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Long-Term Monitoring of Liver Fibrosis and Steatosis in Patients with Chronic Hepatitis C after Achieving a Sustained Virologic Response to Antiviral Therapy

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Aim: to analyze the dynamics of fibrosis and steatosis of the liver according to fibroelastometry in patients with chronic hep-atitis C (CHC) after ≥ 6 months from transient elastometry (TE) achieving a sustained virologic response (SVR) to antiviral therapy.

Materials and methods. At baseline, a prospective observational study included 628 CHC patients with known stage of liver fibrosis (F) before AVT, some of whom were phased out due to non-compliance with the inclusion criteria. The final analysis included 297 patients who had transient elastometry (TE) data with CAP™ technology on the severity of liver fibrosis (± steatosis) before treatment and after ≥ 6 months after reaching SVR (67 % – interferon-free regimens of therapy). Median follow-up from the moment SVR was confirmed was 3 years [2; 6].

Results. At the end of the study, the average age of patients was 49 ± 12 years, of which 53 % were men. In the long-term period after reaching SVR, regression of liver fibrosis was diagnosed in 80 % of cases (including in patients with cirrhosis), and the progression of fibrosis was in 3 % of patient. At the same time, regression of liver steatosis was detected only in 31 % of the patient, worsening of the results was in 23 % (26 % of them had the appearance of steatosis (S) of the liver of 1–3 degrees in persons with no fatty liver before the start of AVT). In the group of patients with liver steatosis, the proportion of men was significantly higher ($p = 0.004$). Clinically significant stages of fibrosis F3–F4 were significantly more often recorded in patients with hepatic steatosis, both before treatment (46 % S1–S3 and 22 % S0, $p < 0.001$) and after ≥ 6 months after reaching SVR (19 % S1–S3 and 9 % S0, $p = 0.023$).

Conclusion. In patients with chronic hepatitis C with SVR achieved in the long term, despite a significant regression of liver fibrosis, a high prevalence of hepatic steatosis remains. The data obtained indicate the feasibility of routine diagnosis of both fibrosis and steatosis of the liver in the management of patients with chronic HCV infection before and after successful antiviral therapy.

Keywords: chronic hepatitis C, sustained virological response, transient elastometry, liver fibrosis, hepatic steatosis, prevalence

Conflict of Interest: authors declare no conflict of interest.

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Долгосрочный мониторинг фиброза и стеатоза печени у больных хроническим гепатитом С после достижения устойчивого вирусологического ответа на противовирусную терапию

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Цель исследования: анализ динамики фиброза и стеатоза печени по данным фиброэластометрии у больных хроническим гепатитом С (ХГС) через ≥ 6 мес. после достижения устойчивого вирусологического ответа (УВО) на противовирусную терапию (ПВТ).

Материалы и методы. Исходно под наблюдением в проспективном обсервационном исследовании было 628 больных ХГС с известной стадией фиброза (F) печени до начала ПВТ, часть которых поэтапно исключались из-за несоответствия критериям включения. В итоговый анализ включены 297 пациентов, имевших данные фиброэластометрии (ТФ) с технологией CAP™ о выраженности фиброза (± стеатоза) печени до начала лечения и через ≥ 6 мес. после достижения УВО (67 % – безинтерфероновые режимы терапии). Медиана наблюдения от момента подтверждения УВО – 3 года [2; 6].
Результаты. На конец исследования средний возраст пациентов – 49 ± 12 лет, из них 53 % мужчин. В отдаленном периоде после достижения УВО в 80 % случаев диагностирован регресс фиброза печени (в том числе и у пациентов с ЦП), а у 3 % пациентов результаты ТФ свидетельствовали о прогрессировании хронического заболевания печени. В то же время регресс стеатоза печени выявлен только у 31 % пациента, ухудшение результатов ТФ – у 23 % (из них у 26 % появление стеатоза (S) печени 1–3-й степени у лиц с отсутствием жировой инфильтрации печени до начала ПВТ). В группе пациентов с наличием стеатоза печени доля мужчин была достоверно выше (p = 0,004). Клинически значимые стадии фиброза F3–F4 достоверно чаще регистрировались у больных со стеатозом печени как до начала лечения (46 % S1–S3 и 22 % S0, $p < 0,001$), так и через ≥ 6 мес. после достижения УВО (19 % S1–S3 и 9 % S0, p = 0,023).
Выводы. У больных ХГС с достижением УВО в отдаленном периоде, несмотря на значительный регресс фиброза печени, сохраняется высокая распространенность стеатоза печени. Полученные данные свидетельствуют о целесообразности рутинной диагностики как фиброза, так и стеатоза печени при ведении пациентов с хронической HCV-инфекцией до и после успешно проведенной противовирусной терапии.
Ключевые слова: хронический гепатит С, устойчивый вирусологический ответ, транзиентная фиброэластометрия, фиброз печени, стеатоз печени, распространенность
Конфликт интересов: авторы заявляют об отсутствии явных и потенциальных конфликтов интересов.

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In chronic HCV infection, the severity of hepatic fibrosis is the most important prognostic factor of the risk of unfavorable disease outcomes. A sustained virologic response (SVR) due to antiviral therapy (AVT) with interferon (IFN)-containing regimens is known to result in hepatic inflammation and fibrosis reversal, which reduces the likelihood of hepatic failure and mortality from hepatic cirrhosis (HC) and hepatocellular carcinoma (HCC). In addition, SVR achievement in patients with clinically significant hepatic fibrosis before AVT is associated with increased overall survival (the risk of all-cause mortality is several times lower than in patients with persisting HCV) [1, 2]. However, serious adverse events and insufficient efficacy (50–80 %) limit the use of this therapeutic regimen. The emerged range of direct-acting antiviral drugs (DAAs) that achieve 90–95 % efficacy in case of 8–12 week treatment duration and a favorable safety profile began to replace IFN-containing AVT regimens from clinical practice [3–5]. Therefore, the long-term clinical outcomes of HCV-associated chronic hepatic disease (CHD) should be evaluated in patients achieving SVR with short courses of DAA treatment.

Previous studies have shown a high prevalence (up to 80 %) of hepatic steatosis in patients with chronic HCV infection, and about half of them have clinically significant fatty liver infiltration [6, 7], which is also associated with an increased risk of hepatic cirrhosis and HCC formation [8]. HCV is known to have a direct steatogenic effect. The most pronounced effect on lipid metabolism is recorded in HCV genotype 3 infection. Thus, when comparing the treatment outcomes for CHC patients using IFN-containing regimens, the hepatic steatosis severity upon SVR achievement reduced significantly in genotype 3 HCV-infected patients (91 % and 19 %, $p < 0.0001$), whereas the hepatic steatosis trends were independent of the response to treatment in patients infected with other HCV genotypes (≥1 degree reduction in fatty liver dystrophy with SVR achievement in 43 % cases, and without SVR achievement, in 34 % cases) [9]. It is also noteworthy that Grade 2–3 hepatic steatosis in patients with chronic HCV infection is a risk factor for HCC even after SVR to treatment with various AVT regimens, if the age is ≥ 55 years, in case of F3–F4 hepatic fibrosis stage, and of diabetes mellitus (DM). It has also been shown that HCC patients in the group that achieved DAA-induced SVR have a higher prevalence of fatty liver infiltration than the patients in whom SVR was induced by IFN-containing regimens [10, 11]. Thus, in CHC patients, the risk of adverse disease outcome is influenced by hepatic steatosis, concomitant to fibrosis, which emphasizes the importance of their combined assessment in the follow-up over time.

The hepatic puncture biopsy is still the “gold” standard for diagnosing hepatic fibrosis and steatosis in CHD patients. However, possible errors in obtaining tissue samples, resulting in underestimation of true pathological changes in the liver [12], the technique invasiveness, risk of severe complications, need for frequent monitoring of hepatic fibrosis trends in CHC patients do not allow for using

hepatic biopsy as a diagnostic method for routine investigation. Currently, according to Russian and international clinical guidelines on the management and treatment of CHC patients, non-invasive diagnosis of hepatic fibrosis is recommended to determine the approach to AVT and further patient monitoring [4, 5, 13]. The most appropriate method for noninvasive diagnosis of hepatic fibrosis and steatosis is transient fibroelastometry (TF), which has high diagnostic accuracy in both CHC and nonalcoholic fatty liver disease (NAFLD) [14, 15]. Currently, most studies on the efficacy of various interferon-free AVT regimens focus on the assessment of hepatic fibrosis trends after SVR achievement using TF. However, the data on the impact of effective DAA treatment regimens on hepatic steatosis and on the trends for pathological changes in the hepatic tissue in the long term, after SVR achievement, are insufficient.

Study purpose: to review the trends for hepatic fibrosis and steatosis using the fibroelastometry data in CHC patients ≥6 months after achieving SVR to antiviral therapy.

Materials and methods

In a prospective cohort longitudinal observational study, data from the outpatient records of 628 patients with confirmed CHC, who were followed up at the Department of Infectious Diseases and Epidemiology of the Moscow State University of Medicine and Dentistry (A.I. Evdokimov University), were reviewed at the baseline since 2000. Then patients (n = 331) who did not meet the inclusion criteria were phased out, which is shown as a flow chart in Fig. 1.

Study inclusion criteria:

- age ≥ 18 years;
- confirmed chronic hepatitis C (anti-HCV Abs and HCV RNAs in blood >6 months);
- full antiviral therapy course with SVR achievement;
- diagnosed hepatic fibrosis (±steatosis) stage before AVT and at the case follow-up ≥6 months after SVR achievement.

Exclusion criteria:

- co-infection with HBV (hepatitis B virus), HIV (human immunodeficiency virus);
- hepatic carcinoma;
- hepatic transplantation before AVT.

As it was impossible to use TF in Russia before 2006, the hepatic fibrosis stage in some CHC patients was diagnosed based on a comprehensive assessment of clinical, laboratory and instrumental data during the follow-up of patients over time. Since 2007, the Department of Infectious Diseases of Moscow State University of Medicine and Dentistry (FSBI HPE) (A.I. Evdokimov University) additionally performed noninvasive diagnosis of hepatic fibrosis using the FibroScan-502 Touch machine (Echosens, France). The elastography findings were taken into account in the comprehensive hepatic fibrosis diagnosis. In 2014, it became possible to determine the fatty liver infiltration severity using additional technology CAP™ (Controlled Attenuation Parameter), which allowed for determination of hepatic steatosis before and after AVT in patients.

TF results were evaluated taking into account the reference values of the hepatic elasticity index and the ultrasound wave controlled attenuation parameter suggested by the developers of this technique and recommended in the studies by V. Wong and T. Karlas [16–18]. To determine hepatic fibrosis, we focused on the threshold values of the hepatic elasticity index expressed in kPa, according to the METAVIR-scale hepatic fibrosis (F) stage assessment system: F0 (no fibrosis): ≤5.8 kPa; F1: 5.9–7.2 kPa; F2: 7.3–9.5 kPa; F3: 9.6–12.5 kPa; F4: >12.5 kPa. To determine the hepatic steatosis (S) degree, the ranges of CAP™ measurements, expressed in decibels per meter (dB/m), were as follows: S0 (no steatosis): < 229.9 dB/m; S1 (5–33 %, mild): 230.0–249.9 dB/m; S2 (33–66 %, moderate): 250.0–276.9 dB/m; S3 (>66 %, severe): ≥277 dB/m.

Data on the presence/absence of fatty liver infiltration before AVT were known in 58 % (366/628) of patients, of whom hepatic steatosis was diagnosed in some patients (n = 39) on the basis of comprehensive instrumental examination (ultrasound examination ± puncture hepatic biopsy or computer tomography), without specifying the degree of fatty liver infiltration severity: after SVR achievement, the hepatic steatosis degree was determined using TF in these patients (as in the other 327 patients).

In the observation period, antiviral therapy was given to 76 % (477/628) patients infected with different HCV genotypes. Given SVR achievement and the absence of hepatic fibrosis, and in some cases, the presence of minor hepatic fibrosis before AVT, 37 % (177/477) patients declined further evaluation in this study. In 0.5 % (n = 3) of cases, hepatic transplantation was performed in patients who did not receive AVT.

A total of 297 patients were included in further review, of whom 33 % (n = 99) were treated with IFN-containing AVT regimens; the rest were treated with DAAs only (glecaprevir/pibrentasvir grazoprevir/elbasvir; dasabuvir/ombitasvir/paritaprevir/ritonavir ± ribavirin; sofosbuvir + daclatasvir; sofosbuvir/velpatasvir, etc.).). In the case follow-up, the severity of steatosis combined with hepatic fibrosis was assessed in 94 % (278/297) patients, because CAP™ determination was not performed within a short period of time for technical reasons.

The hepatic fibrosis and steatosis severity was assessed by TF method ≥6 months after SVR confirmation (after 12 weeks with DAA treatment alone and 24 weeks with IFN-containing regimens). The time interval between repeated hepatic examinations was 6–12–24 months. Follow-up duration after SVR confirmation: 1 year in 17 % (n = 50) patients, 2 years in 22 % (n = 67) patients, 3 years in 20 %

(n = 60) patients, 4 years in 7 % (n = 20) patients, 5 years in 7 % (n = 21) patients, >5 years in 27 % (n = 79) patients. The median follow-up from the SVR confirmation time was 3 years [2; 6].

At the end of the study, deaths were reported in 1.3 % cases (n = 8): HC decompensation due to CHC, no AVT was performed (62 % / n = 5); death unrelated to HCV-associated chronic hepatic disease, a history of AVT with SVR achievement (38 % / n = 3).

The study was conducted in accordance with the principles of the World Medical Association's Helsinki Declaration and complied with ethical standards. Written informed consent to participate in the research was obtained from all patients. The study was approved at the meeting of the Inter-University Ethics Committee on May 19, 2022 (Protocol # 05-22).

Statistical review. The distribution normality was verified using the Kolmogorov-Smirnov criterion. With a normal distribution, quantitative variables are presented as arithmetic mean (M), standard deviation (SD); with a non-normal distribution, they are presented as median (Me) and interquartile range (as 25th and 75th percentiles; 25 %; 75 %). Qualitative variables are presented as absolute values and percentages; the χ^2 test was used to compare them. The level of $p < 0.05$ was considered statistically significant.

Study findings

Key demographic and laboratory data for 628 adult Caucasian patients with a known hepatic fibrosis stage before AVT and after SVR achievement at the end of participation in the study are shown in Table 1.

The study cohort is of working age, predominantly male and predominantly infected with HCV genotypes 1 and 3.

The patients' distribution by hepatic fibrosis (F) and steatosis (S) severity in the groups of CHC patients before AVT and ≥6 months after SVR achievement is shown in Tables 2 and 3.

During the case follow-up ≥6 months after the SVR achievement, a significant decrease in the number of patients with F1–F4 hepatic fibrosis was recorded, which increased the share of patients without this disease respectively ($p < 0.001$). A similar pattern was not detected when reviewing the hepatic steatosis trends. A slight increase in the share of patients both without hepatic steatosis and with Grade 3 steatosis ($p > 0.05$) was found in the group of patients, in whom fatty liver infiltration was diagnosed before AVT using not only TF (and therefore, in some patients its degree was unknown), ≥6 months after SVR achievement. However, when reviewing the results of hepatic steatosis diagnosis in the group of patients examined before and after TF-based AVT, upon SVR achievement, the share of patients with severe hepatic steatosis (S3) became even higher ($p > 0.05$), and that of patients without fatty liver infiltration remained unchanged. Severe hepatic steatosis (S2–S3) in almost 50 % cases of CHC patients before and after AVT is noteworthy.

The ranking of patients into groups, by the HCV genotype the patient was infected with and by fibrosis stage/hepatic steatosis grade, had no effect on the findings on hepatic fibrosis and steatosis severity after SVR achievement ($p > 0.05$).

The share of patients without hepatic steatosis (27 %, n = 9) remained unchanged during the case follow-up after SVR achievement, while the share

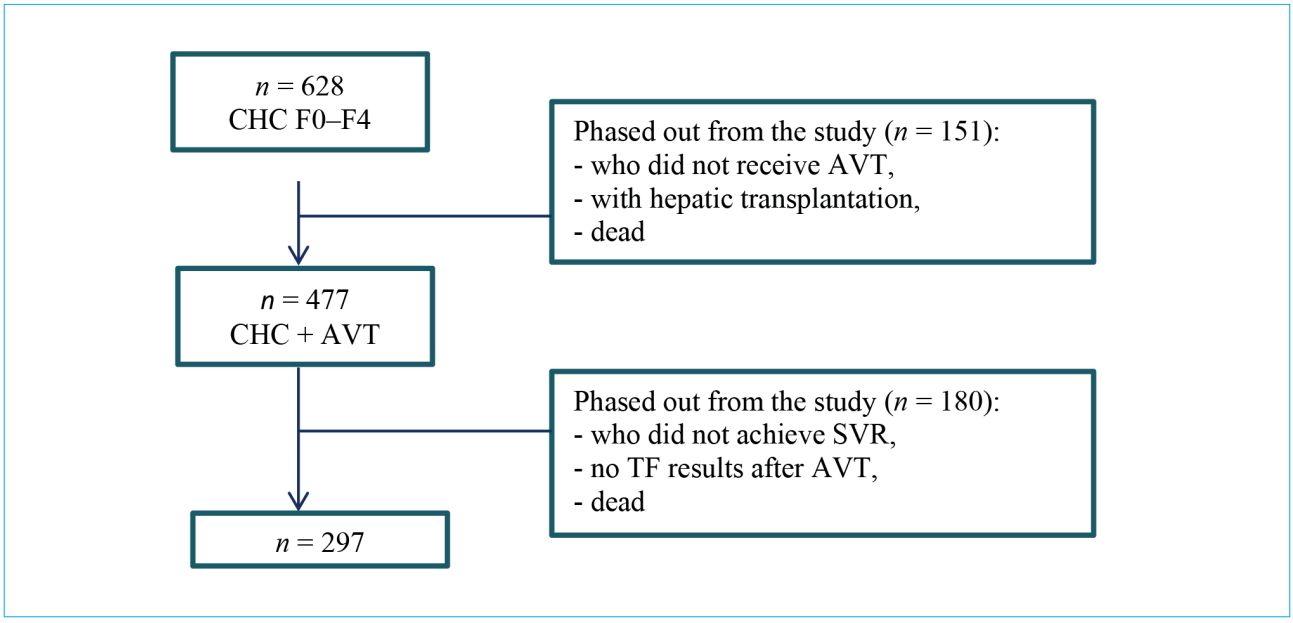


Fig. 1. Flow chart of phasing out of patients from the study

Table 1. Basic patient data before AVT and after SVR achievement as of the end of the study

Parameter	Before AVT	After SVR achievement	*p*-value
Age, years (M ± SD)	48 ± 12	49 ± 12	0.2453
Gender, *n* (%): males females	 345 (55 %) 283 (45 %)	 158 (53 %) 139 (47 %)	<0.001
HCV genotypes, n (%): Genotype 1 Genotype 2 Genotype 3 Genotype 4 Mixed genotypes Unidentified genotype	 354 (56.4 %) 66 (11 %) 170 (27 %) 2 (0.3 %) 21 (3.3 %) 15/(2 %)	–	–
ALT, U/L (M ± SD)	83 ± 72	25 ± 8	<0.001
AST, U/L (M ± SD)	60 ± 43	26 ± 10	<0.001
Platelets, $\times 10^9$/l (M ± SD)	209 ± 80	228 ± 51	0.6526
Albumin, g/l (M ± SD)	44 ± 5.5	45 ± 4.9	0.05
Glycated hemoglobin, % (M ± SD)	5.8 ± 1.2	5.6 ± 0.9	0.1579
Total cholesterol, mmol/l (M ± SD)	4.8 ± 1.2	5.0 ± 1.1	0.1578

Table 2. The patients' distribution by hepatic fibrosis severity in the groups of CHC patients before AVT and ≥6 months after SVR achievement

Stages of hepatic fibrosis, F	Before AVT	After AVT	*p*-value
F0, *n* (%)	112 (18 %)	175 (59 %)	<0.001
F1, *n* (%)	166 (26 %)	53 (18 %)	<0.001
F2, *n* (%)	128 (21 %)	24 (8 %)	<0.001
F3, *n* (%)	77 (12 %)	13 (4 %)	<0.001
F4, *n* (%)	145 (23 %)	32 (11 %)	<0.001
TOTAL, *n* (%)	628 (100 %)	297 (100 %)	–

Table 3. Patients' distribution according to the hepatic steatosis severity in the groups HCV patients before AVT and ≥6 months after SVR achievement

Degrees of hepatic steatosis, S	Results of a comprehensive examination			Fibroelastometry results, *n* = 146		
	Before AVT, *n* = 366	After AVT, *n* = 278	*p*-value	Before AVT	After AVT	*p*-value
S0, *n* (%)	119 (33 %)	108 (39 %)	0.466	53 (36 %)	53 (36 %)	1.000
S1, *n* (%)	38 (10 %)	39 (14 %)	0.910	19 (13 %)	21 (15 %)	0.733
S2, *n* (%)	55 (15 %)	33 (12 %)	0.022	27 (19 %)	16 (11 %)	0.069
S3, *n* (%)	115 (31 %)	98 (35 %)	0.245	47 (32 %)	56 (38 %)	0.270
S (without specifying the degree), *n* (%)	39 (11 %)	–	–	–	–	–

of patients with severe S2–S3 fatty liver infiltration decreased (64 % (*n* = 21) before AVT, 55 % (*n* = 18), after AVT, *p* = 0.631) in the group of genotype 3 HCV-infected patients having TF results before and after AVT (*n* = 33). Only 5 (15 %) patients underwent AVT with IFN-containing regimens (the hepatic steatosis degree remained unchanged after SVR achievement (*n* = 1 — S2, *n* = 3 — S3); *n* = 1 — before and after AVT S0).

The trends for noninvasive hepatic fibrosis diagnosis results ≥6 months after SVR achievement as compared with baseline data before AVT are shown in Fig. 2.

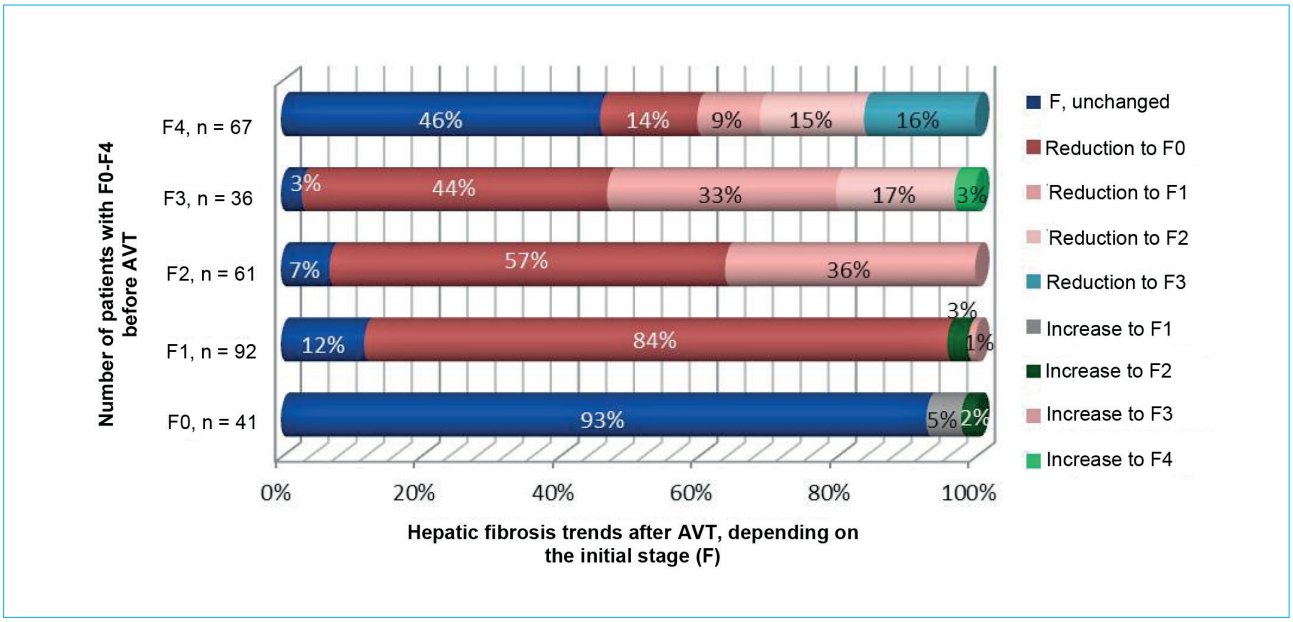


Fig. 2. Hepatic fibrosis trends in CHC patients after ≥6 months after SVR achievement, according to fibroelastometry (n = 297)

The follow-up examination, ≥6 months after SVR achievement, in the group of F1–F4 hepatic fibrosis patients, suggested that:

- in 80 % (204/256) of cases, there was a decrease in hepatic elasticity parameters beyond the threshold values corresponding to the hepatic fibrosis stage before AVT; it is worth noting the fibrosis reversal to F0 in some (24 %, 25/103) patients with severe (F3–F4) hepatic damage (follow-up duration after SVR achievement ranged from 2 years to 17 years);
- in 18 % (47/256) of cases, hepatic fibrosis severity remained unchanged; however, in 59 % of them (n = 28) the hepatic elasticity index decreased within the threshold values corresponding to the hepatic fibrosis stage before AVT: at F1 stage, in 36 % (4/11) patients, at F2 stage, in 25 % (1/4), at F3 — n = 1, F4 stage, in 71 % (22/31) patients, respectively); an increase in hepatic elasticity index from 26.7 kPa to 66.4 kPa was recorded in one patient with F4 stage fibrosis 2 years after SVR achievement;
- in 3 % (8/297) of cases there was an increase in the hepatic elasticity index, which corresponded to an increase in hepatic fibrosis at stage 1–2; in 87.5 % (n = 7) these were males.

Before and after AVT, 164 patients were diagnosed with hepatic steatosis. S2 and S3 hepatic steatosis was diagnosed in 76 % (13/17) cases during the case follow-up after SVR achievement (the follow-up duration is 5–10 years), and no hepatic steatosis was diagnosed in 18 % (3/17) patients (follow-up duration is 8–16 years) among 10 % (n = 17) patients with fatty liver infiltration of unspecified severity before AVT. The hepatic steatosis trends ≥6 months after SVR achievement as compared with baseline data obtained by TF method before AVT are shown in Fig. 3.

According to TF results ≥6 months after SVR achievement, unlike with fibrosis trends, the following percentages were recorded in the group of patients with S1-S3 hepatic steatosis:

- only 31 % (29/94) of cases had a decrease in CAP™ beyond the threshold values corresponding to the degree of hepatic steatosis before AVT;
- in 48 % (45/94) of cases, hepatic steatosis severity remained unchanged; however, in 56 % of them the change in controlled ultrasound wave attenuation within the threshold values corresponding to the degree of hepatic steatosis before the AVT was revealed: 20 % (n = 9) had a decrease in CAP™ (at S2 50 % (2/4), S3 19 % (7/37)), and conversely, 36 % (n = 16) had an increase in CAP™ (at S1 25 % (1/4), S3 41 % (15/37));
- in 23 % (34/147) of cases TF results worsened; of them, 76 % (n = 26) had an increase in CAP™ corresponding to S2–S3; it is worth noting the emergence of hepatic steatosis in 26 % (14/53) of those without fatty liver infiltration before AVT, of which 43 % (n = 6) had severe S2–S3 steatosis (follow-up 2–4 years).

The patients' distribution by gender in the groups of patients with and without hepatic steatosis before AVT (n = 366) and over time, after SVR (n = 278) achievement, is shown in Fig. 4.

Both before and after AVT, the share of males in the subgroup of patients with hepatic steatosis was significantly higher (p = 0.004), while no

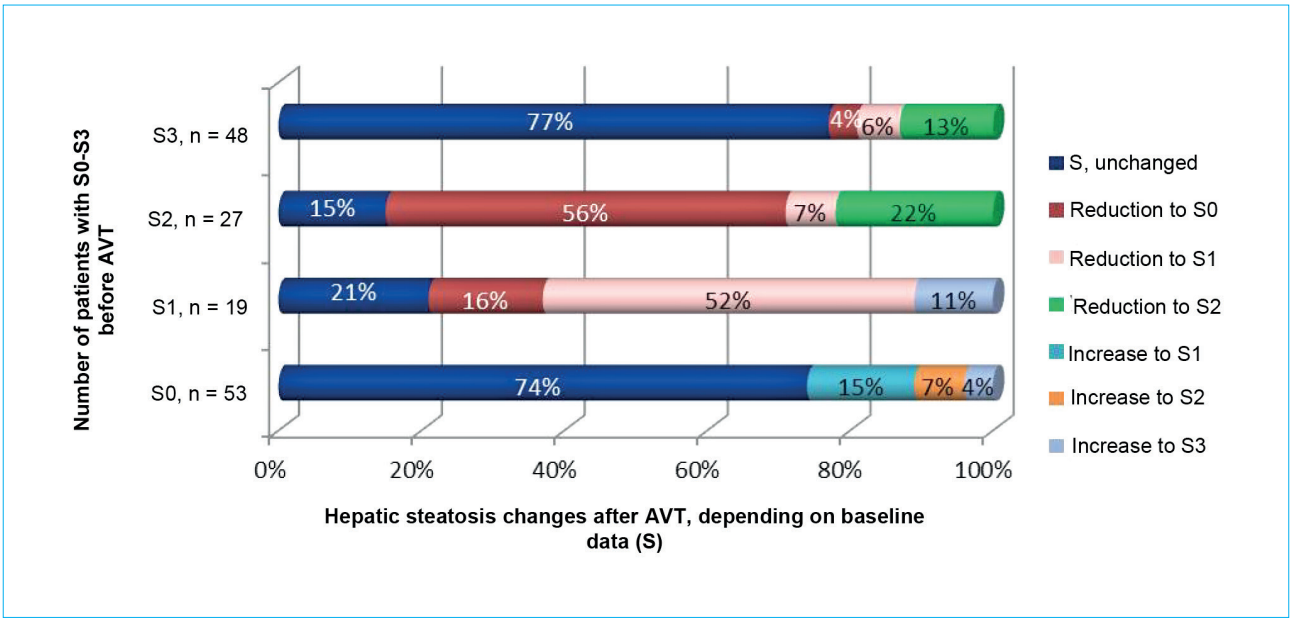


Fig. 3. Hepatic steatosis trends in CHC patients after ≥6 months after SVR achievement, according to fibroelastometry (n = 147)

statistically significant differences by gender were found in the subgroup of patients without hepatic steatosis (p = 0.446).

Hepatic steatosis prevalence before AVT and ≥6 months after SVR achievement in patients with severe hepatic fibrosis (F3–F4) was reviewed further, see Fig. 5.

High hepatic elasticity values according to TF data, which correspond to F3–F4 stages, were recorded much more frequently in patients with hepatic steatosis, both before AVT (46 %, 114/247 (S1–S3) and 22 %, 26/119 (S0), p < 0.001) and ≥6 months after SVR achievement (19 %, 33/170 (S1–S3) and 9 %, 10/108 (S0), p = 0.023).

Discussion

Currently, chronic HCV infection and nonalcoholic fatty liver disease (NAFLD) are the leading causes of CHD, the adverse outcomes of which are the main indications for hepatic transplantation worldwide. The share of patients who achieved SVR has increased significantly in recent years, due to the high efficacy (up to 95 %) of DAAs used to treat chronic HCV infection, while the prevalence of NAFLD continues to grow rapidly [19–21]. SVR achievement is known to be considered as a prognostic marker associated with HCV elimination, reversal of pathological changes in

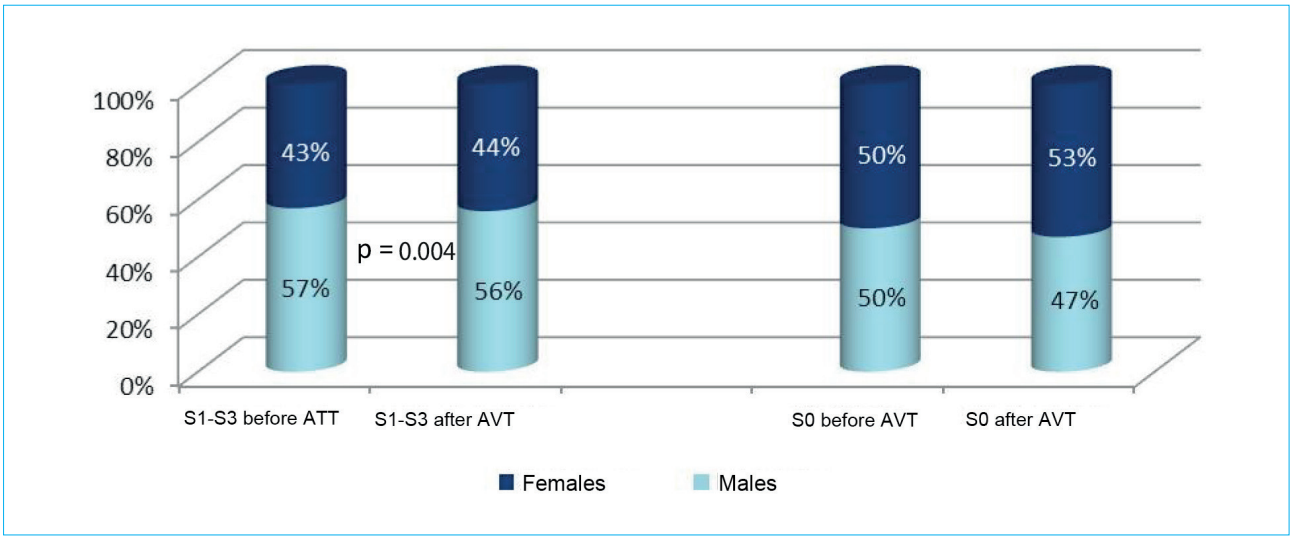
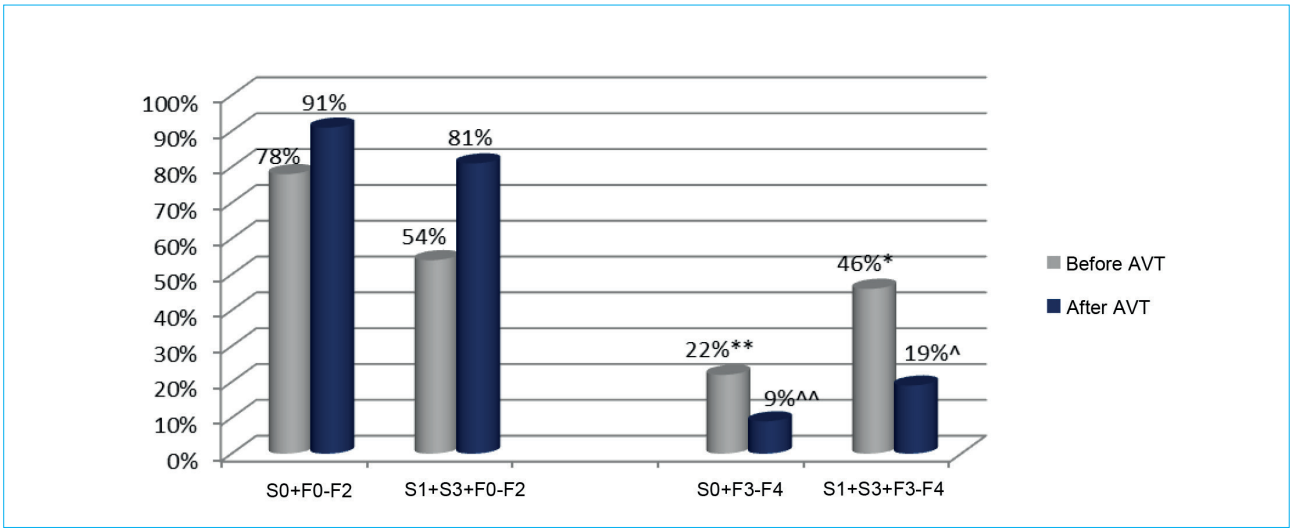


Fig. 4. The patients' distribution by gender, depending on the presence/absence of hepatic steatosis before AVT and after SVR achievement



*,** — $p < 0.001$; ^,^^ — $p = 0.023$

Fig. 5. Hepatic steatosis prevalence in CHC patients with severe hepatic fibrosis before AVT and after SVR achievement

the hepatic tissue, reduced HC and hepatocellulary carcinoma risk. Long-term follow-up studies of patients who achieved SVR with different AVT regimens have shown reversal of hepatic fibrosis in most patients, and it is more significant in those who received DAAs. Significant decrease of hepatic elasticity index according to TF is recorded in the first 6–12 months after SVR achievement, especially in patients with baseline severe hepatic fibrosis and high plasma aminotransferases, with its further gradual decrease in the following 5 years [22–26].

The findings obtained in this study are consistent with the scientific literature that demonstrates the hepatic fibrosis reversal in a significant number of HCV-infected patients when they achieve SVR, even in case of hepatic cirrhosis, regardless of the patient's baseline parameters and the AVT regimen [27, 28]. Long-term monitoring of patients (in 73 % of cases, for 1 year to 5 years) 6 months after SVR achievement revealed the hepatic fibrosis reversal in 80 % cases on the basis of elastometry data and its progression in 3 % cases (n = 8: 50 % — IFN-based AVT, 75 % — infection with 1b HCV genotype), including patients without hepatic fibrosis before AVT. It is worth noting the decrease in 54 % (36/67) cases of hepatic elasticity parameters (kPa), which exceeds the lower threshold value corresponding to F4 stage in the group of HC patients, which indicates the reversal of hepatic fibrosis, in 42 % cases (n = 15), to F0–F1 stages. However, according to the literary data, significant improvement of hepatic elasticity indices after SVR achievement does not always correlate with the change in intra-hepatic venous pressure gradient. Thus, the disease decompensation risk remains in clinically significant portal hypertension (≥10 mmHg), despite successful DAA therapy: 24 weeks after SVR achievement, in 78 % of hepatic cirrhosis patients, after 96 weeks, in 53 % of patients with a history of ascites and intra-hepatic venous pressure gradient of ≥16 mmHg before AVT [29, 30]. Thus, effectively performed AVT in CHC patients without clinically significant portal hypertension leads to a significant reduction in hepatic disease associated mortality; however, hepatic disease progression, in most cases associated with other causes and in some cases unexplained, is observed despite SVR achievement in a small proportion of patients [24]. In patients with clinically significant portal hypertension after successful AVT, it is advisable to focus on intrahepatic venous pressure gradient, in addition to SVR achievement, which will enable to predict the hepatic cirrhosis progression.

Despite a significant reversal of hepatic fibrosis after SVR achievement, we should not forget about fatty liver infiltration that often accompanies hepatic fibrosis. Hepatic steatosis, being the first NAFLD stage, a favorable option of its course, which often occurs in healthy persons, may influence the CHD progression associated, in particular, by HCV infection [31]. Regardless of the causes that induced excessive lipid accumulation in the liver, a small proportion of patients may develop non-alcoholic steatohepatitis, with further progression to hepatic cirrhosis.

The data on hepatic steatosis trends after SVR achievement are contradictory in scientific literature. Some of them demonstrate SAR™ reduction according to TF data, including hepatic cirrhosis patients, 12–24 weeks after completion of DAA therapy [32–35], and others, on the contrary, hepatic steatosis progression [36–38]. The study reported a high prevalence of hepatic steatosis, both before AVT and during long-term follow-up after SVR achievement. The proportion of male patients was significantly higher in the group of patients with hepatic steatosis, which is consistent with numerous data indicating a higher prevalence of NAFLD in men worldwide [20]. Long-term patient monitoring after SVR achievement revealed steatosis progression in those with the baseline fatty liver infiltration and enabled to newly diagnose steatosis in those without this disease before AVT. Overall, the share of patients with severe fatty liver infiltration (S2-S3) was 77 % (131/170) after successful AVT in the group of patients with hepatic steatosis.

Effective treatment of chronic HCV infection leads to significant reversal of hepatic fibrosis over time, while the data on the hepatic steatosis prevalence and severity are quite alarming. Since clinically significant fibrosis (F3–F4) and steatosis (S2–S3) are key predictors of adverse disease outcomes, long-term monitoring of both fibrosis and steatosis change over time is necessary to stratify patients by the CHD progression and decompensation risk and the hepatocellular carcinoma risk. Obviously, a decrease in the hepatic elasticity index and the controlled ultrasound wave attenuation parameter, according to TF data, due to AVT in the long term is a favorable clinically significant factor in forecasting the initial HCV-associated CHD course.

Conclusions

1. After successful AVT, CHC patients remain at risk of hepatic disease progression due to concomitant hepatic steatosis. Despite significant reversal of hepatic fibrosis, the prevalence and severity of hepatic steatosis remained high after SVR achievement.

2. The existing hepatic steatosis in CHC patients years down the line after the SVR achievement, the predominant proportion of individuals with concomitant fatty liver infiltration in case of severe hepatic damage (F3–F4), emphasize the importance of combined long-term monitoring of hepatic fibrosis and steatosis.

3. Long-term studies are needed to assess the true prevalence of hepatic fibrosis and steatosis in the long-term, with histological verification of pathological hepatic changes in patients with CHD progression risk, despite successful AVT.

4. In routine practice, fibroelastometry with SAR™ technology, which enables to identify individuals with a high probability of an adverse disease outcome, is appropriate as a screening study to simultaneously assess the hepatic fibrosis and steatosis severity when monitoring the clinical status of a CHC patient after SVR achievement.

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