

The effect of direct-acting antiviral regimens and telemedicine on the treatment of inmates with hepatitis C virus infection in Israeli prisons

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Abstract

Background Direct-acting antiviral (DAA) regimens and telemedicine services are both options for treating hepatitis C virus (HCV) within the prison setting. We aimed to compare factors associated with HCV treatment success over the past decade in Israeli prisons, specifically the influence of DAAs and telemedicine.

Methods We retrospectively reviewed the medical records of inmates with HCV infection in Israeli prisons from 2010 through 2020. Demographic, clinical, and laboratory data were recorded, including treatment regimens and success rates.

Results A total of 273 inmates were treated; mean age 45 ± 9.36 years; 98.2% males; 63.9% with a history of drug abuse. Advanced fibrosis was documented in 42.9%. The most common genotypes were 1 (46%) followed by 3 (40.7%). Interferon-based regimens were given to 68 inmates between 2010 and 2017. DAA agents were introduced in 2016, with pan-genotype regimens being exclusively used since 2019. Telemedicine services were used in 140 patients (51.3%), starting in February 2019. The sustained viral response (SVR) rate with interferon-based therapy was

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78.8% and 98.8% with DAA treatment, giving an overall SVR of 93.2%. This difference between regimens proved to be the only statistically significant predictor of treatment success. The number of prisoners being treated with DAAs increased exponentially after telemedicine was introduced. Comparable SVR rates were achieved with either in-person or telemedicine consultation.

Conclusion Screening of this high-risk population and using telemedicine for treatment may be an effective strategy for the elimination of HCV from the prison population.

Keywords

hepatitis c virus, inmates, telemedicine, treatment outcomes, direct-acting antiviral (DAA) regimens

Introduction

Hepatitis C virus (HCV) is a major global health concern as chronic infection with HCV is the leading cause of chronic liver disease. The risk of cirrhosis ranges from 15% to 30% within 20 years¹ and of hepatocellular carcinoma from 1% to 4% per year.²

More than 10.35 million people are incarcerated in jails and prisons throughout the world.³ The prevalence of HCV infection among prisoners varies around the world: 2.8% in Geneva post-trial prisons,⁴ 3.4% among Iranian prisoners,⁵ 11.5% in Swedish prisoners in Stockholm County,⁶ and 23.1% in Taiwan.⁷ In the United States, the rate varies by location: 10.1% at two prison facilities in New York State,⁸ and 34.3% at California State correctional facilities.⁹ Qureshi et al. analyzed 20 years of data among 80,681 individuals incarcerated at the Los Angeles County Jail who were tested for HCV infection from 2000 through 2019. Test results for HCV infection were positive in 34.6% but they also included HCV antibody test, and not only detectable HCV RNA or HCV genotype.¹⁰ These rates, however, all exceed the 1% prevalence in the general population¹¹ and this is due to the higher prevalence of risky behaviors among prisoners.¹²

In the past, only a minority of prisoners infected by HCV were tested and treated, mainly because of inaccessible resources, untrained staff, short incarceration time, and the potential interruption of treatment when transferred to the community. Only 16% of prison facilities tested all incarcerated people for HCV antibodies upon entry.¹³ In 2016, Beckman et al. reported that only a minority of the prisoners, about 10%, were screened for HCV infection, and only 0.89% received any therapy.¹⁴ In 2017, MacDonald et al. reported that oral direct-acting antiviral (DAA) treatment is feasible within the prison setting with the advantages of being a short treatment duration (no more than 12 weeks) and limited side effects as compared to interferon-based regimens. These authors reported that the success rate (undetectable load) was 97% in jail-initiated prisoners.¹⁵

The emergence and availability of DAAs, especially pan-genotypic regimens, in correctional institutions have coincided with a transition to telemedicine as a means of providing effective and accessible treatment in prison.^{16,17} Due to the COVID-19 pandemic, the implementation of the telemedicine service has been accelerated in many prisons.

In this study, we aimed to evaluate the trends and factors associated with HCV treatment success over the past decade in Israeli correctional institutions by comparing two

treatment periods--the era of interferon-based treatments versus the era of DAA regimens. In addition, we sought to explore the influence of telemedicine services on the extent and success rate of HCV treatment.

Materials and methods

Population

This study was conducted using the medical records of inmates in the Israeli prison clinic system. A retrospective chart review was undertaken to identify prisoners who were diagnosed with HCV infection and were medically treated between January 2010 and December 2020. Treatment was initiated on most prisoners while in prison; however, some began treatment in the community and were later incarcerated and continued treatment in jail.

The diagnosis of HCV infection was based on the detection of HCV RNA in blood samples, and viral load was recorded as well (Xpert HCV Viral Load assay, Cepheid, Sunnyvale, CA, United States). The limit of detection of this test is 10 IU/mL. HCV Genotype was determined by Sanger sequencing of 5'UTR and NS5A. Demographic data, including sex, age, patients' country of origin, and habits such as smoking and drug abuse were collected. Baseline and post-treatment laboratory tests were also evaluated, and FIB-4 score was calculated.¹⁸ Treatment success was defined as a negative PCR 12-weeks post-treatment (sustained virological response (SVR)).

Since many of the treated patients have been released from the prison system, no data on re-infection rate is available.

Fibrosis stage was established by the results of Fibrotest or Fibroscan, Fibrotest (BioPredictive, Paris, France^{19,20} cut-off for each fibrosis stage: F0: 0.000–0.2100; F0–F1: 0.2101–0.2700; F1: 0.2701–0.310; F1–F2: 0.3101–0.4800; F2: 0.4801–0.5800; F3: 0.5801–0.7200; F3–F4: 0.7201–0.7400; F4: 0.7401–1.00) and Fibroscan (Echosens, Paris, France;²¹ cut-off for each fibrosis stage: F0 to F1: 2 to 7 kPa; F2: 8 to 9 kPa; F3: 9 to 14 kPa; F4: 14 kPa or higher). In the few patients who underwent both Fibroscan and Fibotest, the higher fibrosis value was used. Advanced fibrosis was defined as a result of F3 or F4 since in clinical practice patients with F3 are approached similar to patients with compensated cirrhosis. Treatment was given only to compensated cirrhosis.

Treatment regimens for HCV infection

The protocol of interferon-based treatment in prison was based on peginterferon alfa-2a + ribavirin (1000 mg/day for patients <75 kg, 1200 mg/day for those >75 kg). Boceprevir or telaprevir were not administrated in Israeli prisons. The DAA regimens that were available in prison and were prescribed over the years included: Viekirax (ombitasvir/paritaprevir/ritonavir) + Exviera (dasabuvir), Zepatier (grazoprevir/elbasvir), Harvoni (ledipasvir/sofosbuvir), Maviret (glecaprevir/pibrentasvir), Epclusa (sofosbuvir/velpatasvir), and Vosevi (sofosbuvir/velpatasvir/voxilaprevir). The treatment was administered as a directly observed therapy.

Comparisons were done between patients treated with interferon-based regimens and DAAs regarding demographics, clinical, laboratory, virological factors, severity of liver disease, as well as SVR rate.

Ethics approval was obtained from the Clinical Ethics Research Committee of Shamir Medical Center. Informed consent was waived because of the retrospective nature of the study and because all data was anonymously gathered.

Telemedicine service

Before the introduction of telemedicine, prisoners were transported from various prisons throughout Israel to the central medicine center in Ramla where they were examined by a gastroenterologist. Starting in February 2019, the treatment of prisoners with HCV has been conducted with video teleconferencing once a month. In this framework, the prisoners are escorted to the medical clinic of their prison by a staff member (usually a paramedic), while the gastroenterology consultant and a nurse are located in the central clinic in Ramla. The gastroenterology consultant and a nurse interview the prisoner by using close-up cameras located at both sites with synchronous real-time patient management. The telemedicine facility consists of a computer with access to electronic patient data including medical history, laboratory, and imaging results, as well as medical treatment. All the information is recorded in the patient's medical records. No physical contact or examinations occur.

Statistical analysis

Categorical variables were reported as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram PP plot and Kolmogorov–Smirnov test. Continuous variables were reported as mean and SD. For readers' ease, all laboratory continuous variables were reported as median and IQR. Chi-square test and Fisher's exact test were applied to compare categorical variables, while Independent Samples t-test and Mann–Whitney U test were applied to compare continuous variables.

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS, statistics, Armonk New York, USA, 2016), by the statistics department of Tel Aviv University.

Results

Demographic, clinical, and laboratory data of all patients

A total of 273 inmates with HCV infection who received treatment in prison were included. Out of the study population, 98.2% were males. The mean age of the patients was 45 (± 9.36) years. Most had a history of drug abuse at some point during their life (63.9%) and were smokers (68.1%). Only a minority had HBV or HIV co-infection (6.8% and 7.3%, respectively). The median $\log_{10}$ HCV-RNA level before treatment was 5.9 (IQR: 5.3–6.4). Two hundred and thirty-three prisoners had a Fibroscan or

Fibrotest documented in their medical records. Out of those, 42.9% had advanced fibrosis. No patients decompensated during therapy. Other demographic characteristics and laboratory tests are detailed in Table 1.

Genotype distribution

The genotype distribution is illustrated in Figure 1. The most common genotypes were genotype 1 (46%) and genotype 3 (40.7%). Genotype 1a was more prevalent among prisoners of Israeli origin, whereas genotypes 1b and 3 were more common among prisoners

Table 1. Demographic, clinical, and laboratory data of all prisoners with HCV infection before treatment.

Characteristics	N = 273 n (%)
Male, n (%)	268 (98.2)
Age at initiation, mean (SD)	45 (± 9.36)
Smoking, n (%)	186 (68.1)
Drug abuse, n (%), [†]n = 269	172 (63.9)
Origin, n (%)	
Israel	133 (48.7)
Soviet Union	140 (51.3)
HBV co-infection, n (%), [†]n = 236	16 (6.8)
HIV co-infection, n (%), [†]n = 204	15 (7.3)
Laboratory results, median (IQR)	
AST U/L, [†] n = 244	48 (35-81.7)
ALT U/L, [†] n = 253	61 (40-100)
Platelet K/ul, [†] n = 253	193 (153-242.5)
Hemoglobin g/dl, [†] n = 249	14.6 (13.7-15.7)
WBC K/ul, [†] n = 246	7.4 (5.7-8.9)
Bilirubin mg/dL, [†] n = 251	0.6 (0.4-0.7)
Albumin g/L, [†] n = 236	43 (40.1-45)
Fibrosis*, n (%), [†]n = 233	
F = 0	44 (18.9)
F = 1-2	89 (38.2)
F = 3	37 (15.9)
F = 4	63 (27)
FIB-4 score, n (%), [†]n = 237	
<1.45	119 (50.2)
1.45-3.25	77 (32.5)
>3.25	41 (17.3)
HCV RNA log₁₀, median (IQR) [†]n = 254	5.9 (5.3-6.4)

[†]n, number of prisoners with available data. Percentages have been calculated using valid cases.

*Fibrosis stage was established by the results of Fibrotest or Fibroscan. In the few patients who underwent both Fibroscan and Fibotest, the higher fibrosis value was used.

Abbreviations: HBV, hepatitis B virus; HIV, Human immunodeficiency virus; AST, Aspartate Aminotransferase; ALT, alanine aminotransferase; WBC, White blood cells; HCV, hepatitis C virus; RNA, Ribonucleic acid; SD, standard deviation; IQR, interquartile range.

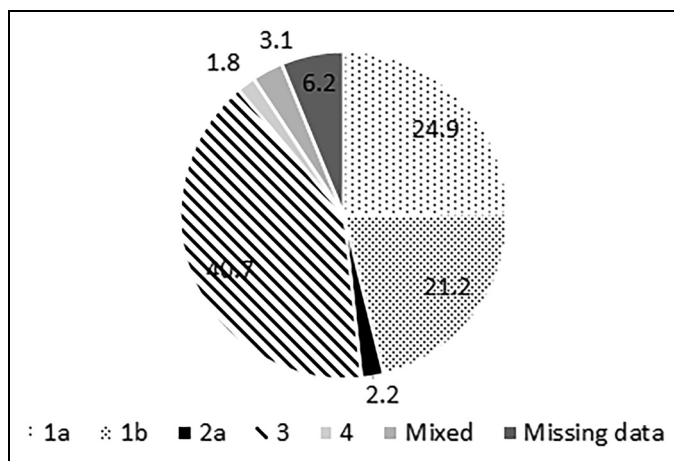


Figure 1. The proportion of genotype distribution among prisoners with hepatitis C virus (HCV) infection.

who immigrated from the former Soviet Union ($p < 0.001$). There was no statistically significant difference in the genotype distribution among prisoners who injected drugs compared to those who did not.

Factors associated with advanced fibrosis

Inmates with advanced fibrosis (F3 or F4) were found to be older and more likely to be of Israeli origin. As expected, patients with advanced fibrosis had higher serum levels of liver transaminases (aspartate transaminase (AST) and alanine aminotransferase (ALT)) and bilirubin, with lower platelet count and serum albumin levels. However, no statistically significant differences were found between genotype and pre-treatment HCV-RNA (Supplementary Table 1).

Treatment regimens for HCV infection

Interferon-based regimens. Interferon-based regimens were the only treatment given between 2010 and 2015 and were last given in February 2017. A total of 69 (25.3%) inmates were treated by this modality (Supplementary Figure 1A + 1B). These patients were younger and had lower rates of smoking and drug use compared to inmates treated with DAAs. The patients treated with interferon-based regimens had significantly higher bilirubin and ALT levels, and significantly lower platelet count (Supplementary Table 2).

DAA treatment. A total of 204 (74.7%) inmates were treated by DAA regimens (Supplementary Figure 1A). Between 2016 and 2018, treatment regimens included: Viekirax and Exviera, grazoprevir + elbasvir, and ledipasvir + sofosbuvir. During the

years 2019–2020 the prisoners were only treated with pan-genotype DAAs; glecaprevir + pibrentasvir, sofosbuvir + velpatasvir, and sofosbuvir + velpatasvir + voxilaprevir. The number of inmates being treated has dramatically increased over the years (Figure 2). Seventy percent of the prisoners have just been treated in the last 3 years of the 11-year study period, including 36.6% in the last year alone.

Telemedicine service

The HCV telemedicine service began in February 2019. Of the 273 inmates treated for HCV, 139 (50.9%) were managed by using telemedicine. During the time that telemedicine was available, the only treatment given was pan-genotype DAAs.

Sustained Virological Response (SVR)

Post-treatment PCR results were unavailable in 36 patients: 15 had no result in the medical record (including four inmates who refused to perform blood tests); 10 were released prisoners who did not perform the test in the community setting; and 11 were inmates who recently finished treatment but were still waiting for 12 weeks to pass to perform the PCR test to validate SVR status. Therefore, treatment success analyses were performed on 237 patients who had a PCR result 12 weeks post-treatment.

The SVR rate with interferon-based therapy was 78.8% and 98.8% with DAA treatment, giving an overall SVR of 93.2%.

Factors associated with sustained virologic response

Analysis of the 237 prisoners that had a PCR result 12 weeks post-treatment revealed that the treatment regimen (interferon-based vs DAAs) was the only statistically significant

Drug regimen	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
INF-based regimen	10	14	17	10	7	5	5	1				69
Viekirax+Exviera							1	2	1			4
Zepatier							1	3	2			6
Harvoni							1	2	4			7
Maviret									16	46	55	117
Epclusa								4	9	10	45	68
Vosevi									1	1		2
Total	10	14	17	10	7	5	8	12	33	57	100	273

Figure 2. The proportion of new prisoners treated according to the year and treatment type.

predictor of SVR ($p < 0.001$). There was no association with age ($p = 0.19$), smoking history ($p = 0.16$), or history of drug abuse ($p = 0.7$). Laboratory data, genotype, viral load, and fibrosis score were not associated with treatment success (Table 2).

We performed an additional statistical analysis that included only interferon-based therapy, and there was no difference in the SVR rate between the different genotypes (75.9%, 85.7%, 77.8%, 100% for genotypes 1,2,3,4, respectively, $p = 0.827$).

To evaluate the efficacy of telemedicine in achieving SVR, this group was compared to those patients who received pan-genotype DAA treatment in person, since the telemedicine group only received this treatment regimen. There were no differences in the

Table 2. Factors associated with sustained virologic response.

	SVR 221	Treatment failure 16	p value
Age, Mean (SD)	44.9 (± 9.4)	41.6 (± 11.3)	0.19
Smoking, n (%)	148 (67)	8 (50)	0.16
Drug abuse, n (%) , $^{\dagger}n = 218/16$	133 (61)	9 (56.3)	0.70
HBV co-infection, n (%) , $^{\dagger}n = 196/13$	13 (6.6)	0	1
HIV co-infection, n (%) , $^{\dagger}n = 166/16$	10 (6)	3 (18.8)	0.09
Origin, n (%)			
Israel	108 (48.9)	7 (43.7)	0.69
Soviet Union	113 (51.1)	9 (56.3)	
Laboratory results, median (IQR)			
AST U/L , $^{\dagger}n = 202/13$	46 (34-80)	57 (35.5-90.5)	0.31
ALT U/L , $^{\dagger}n = 208/13$	65.5 (39.2-97.7)	71 (42-217.5)	0.23
Platelet K/ul , $^{\dagger}n = 206/14$	191 (152.7-245)	197.5 (170.7-254)	0.51
Hemoglobin g/dl , $^{\dagger}n = 202/14$	14.6 (13.7-15.7)	14.9 (14.4-15.5)	0.54
WBC K/ul , $^{\dagger}n = 199/14$	7.4 (5.7-9)	7.6 (5.8-10)	0.43
Bilirubin mg/dL , $^{\dagger}n = 205/14$	0.6 (0.45-0.77)	0.65 (0.4-0.73)	0.97
Albumin g/L , $^{\dagger}n = 194/11$	43 (40-45)	41 (39-45)	0.62
HCV RNA log₁₀, median (IQR) , $^{\dagger}n = 209/15$	5.9 (5.3-6.4)	6.3 (5.3-6.8)	0.10
Genotype , $^{\dagger}n = 212/16$			
Genotype 1	105 (49.5)	7 (43.8)	0.65
Genotype non-1	107 (50.5)	9 (56.3)	
Fibrosis[*], n (%) , $^{\dagger}n = 190/13$			
F-0	36 (18.9)	3 (23.1)	0.80
F-1	24 (12.6)	1 (7.7)	
F-2	52 (24.7)	2 (15.4)	
F-3	31 (16.3)	4 (30.8)	
F-4	47 (24.7)	3 (23.1)	
FIB-4 score, n (%) , $^{\dagger}n = 195/13$			
<1.45	98 (50.3)	9 (69.2)	0.45
1.45-3.25	64 (32.8)	3 (23.1)	
>3.25	33 (16.9)	1 (7.7)	

$^{\dagger}n$, number of prisoners with available data (resolved/treatment failure).

^{*}Fibrosis stage was established by the results of Fibrotest or Fibroscan. In the few patients who underwent both Fibroscan and Fibotest, the higher fibrosis value was used.

Abbreviations: AST, Aspartate Aminotransferase; ALT, alanine aminotransferase; WBC, White blood cells; HCV, hepatitis C virus; RNA, Ribonucleic acid; SD, standard deviation; IQR, interquartile range.

demographic, clinical, laboratory, and virological characteristics of the prisoner population that were treated by usual clinical practice versus telemedicine (Supplementary Table 3). Only one prisoner failed to achieve SVR in each group.

Discussion

Our study supports the idea that a prison is an optimal place for micro-elimination of HCV infection. In addition, the use of telemedicine allows more accessible treatment for a greater number of prisoners.

Israel currently has 33 prisons with 14,000 prisoners. All prisons offer Harm Reduction Programs with opioid and other drug substitution therapies, safe sex education and supplies, and HIV and viral hepatitis testing and treatment. Screening for HCV is offered to inmates with high-risk behaviors such as injection drug users, a history of HIV or hepatitis B, or immigrants from an endemic region. However, prisoners may refuse to be screened.

In our study, the SVR of the interferon-based regimen was 78.8%, higher than reported in the literature. One explanation for this high SVR might be that treatment in prison was more strictly enforced than in the real world. However, Vroiling et al., in a systemic review of the prison setting, reported SVRs of only 43–74% following interferon-based treatment.²² Past studies reported higher response rates with interferon-based therapy for other genotypes compared with genotype 1.^{23–25} The high prevalence of genotype 3 in our study might be another explanation for this high SVR. Nonetheless, there was no significant difference in the SVR rate between the different genotypes, and therefore this does not explain the high SVR rate. In Israeli prisons, the prisoner may refuse to perform a blood test. Hence, we assume that those who agreed to be screened are the ones who were interested in medical care and therefore were more likely to adhere to treatment.

Treatment with DAAs in Israeli prisons started in 2016. Pan-genotype DAA regimens were introduced in prisons only in 2017 and have since become the treatment of choice. The high success rate of 98.8% found in our study correlates well with previously reported results.^{5,7,26–28}

Several factors have been reported to be associated with achieving higher SVR rates in prisoners. In the era of interferon-based therapy, these included younger age, better pre-treatment liver fibrosis status, HCV genotype other than 1, and lower baseline viral load.^{24,40} In the era of DAAs, the predictors of SVR in prisons have not been elucidated. Fiore et al. did not find any statistically significant association between SVR12 and incarceration status, Italian nationality, injection drug use, or opioid use when evaluating incarcerated patients.²⁷ However, studies performed outside of prisons have documented that African-American origin, high BMI, advanced liver disease, signs of portal hypertension, especially platelet count <100/nL, genotype 3, and proton pump inhibitors administration have higher rates of treatment failure.^{29,30} The analysis in our study included both prisoners treated either by DAA or interferon-based regimens. We did not find any factors significantly associated with SVR. This may be due to the extremely high success rate of DAA regimens which do not leave a large enough group of treatment failures (only 16 in our study) to analyze predictors of treatment failure.

According to the micro-elimination strategy to eradicate HCV, breaking down national elimination goals into more specific goals for individual population segments enables faster and more efficient treatment.³¹ This concept may allow treatment of HCV to be tailored to overcome the specific difficulties inherent in treating incarcerated patients. During the COVID-19 pandemic, many HCV elimination programs were delayed, mainly due to the fear of close contact.³² Telemedicine may help overcome many of these difficulties.

Telemedicine has been well-described in and out of prisons.^{33,34} Treatment of HCV with telemedicine has been found to be effective in correctional facilities in many countries around the world.^{16,35–39} Since February 2019, when telemedicine was introduced into Israeli prisons to treat HCV infection, it has become the main method of treatment during the COVID-19 era. We demonstrated a substantial increase in the number of prisoners receiving HCV treatment since the introduction of telemedicine, as 51.2% of all prisoners were treated by this method within the last two years. For example, in 2018, even though the use of pan-genotype DAA treatment had already been introduced, only 33 inmates were treated. This number jumped to 57 in 2019 and 101 in 2020 when telemedicine was also available. Some people fear that the lack of in-person doctor visits may lead to an inferior treatment, but the rate of SVR in telemedicine patients was just as high. It is important to note that there was no difference between the patient population in usual clinical practice versus telemedicine clinical practice.

The strength of this study is that it describes the significant changes that have taken place in HCV treatment over the last decade in Israeli prisons. Despite this, our study does have some limitations. First, we were unable to estimate the prevalence of HCV infection in the Israeli correctional institutions since there was no routine screening policy until August 2020. Second, this is a retrospective cohort of data, and therefore some of the relevant data, such as data on the length of HCV infection and the rate of reinfection, were missing. Third, in a small number of patients, the doctor documented achieving SVR without mentioning the specific date of the blood test was performed, so we could not verify that it was indeed done 12 weeks after the end of treatment. However, as the physicians were all knowledgeable and trained in treating HCV, it is likely that they worked according to the accepted guidelines. Fourth, the small sample size limits the statistical comparison of interferon-based and all DAA treatments (type 2 error). Lastly, there was no uniform treatment policy in the various prisons and the treatment decisions were made by the local treating physician on staff.

Conclusion

The concept that HCV may be eradicated even in the absence of a vaccine is no longer a fantasy. We have shown that in the era of DAAs and telemedicine, extremely high SVR rates can be obtained even in difficult-to-treat populations such as prisoners. Screening high-risk populations for HCV infection, the use of pan-genotype DAAs, and better access to telemedicine present a feasible and beneficial strategy to eliminate HCV infection.

Abbreviations

DAA	Direct-acting antiviral
HCV	Hepatitis C virus
SVR	Sustained Viral Response
HBV	hepatitis B virus
HIV	Human immunodeficiency virus
AST	Aspartate transaminase
ALT	Alanine aminotransferase
WBC	White blood cells
RNA	Ribonucleic acid
SD	Standard deviation
IQR	Interquartile range

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Author contributions

Conceptualizing: VR, RR, MM, EB, LG; Design of the work: VR, RR, MM, HS, EB, LG; Acquisition of data: VR, RR, MM, EB, LG; Analysis and interpretation of data: VR, DLC, AB, DZY, HS, EB, LG; Drafting of the manuscript: VR, DLC, EB, HS; Critical review of the manuscript: DLC, AB, DZY, MM, LG, HS, LG. All authors approved the final version of the manuscript.

Conflict-of-interest statement

All the authors have no conflict of interest related to the manuscript.

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The original anonymous dataset is available on request from the corresponding author at broidcef@mail.tau.ac.il

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Supplemental material

Supplemental material for this article is available online.

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