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Research Article

Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C

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Abstract

Cardiovascular diseases are the most common and important cause of morbidity, hospitalisation, and mortality in Poland and worldwide. Hence, in recent years there has been a strong emphasis on preventive cardiology, aimed at early identification and prevention of cardiovascular risk factors and lifestyle changes. The main classical risk factors include lipid disorders, hypertension, diabetes, obesity, and smoking. A new non-classical risk factor is HCV infection.

The study group consisted of 320 patients with a mean age of 43 years, diagnosed with chronic hepatitis C. In the study group, ischaemic heart disease was diagnosed in 4 patients, representing 1.25%. Six people had a history of ischaemic stroke, representing 1.87% of the study group.

Among the subjects, the most common cardiovascular risk factor was hyperlipidaemia (28%); there was no correlation with the severity of liver fibrosis for total cholesterol, LDL fraction, or TG, but more advanced liver fibrosis was observed in patients with low HDL fraction cholesterol values. Hypertension was present in 25% of patients and occurred in patients with more advanced liver fibrosis and steatosis. Diabetes was found in 11,56% of patients, also the mean fasting glucose level was elevated and was associated with more advanced liver fibrosis. The majority of patients were overweight and 32% were diagnosed as obese. The mean CRP value was 1.73 which may indicate moderate -cardiovascular risk.

The results obtained may contribute to the awareness of physicians and the attempt to create recommendations for comprehensive - interdisciplinary care of patients chronically infected with HCV, concerning the need for systematic periodic examinations to assess individual cardiovascular risk factors, with the aim of prevention and early prevention of cardiovascular events.

Introduction

Atherosclerotic Cardiovascular Disease (ASCVD), including ischaemic heart disease, ischaemic stroke, and peripheral vascular disease, is the most common and important cause of morbidity, hospitalisation, and mortality in Poland and worldwide and is still a current problem for modern medicine. Despite advances in diagnosis and both conservative and invasive treatment, cardiovascular disease prevention aimed at reducing risk factors remains a problem [1-4].

The main classical risk factors for the development of

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cardiovascular disease in Poland include lipid disorders, hypertension, obesity, diabetes, and smoking. New non-classical risk factors also include infectious factors, such as influenza virus infection and Human Immunodeficiency Virus (HIV) infection.

In recent years, hepatitis C virus (HCV) infection has been identified as a possible cause of the development of cardiovascular disease [5-10].

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) worldwide, contributing to poorer quality and length of life. Despite highly effective non-interferon therapies with direct-acting antiviral agents (DAAs), HCV is still a current medical problem.

The risk of HCV infection is due to the high spread of the virus in the population, the long-standing sparse or asymptomatic course, extrahepatic manifestations of HCV infection, the low detection rate, and the lack of nationwide screening programmes, and the lack of a vaccine [11-14].

Studies in recent years show that HCV infection also leads to the development of metabolic disorders, which play an important role as a risk factor for the development of cardiovascular disease. The observable influence of HCV on the development of obesity, insulin resistance, the development of diabetes, lipid disorders, or hepatic steatosis has led some authors to call metabolic disorders in the course of HCV infection the "metabolic-viral syndrome", and hepatic steatosis is described as an organ form of the metabolic syndrome [15-20].

In recent years, there has been increasing discussion of the extrahepatic manifestations of HCV infection, including its possible influence on the development of cardiovascular disease, hence the observed increased incidence of cardiovascular disease in patients with hepatitis C has contributed to the identification of HCV as a new risk factor for cardiovascular disease, and its occurrence as an extrahepatic manifestation of HCV infection. The potential role of HCV as a risk factor for the development of cardiovascular disease is complex. On the one hand, infection directly leads to chronic inflammation, contributing to the development of vascular atherosclerosis and vascular endothelial dysfunction; on the other hand, HCV infection indirectly leads to the development of other key risk factors - insulin resistance, pre-diabetes, diabetes, obesity, lipid disorders, hypertension or chronic kidney disease [11,21-23].

The aforementioned metabolic abnormalities described in HCV infection are similar to those observed in the so-called metabolic syndrome, which is recognised today as a major cause of the increased risk of cardiovascular disease [15].

In view of the above, the aim of this analysis was to analyse the prevalence of cardiovascular risk factors among a population of Polish patients with chronic hepatitis C according to sex, age, stage of liver fibrosis, duration of infection, and HCV genotype.

Taking into account the impact of chronic HCV infection on the risk of developing metabolic disorders and the risk of developing cardiovascular disease, the results obtained may contribute to increasing the awareness of physicians and attempts to create recommendations for comprehensive - interdisciplinary care of patients with chronic HCV infection, concerning the need for a change in lifestyle and the systematic performance of periodic tests to assess blood glucose levels (fasting glycaemia, oral glucose load test -OGTT), lipidogram, as well as blood pressure measurement, control of body weight and waist circumference, with the aim of prevention and early prevention of cardiovascular events.

Purpose of the work

The aim of this study is to analyse the prevalence of selected cardiovascular risk factors and the incidence of cardiovascular disease among patients with chronic hepatitis C and to assess their association in relation to gender, age, duration of infection, stage of liver fibrosis, and HCV genotype.

Material and methods

The study group consisted of 320 patients of both sexes, 149 women (46.56%) and 171 men (53.44%) aged between 21 and 93 years (mean age 43 years) with chronic hepatitis C. All diagnosed and treated patients were hospitalised at the Regional Observational and Infectious Diseases Hospital in Bydgoszcz between 2018 and 2024 (Table 1).

The analysis was based on a retrospective statistical evaluation of clinical data - a detailed review of patients' medical histories.

Medical records were analysed for cardiovascular risk factors: total cholesterol, LDL, HDL, triglycerides, glucose, body weight, body mass index - BMI and glomerular filtration rate - GFR, C-reactive protein - CRP, and smoking. The degree of liver fibrosis and steatosis, HCV genotype, and time since the detection of HCV infection - up to 5 years, between 5 and 10 years, and more than 10 years - were also analysed.

Each patient's medical history was analysed for cardiovascular disease - hypertension, ischaemic heart disease, myocardial infarction, previous coronary angioplasty, previous coronary artery bypass grafting (CABG), stroke or TIA, peripheral vascular disease (carotid atherosclerosis, lower limb atherosclerosis, previous lower limb artery angioplasty, and aortic aneurysm) and metabolic disease - diabetes, dyslipidaemia. Also, a history of family history of cardiovascular disease in men < 55 years of age and women < 60 years of age was taken.

The degree of liver fibrosis and steatosis was assessed by liver elastography performed by fibroscan with Echosens' FibroScan

Table 1: Basic descriptive statistics for age and BMI.

N 320	M	Me	Mo	SD	γ	K	Min	Max
Age (years)	43.40	40.00	31.00[a]	13.31	1.14	.796	21.00	93.00
BMI (kg/m)[2]	26.47	25.73	22.00[a]	4.73	.475	-.29	16.70	39.91

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Expert 630 and Compact 530. The assessed parameters LSM by VCTE - Liver Stiffness Measurement by Vibration Controlled Transient Elastography expressed in kPa and CAP - controlled attenuation parameter expressed in dB/m, were respectively converted to a degree of fibrosis and steatosis using Echosens' validation for HCV infection.

The determination of HCV RNA and HCV genotype was performed in standardised laboratories by PCR and nucleic acid hybridisation methods.

The analysis performed had some limitations in the overall assessment of cardiovascular disease risk factors, as it was based on the analysis of medical records and the collection of patients' medical history. Limitations include the lack of waist circumference measurement, non-HDL cholesterol and apolipoprotein A (apoA) and B (apoB) levels, carotid artery Doppler ultrasound to measure intima-media complex thickness (IMT, intima-media thickness), computed tomography coronary artery angiography (CCTA, contrast computed tomography angiography) or coronary artery calcification index (CAC, coronary artery calcium) assessment to detect subclinical features of cardiovascular disease. However, as patients did not report clinical symptoms, these tests were not performed and the study was a retrospective medical history review. Medical history was reviewed for cigarette smoking, but electronic cigarette use and alcohol consumption, type of diet and frequency and type of physical activity, and environmental exposures (air pollution, soil, noise levels) were not assessed.

Statistical methods

The results were presented as mean ± standard deviation for quantitative data and as counts expressed in numbers and percentages for qualitative data. Normal distribution of the data was checked using the Shapiro-Wilk test. When the data met the assumptions of parametric analysis for comparing two dependent variables, either the Student's t-test for dependent samples or the Wilcoxon paired rank-order test was used when the data did not have a natural distribution and/or homogeneous variance. Pearson's chi^2 test was used to compare abundances. Due to not meeting the assumptions for the Student's t-test for independent samples, the non-parametric U-Mann -Whitney rank-sum test was also used. The Leveve test was also used to check the homogeneity of variance,

On the other hand, quantitative data were subjected to correlation analysis using Pearson's correlation coefficient for data with a normal distribution or Spearman's rank correlation coefficient for data that did not meet the assumption of normality of distribution. Linear regression and analysis of covariance (ANOVA/ANCOVA) were used in the statistics to account for confounding factors. The level of statistical significance was taken as $p < 0.05$. Statistical analysis was performed using STATISTICA 12.0, StatSoft, Inc. (2014), www.statsoft.com (StatSoft Poland, Krakow, Poland).

Results

The study enrolled 320 patients, of both sexes, aged between 21 and 93 years (mean age 43 years). In the study group, the mean value of liver elasticity was 10.35 kPa, corresponding to fibrosis at level F3 according to the Metavir scale. The level of hepatic steatosis, on the other hand, averaged 223.89 dB/m, corresponding to steatosis at level S0 according to the Brunt scale.

Based on the analysis of medical records in the study group, ischaemic heart disease was diagnosed in 4 patients, representing 1.25% of the study group, including myocardial infarction in 3 patients (0.94%), 2 patients underwent percutaneous coronary angioplasty and 1 patient CABG. Six subjects had a history of stroke, representing 1.87% of the study group. Patients in the study group, following cardiovascular incidents, were administered the following medications: 4 patients received a beta-blocker (bisoprolol at a dose of 5 mg), 1 patient received nebivolol at a dose of 5 mg, 4 patients were administered ramipril at 5 mg, and 2 patients received telmisartan at a dose of 80 mg. Additionally, 10 patients received statins (atorvastatin at 20 mg for 6 patients and at 40 mg for 2 patients, rosuvastatin at 10mg for 2 patients). One patient also received ezetimibe, and all patients were given acetylsalicylic acid at a dose of 75 mg. There was no family history of early cardiovascular disease - <55 years of age in men and <60 years of age in women.

Among the subjects, the most common cardiovascular risk factor was hyperlipidaemia, which was treated in 88 subjects, representing 28% of the study group. Hypertension was present in 80 subjects (25%), cigarette smoking was present in 67 subjects (20.94%), and more often in men. Hyperlipidemia was treated in 70% of patients with statins, primarily atorvastatin at doses from 10 to 40 mg and rosuvastatin from 10 to 20 mg. About 20% received a combination of a statin with ezetimibe, 5% received ezetimibe alone, and the remaining patients were given fenofibrate at doses of 160 and 200 mg.

For patients with hypertension, combination therapy was commonly used. ACE inhibitors, mainly ramipril at doses from 2.5 mg to 10 mg, were combined with a diuretic: indapamide at 1.5 mg for approximately 30% of participants, or hydrochlorothiazide at 12.5 mg for around 15% of participants, or combined with a calcium channel blocker, amlodipine at 5 mg, in about 20% of cases. Additionally, 10% of patients used ARBs (angiotensin II receptor blockers) — telmisartan at doses from 40 to 80 mg or valsartan at 160 mg. Beta-blockers were used by 35% of patients, either bisoprolol at doses of 5 mg -10 mg or nebivolol at 2.5 mg - 5 mg. Approximately 5% used loop diuretics, such as furosemide or torsemide 10 mg.

Type 2 diabetes was found in 37 patients, representing 11.56% of patients in the study group. Diabetes was more common in men. 74% of patients received metformin at doses ranging from 500 mg to 1000 mg, usually twice daily. 8% were treated with SGLT2 inhibitors — empagliflozin at 10 mg, 14% with sulfonylurea derivatives — glimepiride at doses of 2 mg and 3 mg, 4% received insulin therapy, and 1% received GLP-1 analogs — liraglutide

The mean fasting glucose level in the study group was 100.40 mg/dl (SD = 23.12 mg/dl), mean total cholesterol 173.98

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mg/dl (SD = 38.18 mg/dl), LDL fraction 98.85 mg/dl (SD = 39.11 mg/dl), HDL fraction 52.81 mg/dl (SD = 15.36 mg/dl) and TG 123.32 mg/dl (SD = 51.17 mg/dl).

In the study group, the majority of patients were overweight with a mean BMI of 26.47kg/m² (SD = 4.73 kg/m²), a minimum of 16.70 kg/m², and a maximum of 39.91 kg/m². Obesity was diagnosed in 27.14% of the subjects.

The concentration of c reactive protein - CRP - averaged 1.73 mg/l.

Renal function determined by glomerular filtration rate - GFR showed an average of 103.34 ml/min/1.73m². Five patients in the study group had chronic kidney disease with GFR < 60 ml/min/1.73 m², and impaired glomerular filtration did not correlate with the amount of hepatic steatosis and fibrosis (Tables 1-4).

In the first step of data analysis, quantitative data related to descriptive statistics were calculated and interpreted: age, BMI, total cholesterol, LDL, HDL, TG, glucose, GRF, CRP, HCV RNA, LSM, and CAP.

In the study group (N = 320), the mean age was just over 43 years (M = 43.40; SD = 13.31) and the median was 40, meaning that 50% of the subjects were under 40 years of age. The most common ages were 31 and 37, with 20 respondents each declaring this age. The standard deviation SD = 13.31 indicates that the majority of respondents were between 30 and just under 57 years of age. The skewness γ is right-skewed and indicates that the age of the subjects was mostly below average.

Table 2: Basic descriptive statistics for total cholesterol, LDL, HDL and glucose.

N 320	M	Me	Mo	SD	γ	K	Min	Max
Total cholesterol (mg/dl)	173.98				.379	-.110	85	267
LDL (mg/dl)	98.85	93.50	51	39.11	.88	.73	37	213
HDL (mg/dl)	52.81	54.00	43[a]	15.36	.54	.00	25	103
Glucose (mg/dl)	100.40	97.00	90	23.12	3.07	17.28	66	260
TG (mg/dl)	123.32	115.00	156	51.17	1.12	1.77	42	321

Table 3: Descriptive statistics for GRF, CRP, HCV RNA.

N 320	HCV RNA	GFR (ml/min./1.73m²)	CRP (mg/l)
Average	1.8911E+007	103.34	1.726
Median	1.5650E+006	102.00	.700
Dominant	1.12E+006	102	.6
Skewness	12.918	.607	5.194
Kurtosis	178.667	3.660	33.078
Minimum	1.57E+003	23	.0
Maximum	2.60E+009	232	24.0

Table 4: Descriptive statistics for LSM and CAP.

N 320	M	Me	Mo	SD	γ	K	Min	Max
LSM (kPa)					3.52			
CAP (dB/m)	223.89	217.00	167.00	53.75	.23	1.20	190	400

The kurtosis (K = 0.797) indicates a leptokurtic distribution, where most of the results were close to the mean. The youngest of the data was aged 21 years while the oldest was 93 years.

The subjects had a mean body weight of 77.46 kg (SD = 16.96 kg) and the median value indicates that 50% of the subjects weighed 78 kg or less. The dominant value was 60 kg, which was the weight reported by 12 subjects. The standard deviation SD = 16.96 kg indicates that the majority of subjects had a weight between 60.50 and 94.42 kg. The skewness value γ is negative and indicates that the weight of the subjects was mostly above average. The kurtosis (K = - 0.392) indicates a platykurtic distribution, where most of the results were dispersed from the mean. The lowest weight of the subject was 46 kg, while the highest weight was 129 kg.

The subjects had a mean BMI of 26.47 kg/m² (SD = 4.73 kg/m2) and the majority of subjects had a BMI between 21.74 kg/m² and 31.20 kg/m². The median value indicates that 50% of the subjects had a BMI of at least 25.73 kg/m² and the remaining 50% had a BMI of at most 25.73 kg.m².The most common indices were values of 22 and 23 (6 subjects each). The skewness γ is positive and indicates that the BMI of the subjects was mostly below the mean, while kurtosis indicates a platykurtic distribution, where most of the results were dispersed from the mean. The lowest BMI of the subjects was 16.70 kg/m² and the highest was 39.91 kg/m² (Table 1).

The mean total cholesterol level of the subjects was 173.98 mg/dl(SD = 38.18,g/dl) while the median was 173 mg/dl, meaning that 50% of the subjects had a total cholesterol level of less than 173 mg/dl. The predominant value was 178 mg/dl and this was the result of 9 subjects. The standard deviation SD = 38.18 mg/dl gives an estimate of the total cholesterol level of the majority of subjects in the range of 135.80 mg/dl to 212.17 mg/dl. The skewness γ = 0.379 is right-skewed and indicates that the cholesterol of the subjects was mostly below average. Kurtosis (K = - 0.11) indicates a platykurtic distribution, where the majority of results were away from the mean. The lowest cholesterol level was 85 mg/dl, while the highest level was 267 mg/dl (Table 2).

Descriptive statistics for LDL, HDL, and TG are shown in Table 2.

The subjects had a mean glucose level of 100.40 mg/dl (SD = 23.12 mg/dl) and the median value indicates that 50% of the subjects had a glucose level of at most 97 mg/dl. The dominant value was 90 - such a result was obtained in 24 subjects. The standard deviation SD = 23.12 mg/dl indicates that the majority of subjects had glucose levels between 77.28 mg/dl and 123.52 mg/dl. The skewness value γ is positive and indicates that the subjects' glucose was mostly below average. The kurtosis (K = 17.279) is indicative of a leptokurtic distribution, where the majority of results were close to the mean. The subject's lowest result was 66 mg/dl while the highest was 260 mg/dl (Table 2).

In the study group, the mean HCV RNA result was 1.8911E+007 and the median value indicates that 50% of the subjects had an index below 1.5650E+006. The dominant value

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was 1.12E+006 - such a result was obtained in 3 subjects. The skewness value γ is positive and indicates that HCV RNA in the subjects was mostly below average. The positive kurtosis indicates a leptokurtic distribution, where the majority of the results were close to the mean. The lowest score of a subject was 1.57E+003, while the highest was 2.60E+009 (Table 3).

The mean glomerular filtration rate in the subjects was 103.34 ml/min./1.73 m², and the median was 102 ml/min./1.73m², meaning that 50% of the subjects had a GFR level greater than 102 ml/min./1.73 m². The predominant value was a factor level of 102 and 12 subjects had this result. The skewness γ = 5.194 is right-skewed and indicates that the GFR of the subjects was mostly below average. The kurtosis (K = 33.078) indicates a platykurtic distribution, where the majority of the results were away from the mean. The lowest GFR was 23 ml/min./1.73 m², while the highest level was 232 ml/min./1.73 m² (Table 3).

Descriptive statistics for the CRP are presented in Table 3.

Subjects had a mean liver stiffness level of 10.35 kPa, corresponding to Metavir level F3 fibrosis (M = 10.346 kPa; SD = 10.139 kPa), and the median value indicates that 50% of subjects had a level of at least 6.5 kPa. The dominant value was 5.3kPa - such a result was obtained in 13 subjects. The skewness value γ is positive and indicates that the index was mostly below average. The kurtosis (K = 15.69) indicates a leptokurtic distribution, where most of the results were close to the mean. The lowest score of the subject was 2.8 kPa, while the highest score was 74.6 kPa.

The mean CAP factor level in the subjects was 223.89 dB/m, which corresponds to S0 level steatosis according to Brunt, while the median was 217 dB/m, meaning that 50% of the subjects had CAP levels greater than 217 dB/m. The predominant value was a factor level of 167 dB/m and this was the result of 5 subjects. The skewness γ = 3.52 is right-skewed and means that the levels of the subjects were mostly below average. The kurtosis (K = 1.199) indicates a leptokurtic distribution, where most of the results were close to the mean. The lowest Fibroscan CAP level was 190 dB/m, while the highest level was 400 dB/m (Table 4).

In the next step, the correlation between the variables measured on the ratio scale, i.e. age, weight, BMI, glucose levels, GFR, CRP, total cholesterol, LDL, HDL, TG, HCV RNA, LSM, and CAP, was checked. These relationships were checked using the r-Person correlation coefficient.

In the next step, the correlation between variables measured on an ordinal scale, i.e. duration of infection, normal weight - overweight - obesity, age, and HCV RNA, LSM, and CAP was checked for co-existence. These relationships were checked using Spearman's RHO correlation coefficient (Table 5).

As shown in Table 5, there is a significant negative association between HCV RNA and CAP. The value r = - 0.266; $p < 0.001$ indicates that the higher the HCV RNA level, the lower the CAP. This association is a weak association - in the absolute range |0.0 - 0.3|.

There was also a significant association between LSM and the age of the subjects. The value r = 0.175; $p < 0.01$ indicates a positive association (LSM increases with age). This association is a weak association - in the absolute range |0.0-0.3|.

For CAP, there are additional associations between body weight (r = 0.364; $p < 0.001$) and BMI (r = 0.454; $p < 0.001$). These associations are positive associations (CAP increases with increasing body weight and BMI) and moderate in the absolute range |0.3 - 0.5| (Table 5).

Correlations

There is a negative association for LSM with HDL (r = - 0.189; $p < 0.05$). This association is a negative association (LSM increases when HDL decreases) and a weak association in the absolute range |0.0 - 0.3| (Table 6).

Table 5: Correlations.

		HCV RNA	LSM (kPa)	CAP (dB/m)	Age(years)	body weight (kg)	BMI(kg/m)²
HCV RNA	Pearson correlation	1	-.025	-.266**	.022	.022	-.019
	Relevance (bilateral)		.653	<.001	.697	.704	.737
	N	320	320	169	320	309	306
LSM (kPa)	Pearson correlation	-.025	1	.054	.175**	.079	.048
	Relevance (bilateral)	.653		.485	.002	.167	.401
	N	320	320	169	320	309	306
CAP(dB/m)	Pearson correlation	-.266**	.054	1	.102	.364**	.454**
	Relevance (bilateral)	<.001	.485		.187	<.001	<.001
	N	169	169	169	169	165	164
Age (years)	Pearson correlation	.022	.175**	.102	1	-.013	.114*
	Relevance (bilateral)	.697	.002	.187		.819	.046
	N	320	320	169	320	309	306
body weight (kg)	Pearson correlation	.022	.079	.364**	-.013	1	.826**
	Relevance (bilateral)	.704	.167	<.001	.819		<.001
	N	309	309	165	309	309	306
BMI (kg/m)²	Pearson correlation	-.019	.048	.454**	.114*	.826**	1
	Relevance (bilateral)	.737	.401	<.001	.046	<.001	
	N	306	306	164	306	306	306

**. Correlation significant at the 0.01 level (two-sided).

*. Correlation significant at the 0.05 level (two-sided).

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Table 7 shows the remaining correlations, made using the r-Pearson coefficient.

There is a significant positive association between LSM and glucose. The value r = 0.255; $p < 0.001$ indicates that the higher the glucose level, the higher the LSM level. This association is a weak association - in the absolute range |0.0 - 0.3| (Table 7).

For CAP, the significant positive associations are with glucose (r = 0.160; $p < 0.05$) and with CRP (r = 0.205; $p < 0.05$). These associations are weak associations - in the absolute range |0.0 - 0.3| (Table 7).

For variables measured on an ordinal scale (duration of infection, normal weight - overweight - obese, age), and HCV RNA, LSM, and CAP, non-parametric correlations were tested using Spearman's RHO.

A significant positive association was shown between CAP and BMI in the ranges for normal weight, overweight, and obesity (rS = 0.283; $p < 0.001$) and LSM and age – rS = 0.287; $p < 0.001$. These associations are weak associations in the absolute range |0.0 - 0.3| (Table 8).

In order to test whether there was a significant difference between HCV RNA, LSM, and CAP in relation to the subjects' sex, diabetes, coronary heart disease, myocardial infarction, coronary interventions, stroke, hypertension, total cholesterol, LDL cholesterol, and triglycerides, the subjects were analysed using a test for independent samples. According to the methodological assumptions, the assumptions (parameters) for this test were checked.

The first parameter in the test for 2 independent samples is the assumption that the dependent variables (HCV RNA, LSM, CAP) are quantitative variables. The assumption is met - results are given on a quantitative scale in the range as shown in Tables 3 and 4.

Table 6: Correlations.

		HCV RNA	LSM (kPa)	CAP (dB/m)	Total cholesterol (mg/dl)	LDL (mg/dl)	HDL(mg/dl)
HCV RNA	Pearson correlation	1	-.025	-.266**	-.061	-.080	.010
	Relevance (bilateral)		.653	<.001	.503	.625	.916
	N	320	320	169	124	40	119
LSM (kPa)	Pearson correlation	-.025	1	.054	-.148	.009	-.189*
	Relevance (bilateral)	.653		.485	.100	.957	.039
	N	320	320	169	124	40	119
CAP (dB/m)	Pearson correlation	-.266**	.054	1	-.042	.043	-.061
	Relevance (bilateral)	<.001	.485		.749	.846	.646
	N	169	169	169	61	23	60
Total cholesterol (mg/dl)	Pearson correlation	-.061	-.148	-.042	1	.887**	.275**
	Relevance (bilateral)	.503	.100	.749		<.001	.003
	N	124	124	61	124	40	118
LDL (mg/dl)	Pearson correlation	-.080	.009	.043	.887**	1	.013
	Relevance (bilateral)	.625	.957	.846	<.001		.938
	N	40	40	23	40	40	40
HDL (mg/dl)	Pearson correlation	.010	-.189*	-.061	.275**	.013	1
	Relevance (bilateral)	.916	.039	.646	.003	.938	
	N	119	119	60	118	40	119

**. Correlation significant at the 0.01 level (two-sided).

*. Correlation significant at the 0.05 level (two-sided).

Table 7: Correlations.

		HCV RNA	LSM (kPa)	CAP (dB/m)	Glucose (mg/dl)	GFR (ml/min./1.73m)^2	CRP (mg/l)
HCV RNA	Pearson correlation	1	-.025	-.266**	-.061	.028	-.030
	Relevance (bilateral)		.653	<.001	.278	.616	.671
	N	320	320	169	318	319	200
LSM (kPa)	Pearson correlation	-.025	1	.054	.255**	.084	.044
	Relevance (bilateral)	.653		.485	<.001	.136	.540
	N	320	320	169	318	319	200
CAP (dB/m)	Pearson correlation	-.266**	.054	1	.160*	.018	.205*
	Relevance (bilateral)	<.001	.485		.038	.820	.035
	N	169	169	169	168	169	107
Glucose (mg/dl)	Pearson correlation	-.061	.255**	.160*	1	-.091	.000
	Relevance (bilateral)	.278	<.001	.038		.104	.997
	N	318	318	168	318	317	199
GFR (ml/min./1.73m)^2	Pearson correlation	.028	.084	.018	-.091	1	-.226**
	Relevance (bilateral)	.616	.136	.820	.104		.001
	N	319	319	169	317	319	200
CRP (mg/l)	Pearson correlation	-.030	.044	.205*	.000	-.226**	1
	Relevance (bilateral)	.671	.540	.035	.997	.001	
	N	200	200	107	199	200	200

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

Table 8: Correlations.

			HCV RNA	LSM (kPa)	CAP (dB/m)	Time of infection	BMI range	Age
Spearman's rho	HCV RNA	Correlation coefficient	1.000	.004	-.055	-.079	.087	.074
		Relevance (bilateral)	.	.942	.476	.157	.131	.186
		N	320	320	169	320	304	320
	LSM (kPa)	Correlation coefficient	.004	1.000	.062	-.057	.110	.287**
		Relevance (bilateral)	.942	.	.423	.311	.056	<.001
		N	320	320	169	320	304	320
	CAP (dB/m)	Correlation coefficient	-.055	.062	1.000	.051	.283**	.068
		Relevance (bilateral)	.476	.423	.	.513	<.001	.381
		N	169	169	169	169	163	169
	Time of infection	Correlation coefficient	-.079	-.057	.051	1.000	.126*	.045
		Relevance (bilateral)	.157	.311	.513	.	.028	.418
		N	320	320	169	320	304	320
	BMI	Correlation coefficient	.087	.110	.283**	.126*	1.000	.096
		Relevance (bilateral)	.131	.056	<.001	.028	.	.095
		N	304	304	163	304	304	304
	Age	Correlation coefficient	.074	.287**	.068	.045	.096	1.000
		Relevance (bilateral)	.186	<.001	.381	.418	.095	.
		N	320	320	169	320	304	320

**. Correlation significant at the 0.01 level (two-sided).

*. Correlation significant at the 0.05 level (two-sided).

The second assumption is that the groups are equal. This assumption was verified using the $\chi 2$ test.

The result of the test $\chi 2$ indicates that only for gender are the groups equal $\chi 2 = 1.513$; $p = .219 > .05$ - non-significant result). The remaining groups are unequal groups with a significance level of less than 0.001 (Table 9).

The third parameter to be verified is the assumption of normality of the distribution of the dependent variable, which in this study was tested using the Shapiro-Wilk test.

Analysing the results of the Shapiro-Wilk test, it can be seen that only some groups of variables show conformity to a normal distribution ($p > 0.05$). Thus, it can be considered that assumption two is partially met for some variables (highlighted in yellow) (Table 9).

The last parameter to be confirmed is the test for homogeneity of variance, which was performed using Levene's test. As it is not the case for all groups that both assumptions are met, this assumption was dropped as not valid.

As the assumptions for the Student's t-test for independent samples were not met, a non-parametric U-Mann -Whitney rank-sum test was performed.

The results of the U-Mann-Whitney test indicate that there are significant differences ($p < 0.05$) in HCV RNA and LSM levels according to gender. Men had higher results. There were no significant gender differences for CAP (Table 10a,b).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA LSM and CAP levels according to cigarette smoking (Table 11).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels in relation to coronary artery disease (Table 12).

Table 9: *Equality of groups test χ2.*

Tested value					
	Chi-square	df	Asymptotic significance	Group size 1	Group size 2
Sex M/F	1.513[a]	1	.219	149K	171M
Diabetes	189.113[a]	1	<.001	283N	37T
Smoking 0 NO 1 YES	107.288[b]	1	<.001	252N	67T
Coronary heart disease 0 NO 1 YES	304.200[a]	1	<.001	316N	4T
Myocardial infarction 0 NO 1 YES	308.113[a]	1	<.001	317N	3T
Coronary interventions 1 PTCA 2 CABG	622.131[c]	2	<.001	317T	3T
Brain stroke 0 NO 1 YES	295.451[b]	1	<.001	313N	6T
Arterial hypertension 0 NO 1 YES	80.000[a]	1	<.001	240N	80T
Cirrhosis 0 NO 1 YES	97.409[d]	1	<.001	247N	71T
Cholesterol range	27.129[a]	1	<.001	91 (<190mg/dl)	33 (>190 mg/dl)
LDL range	8.100[b]	1	.004	29 (<115mg/dl)	11 (>115 mg/dl)
TG range	25.420[c]	1	<.001	87 (<150)	32 (>150)

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels in relation to MI (Table 13).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels according to the type of coronary intervention (Table 14).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels according to stroke history (Table 15).

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

Table 10a: Normality of distribution test.

	Sex M/F	Shapiro-Wilk		
HCV RNA	Woman	.351	79	.000
	Male	.237	90	.000
LSM (kPa)	Woman	.738	79	.000
	Male	.649	90	.000
CAP (dB/m)	Woman	.940	79	.001
	Male	.966	90	.019
	Diabetes	**Shapiro-Wilk**		
HCV RNA	Not	.244	151	.000
	Yes	.646	18	.000
LSM (kPa)	Not	.654	151	.000
	Yes	.637	18	.000
CAP (dB/m)	Not	.975	151	.008
	Yes	.938	18	.267
	smoking 0 NO 1 YES	**Shapiro-Wilk**		
HCV RNA	Not	.264	136	.000
	Yes	.786	32	.000
LSM (kPa)	Not	.674	136	.000
	Yes	.687	32	.000
CAP (dB/m)	Not	.972	136	.007
	Yes	.947	32	.115
	Coronary heart disease 0 NO 1 YES	**Shapiro-Wilk**		
HCV RNA	Not	.258	166	.000
	Yes	1.000	3	.995
LSM (kPa)	Not	.628	166	.000
	Yes	1.000	3	.982
CAP (dB/m)	Not	.974	166	.004
	Yes	.958	3	.605
	Heart attack 0 NO 1 YES	**Shapiro-Wilk**		
HCV RNA	Not	.258	166	.000
	Yes	1.000	3	.995
LSM (kPa)	Not	.628	166	.000
	Yes	1.000	3	.982
CAP (dB/m)	Not	.974	166	.004
	Yes	.958	3	.605
	Brain stroke 0 NO 1 YES	**Shapiro-Wilk**		
HCV RNA	Not	.258	165	.000
	Yes	.861	3	.271
LSM (kPa)	Not	.628	165	.000
	Yes	.777	3	.060
CAP (dB/m)	Not	.973	165	.003
	Yes	.784	3	.077
	Arterial hypertension 0 NO 1 YES	**Shapiro-Wilk**		
HCV RNA	Not	.251	124	.000
	Yes	.596	45	.000
LSM (kPa)	Not	.592	124	.000
	Yes	.891	45	.000
CAP (dB/m)	Not	.973	124	.013
	Yes	.959	45	.108
Normality of distribution tests				
	Cirrhosis 0 NO 1 YES	**Shapiro-Wilk**		
HCV RNA	Not	.408	126	.000
	Yes	.264	41	.000
LSM (kPa)	Not	.634	126	.000
	Yes	.741	41	.000
CAP (dB/m)	Not	.957	126	.000
	Yes	.967	41	.270
Normality of distribution tests				
	Cholesterol range	**Shapiro-Wilk**		
HCV RNA	cholesterol below 190 mg/dl	.892	17	.051
	cholesterol above 190 mg/dl	.866	6	.211
LSM (kPa)	cholesterol below 190 mg/dl	.826	17	.005
	cholesterol above 190 mg/dl	.814	6	.078

Table 10b: U-Mann-Whitney test – gender.

Ranks

	Sex M/F	N	Average rank	Sum of ranks
HCV RNA	Woman	149	148.16	22076.50
	Male	171	171.25	29283.50
	Total	320		
LSM (kPa)	Woman	149	148.11	22068.00
	Male	171	171.30	29292.00
	Total	320		
CAP (dB/m)	Woman	79	77.84	6149.50
	Male	90	91.28	8215.50
	Total	169		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	10901.500	10893.000	2989.500
In Wilcoxon	22076.500	22068.000	6149.500
Z	-2.226	-2.237	-1.782
Asymptotic significance (two-sided)	.026	.025	.075

a. Grouping variable: Sex M/F

Table 11: U-Mann-Whitney test - cigarette smoking.

Ranks

	Smoking 0 NO 1 YES	N	Average rank	Sum of ranks
HCV RNA	Not	252	157.49	39688.00
	Yes	67	169.43	11352.00
	Total	319		
LSM (kPa)	Not	252	157.76	39755.00
	Yes	67	168.43	11285.00
	Total	319		
CAP (dB/m)	Not	136	83.37	11338.50
	Yes	32	89.30	2857.50
	Total	168		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	7810.000	7877.000	2022.500
In Wilcoxon	39688.000	39755.000	11338.500
Z	-.942	-.842	-.620
Asymptotic significance (two-sided)	.346	.400	.535

[a]Grouping variable: smoking 0 NO 1 YES.

Table 12: U-Mann-Whitney test - coronary artery disease.

Ranks

	Coronary heart disease 0 NO 1 YES	N	Average rank	Sum of ranks
HCV RNA	Not	316	160.15	50606.00
	Yes	4	188.50	754.00
	Total	320		
LSM (kPa)	Not	316	160.41	50688.50
	Yes	4	167.88	671.50
	Total	320		
CAP (dB/m)	Not	166	85.59	14208.50
	Yes	3	52.17	156.50
	Total	169		

Tested value[a]

	HCV RNA	Fibroscan or SWE (kPa)	Fibroscan (CAP)
At Mann-Whitney	520.000	602.500	150.500
In Wilcoxon	50606.000	50688.500	156.500
Z	-.609	-.160	-1.173
Asymptotic significance (two-sided)	.542	.873	.241

[a]Grouping variable: coronary heart disease 0 NO 1 YES

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

The results of the U-Mann-Whitney test indicate that there are significant differences ($p < 0.05$) in LSM and CAP levels according to hypertension. Higher scores were obtained by subjects who were diagnosed with hypertension. There were no significant differences according to the fact of hypertension for HCV RNA (Table 16).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels in relation to total cholesterol (cut-off point 190 mg/dl) (Table 17).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels in relation to LDL (cut-off point 115 mg/dl) (Table 18).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels according to TG (cut-off point 150 mg/dl) (Table 19).

The results of the U-Mann-Whitney test indicate that there are no significant differences in HCV RNA, LSM, and CAP levels according to GFR (cut-off point 60 ml/min. / 1.73 m²).

In order to test whether there was a significant difference between HCV RNA, LSM, and CAP in relation to HCV genotype, age of subjects, time of infection, BMI, and HDL, a one-way analysis of variance ANOVA test was performed. According to the methodological assumptions, the assumptions (parameters) for this test were checked (Table 20).

The first parameter in the ANOVA test is the assumption that the dependent variables (HCV RNA, LSM, and CAP) are quantitative variables. The assumption is met - results are reported on a quantitative scale in the range as shown in Tables 3 and 4.

Table 13: U-Mann-Whitney test - myocardial infarction.

Ranks				
	Heart attack 0 NO 1 YES	N	Average rank	Sum of ranks
HCV RNA	Not	317	159.76	50645.00
	Yes	3	238.33	715.00
	Total	320		
LSM (kPa)	Not	317	160.23	50793.50
	Yes	3	188.83	566.50
	Total	320		
CAP (dB/m)	Not	166	85.59	14208.50
	Yes	3	52.17	156.50
	Total	169		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	242.000	390.500	150.500
In Wilcoxon	50645.000	50793.500	156.500
Z	-1.464	-.533	-1.173
Asymptotic significance (two-sided)	.143	.594	.241

[a]Grouping variable: heart attack 0 NO 1 YES

Table 14: U-Mann-Whitney test - coronary interventions.

Ranks				
	Coronary interventions 1 PTCA 2 CABG	N	Average rank	Sum of ranks
HCV RNA	PTCA	2	2.00	4.00
	CABG	1	2.00	2.00
	Total	3		
LSM (kPa)	PTCA	2	2.00	4.00
	CABG	1	2.00	2.00
	Total	3		
CAP (dB/m)	PTCA	2	2.00	4.00
	CABG	1	2.00	2.00
	Total	3		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	1.000	1.000	1.000
In Wilcoxon	2.000	2.000	2.000
Z	.000	.000	.000
Asymptotic significance (two-sided)	1.000	1.000	1.000
Exact significance [2*(one-sided)].	1.000[b]	1.000[b]	1.000[b]

[a]Grouping variable: Coronary interventions 1 PTCA 2 CABG

[b]Unadjusted for bonding.

Table 15: U-Mann-Whitney test – stroke.

Ranks				
	Brain stroke 0 NO 1 YES	N	Average rank	Sum of ranks
HCV RNA	Not	313	160.05	50096.00
	Yes	6	157.33	944.00
	Total	319		
LSM (kPa)	Not	313	161.21	50458.00
	Yes	6	97.00	582.00
	Total	319		
CAP (dB/m)	Not	165	84.91	14009.50
	Yes	3	62.17	186.50
	Total	168		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	923.000	561.000	180.500
In Wilcoxon	944.000	582.000	186.500
Z	-.071	-1.689	-.803
Asymptotic significance (two-sided)	.943	.091	.422

[a]Grouping variable: Brain stroke 0 NO 1 YES

Table 16: U-Mann-Whitney test – hypertension.

Ranks				
	Arterial hypertension 0 NO 1 YES	N	Average rank	Sum of ranks
HCV RNA	Not	240	155.68	37362.00
	Yes	80	174.98	13998.00
	Total	320		
LSM (kPa)	Not	240	153.75	36900.00
	Yes	80	180.75	14460.00
	Total	320		
CAP (dB/m)	Not	124	76.62	9500.50
	Yes	45	108.10	4864.50
	Total	169		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	8442.000	7980.000	1750.500
In Wilcoxon	37362.000	36900.000	9500.500
Z	-1.616	-2.261	-3.698
Asymptotic significance (two-sided)	.106	.024	<.001

[a]Grouping variable: hypertension 0 NO 1 YES

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

The second assumption is that the groups are equal. This assumption was verified using the $\chi 2$ test.

The result of the test $\chi 2$ indicates that only for BMI the groups are equi-groups ($\chi 2(2) = 2.770$; $p = .250 > .05$ - non-significant result). The remaining groups are unequal groups with a significance level of less than 0.001 (Table 21).

The third and fourth parameters requiring verification are the assumption of normality of the distribution of the dependent variable, which in this study was tested using the Shapiro-Wilk test, and the assumption of homogeneity of variance using the Levee test (Tables 22,23).

As the assumptions are only met for the BMI factor for the LSM variable, only in this relationship was the statistic analysed using ANOVA (Table 24). For the remaining correlations, the Kruskal-Wallis non-parametric H test was used (Table 25a).

Table 17: U-Mann-Whitney test - total cholesterol.

Ranks				
	Cholesterol range	N	Average rank	Sum of ranks
HCV RNA	cholesterol below 190 mg/dl	91	61.91	5633.50
	cholesterol above 190 mg/dl	33	64.14	2116.50
	Total	124		
LKM (kPa)	cholesterol below 190 mg/dl	91	63.75	5801.00
	cholesterol above 190 mg/dl	33	59.06	1949.00
	Total	124		
CAP (dB/m)	cholesterol below 190 mg/dl	44	30.05	1322.00
	cholesterol above 190 mg/dl	17	33.47	569.00
	Total	61		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	1447.500	1388.000	332.000
In Wilcoxon	5633.500	1949.000	1322.000
Z	-.305	-.642	-.676
Asymptotic significance (two-sided)	.760	.521	.499

[a]Grouping variable: Cholesterol range

Table 18: U-Mann-Whitney test – LDL.

Ranks				
	LDL range	N	Average rank	Sum of ranks
HCV RNA	LDL below 115 mg/dl	29	19.05	552.50
	LDL over 115 mg/dl	11	24.32	267.50
	Total	40		
LSM (kPa)	LDL below 115 mg/dl	29	20.33	589.50
	LDL over 115 mg/dl	11	20.95	230.50
	Total	40		
CAP (dB/m)	LDL below 115 mg/dl	17	11.29	192.00
	LDL over 115 mg/dl	6	14.00	84.00
	Total	23		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	117.500	154.500	39.000
In Wilcoxon	552.500	589.500	192.000
Z	-1.272	-.152	-.840
Asymptotic significance (two-sided)	.203	.880	.401
Exact significance [2*(one-sided)].	.207[b]	.881[b]	.431[b]

[a]Grouping variable: LDL range

[b]Unadjusted for bonding.

Table 19: U-Mann-Whitney test – triglycerides.

Ranks				
	TG range	N	Average rank	Sum of ranks
HCV RNA	TG less than 150	87	60.09	5228.00
	TG over 150	32	59.75	1912.00
	Total	119		
LSM (kPa)	TG less than 150	87	56.50	4915.50
	TG over 150	32	69.52	2224.50
	Total	119		
CAP (dB/m)	TG less than 150	45	30.40	1368.00
	TG over 150	13	26.38	343.00
	Total	58		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	1384.000	1087.500	252.000
In Wilcoxon	1912.000	4915.500	343.000
Z	-.048	-1.825	-.755
Asymptotic significance (two-sided)	.962	.068	.450

[a]Grouping variable: TG range

Table 20: U-Mann-Whitney test – GFR.

Ranks				
	GFR range	N	Average rank	Sum of ranks
HCV RNA	GFR less than 60 ml/ min./1.73m^2	8	147.63	1181.00
	GFR greater than 60 ml/ min./ 1.73m^2	311	160.32	49859.00
	Total	319		
LSM (kPa)	GFR less than 60 ml/ min./ 1.73m^2	8	188.25	1506.00
	GFR greater than 60 ml/ min./ 1.73m^2	311	159.27	49534.00
	Total	319		
CAP (dB/m)	GFR less than 60 ml/ min./ 1.73m^2	7	73.14	512.00
	GFR greater than 60 ml/ min./ 1.73m^2	162	85.51	13853.00
	Total	169		

Tested value[a]

	HCV RNA	LSM (kPa)	CAP (dB/m)
At Mann-Whitney	1145.000	1018.000	484.000
In Wilcoxon	1181.000	49534.000	512.000
Z	-.384	-.878	-.655
Asymptotic significance (two-sided)	.701	.380	.513

[a]Grouping variable: GFR range

Table 21: *Equality of groups test χ2.*

Tested value			
	Chi-square	df	Asymptotic significance
HCV genotype	819.241[a]	7	<.001
Age ranges	91.475[b]	3	<.001
Time of infection	122.369[c]	2	<.001
BMI range	2.770[d]	2	.250
HDL range	28.395[e]	3	<.001

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

Table 22: Normality of distribution test.

	HCV genotype	Shapiro-Wilk		
HCV RNA	1a	.859	7	.148
	1b	.346	100	.000
	3	.730	21	.000
	4	.503	16	.000
LSM (kPa)	1a	.617	7	.000
	1b	.677	100	.000
	3	.712	21	.000
	4	.557	16	.000
CAP (dB/m)	1a	.949	7	.716
	1b	.972	100	.034
	3	.972	21	.772
	4	.890	16	.055
Normality of distribution tests				
	Time of infection	**Shapiro-Wilk**		
HCV RNA	up to 5 years	.384	116	.000
	between 5 and 10 years	.344	19	.000
	Over 10 years	.688	34	.000
LSM (kPa)	up to 5 years	.638	116	.000
	between 5 and 10 years	.563	19	.000
	over 10 years	.733	34	.000
CAP (dB/m)	up to 5 years	.964	116	.003
	between 5 and 10 years	.903	19	.055
	over 10 years	.939	34	.059
Normality of distribution tests				
	BMI (kg/m²) range	**Shapiro-Wilk**		
HCV RNA	BMI normal to 25	.395	61	.000
	BMI from 25-29 overweight	.228	49	.000
	BMI over 30 - obesity	.671	53	.000
LSM (kPa)	BMI normal to 25	.545	61	.000
	BMI from 25-29 overweight	.675	49	.000
	BMI over 30 - obesity	.708	53	.000
CAP (dB/m)	BMI normal to 25	.937	61	.004
	BMI from 25-29 overweight	.932	49	.007
	BMI over 30 - obesity	.971	53	.215
Normality of distribution tests				
	HDL range	**Shapiro-Wilk**		
HCV RNA	HDL below 50 in women	.935	9	.528
	HDL over 50 in women	.849	15	.017
	HDL below 40 in men	.539	6	.000
	HDL over 40 in men	.859	30	.001
LSM (kPa)	HDL below 50 in women	.782	9	.013
	HDL over 50 in women	.724	15	.000
	HDL below 40 in men	.930	6	.583
	HDL over 40 in men	.827	30	.000
CAP (dB/m)	HDL below 50 in women	.929	9	.476
	HDL over 50 in women	.978	15	.955
	HDL below 40 in men	.916	6	.479
	HDL over 40 in men	.974	30	.642
Normality of distribution tests				
	Age ranges	**Shapiro-Wilk**		
HCV RNA	Age 20 to 30	.621	15	.000
	Age 30 to 40	.690	70	.000
	Age 40 to 45	.389	28	.000
	Age over 45	.250	56	.000
LSM (kPa)	Age 20 to 30	.498	15	.000
	Age 30 to 40	.545	70	.000
	Age 40 to 45	.724	28	.000
	Age over 45	.880	56	.000
CAP (dB/m)	Age 20 to 30	.963	15	.751
	Age 30 to 40	.957	70	.018
	Age 40 to 45	.953	28	.231
	Age over 45	.953	56	.029

Table 23: Test for homogeneity of distribution variance.

Homogeneity of variance test					
		Levene's statistics	**df1**	**df2**	**Relevance**
HCV RNA	Based on the average	9.469	2	166	<.001
	Based on the median	3.166	2	166	.045
	Based on median and adjusted df	3.166	2	31.256	.056
	Based on the truncated average	3.641	2	166	.028
LSM (kPa)	Based on the average	1.535	2	166	.219
	Based on the median	.667	2	166	.515
	Based on median and adjusted df	.667	2	148.592	.515
	Based on the truncated average	.956	2	166	.386
CAP (dB/m)	Based on the average	.304	2	166	.738
	Based on the median	.255	2	166	.775
	Based on median and adjusted df	.255	2	140.874	.775
	Based on the truncated average	.337	2	166	.715
Homogeneity of variance test					
		Levene's statistics	**df1**	**df2**	**Relevance**
HCV RNA	Based on the average	1.776	2	160	.173
	Based on the median	.818	2	160	.443
	Based on median and adjusted df	.818	2	75.325	.445
	Based on the truncated average	.859	2	160	.425
LSM (kPa)	Based on the average	.236	2	160	.790
	Based on the median	.021	2	160	.980
	Based on median and adjusted df	.021	2	146.830	.980
	Based on the truncated average	.070	2	160	.932
CAP (dB/m)	Based on the average	.426	2	160	.654
	Based on the median	.490	2	160	.613
	Based on median and adjusted df	.490	2	155.699	.613
	Based on the truncated average	.504	2	160	.605
Homogeneity of variance test					
		Levene's statistics	**df1**	**df2**	**Relevance**
HCV RNA	Based on the average	18.484	3	56	<.001
	Based on the median	3.442	3	56	.023
	Based on median and adjusted df	3.442	3	5.124	.106
	Based on the truncated average	12.561	3	56	<.001
LSM (kPa)	Based on the average	.467	3	56	.706
	Based on the median	.362	3	56	.780
	Based on median and adjusted df	.362	3	51.773	.780
	Based on the truncated average	.474	3	56	.702
CAP (dB/m)	Based on the average	2.244	3	56	.093
	Based on the median	2.175	3	56	.101
	Based on median and adjusted df	2.175	3	31.582	.111
	Based on the truncated average	2.216	3	56	.096
Homogeneity of variance test					
		Levene's statistics	**df1**	**df2**	**Relevance**

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

HCV RNA	Based on the average	1.600	3	165	.191
	Based on the median	.795	3	165	.498
	Based on median and adjusted df	.795	3	81.142	.500
	Based on the truncated average	.807	3	165	.492
LSM (kPa)	Based on the average	8.724	3	165	<.001
	Based on the median	4.214	3	165	.007
	Based on median and adjusted df	4.214	3	87.653	.008
	Based on the truncated average	6.812	3	165	<.001
CAP (dB/m))	Based on the average	1.202	3	165	.311
	Based on the median	.970	3	165	.408
	Based on median and adjusted df	.970	3	134.360	.409
	Based on the truncated average	1.160	3	165	.327

Table 24: Anova test for the LSM variable - BMI factor.

One-way ANOVA					
LSM					
	Sum of squares	df	Mean square	F	Relevance
Between groups	292.223	2	146.111	1.432	.240
Within the groups	30715.057	301	102.043		
Total	31007.280	303			

Table 25a: Kruskal-Wallis H test for the HCV RNA variable and CAP factor BMI.

Ranks			
	BMI range	N	Average rank
HCV RNA	BMI normal to 25	115	142.45
	BMI from 25-29 overweight	94	156.88
	BMI over 30 - obesity	95	160.33
	Total	304	
CAP (dB/m)	BMI normal to 25	61	66.76
	BMI from 25-29 overweight	49	82.91
	BMI over 30 - obesity	53	98.7
	Total	163	
Tested value[a,b]			
		HCV RNA	CAP (dB/m)
H Kruskal-Wallis		2.492	13.012
df		2	2
Asymptotic significance		0.288	0.001
[b]Grouping variable: BMI range			

Table 25b: Kruskal-Wallis H test for the HCV RNA variable, LSM and CAP - HCV genotype.

Ranks			
	HCV genotype	N	Average rank
HCV RNA	1	5	151.90
	1a	16	144.19
	1b	193	154.17
	3	39	115.33
	4	34	135.46
	-	1	13.00
	1+4	1	196.00
	indefinite	1	61.00
	Total	290	
CAP (dB/m)	1	2	43.25
	1a	7	81.93
	1b	100	71.41
	3	21	86.45
	4	16	83.06
	-	1	92.50
	1+4	1	77.00
	indefinite	1	60.50
	Total	149	
LSM (kPa)	1	5	179.70
	1a	16	116.03
	1b	193	144.86
	3	39	174.50
	4	34	121.25
	-	1	231.00
	1+4	1	166.00
	indefinite	1	156.50
	Total	290	
Tested value[a,b]			
	HCV RNA	CAP (dB/m)	LSM (kPa)
H Kruskal-Wallis	11.505	4.274	11.447
df	7	7	7
Asymptotic significance	.118	.748	.120
[a]Kruskal-Wallis test			
[b]Grouping variable: HCV genotype			

Table 26: Kruskal-Wallis H test for the variable HCV RNA, LSM and CAP - age of subjects.

Ranks			
	Age ranges	N	Average rank
HCV RNA	Age 20 to 30	22	157.18
	Age 30 to 40	135	154.00
	Age 40 to 45	60	157.57
	Age over 45	103	171.44
	Total	320	
CAP (dB/m)	Age 20 to 30	15	80.30
	Age 30 to 40	70	80.32
	Age 40 to 45	28	96.50
	Age over 45	56	86.36
	Total	169	
LSM (kPa)	Age 20 to 30	22	119.27
	Age 30 to 40	135	136.44
	Age 40 to 45	60	176.37
	Age over 45	103	191.60
	Total	320	
Tested value[a,b]			
	HCV RNA	Fibroscan (CAP)	Fibroscan or SWE (kPa)
H Kruskal-Wallis	2.195	2.369	26.909
df	3	3	3
Asymptotic significance	.533	.500	<.001
[a]Kruskal-Wallis test			
[b]Grouping variable: Age in intervals			

The results of the ANOVA test indicate that there are no significant differences in LSM levels according to BMI (normal weight - overweight – obese) (Table 24).

The result of the Kruskal-Wallis test shows that there are no significant differences in HCV RNA levels for the BMI factor, while for CAP the test result is significant ($H(2) = 13.012$; $p < 0.001$) and indicates that the lowest CAP level is for BMI up to 25 kg/m² and the highest for BMI above 30 kg/m² (Table 25b).

The result of the Kruskal-Wallis test indicates that there are no significant differences in HCV RNA, CAP, and LSM levels for the HCV genotype factor (Table 25b).

The result of the Kruskal-Wallis test shows that there are no significant differences in the levels of HCV RNA and CAP for

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Table 27: Kruskal-Wallis H test for the variable HCV RNA, LSM and CAP - time of infection.

Ranks			
	Time of infection	N	Average rank
HCV RNA	up to 5 years	199	166.58
	between 5 and 10 years	49	148.31
	over 10 years	72	152.00
	Total	320	
CAP (dB/m)	up to 5 years	116	83.24
	between 5 and 10 years	19	90.13
	over 10 years	34	88.15
	Total	169	
LSM (kPa)	up to 5 years	199	164.75
	between 5 and 10 years	49	152.95
	over 10 years	72	153.89
	Total	320	

Tested value[a,b]

	HCV RNA	CAP (dB/m)	LSM (kPa)
H Kruskal-Wallis	2.318	.500	1.115
df	2	2	2
Asymptotic significance	.314	.779	.573

[a]Kruskal-Wallis test

[b]Grouping variable: Time of infection

the factor age of the designated ranges, while for LSM the test result is significant ($H(3) = 26.909$; $p < 0.001$) and indicates that the lowest level of LSM is for those in the age range 20 to 30 years and the highest for those in the range above 45 years (Table 26).

The result of the Kruskal-Wallis test indicates that there are no significant differences in HCV RNA levels and CAP and LSM for the time of infection factor (Table 27).

Discussion

Cardiovascular diseases are also a major cause of disability, hospitalisation, and rising costs in health care. Poland is one of the countries at high cardiovascular risk [1,2,4,9,24]

Large population-based studies have shown that the prevalence of ischaemic heart disease increases with age, from 5% - 7% in women aged 45 - 64 years to 10% - 12% in women aged 65-84 years and from 4% - 7% in men aged 45 - 64 years to 12% - 14% in men aged 65 - 84 years [25]. Recent studies show an association of chronic HCV infection with an increased risk of cardiovascular disease, its complications, and a 1.65-fold increase in mortality compared to the uninfected population. The increased risk of cardiovascular disease in patients with HCV C is 1.75-fold higher compared to uninfected individuals when an additional risk factor such as diabetes or hypertension is present [21,22]. Another observational study from Taiwan showed that HCV is an independent factor in stroke and increases the risk of peripheral arteriosclerosis by 1.43-fold. A US observational study showed that patients with detectable HCV RNA viral load had a statistically significant higher incidence of coronary events [23,26].

In the study group, ischaemic heart disease was diagnosed in 4 patients, representing 1.25% of the study group, including myocardial infarction in 3 patients (0.94%); also, 2 patients underwent percutaneous coronary angioplasty and 1 patient CABG. Six subjects had a history of stroke, representing 1.87% of the study group. There was no family history of early cardiovascular disease - <55 years of age in men and <60 years of age in women. Thus, although many studies in recent years confirm an increased cardiovascular risk in HCV-infected patients, this was not demonstrated in the study group and the incidence was lower than the population prevalence. This may be related to the fact that the mean age of the subjects was 43 years (ranging from 21 to 93 years) and indeed the 10 cardiovascular incidents found in the study were in people over 60 years of age, with a male predominance of 8:2, which may confirm the relevance of the risk factor of age and sex. Older age reflects the likelihood of other cardiovascular risk factors and their accumulation and is an independent non-modifiable factor. Older age represents a potentially longer overlap of individual cardiovascular risk factors - diabetes, hypertension, and hypelipidaemia. In the general population, male gender is associated with a 3-fold higher risk of coronary events (myocardial infarction, unstable angina) and a 4-fold higher risk of death from coronary causes. This is associated with a higher prevalence of other cardiovascular risk factors, such as smoking, elevated total cholesterol, reduced HDL fraction cholesterol, and the presence of hypertension. The gender difference phenomenon is explained by the protective effect of oestrogens in premenopausal women, which have a beneficial effect on carbohydrate metabolism, lipid metabolism, vascular endothelial function, and the haemostatic system [1,5,10,27,28].

The lower incidence of cardiovascular diseases in the studied group of HCV patients may have been due to certain limitations, including the average age of the patients mentioned above, as well as the group size. In larger population studies, the incidence might be higher. This requires further research.

In addition, another Polish study showed that HCV infection does not increase cardiovascular risk in young adults up to 45 years of age [29].

The main causal and modifiable risk factors for ASCVD are elevated LDL fraction cholesterol, hypertension, smoking, obesity, and diabetes.

Based on large Polish population-based studies (WOBASZ II 2013-2014, NATPOL 2011 and PolSenior2 2016-2020), hypercholesterolaemia may affect 61% of the adult population, hypertension 35%, smoking 26%, diabetes 9% and obesity 22% [6-10].

Among the subjects, the most common cardiovascular risk factor was hyperlipidaemia, which was treated by 88 subjects, representing 28% of the study group. The mean concentration of total cholesterol was 173.98 mg/dl (SD = 38.18 mg/dl), LDL fraction 98.85 mg/dl (SD = 39.11 mg/dl), HDL fraction 52.81 mg/dl (SD = 15.36 mg/dl) and TG 123.32 mg/dl (SD = 51.17 mg/dl). Total cholesterol, LDL fraction, and TG levels did not correlate with the severity of liver fibrosis and steatosis, HCV genotype, or duration of infection. Lipid abnormalities were found more frequently, as in the general population in older

Citation: Rajewski P, Pawłowska M, Kwiatkowska J, Fadzina-Abukhouska A, Nowicka-Matuszewska A, Kozielewicz D, et al. Analysis of the Prevalence of Cardiovascular Risk Factors in Patients with Chronic Hepatitis C. J Cardiovasc Med Cardiol. 2024;11(4):049-067. Available from: https://dx.doi.org/10.17352/2455-2976.000210

patients. More advanced liver fibrosis was observed in patients with low values for HDL fraction cholesterol, which requires further study. The liver is actively involved in lipid metabolism. In the cytoplasm of hepatocytes, fatty acids are biosynthesised and metabolised, converted into triglycerides, esterified with cholesterol, and incorporated into phospholipids or formed by oxidation of ketone bodies.

Most fatty acids are converted to lipoproteins in the liver.

Hepatic dysfunction usually leads to lower serum total cholesterol concentrations in patients, except in cholestatic diseases or alcoholic hepatitis, where an increase in lipid concentrations is observed.

Most studies to date have shown that HCV infection has an impact on lipid disorders. The majority of patients with chronic hepatitis C show a reduction in total cholesterol, LDL, and HDL fractions.

The disruption of lipid metabolism caused by HCV infection causes damage to membrane structures, which probably facilitates viral replication and spread in liver tissue. This can be confirmed by studies using statins, which, by affecting lipid metabolism, simultaneously inhibited HCV replication [15,30,31]. The analysis performed confirms this, as the prevalence of lipid disorders is lower than in the general population 28% vs. 61%.

The second most common cardiovascular risk factor in the study group was excessive body weight - overweight and obesity. In the study group, the majority of patients were overweight, with a mean BMI of 26.47kg/m^2 (SD = 4.73 kg/m^2), a minimum of 16.70 kg/m^2, and a maximum of 39.91 kg/m^2. Obesity was found in 27.14%. The percentage of HCV patients with excessive body weight was higher than in the general population. In the analysed group, obesity was found in more than 5% more patients compared to population studies. In the general Polish population, obesity is found in 22%, while in the HCV patient population, obesity is found in 17% - 38% of patients. The higher proportion of overweight and obese patients may be related to the effect of HCV infection on the activity of cytokines produced by adipose tissue and the associated increase in body weight. Decreased levels of adiponectin, which acts as an endogenous factor to increase insulin sensitivity (lowers glycaemia without increasing insulin levels), stimulates adipose tissue metabolism and increases the sensitivity of muscle tissue and liver cells to insulin, thereby increasing tissue insulin sensitivity, are observed in this group of patients. A decrease in leptin, responsible for regulating feelings of hunger and satiety, is also observed in HCV patients, decreasing hunger, increasing metabolism, stimulating glucose consumption, activating the breakdown of adipose tissue, and inhibiting adipose tissue production. In contrast, there is an increase in resistin, which has a pro-inflammatory effect and exacerbates insulin resistance, and an increase in ghrelin, which causes an increase in appetite, also increases adiposity by decreasing fat oxidation, has a local effect on gastric emptying and decreases energy expenditure, and is involved in blood glucose regulation through its effect on insulin and glucagon secretion [32-39].

The increased body weight in the study group may also have been influenced by the SARS-CoV-2 coronavirus pandemic and the post-pandemic period, in which the average increase in body weight in Poland was about 5 kg [40]. As BMI increased, the CAP parameter, indicating the degree of hepatic steatosis, increased, which seems obvious. There was no statistically significant effect of HCV genotype or duration of infection on body weight and BMI in the study group.

The next most common cardiovascular risk factor was hypertension, which was found in 25% of the subjects, which was 10% lower than in the general population [7,9]. It was more common in those with advanced liver fibrosis and steatosis, which was also confirmed by other researchers. However, the mean value of liver fibrosis in the study group was F3 according to Metavir (10.35 kPa); in other studies evaluating the effect of HCV on hypertension, the percentage of advanced F4 liver fibrosis according to Metavir and clinical cirrhosis was higher and the population of HCV subjects was also older [10].

Several studies to date have confirmed an increase in the prevalence of hypertension in people with chronic hepatitis C. This is related to the effect of HCV on the development of inflammation, which can lead to atherosclerosis and vascular endothelial damage. There is apoptosis of adipocytes and impaired activity of individual adipocytokines, activation of macrophages, formation of inflammatory infiltrates, release of oxygen free radicals - formation of oxidative stress, TNF alpha, FFA, PAI 3, which are involved in the development of hepatic steatosis, insulin resistance, obesity and consequently the development of atherosclerosis and hypertension [16,17,35,41-42].

Also, extrahepatic manifestations of HCV infection, such as glomerulonephritis-membranous or membranoproliferative, leading to chronic kidney disease, can cause hypertension and were not analysed in this study [10,16,17]. In the study group, renal function determined by glomerular filtration rate - GFR showed an average of 103.34 ml/min/1.73 m^2. Five patients in the study group had chronic kidney disease with GFR < 60 ml/min/1.73 m^2, and impaired glomerular filtration did not correlate with the amount of hepatic steatosis and fibrosis.

Another cardiovascular risk factor analysed was cigarette smoking, which was found in 20.94% of participants, more often in men. The percentage of cigarette-smoking HCV patients was lower than in the general population - 20.94% *vs.* 26%. In recent years, there has been a reduction in the number of cigarette smokers, especially among young people, and an increased vogue for electronic cigarettes. In the study group, the mean age was 43 years, hence it is possible that there was an increased proportion of non-smokers or e-cigarette smokers who were not analysed. Cigarettes were mainly smoked by older people [1,9,43-46]. Passive smoking, which can also increase cardiovascular risk, was also not analysed. Another risk factor for cardiovascular disease analysed was cigarette smoking.

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Abnormal carbohydrate metabolism in the study group was a significant cardiovascular risk factor. The majority of patients had abnormal fasting glycaemia - the mean fasting glucose level in the study group was 100.40 mg/dl (SD = 23.12 mg/dl). Type 2 diabetes was found in 11.56% of HCV patients in the study group, which was more than 2% higher than in the general population (9%). Diabetes was more common in men. Higher glucose levels also correlated with the severity of liver fibrosis, which is consistent with the results obtained by other researchers. It has been shown that as liver fibrosis progresses, the risk of developing carbohydrate disorders increases. Liver function is impaired in 50% (liver fibrosis at levels F2 and F3 according to the Metavir 5-point scale - from F0 - no fibrosis to F4 - cirrhosis) of cases and, in the case of clinically overt cirrhosis, leads to the development of glucose intolerance in 80% of cases and diabetes in 10%. In the study group, mean liver fibrosis was F3 according to the Metavir scale [18,20,47-50].

Previous studies confirm the impact of chronic HCV infection on the development of insulin resistance, pre-diabetes, and diabetes. The prevalence of carbohydrate disorders in patients with chronic hepatitis C is four to ten times higher than in the healthy population and occurs in 14% - 30% of patients. In the population-based Third National Health and Nutrition Examination Survey (NHA-NES III), diabetes was 3-fold more common in patients over 40 years of age with HCV than in the HCV-uninfected population, while in patients with risk factors for diabetes, its incidence in the HCV-infected group increased up to 11-fold. Thus, HCV infection is now recognised as a risk factor for the development of diabetes, and diabetes as an extrahepatic manifestation of HCV infection. Risk factors for the development of diabetes in patients with HCV include older age, HCV genotype 3, markedly severe fibrosis or cirrhosis, a positive family history of diabetes, and kidney or liver transplantation [18,50-52].

The development of abnormal carbohydrate metabolism in HCV infection is complex and is mainly associated with insulin resistance and a chronic inflammatory response due to increased synthesis of pro-inflammatory cytokines - mainly tumour necrosis factor (TNF alpha) and interleukin 6 (IL-6). As a result of insulin resistance, there is an increase in insulin that is not efficiently utilised by the tissues, secondary hyperinsulinaemia, and consequently an increase in serum glucose levels and the development of carbohydrate disorders.

The development of insulin resistance is also associated with the direct effect of the virus on the pathway of insulin signalling. In HCV genotype 3, viral proteins can directly affect intrahepatic insulin signalling by downregulating the expression of peroxisome proliferator-activated receptor alpha (PPAR alpha). It controls the gene expression of mitochondrial carnitine palmitoyltransferase-1 (CPT-1), which reduces mitochondrial beta-oxidation responsible for fatty acid catabolism and acetyl CoA oxidase (AOX). One mechanism of insulin resistance in patients with chronic liver disease is acquired resistance to growth hormone (GH-growth hormone), which is caused by an increase in pro-inflammatory cytokines, mainly TNF-alpha. Acquired GH resistance consequently causes a decrease in insulin-like growth factor 1 (IGF -1 - insulin-like growth factor-1) and a compensatory increase in GH, exacerbating insulin resistance secondarily. Insulin resistance through the increased influx of free fatty acids (FFA) into the liver, hypertriglyceridaemia, and hyperinsulinaemia exacerbates hepatic steatosis and fibrosis. In recent studies, it has been shown that decreased insulin receptor substrate-1 (IRS-1 insulin receptor substrate-1) and kinase B (PKB/Akt) phosphorylation plays an important role in the pathomechanism of insulin resistance in HCV patients. In addition, HCV affects the insulin signalling pathway through the suppressor of cytokines signalling proteins (SOCS-3), which are directly stimulated by HCV core proteins and cause degradation of IRS-1[41,42,52,53-58].

The increased risk of developing diabetes is also associated with an increase in ghrelin secretion, resistin, and a decrease in adiponectin and leptin secretion by adipose tissue, resulting in increased insulin resistance and weight gain [15,35,36-37].

There were no statistically significant differences according to HCV genotype or duration of infection.

In recent years, chronic inflammation has been cited as an increased risk factor for cardiovascular disease. In chronic hepatitis C, an increase in pro-inflammatory cytokines is observed - mainly interleukin 1 and 6 (IL-1, IL-6) and tumour necrosis factor-alpha - TNF alpha. Under the influence of these cytokines, C-reactive protein - CRP - is synthesised, which plays an important role in the process of atherosclerosis. It can damage vascular walls, accelerate the formation of atherosclerotic plaques and cause an increased risk of plaque rupture - destabilisation. Elevated CRP levels are associated with inflammation in the arteries, which promotes cholesterol accumulation and plaque deposition. Recent studies suggest that CRP levels correlate with the risk of cardiovascular events. Based on the available studies, CRP values below 1 mg/L correspond to a low cardiovascular risk, while values above 3 mg/L correspond to a high risk. Values between 1 and 3 mg/L are associated with intermediate - moderate cardiovascular risk [58-62]. In the analysed group of HCV-infected patients, the mean CRP concentration was 1.73 mg/L, which corresponds to intermediate (moderate) cardiovascular risk.

Although CRP levels are not specific for heart disease, when combined with the presence of other cardiovascular factors, they can help assess the likelihood of cardiovascular incidents.

Most studies on the effect of HCV infection on CRP levels do not show statistically significant differences in CRP levels. Some of them show a slight increase in CRP levels mainly in patients with HCV genotype 2; on the other hand, some studies show a reduction in CRP levels through a decrease in IL-6 production in an immune tolerance mechanism caused by continuous HCV replication in the liver [63-66]. On the other hand, in a recent study of young adults with chronic hepatitis C, CRP was high and measured at 1.43 mg/L [29].

The effect of HCV on C-reactive protein levels and its

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association with increased cardiovascular risk in this group of patients requires further study.

On the basis of the analysis, it can be assumed that the cardiovascular risk in patients with chronic hepatitis C may be higher than in the general population, especially in older patients and advanced liver fibrosis. The effect of HCV on the development of carbohydrate disorders, including diabetes and excessive body weight, is particularly notable.

The metabolic abnormalities present in chronic hepatitis C are characteristic of the so-called metabolic syndrome, a cluster of risk factors for cardiovascular disease which, when present together, significantly increase this risk. Therefore, in recent years, HCV infection has been treated as a metabolic liver disease, which is also a risk factor for atherosclerosis and cardiovascular disease - coronary heart disease, stroke, or peripheral vascular disease. Therefore, it seems necessary in all HCV-infected patients to pay attention to the presence of possible cardiometabolic factors and to carry out systematic, periodic check-ups, especially in patients with other risk factors for cardiovascular disease or after a myocardial infarction or stroke. Attention should also be paid to an appropriate healthy lifestyle, i.e. dietary and physical activity recommendations, as well as the abstinence from smoking, including electronic cigarettes, and alcohol consumption. Prompt recognition of HCV infection and the initiation of treatment with drugs that act directly on the virus reduces the severity of metabolic disorders, particularly incidents of insulin resistance and diabetes, and reduces the risk of cardiovascular incidents. It is therefore important to screen for anti-HCV antibodies in all patients with already diagnosed carbohydrate disorders as well as in the general population as a broad prevention of metabolic disorders, including diabetes, and prevention of cardiovascular disease [5,29,67-70].

Conclusion

HCV increases cardiovascular risk. Lipid disorders are the most common cardiovascular risk factor in patients with HCV, however, HCV does not increase their prevalence compared to the general population. The low levels of HDL fraction cholesterol in patients with HCV correlate with the severity of liver fibrosis. Overweight and obesity in HCV patients are more common than in the general population and correlate with the severity of hepatic steatosis. Also, elevated fasting glucose levels and diabetes in patients with HCV are more common than in the general population and correlate with the severity of liver fibrosis.

HCV does not increase the risk of hypertension. It increases C-reactive protein levels which may increase cardiovascular risk. The HCV genotype and HCV RNA viral load size had no effect on the prevalence of cardiovascular factors. It is important that patients with HCV should be screened for cardio-metabolic factors in the prevention of cardiovascular disease.

Institutional review board statement

This observational study was conducted in a real-world setting with approved drugs. The patients were not exposed to any experimental interventions nor did the study intervene with the clinical management of the patients. This study only collected information from patients' medical records. The analysis included routine examinations and tests performed on patients treated within the therapeutic program of the National Health Fund. The data were originally collected to assess the treatment efficacy and safety in individual patients, not for scientific purposes. The study was approved by the ethical committee in January 2024 – number KB 146/2024 (The Bioethics Committee Nicolaus Copernicus University in Torun at the Collegium Medicum. Ludwik Rydygier in Bydgoszcz). The study was not conducted on animals.

Informed consent statement

Patient consent was waived due to the retrospective design of the study.

Author contributions

Conceptualization, P.R.; Methodology, P.R.; Software, P.R.; Validation, P.R.; Formal analysis, P.R., J.K., A.M.N., A.F.A..; Investigation, P.R.; Data curation, D.K., D.D., J.K, A.M.N, A.F.A., A.O. and J.C.; Writing—original draft, P.R.; Writing—review & editing, P.R., M.P. and J.C.; Visualization, J.C.; Supervision, P.R, M.P.; Project administration, M.P. All authors have read and agreed to the published version of the manuscript.

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