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Renal Safety in HCV Infected Patients Treated with Sofosbuvir-Based Regimens: A 144-Week Follow-Up

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Abstract

Background: Sofosbuvir (SOF) is widely used for treating hepatitis C virus (HCV) infection. GS-331007, the major metabolite of SOF, is mainly eliminated through kidney. Short-term impact of SOF on renal function has been reported, long-term observation on renal safety of sofosbuvir is lacking.

Methods: Patients who completed sofosbuvir-based treatment and 120-week follow-up after the end of treatment (EOT) were included. Estimated glomerular filtration rate (eGFR) was dynamically monitored for the evaluation of renal function.

Results: Patients presented significantly decrease in eGFR on-treatment and off-treatment. The changes of eGFR (△eGFR) on-treatment, at EOT, EOT-24W, EOT-72W, and EOT-120W from the baseline were -1.61, -1.52, -2.37, -3.01, and -4.01 mL/min/1.73m^2. Adverse renal event, namely eGFR decline ≥ 3mL/min/1.73m^2 at the end of follow-up, was observed in 64 (62.7%) patients. Age ≥ 60 years and Child-Turcotte-Pugh grade B or C (CTP-B/C) cirrhosis were identified as independent predictors of adverse renal event through logistic regression analysis. Patients with CTP-B/C cirrhosis and age ≥ 60 years were observed continuous eGFR decrease during and after treatment, △eGFR on-treatment, EOT-24W, EOT-72W and EOT-120W were -1.06, -3.46, -4.03, and -4.33 mL/min/1.73m^2.

Conclusion: Patients with CTP-B/C cirrhosis and age ≥ 60 years need to monitor renal function for long time during and af-

ter sofosbuvir-based treatment.

Keywords: HCV; Renal Safety; Liver Cirrhosis; Sofosbuvir

List of Abbreviations: Hepatitis C virus (HCV); hepatocellular carcinoma (HCC); Direct-acting antiviral agents (DAA); Sofosbuvir (SOF); end stage renal disease (ESRD); end of treatment (EOT); Child-Turcotte-Pugh (CTP).

Introduction

Hepatitis C virus (HCV) infection is among the leading causes of chronic liver disease, cirrhosis, hepatocellular carcinoma (HCC), and liver-related death. It has been estimated that more than 71 million people have HCV viremia worldwide [1]. Eradication of HCV through antiviral treatment improves the long-term prognosis of patients with HCV infection [2,3]. Direct-acting antiviral agents (DAA) are the first-line therapies for HCV infection because of their excellent efficacy and safety [4]. Sofosbuvir (SOF) based DAAs are the most widely used antiviral regimens for treating patients with HCV infection [5].

Sofosvel (Sofosbuvir and Velpatasvir Tablets) was approved to be used in patients with end stage renal disease (ESRD) with or without dialysis, and the dose adjustment is not needed [6]. Nevertheless, renal safety of SOF remains a major concern for clinicians when SOF or SOF-contained agents are used in HCV infection. The major metabolite of SOF, GS-331007, is mainly eliminated through the renal pathway [7]. Moreover, a lot of studies reported the SOF-associated renal injury, patients were observed significantly decrement in eGFR or increment of serum creatinine during the treatment course [8]. Up to now, most reports of the SOF-associated renal injury were short-term observations. The follow-up period of most studies was less than 1 year, and long-term observations on the renal safety of sofosbuvir were rare.

In real world, patients with HCV infection have many risk factors of kidney damage, including HCV infection itself, aging, liver cirrhosis, drug-related, and underlying diseases, such as hypertension, diabetes, and even chronic renal disease. On account of these potential factors for kidney damage, clinicians should consider the renal safety of SOF when they decide on the therapeutic regimens for patients with HCV infection. Here, we performed a retrospective study to evaluate the long-term renal safety of SOF-containing regimens for HCV-infected patients.

Materials and Methods

Patients

In this study, patients with HCV infection and treated with SOF-based regimens in the period from January 2015 and April 2018 in the First Affiliated Hospital of Xi'an Jiaotong University were included. Inclusion criteria were as follows: (1) patients with positive HCV RNA; (2) those aged ≥18 years; (3) those receiving SOF-based antiviral therapies. Patients who had one of the following criteria were excluded: (1) patients with eGFR of <30mL/min/1.73m^2; (2) patients receiving organ transplantation; (3) patients receiving sofosbuvir-based treatment but did not complete the treatment or was followed less than 24 weeks after the end of treatment (EOT). Before starting treatment, written informed consent was obtained from all patients and/or their family members. This retrospective protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Laboratory Assessment

All biochemical and virological markers were performed in the laboratory of the First Affiliated Hospital of Xi'an Jiaotong University. Serum HCV RNA levels were measured using a real-time polymerase chain reaction (PCR)-based method (COBAS TaqMan HCV Test; Roche Diagnostics, Branchburg, NJ, USA). The lower detection limit for HCV RNA quantification was 15 IU/mL. Liver function, kidney function, and HCV RNA were monitored at the following points: before treatment, on-treatment, EOT, week 24, week 72, week 120 after the EOT (EOT-24W, EOT-72W, and EOT-120W).

Renal Outcomes

Sarcosine Oxidase method was used to test serum creatinine. The eGFR was calculated using the CKD-EPI formula [9]. The adverse renal event was defined as the decrement of eGFR ≥ 3 mL/min/1.73m^2 from the baseline to the end of follow-up.

Statistical Analysis

Baseline characteristics of all subjects were described as mean ± SD, median (interquartile range), or percentage (%). The Chi-square test was used to calculate the difference between categorical variables. Paired samples t-test or nonparametric test was used to compare the variables of two different observation time points. Univariate and multivariate logistic regression analyses were conducted for the predictive analysis of adverse renal events. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 13.0.

Results

Baseline Characteristics

A total of 102 HCV-infected patients treated with SOF-based regimens were enrolled. All patients completed the 24-week anti-HCV treatment and at least 6-month follow-up after the EOT. Patients were followed up for 133.6 ± 32.9 weeks. The characteristics at baseline were presented in Table 1. of the 102 patients, 39.2% (40/102) were male, 52.0% (53/102) were over 60 years old, 73.5% (75/102) were HCV-related liver cirrhosis, and 39.2% (40/102) had interferon-treatment history. The Child-Turcotte-Pugh (CTP) score of these patients was 6.4 ± 1.7; 29 (38.7%); 28 (37.3%), and 18 (24.0%) patients were evaluated as grade A (CTP-A), B (CTP-B), and C (CTP-C), respectively. Patients with baseline eGFR ≥ 90 ml/min/1.73m2account for 84.3% (86/102). Most of the patients were infected with genotype 1b (45.1%) or 2a (50.0%) HCV. The baseline HCV RNA load was Log_{10}5.84 ± 1.01 IU/mL; and 18 (17.6%), 25 (24.5%), 18 (17.6%), and 41 (40.2%) patients received sofosbuvir only, sofosbuvir and interferon with or without ribavirin, sofosbuvir combined with ledipasvir, and sofosbuvir combined with daclatasvir, respectively. All patients achieved sustained virologic response.

Characteristics	Overall (n = 102)
Male, n, (%)	40 (39.2%)
Age* (years)	58 (22, 76)
Age ≥ 60 years, n, (%)	53 (52.0%)
Hypertension, n, (%)	25 (24.5%)
Diabetes, n, (%)	22 (21.6%)
Cirrhosis, n, (%)	75 (73.5%)
Child-Turcotte-Pugh score Grade A, n, (%) Grade B, n, (%) Grade C, n, (%)	6.4 ± 1.729 (38.7%)28 (37.3%)18 (24.0%)
HCV RNA (Log_{10} IU/mL)	5.84 ± 1.01
HCV genotype 1b 2a 3a 3b	46 (45.1%)51 (50.0%)4 (3.9%)1 (1.0%)
Alanine transaminase* (U/L)	32.7 (8.0, 135.0)
Aspartate aminotransferase* (U/L)	42.0 (15.0, 151.0)
Albumin* (g/L)	37.2 (25.9, 48.0)
Total bilirubin* (μmol/L)	17.6 (5.0, 109.0)
International normalized ratio*	1.20 (0.81, 2.10)
Platelet* ($\times 10^9$/L)	77 (20, 335)
Creatinine* (μmol/L)	52.9 (30.0, 112.0)
eGFR* (ml/min/1.73m^2)≥90 ml/min/1.73m^2, n, (%)60-89 ml/min/1.73m^2, n, (%)30-59 ml/min/1.73m^2, n, (%)	105.40 (45.01, 152.13)86 (84.3%)13 (12.7%)3 (2.9%)
Interferon-treatment experience, n, (%)	40 (39.2%)
Therapeutic regimensSOF, n, (%)SOF + IFN ± RBV, n, (%)SOF + LDV, n, (%)SOF + DCV, n, (%)	18 (17.6%)25 (24.5%)18 (17.6%)41 (40.2%)

Table 1: Baseline characteristics of the patients with HCV infection and treated by sofosbuvir-based regimens

HCV, hepatitis C virus; SOF, sofosbuvir; IFN, interferon; RBV, ribavirin; LDV, ledipasvir; DCV, daclatasvir; *, the variable was described as median (rang)

Changes of eGFR and Creatinine During the Follow-Up

Figure 1 shows the changes of eGFR and creatinine during the follow-up. The eGFR decreased significantly in patients who received SOF-based regimens during the follow-up (Figure 1A). We observed a significant decrease in eGFR during treatment (median of eGFR at pre-treatment vs EOT: 105.40 vs 103.86 mL/min/1.73m^2, P = 0.001, z = -3.277), stable eGFR at the EOT-24W (median of eGFR at EOT vs EOT-24W: 103.86 vs 104.26 mL/min/1.73m^2, P = 0.454, z = -0.749), and the eGFR decreased gradually over time after EOT-24W (median of eGFR at EOT vs EOT-120W: 104.26 vs 98.41 mL/min/1.73m^2, P = 0.0.42, z = -2.031). Compared with baseline, the median values of eGFR changes on-treatment, at EOT, EOT-24W, EOT-72W, and EOT-120W from pre-treatment were -1.61, -1.52, -2.37, -3.01, and -4.01 mL/min/1.73m2, respectively. The serum creatinine also showed an increasing trend over time (Figure 1B), the levels of serum creatinine at pre-treatment, on-treatment, EOT, EOT-24W, EOT-72W, and EOT-120W were 52.9, 55.6, 55.3, 56.7 and 57.2 μmol/L, respectively.

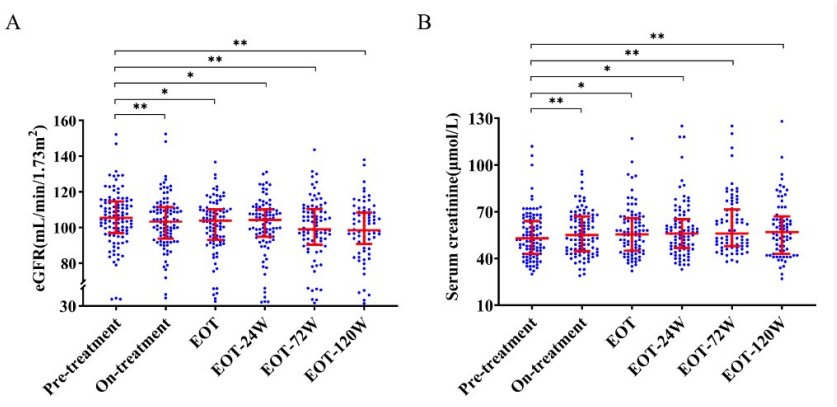

Figure 1: Changes of eGFR and serum creatinine during the follow-up in patients infected with HCV and treated by sofosbuvir-based antiviral regimens. eGFR, estimated glomerular filtration rate; *, $P < 0.01$ (compared to the eGFR at baseline); EOT, End of treatment; **, $P < 0.001$ (compared to the eGFR at baseline); EOT, End of treatment

Risk Factors for eGFR Decline in Patient Treated by SOF-Based Regimens

At the end of the follow-up, 64 (62.7%) patients were observed a decline in eGFR more than 3mL/min/1.73m^2. As shown in Table 2, patients were divided into two groups according to the eGFR decrement. Patients with eGFR decrease more than 3mL/min/1.73m2 had significantly higher percentages of those aged 60 years above (62.5% (27/64) vs 34.2% (13/34), P = 0.006), hypertension (31.3% (20/64) vs 13.2% (5/38), P = 0.040), diabetes (28.1% (18/64) vs 10.5% (4/38), P = 0.037), liver cirrhosis with CTP grade B or C (54.7% (35/64) vs 28.9% (11/38), P = 0.012) compared to the patients with eGFR decrease less than 3 mL/min/1.73m^2. Other characteristics including gender, history of IFN-treatment, baseline eGFR, and therapeutic regimen were comparable between the two groups.

	eGFR decrement≤ 3mL/min/1.73m^2 (n = 38)	**eGFR decrement> 3mL/min/1.73m^2 (n = 64)**	*P*
Male, n, (%)	13 (34.2%)	27 (42.2%)	0.425
Age ≥ 60 years, n, (%)	13 (34.2%)	40 (62.5%)	0.006
Hypertension, n, (%)	5 (13.2%)	20 (31.3%)	0.040
Diabetes, n, (%)	4 (10.5%)	18 (28.1%)	0.037
eGFR < 90 ml/min/1.73m^2, n, (%)	7 (18.4%)	9 (14.1%)	0.558
Cirrhosis, n, (%)	26 (68.4%)	49 (76.6%)	0.368
Liver disease statusCHC, n, (%)	12 (31.6%)	15 (23.4%)	0.050
CTP-A cirrhosis, n, (%) CTP-B cirrhosis, n, (%) CTP-C cirrhosis, n, (%)	15 (39.4%)5 (13.2%)6 (15.8%)	14 (21.8%)23 (35.9%)12 (18.8%)	
IFN-treatment experience, n, (%)	13 (34.2%)	27 (42.2%)	0.425
Therapeutic regimenSOF, n, (%)SOF + IFN ± RBV, n, (%)SOF + LDV, n, (%)SOF + DCV, n, (%)	7 (18.4%)4 (10.5%)7 (18.4%)20 (52.6%)	11 (17.2%)21 (32.8%)11 (17.2%)21 (32.8%)	0.066

Table 2: Comparison of the characteristics between patients with eGFR decrease more than 3mL/min/1.73m^2 and less than 3mL/min/1.73m^2 from the baseline to the end of follow-up

eGFR, estimated glomerular filtration rate; CTP, Child-Turcotte-Pugh; SOF, sofosbuvir; IFN, interferon; RBV, ribavirin; LDV, ledipasvir; DCV, daclatasvir.

To explore risk factors of eGFR decline in SOF-treated patients, we further performed the univariate and multivariate logistic regression analyses. As shown in Table 3, gender, age, hypertension, diabetes, CTP grade, eGFR at baseline, and the therapeutic regimen were all enrolled as potential influence factors for the analysis. The univariate logistic regression analysis revealed that age ≥ 60 years old, hypertension, diabetes, and CTP-B or C (CTP-B/C) were the risk factors for eGFR decline in SOF-treated patients (age, OR 3.205, 95%CI [1.384 – 7.423], P = 0.007; hypertension, OR 3.000, 95%CI [1.020 – 8.825], P = 0.046; diabetes, OR 3.326, 95%CI [1.032 – 10.723], P = 0.044; CTP-B/C, OR 2.962, 95%CI [1.258 – 6.977], P = 0.013). In multivariate regression analysis, age ≥ 60 years old, and CTP-B/C were independent predictors of eGFR decline more than 3mL/min/1.73m^2 (age, OR 2.754, 95%CI [1.132 – 6.755], P = 0.027; CTP-B/C, OR 3.298, 95%CI [1.086 – 6.582], P = 0.032).

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male	1.403 (0.610 – 3.231)	0.426		
Age ≥ 60 years	3.205 (1.384 – 7.423)	0.007	2.754 (1.123 – 6.755)	0.027
Hypertension	3.000 (1.020 – 8.825)	0.046	1.421 (0.384 – 5.265)	0.599
Diabetes	3.326 (1.032 – 10.723)	0.044	2.086 (0.518 – 8.403)	0.301
eGFR < 90 mL/min/1.73m^2	0.725 (0.246 – 2.137)	0.559		
CTP-B/C	2.962 (1.258 – 6.977)	0.013	3.298 (1.086 – 6.582)	0.032
Therapeutic regimenSOFSOF + IFN ± RBVSOF + LDVSOF + DCV	13.341 (0.081 – 13.942)1.000 (0.262 – 3.820)0.668 (0.216 – 2.065)	0.0880.0981.0000.484		

Table 3: Univariate and multivariate logistic regression analysis of the factors for eGFR decrease>3mL/min/1.73m^2

eGFR, Estimated glomerular filtration rate; CTP, Child-Turcotte-Pugh; SOF, sofosbuvir; IFN, interferon; RBV, ribavirin; LDV, ledipasvir; DCV, daclatasvir.

The Impact of Risk Factors on eGFR Changes

In this study, hypertension, diabetes and liver cirrhosis with CTP-B/C were the four risk factors of eGFR decline more than 3mL/min/1.73m^2. To understand the impacts of these factors on renal function, 102 patients were divided into different groups according to whether they had risk factors. As shown in Figure 2, patients with age ≥ 60 years, hypertension, diabetes, or CTP-B/C cirrhosis had more significant downward trend of eGFR and more obvious eGFR changes (described as median and IQR) at EOT-120W than those without risk factors (age ≥ 60 years vs age < 60 years: -4.67 (-0.47, -8.07) vs -2.22 (1.18, -6.67) mL/min/1.73m2, P = 0.618, z = -0.498; hypertension vs non-hypertension: -5.04 (-0.07, -7.84) vs -3.39 (0.82, -6.02) mL/min/1.73m2, P = 0.630, z = -0.481; diabetes vs non-diabetes: -4.44 (-0.08, -7.93) vs -3.79 (0.74, -7.36) mL/min/1.73m2, P = 0.568, z = -0.571; cirrhosis with CTP-B/C vs CHC and cirrhosis with CTP-A: -4.33 (-0.80, -7.25) vs -3.39 (0.31, -8.24) mL/min/1.73m^2, P = 0.805, z = -0.247).

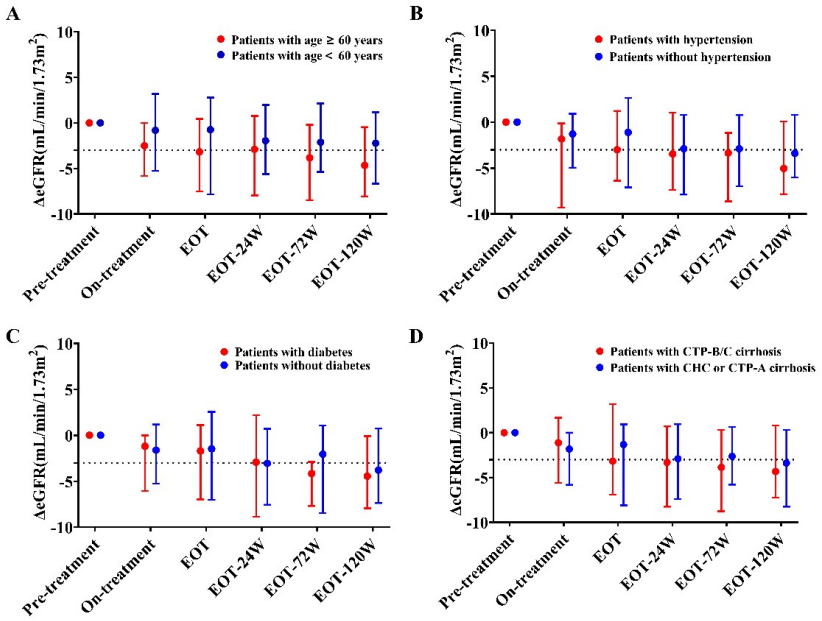

Figure 2: Changes of eGFR in patients with and without risk factors. △eGFR, eGFR changes from the baseline to the time point of follow-up; eGFR, estimated glomerular filtration rate; CTP, Child-Turcotte-Pugh; EOT, End of treatment

As shown in Figure 3, patients were divided into four groups based on age and CTP grade (Group 1: age < 60 years, CHC or CTP-A cirrhosis; Group 2: age < 60 years, CTP-B/C cirrhosis; Group 3: age ≥ 60 years, CHC or CTP-A cirrhosis; Group 4: age ≥ 60 years, CTP-B/C cirrhosis). We observed significant eGFR decrease on-treatment in all groups and various changing trend off-treatment in different groups. In Group 1 (Figure 3A) and Group 3 (Figure 3C), eGFR decreased obviously on-treatment and at EOT-24W, then remained stable levels (changes of eGFR on-treatment, at EOT, EOT-24W, EOT-72W, and EOT-120W, Group 1: -1.29, -0.77, -2.32, -1.69, and -3.21 mL/min/1.73m^2; Group 3: -2.67, -1.20, -3.35, -3.29, and -3.55 mL/min/1.73m^2).

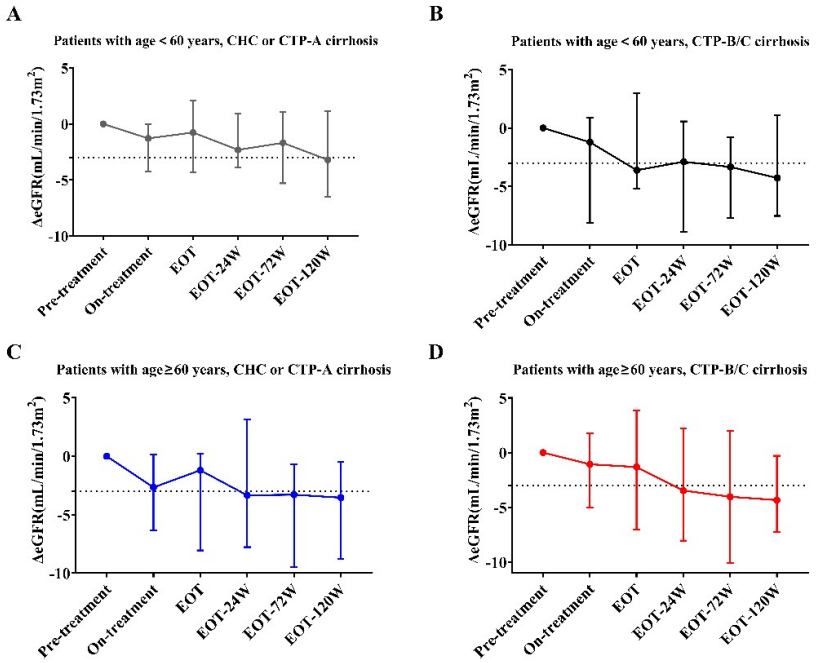

Figure 3: Changes of eGFR in different groups based on age and CTP grade. △eGFR means the decrement of eGFR from baseline to the end of the follow-up; eGFR, estimated glomerular filtration rate; CTP, Child-Turcotte-Pugh; EOT, End of treatment

In Group 2 (Figure 3B) and Group 4 (Figure 3D), the eGFR presented continuous decrease from the baseline to EOT-120W (changes of eGFR on-treatment, at EOT, EOT-24W, EOT-72W, and EOT-120W, Group 2: -1.22, -3.62, -2.89, -3.34, and -4.28 mL/min/1.73m^2; Group 4: -1.06, -1.32, -3.46, -4.03, and -4.33 mL/min/1.73m^2).

Discussion

The study aims to assess the long-term renal safety of HCV-infected patients receiving SOF-based therapeutic schemes. We investigated the dynamic changes in kidney function during and after 120 weeks of SOF-based treatment in 102 patients. In this "real--world" study, patients with age ≥ 60 years showed a persistent decrease in eGFR during the 144-week follow-up. Age ≥ 60 years and liver cirrhosis of CTP-B/C grade were identified to be the risk factors of the adverse renal outcome.

Majority of prior studies reported short-term renal safety of SOF. Patients receiving SOF-based regimens usually presented a significant decline in eGFR on treatment and improved kidney function after drug discontinuation [10-14]. Our data is partially consistent with previous studies, ie., obvious decrement in eGFR on treatment was observed. However, we notice that the changing trend of post-treatment eGFR in sub-population in this study varies. In the overall population, the kidney function continued to deteriorate, rather than recovered to baseline levels off treatment. The mean decrement of eGFR from the baseline to EOT-120W was 4.01 mL/min/1.73m^2. The persistent renal function deterioration was more apparent in patients aged over 60 years. The decline of eGFR on-treatment and off-treatment in patients with age < 60 years was not apparent. Several large real-life studies reveal that patients with poor kidney function were more likely to get renal function improvement after the anti-HCV treatment. When CKD patients received SOF-based treatment, renal function improved in patients with CKD stage 3-5 and significantly declined in those with CKD stage 1-2; and higher baseline stage of CKD was a independent predictor of renal function worsening after the treatment [15-17]. In the present study, about 90% of the patients had baseline eGFR ≥ 90 ml/min/1.73m^2 and received 24-week therapy containing sofosbuvir, which is mainly eliminated by the kidney. Therefore, we speculate that the better renal function at baseline and the longer duration of sofosbuvir exposure were probably main reasons for the persistent decline of eGFR. Certainly, it is easy to understand that the progressive decline of eGFR in patients with age over 60 years was more apparent because older age is an important factor contributing to the degradation of kidney function. Taken these findings together, assessment of renal safety is strongly necessary for elderly patients when sofosbuvir is used as anti-HCV treatment.

This study demonstrates the long-term renal safety among the patients treated by an SOF-based regimen. A 5-year observation of the natural eGFR decline in healthy individuals indicated that the average annual decline of eGFR was close to 1 mL/min/1.73m^2 [18]. In this study, patients were followed up for nearly 3 years and the decline of eGFR from the baseline to EOT was 4.01 mL/min/1.73m2. We showed that the eGFR decline in these SOF-treated patients was significantly higher than the natural decline of eGFR in a healthy population. Taking the changes of eGFR within the 3-year observation into consideration, we defined the decrement of eGFR > 3 mL/min/1.73m^2 as the adverse renal outcome. Our data show that nearly 2/3 of patients exhibited eGFR decline over 3 mL/min/1.73m^2. The proportions of hypertension, diabetes, liver cirrhosis, and age ≥ 60 years were high among these patients with adverse renal outcome. Furthermore, liver cirrhosis with CTP-B/C and age ≥ 60 years were identified as independent risk factors for adverse renal outcome. It is well known that HCV infection, hypertension, diabetes, liver cirrhosis, and aging all have an impact on kidney function [19,20]. HCV infection, hypertension, and diabetes can be controlled through corresponding treatment; aging is a natural process; liver cirrhosis is hard to be removed because it results from a long-term progression of chronic hepatitis. Hence, patients with CTP-B/C liver cirrhosis and age ≥ 60 years were at high risk of renal injury for a long time even though HCV infections were cured. The results indicate that SOF-treated patients, especially those elderly patients with CTP-B/C liver cirrhosis, would exhibit renal function worsening for a long time.

There are several limitations in this study. First, the relatively small sample size of enrolled patients may limit the power of our conclusions, and data from a larger population are necessary. Second, a longer follow-up period for the patients treated with SOF, especially those aged patients with liver cirrhosis are required for evaluating the changes in renal function. The current labeling of SOF is permitted to treat patients with severe renal injury or end-stage renal disease, although sofosbuvir has a potential renal injury which is related to its pharmacology. Our data were drawn from a real-world clinical observation, the patients who were treated with SOF-based therapies and followed up for nearly 3 years, and showed that age ≥ 60 years old, and liver cirrhosis with grade CTP-B/C were the independent risk factors for decrease in eGFR more than 3mL/min/1.73m^2. Although SOF was not the main predictor of renal function decrease, renal function should be monitored in those aged patients with liver cirrhosis when they receive SOF to treat HCV infection.

Conclusion

Persistent decline in eGFR was observed in patients with HCV infection and treated with SOF-based regimens through 3-year follow-up. Age of over 60 years and liver cirrhosis with CTP-B/C grade were independent risk factors for the decrease of eGFR.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgment

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Authors' Contributions

Study design, Taotao Yan, Yingli He, Li Jin, Yingren Zhao; Data collection, Taotao Yan, Weicheng Xu, Xiaonan Wu, BAIMA Yangjin, Tianzhi Ni, Shan Fu; Data analysis, Taotao Yan, Yingli He, Danfeng Ren, Jinfeng Liu; Writing – original draft, Taotao Yan, Weicheng Xu, Li Jin, Yingli He. All authors read and approved the final version of the report.

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Potential Competing Interests

None to report

Clinical Trial Registration

The study was registered on Clinicaltrials.gov (registration number: NCT05653830), accessible at: https://clinicaltrials. gov/ct2/show/NCT05653830.

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