepatite c; fator de risco de doenças cardíacas; assistência farmacêutica; diabetes mellitus; hipertensão.

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Introduction

Hepatitis C affects approximately 150 million people in the world, causing liver disorders that result in up to half a million annual deaths.[1] Chronic infection by the HCV virus is predominantly associated with countless extra-hepatic manifestations, which include cardiovascular diseases (CVDs).[2] In the world context, CVDs remain among the leading causes of death and represent half of all deaths due to chronic non-communicable diseases (CNCDs), causing nearly 17 million deaths per year.[3]

In 2013, the Brazilian Society of Cardiology, in line with the CNCD reduction targets proposed by the World Health Organization, published the I Brazilian Guidelines on Cardiovascular Prevention, with the objective of expanding prevention of CVD and modifying this epidemiological reality in Brazil.[4]

Since mid-20th century, assessing cardiovascular risk (CVR) is of great importance in the prevention of CVDs and interventions.[5] The *Framingham Risk Score* (FRS) is a good assessment method due to its simplicity and predictive ability to estimate CVD over ten years in people who do not have any overt coronary artery disease.[6]

On the other hand, the role of the clinical pharmacist is fundamental in preventing the occurrence of CVD in patients with hepatitis C. This professional can directly assist the multidisciplinary team, collecting information and offering the user various pharmaceutical services (such as screening and education in health, medication reconciliation and pharmacotherapy review, among others) to improve therapeutic results related to safety and efficacy of the medications.[7] The pharmaceutical intervention with the patient is part of the pharmacotherapy follow-up process, which aims at solving or preventing negative results arising from the use of medications. Diverse scientific evidence has shown that pharmaceutical care measures improve the patients' clinical and economic outcomes.[8]

Thus, the objective is to analyze the risk of occurrence of coronary events in up to 10 years in a group of patients with hepatitis C, under pharmacotherapy follow-up, with application of the *Framingham Risk Score*.

Methods

Study design

This is a cross-sectional and observational study, with data collection based on information contained in medical records of patients with hepatitis C, at the Viral Hepatitis Outpatient Clinic in the municipality of Uruguaiana, Rio Grande do Sul, Brazil.

Study locus and data collection period

The Viral Hepatitis Outpatient Clinic is linked to the Specialized Assistance Service in STIs/HIV, AIDS and Viral Hepatitis at the Municipal Health Secretariat and its objectives is to diagnostic and laboratory monitoring, as well as medical and pharmacotherapy treatment, thus promoting full attention to the needs of patients with viral hepatitis, in accordance with the Therapeutic Protocols and Guidelines established by the Ministry of Health.

The Viral Hepatitis Outpatient Clinic is composed of a multidisciplinary team that includes pharmacists trained in the pharmacotherapy follow-up of patients with hepatitis C. During treatment, the pharmacists dispense Direct-Acting Antiviral (DAA) drugs and monitor the progress of the monthly consultations, where requests and evaluations of laboratory tests are conducted in order to monitor the pharmacological treatment, as well as investigation of the use of other drugs for other comorbidities, in addition to hepatitis C. In this way, it is possible to identify possible and potential interactions and other drug-related problems (DRPs) that may arise, thus promoting rational use of medications (RUM).

The collection period for the information contained in the patients' medical records was conducted between January 2018 and June 2019. All the necessary information for this study was collected at the beginning of the treatment with DAAs.

Eligibility criteria

The patients included were those with a positive HCV reagent and detectable RNA-HCVRNA-HCV, age over 18 years old, and undergoing pharmacotherapy monitoring in the service. The individuals excluded were those whose medical records lacked a description of the necessary criteria for the assessment proposed.

Data collection

All the records in the medical charts of the patients undergoing pharmacotherapy monitoring during the study period were assessed. To compose the profile of this sample, the following factors were considered: gender, age, family history of cardiovascular diseases (paternal and/or maternal), use of medications (antihypertensive and antidiabetic drugs), consumption of alcoholic beverages (never drank; yes, but stopped; currently consumes alcoholic beverages), physical activity (yes/no) and time since hepatitis C diagnosis (in years).

Stratification of the cardiovascular risk

Cardiovascular risk was stratified using the *Framingham Risk Score* (FRS),[9] whereby it was possible to calculate the risk of cardiovascular disease, based on six coronary risk factors, namely: age, smoking habit, total cholesterol, blood pressure, HDL-cholesterol and diabetes mellitus (previous diagnosis established by the use of hypoglycemic drugs and/or blood glucose ≥ 100 mmHg).[10] The percentage risk of CVDs in 10 years was calculated by the total points. When the score result was < 10% of risk events, it was considered as low risk; between 10% and 20%, as medium risk; and > 20% was considered as high risk.[9]

Statistical analysis

Data normality was analyzed by means of the *Kolmogorov-Smirnov* test. For all the continuous variables that presented normal distribution, the data were presented as mean and Standard Deviation (SD); the categorical variables were expressed as absolute numbers and percentages.

To verify the association of possible risk factors with CVR, the sample was first divided into two groups: low risk of cardiovascular disease and moderate/high risk of cardiovascular disease. Subsequently, analyses were performed by means *Pearson*'s chi-square test for the categorical variables and through the *Student*'s t test to compare the mean values.

Pearson's (parametric data) or *Spearman*'s (non-parametric) correlation tests were used to assess possible correlations of intervening continuous variables with the risk of cardiovascular disease. The correlation coefficients were interpreted considering weak (from 0.1 to 0.3), moderate (from 0.4 to 0.7) and strong (from 0.8 to 1) correlation strengths.[11] After a univariate analysis, the influence of potential predictive variables was determined by using multiple linear regression. To select the variables in the regression model, the *Enter* method was used; consequently, the variables were manually included one by one. The cutoff point established for the variables to enter the model was p-value < 0.05.

All the data were introduced into electronic spreadsheets and the statistical analyses were performed in the IBM SPSS® (*Statistical Package for Social Sciences*) software, version 25. In all the cases, the differences were considered statistically significant when p < 0.05.

Ethical aspects

This study was approved by the Research Ethics Committee (*Comitê de Ética em Pesquisa*, CEP) of the Federal University of Pampa, registered under CAAE 06063118.1.0000.5323 according to resolution No. 466/12.[12] The researchers signed the DUCF (Data Use Commitment Form) to ensure confidentiality of the patients' personal data. After data collection, the names of the individuals were substituted with an identification number.

Results

During the study period, 92 patients were considered eligible, having their medical records evaluated On the other hand, 21 patients were excluded for not presenting the necessary information for the analyses performed.

The mean age of the 71 patients that were suitable for inclusion in this study was 56.4 years old, varying from 34 to 76. In relation to the 10-year risk for coronary diseases, in general, the presented a medium risk range (10%-20%) with a mean risk value of 11.5. High risk for cardiovascular diseases was present in 15.5% of the patients with Hepatitis C, and the percentage for moderate risk was 36.6%.

The time between Hepatitis C diagnosis and beginning of treatment with Direct-Acting Antivirals presented a mean of 5.7 years. The characterization of the sample is presented in Table 1, as well as the patients' habits.

The *Spearman* analysis showed that there is a moderate correlation between CVR and the levels of total cholesterol and fasting glucose, evidencing that the higher these values, the greater the risk of developing coronary heart disease in 10 years. This was also noticed in *Pearson*'s correlation, where the results presented a moderate and positive correlation strength, for the age and systolic blood pressure variables. On the other hand, HDL-c presented an inverse correlation coefficient, indicating that, as HDL-c increases, the risk of cardiovascular diseases is reduced (Table 2).

The multiple linear regression analysis resulted in a significant regression model to foresee the cardiovascular risk (p<0.05), showing that the variables evaluated would explain up to 62%of the cardiovascular risk (R^2 = 0.628; p<0.05). In this case, variables such as age, systolic blood pressure, total cholesterol, HDL-c and diabetes diagnosis were related with the CVR, with a significance level of <0.05.

Table 1. Characterization of the study sample.

Variables evaluated	Total sample (n=71)	Low Risk of CVDs (n=34)	Moderate/ High Risk of CVDs (n=37)	p-value*
Gender n (%)				
Male	39	17 (50,0)	22 (59.5)	0.424
Female	32	17 (50,0)	15 (40.5)	
Smoking habit n (%)				
Never smoked	36	20 (58.8)	16 (43.2)	0.265
Yes, but stopped	21	7 (20.6)	14 (37.8)	
Active smoker	14	7 (20.6)	7 (18.9)	
Consumption of alcoholic beverages n (%)				
Never drank	22	9 (26.5)	13 (35.1)	0.495
Yes, but stopped	36	17 (50.0)	19 (51.4)	
Currently drinks	13	8 (23.5)	5 (13.5)	
Diabetes n (%)				
No	43	25 (73.5)	18 (48.6)	0.032
Yes	28	9 (26.5)	19 (51.4)	
Family history of CVDs n (%)				
No	19	12 (35.3)	7 (18.9)	0.119
Yes	52	22 (64.7)	30 (81.1)	
Sedentary lifestyle n (%)				
Yes	49	23 (67.6)	26 (70.3)	0.811
No	22	11 (32.4)	11 (29.7)	
Hypoglycemic agents n (%)				
No	56	29 (85.3)	27 (73.0)	0.204
Yes	15	5 (14.7)	10 (27.0)	
Antihypertensive drugs n (%)				
No	41	24 (70.6)	17 (45.9)	0.036
Yes	30	10 (29.4)	20 (54.1)	
Time since diagnosis (years) Mean (SD)		5.71 (3.52)	5.49 (5.31)	0.840**

SD: Standard Deviation. CVDs: Cardiovascular Diseases Statistical Treatment: Data descriptive analysis. Results presented as absolute numbers and percentages and as Mean ± SD. *Chi-square test. **Student's t test. Significance level p<0.05.

Table 2. Assessment of the patients' characteristics and correlation with Cardiovascular Risk

Domains evaluated	Mean (SD)	Median (variation)	Correlation with CVR	p-value
Age	56.4 (9.2)	56.0 (34.0 – 76.0)	0.559	0.000
Time since diagnosis	5.6 (4.5)	4.0 (2.0 – 23.0)	-0.071	0.556
SBP	136.1 (21.9)	135.0 (99.0 – 206.0)	0.532	0.000
HDL-c	45.4 (13.9)	45.0 (12.0 – 82.0)	-0.218	0.034
TCh	157.3 (44.0)	148.0 (101.0 – 362.0)	0.410*	0.000
FG	104.4 (39.5)	93.0 (68.0 – 290.0)	0.376*	0.001

BMI: Body Mass Index; SBP: Systolic Blood Pressure; HDL-c: High Density Lipoprotein. TCh: Total Cholesterol; FG: Fasting Glycaemia.

*Spearman's correlation. In the domains not indicated, Pearson's correlation was used.

Table 3. Multiple linear regression model including predictive variables and Framingham Score.

Parameters	B	B standard error	p-value
Constant	-34.253	5.216	0.000
Age	0.410	0.068	0.000
Gender	2.218	1.241	0.079
SBP	0.131	0.029	0.000
TCh	0.052	0.013	0.000
HDL-c	-0.182	0.042	0.000
Diabetes	3.411	1.210	0.006
Smoking Habit	1.478	1.466	0.317

B: Non-standardized coefficient; SBP: Systolic Blood Pressure; TCh: Total Cholesterol; HDL-c: High Density Lipoprotein.

Discussion

Estimates of cardiovascular risk determination in patients with hepatitis C are important measures in an attempt to control and minimize possible cardiovascular events that may debilitate the patient or lead to their future death. As already verified in another cross-sectional study, it was also possible to observe that the patients with positive HCV tend to present an intermediate risk range, as identified in our study.[13] Cardiovascular risk was significantly associated with HCV infection, which makes it highly important to initiate antiviral therapy regardless of the degree of liver damage, with the possibility of improving the risk of cardiovascular disease and liver complications resulting from chronic infection.[13]

The analysis of a population with HCV showed that patients treated with DAAs had a significant improvement in some CVR biomarkers.[14] The treatment with DAAs significantly reduced the number of cardiovascular events, regardless of the degree of liver fibrosis, contributing clinical and economic benefits.[15]

In addition to that, our results showed that most of the patients were classified as with some type of CVR, according to the classical FRS risk factors. The low risk found in 47.8% (n=34) of the patients is only based on Framingham's traditional criteria.

Currently, the reality of the population includes other risk factors that can be related to the higher degree of CVR, as observed in our study. In this case, the use of antihypertensive medications was significantly associated with CVR, as well as with occurrence of diabetes. Other studies show that nearly one-fifth of the patients with hypertension (21,5%) were classified as with high CVR, and having a previous diabetes diagnosis is considered as high CVR.[16]

Thus, the use of FRS modified by the inclusion of emerging and aggravating risk factors sensitizes risk prediction, when compared to the traditional score, thus making CVR detection more interesting when incorporating variables related to lifestyle and family history.[17]

Although only the use of antihypertensive drugs and the diagnosis of diabetes have been significant in the association with CVR, new assessments should be considered, as the intention of current Medicine is, increasingly, to use models to estimate risks, with the purpose of establishing goals that assist in the therapeutic decision.[18]

Active smoking was a variable equally distributed among the people who were at low risk and those who were at moderate/high risk, showing no correlation with CVR in this sample. Likewise, alcohol consumption, family history of cardiovascular disease and time since diagnosis were factors that were not associated with moderate/high risk of CVD.

Regarding physical activity, 69% of the patients presented low levels or even sedentary lifestyles. This fact can lead to low energy expenditure and contribute to the overweight/obesity found in patients with hepatitis C, in this same study locus, in which the results were previously published.[19] Bertani et al. (2016) believe that it is possible that the high percentage of body fat is a relevant risk factor in the development of heart disease and complications in individuals who have chronic hepatitis C. In addition to that, these comorbidities exert a direct impact on the quality of life of these patients.[20]

As expected, in this study, CVR increased with age, and total cholesterol and blood pressure also showed a moderate correlation with FRS, being similar to other studies where Metabolic Syndrome (MS) parameters such as blood pressure and blood serum fasting glycaemia were associated with a significantly increased risk of CVD,[21] as well as total cholesterol, which consequently influences other diagnostic parameters of MS such as waist circumference, fasting glucose, and triglycerides.[22]

The model evaluated through linear regression included the Framingham risk variables and was able to predict 62% of the cardiovascular risk in this group of patients with hepatitis C. Therefore, risk stratification using *Framingham Risk Score* proved to be an effective and simple strategy in the predictive assessment of CVD. Therefore, this evaluation method offers easy access to clinical pharmacists and is important for devising the care plan for patients with Hepatitis C.

Regarding the new FRS predictive studies, the use of models with *Machine learning* seems to be superior to the standard linear regression models.[23] These innovative tools are important in the health field; however, it is necessary to gain knowledge that is not commonly found in pharmacists and other health workers.[24] Consequently, the method used in our research also presents advantages in relation to the simplicity of the risk stratification instrument.

Some observations must be made regarding the limitations of this study. The study design does not allow us to determine causality, as we lack the information about the order of the events. In addition to that, the data used in this research were collected in a retrospective manner from the elements contained in the medical records of a convenience sample. Thus, it cannot be asserted that the lipid and glycemic profile followed collection standardization. Information on the consumption of alcoholic beverages and cigarettes referring to the amount and period, and on physical activities regarding the frequency and intensity of exercise were not available. This study included cases from a single institutions, with characteristics that are inherent to the care provided to patients with Hepatitis C and, for this reason, it is not possible to generalize findings to other situations.

Conclusion

The presence of comorbidities and complications associated with hepatitis C makes the care of these patients even more challenging. In this study, FRS proved to be a simple and easily available assessment method for the clinical pharmacists who work in the pharmacotherapy follow-up of patients with hepatitis C. Its use allowed verifying the presence of a moderate/high

level for the risk of occurrence of cardiovascular events in up to 10 years in the group of patients evaluated. Therefore, knowing the characteristics of hepatitis C patients and its cardiovascular risk can assist pharmacists in the execution of care, detecting and preventing drug-related problems with the goal of achieving better therapeutic outcomes regarding safety and efficacy of the medications.

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Collaborators

MBR, MIZ, RAB, LDQ and EAB participated in the conception of the article, data analysis and interpretation, writing, critical review and approval of the final version of the article. The authors are responsible for all the aspects of the paper in ensuring the accuracy and integrity of any part of the article.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding this article

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