

Original article

Sofosbuvir-based regimens for HCV in stage 4–stage 5 chronic kidney disease. A systematic review with meta-analysis

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ARTICLE INFO

Article history:

Received 5 May 2020

Accepted 18 January 2021

Available online 19 June 2021

Keywords:

Adverse events

Dialysis

Direct-acting antivirals

Hepatitis C

Sofosbuvir

Virological response

ABSTRACT

Background: Hepatitis C is an important agent of liver damage in patients with chronic kidney disease and the advent of DAAs has dramatically changed the management of HCV positive patients, including those with advanced CKD. Sofosbuvir is the backbone of many anti-HCV regimens based on DAAs but it remains unclear whether it is appropriate for HCV-infected patients with stage 4–5 CKD.

Study aims and design: We performed a systematic review of the literature with a meta-analysis of clinical studies in order to evaluate the efficacy and safety of SOF-based DAA regimens in patients with stage 4–5 CKD. The primary outcome was sustained viral response (as a measure of efficacy); the secondary outcomes were the frequency of SAEs and drop-outs due to AEs (as measures of tolerability). The random-effects model of DerSimonian and Laird was adopted, with heterogeneity and stratified analyses.

Results: Thirty clinical studies ($n = 1537$ unique patients) were retrieved. The pooled SVR12 and SAEs rate was 0.99 (95% confidence intervals, 0.97; 1.0, $I^2 = 99.8\%$) and 0.09 (95% CI, 0.05; 0.13, $I^2 = 84.3\%$), respectively. The pooled SVR12 rate in studies with high HCV RNA levels at baseline was lower, 0.87 (95% CI, 0.75; 1.0, $I^2 = 73.3\%$) ($P < 0.001$). The pooled drop-out rate due to AEs was 0.02 (95% CI, -0.01 ; 0.04, $I^2 = 16.1\%$). Common serious adverse events were anemia ($n = 26$, 38%) and reduced eGFR ($n = 14$, 19%). SAEs were more common in studies adopting full-dose sofosbuvir (pooled rate of SAEs 0.15, 95% CI, 0.06; 0.25; $I^2 = 80.1\%$) and in those based on ribavirin (0.15, 95% CI, 0.07; 0.23, $I^2 = 95.8\%$). Six studies ($n = 69$ patients) reported eGFR levels at baseline/post-antiviral therapy; no consistent changes were found.

Abbreviations: AUC, area under curve; CI, confidence intervals; CKD, chronic kidney disease; DAAs, direct-acting antiviral agents; DM, diabetes mellitus; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; ITT, intention-to-treat; HD, haemodialysis; PD, peritoneal dialysis; RCT, randomized controlled trial; RT, renal transplant; SAEs, severe adverse events; SOF, sofosbuvir; SVR, sustained virological response.

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<https://doi.org/10.1016/j.nefro.2021.01.008>

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Conclusions: SOF-based regimens appear safe and effective in patients with stage 4-5 CKD. Serum creatinine should be carefully monitored during therapy with SOF in patients with CKD. Randomized controlled studies in order to expand our knowledge on this point are under way.

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Tratamientos basados en sofosbuvir en la infección por el VHC en la enfermedad renal crónica en estadio 4 o estadio 5. Una revisión sistemática con metaanálisis

R E S U M E N

Palabras clave:

Acontecimientos adversos
Diálisis
Antiviricos de acción directa
Hepatitis C
Sofosbuvir
Respuesta virológica

Antecedentes: La hepatitis C es un importante agente de daño hepático en los pacientes con enfermedad renal crónica. La aparición de los antiviricos de acción directa (AAD) ha cambiado espectacularmente el tratamiento de los pacientes con positividad para el virus de hepatitis C (VHC), incluidos los que presentan enfermedad renal crónica (ERC) avanzada. El sofosbuvir es la piedra angular de muchos tratamientos contra la infección por el VHC basados en AAD, pero sigue habiendo dudas sobre si es apropiado en los pacientes con infección por el VHC y ERC en estadio 4-5.

Objetivos y diseño del estudio: Realizamos una revisión sistemática de la literatura médica con un metaanálisis de estudios clínicos para evaluar la eficacia y la seguridad de tratamientos con AAD basados en el sofosbuvir en pacientes con ERC en estadio 4-5. El criterio principal de valoración fue la respuesta virológica sostenida (como indicador de la eficacia); los criterios secundarios de valoración fueron la frecuencia de acontecimientos adversos graves (AAG) y los abandonos por acontecimientos adversos (AA) (como indicadores de la tolerabilidad). Se adoptó el modelo de efectos aleatorios de DerSimonian y Laird, con análisis estratificados y de heterogeneidad.

Resultados: Se recuperaron 30 estudios clínicos ($n = 1.537$ pacientes individuales). La tasa agrupada de respuesta virológica sostenida a las 12 semanas (RVS12) y de AAG fue de 0,99 (intervalos de confianza del 95%, 0,97; 1,0, $I^2 = 99,8\%$) y 0,09 (IC del 95%, 0,05; 0,13, $I^2 = 84,3\%$), respectivamente. La tasa agrupada de RVS12 en estudios con niveles altos de ARN del VHC al inicio fue menor, 0,87 (IC del 95%, 0,75; 1,0, $I^2 = 73,3\%$) ($p < 0,001$). La tasa agrupada de abandonos por AA fue 0,02 (IC del 95%, -0,01; 0,04, $I^2 = 16,1\%$). Los acontecimientos adversos graves frecuentes fueron anemia ($n = 26$, 38%) y filtración glomerular estimada (FGe) reducida ($n = 14$, 19%). Los AAG fueron más frecuentes en los estudios que administraron sofosbuvir en la dosis completa (tasa agrupada de AAG 0,15, IC del 95%, 0,06; 0,25; $I^2 = 80,1\%$) y en los que se administró ribavirina (0,15, IC del 95%, 0,07; 0,23, $I^2 = 95,8\%$). En seis estudios ($n = 69$ pacientes) se notificaron niveles de FGe al inicio/después del tratamiento antivirico; no se observaron variaciones sistemáticas.

Conclusiones: Los tratamientos basados en SOF parecen seguros y eficaces en los pacientes con ERC en estadio 4-5. La creatinina sérica debe vigilarse atentamente durante el tratamiento con SOF en los pacientes con ERC. Se están llevando a cabo estudios controlados aleatorizados para ampliar nuestros conocimientos al respecto.

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Introduction

Hepatitis C virus infection and CKD are important public health issues globally; it has been estimated that around 71 million people are chronically infected with HCV and the frequency of CKD is 10-15% in the adult general population of industrialized countries. The relationship between HCV infection and CKD is complex; some types of kidney disease are precipitated by HCV infection and patients on haemodialysis are at increased risk of acquiring HCV.¹ The prevalence rates of

HCV in dialysis population range from 3 to 50% within dialysis units of developed or less-developed countries.²

Chronic HCV infection has been associated with both liver disease-related deaths and cardiovascular mortality in HD patients.³ Although there are scarce data demonstrating that the sustained viral response improves survival in CKD, accumulated evidence shows a decreased mortality risk in CKD patients who had undergone antiviral therapy for HCV. According to a recent longitudinal study ($n = 93,894$ Taiwanese adults diagnosed with CKD), the 16-year cumulative incidence

of death was greater in the untreated cohort, 58% (95% CI, 51.5–63.9%) as compared to the treated one, 41.4% (95% CI, 8.1%–54.1%), $P < 0.0001$.⁴

The advent of direct-acting antiviral agents has profoundly changed the treatment of HCV not only in the general population, but also in ‘special populations’ (patients with CKD, HCV/HIV co-infection, HCV/HBV co-infection and unsuccessful previous DAA regimens). Sofosbuvir, a non-structural NS5B polymerase inhibitor, has been approved in 2013 and is now the backbone of many DAA treatment regimens. Sofosbuvir has large renal excretion and has been initially licensed for patients with a GFR more than 30 mL/min. The SOF-free combination therapies grazoprevir/elbasvir and glecaprevir/pibrentasvir proved to be effective and safe in patients with advanced CKD, based on C-SURFER and EXPEDITION-4 trials, respectively.⁵

Numerous ‘real life’ studies have suggested the efficacy and safety of SOF-based regimens in those with an eGFR < 30 mL/min. AASLD now recommend all DAAs for GFR ≤ 30 mL/min.⁵ We have conducted a systematic review and meta-analysis in order to assess efficacy and tolerability of SOF-containing therapies in the setting of stage 4–5 chronic kidney disease.

Material and methods

Search strategy and data extraction

We followed PRISMA (Preferred reporting items for systematic review and meta-analysis) statement guidelines to conduct this study.⁶ National Library of Medicine MEDLINE and manual searches were combined, as it had been previously demonstrated that a MEDLINE search alone may not be sensitive enough.⁷ The following key words were adopted: (sofosbuvir OR Sovaldi OR Harvoni OR Hepclusa OR Vosevi) AND (advanced chronic kidney disease OR severe kidney impairment OR end stage renal disease OR ESRD OR severe renal insufficiency) AND (Dialysis OR Haemodialysis OR Peritoneal Dialysis). General reviews, references from published clinical trials, letters to pharmacological companies, and Current Contents were also used. All articles were retrieved by a search from January 2013 to May 15, 2020. Data extraction was conducted independently by two investigators (F.F., and V.D.), and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Inclusion and exclusion criteria were pre-specified.

Criteria for inclusion

To be included in this systematic review, a clinical study had to fulfill a set of criteria. It had to be published as a peer-reviewed paper; report the results of SOF-based regimens; and use the sustained viral response (and/or dropout rate) as a clinical endpoint. We enrolled patients who underwent primary antiviral therapy (naïve patients) or those who had already completed an antiviral course (non responder or relapser patients).

Criteria for exclusion

Studies were excluded if they reported inadequate data on treatment or measures of response. Patients with antibody response against human immunodeficiency virus were not considered. Studies that were only published as abstracts, case reports or interim reports were excluded; review articles were not evaluated for the current analysis. Studies reporting viral response rates by methods other than polymerase chain reaction (PCR) (i.e., bDNA assay) were excluded.

Definitions

The primary outcome of interest in this systematic review was SVR, as a measure of efficacy; SVR was defined as clearance of HCV viremia by PCR for at least 12 weeks after completion of antiviral therapy. Secondary end-points were the frequency of AEs, SAEs, and discontinuation rate of therapy due to SAEs, as measures of tolerability.

Quality assessment

The methodological quality of included observational studies was assessed by two authors independently using the Newcastle-Ottawa scale (NOS).⁸ The NOS is usually used for observational studies. In the NOS scale, observational studies are scored across three categories: selection (up to four points), comparability (up to two points) and outcome of study participants (up to three points). Reports showing cumulative scores ranging between 4 and 6 are commonly defined as of fair quality. Disagreements in the above procedures were resolved by full discussions between the two independent reviewers with the corresponding author.

Statistical methods

Outcomes were analyzed on an intention-to-treat basis, that is, all patients included in these studies were considered for the calculation of the response rate, while patients without the end-point were classified as failures. Quantitative, pooled, summary estimates of the SVR and discontinuation rate of antiviral therapy (due to SAEs) across individual studies were generated using the random-effects model of Der Simonian and Laird.⁹ Confidence intervals for point estimates were computed adopting non-parametric (bootstrap) resampling methods. The estimate for each study was weighted inversely to its squared standard error when computing the overall estimate and its confidence intervals. The confidence intervals for the random-effects model were quoted, since the standard error under the fixed-effect model may be misleading, and the test for homogeneity was rejected. The Cochrane’s chi-squared test (χ^2) was adopted to quantify the heterogeneity, a value of < 0.10 was considered indicative of a statistically significant heterogeneity.¹⁰ In addition, the consistency of effects across studies was measured by I^2 index, and was considered significant if I^2 value was 50% or greater.¹¹ To further explore the origin of heterogeneity, we restricted the analysis to subgroups of studies defined by study characteristics such as country of origin (Asia, United States), study design, and DAA regimen, among others. Sensitivity analysis using a

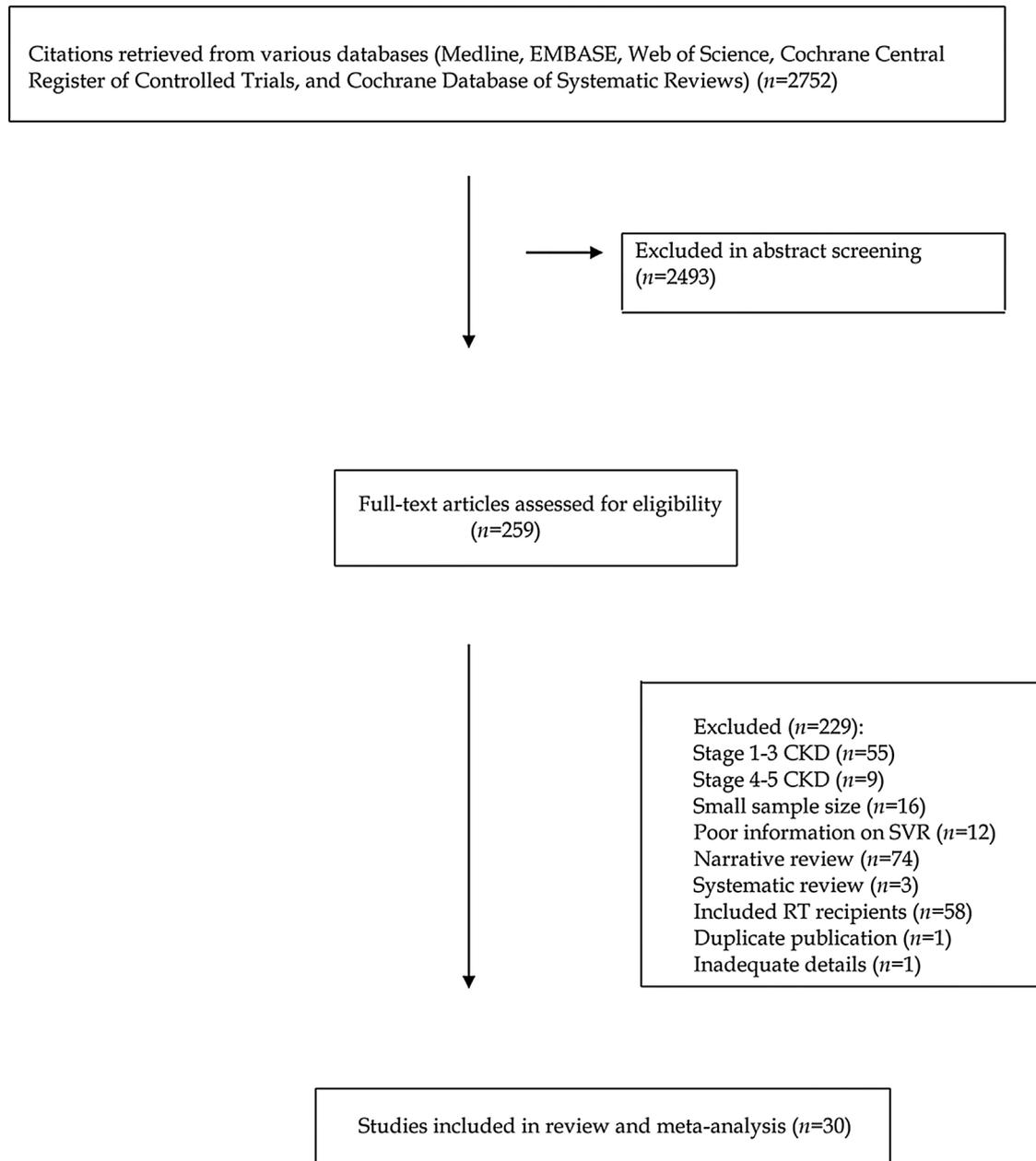


Fig. 1 – Flow diagram of literature search and selection.

fixed-effects model was also performed to assess the consistency of results. We made a funnel plot to detect a publication bias in the relation exposure at hand. Every estimate was given with 95% confidence intervals (CIs). The 5% significance level was adopted for alpha risk. All the statistical analyses were performed using Rev Man (Review Manager) 5.0, The Cochrane Collaboration (2020).

Results

Literature review

Our electronic and manual searches identified 2747 articles that were considered potentially relevant and selected for

review. Fig. 1 shows the flow diagram of literature review and study selection. A complete list of the 259 full-text articles reviewed is reported in supplementary file.

A total of 30 reports giving information on 1537 unique patients with stage 4–5 CKD were included in our meta-analysis.^{12–42} There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies based on predefined and exclusion criteria.

Patient characteristics

Shown in Table 1 are the list of reports evaluated, the countries where the studies were conducted, the reference year and some background data. All the selected studies were conducted between 2015 and 2020. As listed in Table 2, the fre-

Table 1 – Baseline characteristics of studies included in the meta-analysis: background and clinical data.

Author	Publication year	Country	Males (%)	Age
Bhamidimarri K.	2015	USA	11 (73%)	59.7 ± 7.2
Hundemer G.	2015	USA	5 (83%)	60 ± 14
Beinhardt S.	2016	Austria	NA	50.6 ± 10.9
Saxena V.	2016	USA	4 (22%)	NA
Nazario H.	2016	USA	14 (82%)	57 (46–69)
Desnoyer A.	2016	France	10 (83%)	52 (42–62)
Dumortier J.	2017	France	36 (72%)	60.5 ± 7.5
Aggarwal A.	2017	USA	13 (93%)	61 ± 4.9
Choudhary N.	2017	India	7 (70%)	48.5 (26–68)
Sperl J.	2017	Czech	6 (100%)	39 (25–53)
Cox-North P.	2017	USA	NA	NA
Saab S.	2017	USA	8 (67%)	62.2 (52–73)
Kumar M.	2018	India	54 (76%)	42 (22–80)
Singh A.	2018	India	39 (83%)	39.6 ± 15.4
Mehta R.	2018	India	26 (68%)	49.5 (36–58)
Akhil M.	2018	India	15 (68%)	49.7 (32–68)
He Y.	2018	China	24 (73%)	52.8 (19–74)
Taneja S.	2018	India	40 (61.5%)	42.9 ± 13
Butt A.	2018	USA	NA	NA
Garcia Agudo R.	2018	Spain	NA	NA
Surendra M.	2018	India	13 (68%)	44 (19–77)
Borgia S.	2019	Canada	35 (59%)	60 (33–91)
Eletreby R.	2019	Egypt	205 (35.5%)	52 ± 17
Wiegand J.	2019	Germany	NA	NA
Butt N.	2019	Pakistan	11 (35%)	36.5 ± 10.9
Seo H.	2019	Korea	6 (67%)	59.9 (27–82)
Goel A.	2019	India	25 (61%)	48 (19–75)
Debnath P.	2020	India	14 (78%)	39.4 ± 8.3
Michels F.	2020	Brazil	NA	NA
Poustchi H.	2020	Iran	76 (73.8%)	50.3 ± 13.5

Table 2 – Baseline characteristics of studies included in the meta-analysis: clinical data Co = cohort, P = prospective, R = retrospective.

Author	Dialysis, pts (%)	Cirrhosis (%)	Study design	HCV RNA, log ₁₀ IU/mL
Bhamidimarri K.	12 (80%)	9 (60%)	Co, P	NA
Hundemer G.	2 (33%)	3 (50%)	Co, R	6.47
Beinhardt S.	10 (100%)	4 (40%)	Co, R	6.1 ± 0.8
Saxena V.	5 (28%)	7 (39%)	Multicenter, longitudinal	6.11
Nazario H.	15 (88%)	8 (47%)	NA	NA
Desnoyer A.	12 (100%)	10 (83%)	Co, P	6.59 (6.1–6.9)
Dumortier J.	35 (70%)	34 (68%)	Co, R	6.41 ± 5.63
Aggarwal A.	14 (100%)	3 (21%)	Co, R	6.92 ± 7.09
Choudhary N.	10 (100%)	2 (20%)	Co, P	7 (5–8)
Sperl J.	6 (100%)	2 (33%)	Co, R	6.61
Cox-North P.	20 (69%)	13 (65%)	Co, R	NA
Saab S.	12 (100%)	1 (8%)	Co, R	7.48 ± 7.47
Kumar M.	11 (17%)	17 (26%)	Co, P	6.12 (3–7.8)
Singh A.	39 (83%)	12 (25%)	Co, P	6.05
Mehta R.	38 (100%)	NA	Co, P	5.75 (5.1–6.4)
Akhil M.	22 (100%)	NA	Co, R	6.42
He Y.	33 (100%)	0	Co, P	6.8 (1.7–7.9)
Taneja S.	54 (83%)	21 (32%)	Co, P	6.21
Butt A.	NA	NA	National cohort	NA
Garcia Agudo R.	NA	NA	Co, R	NA
Surendra M.	19 (100%)	0	Co, P	NA
Borgia S.	59 (100%)	17 (29%)	Co, P	5.8 (3.1–7.7)
Eletreby R.	4 (0.7%)	107 (11%)	Multicenter cohort, R	5.59
Wiegand J.	NA	107 (18%)	Co, R	NA
Butt N.	31 (100%)	0	Co, P	NA
Seo H.	9 (100%)	2 (22%)	Co, R	5.6 (2.9–6.7)
Goel A.	31 (76%)	5 (12%)	Co, R	5.9 (4.1–9.9)
Debnath P.	18 (100%)	0	Co, P	5.37
Michels F.	34 (100%)	NA	Co, P	NA
Poustchi H.	75 (72.8%)	39 (37.9%)	Co, P	NA

Table 3 – Baseline characteristics of studies included in the meta-analysis: clinical data.

Author	HCV genotype 1	SOF-based regimen	SOF-dose	Prior antiviral therapy
Bhamidimarri K.	15 (100%)	SOF/SMV	400 mg QD 200 mg QD	9 (60%)
Hundemer G.	6 (100%)	SOF + SMV (n = 3) SOF + pegIFN ± RBV (n = 3)	400 mg QD	3 (50%)
Beinhardt S.	6 (60%)	SOF + DCV (n = 5), SOF + SMV (n = 3) SOF + pegIFN ± RBV (n = 2)	400 mg QD	4 (40%)
Saxena V.	14 (78%)	SOF + pegIFN, SOF + RBV SOF/LDV ± RBV	400 mg QD	10 (55%)
Nazario H.	13 (76%)	SOF + SMV	400 mg QD	3 (18%)
Desnoyer A.	11 (92%)	SOF/LDV (n = 1) SOF + RBV (n = 1) SOF + DCV (n = 8) SOF + SMV (n = 2)	400 mg QD (n = 7) 400 mg 48 h (n = 5)	7 (58%)
Dumortier J.	28 (56%)	SOF/SMV ± RBV (n = 11), SOF + DCV + RBV (n = 30) SOF + pegIFN + RBV (n = 9)	400 mg QD or 400 mg/48 h	36 (72%)
Aggarwal A.	9 (64%)	SOF + SMV (n = 6), SOF + pegIFN ± RBV (n = 2) SOF/LDV ± RBV (n = 5), SOF + DCV (n = 1)	400 mg QD (n = 7) 200 mg QD (n = 7)	9 (64%)
Choudhary N.	7 (70%)	SOF + RBV + pegIFN (n = 8), SOF + DCV (n = 2)	400 mg/48 h	NA
Sperl J.	0	SOF + DCV	200 mg QD	1 (17%)
Cox-North P.	21 (72%)	SOF + RBV (n = 2) SOF/LDV ± RBV (n = 20) SOF + DCV ± RBV (n = 7)	400 mg QD	12 (43%)
Saab S.	10 (83%)	SOF + RBV (n = 9), SOF/LDV ± RBV (n = 3)	400 mg QD	NA
Kumar M.	NA	SOF + DCV (n = 16), SOF/LDV (n = 25) SOF + RBV (n = 23)	400 mg QD	13 (20%)
Singh A.	32 (68%)	SOF + LDV (n = 34), SOF + DCV (n = 13)	400 mg QD	2 (4%)
Mehta R.	38 (100%)	SOF/LDV (n = 12), SOF + DCV (n = 26)	400 mg QD (n = 13) 200 mg QD (n = 13)	NA
Akhil M.	14 (63%)	SOF + RBV	400 mg QD	9 (41%)
He Y.	7 (21%)	SOF + DCV	200 mg QD	11 (33%)
Taneja S.	42 (65%)	SOF + DCV	200 mg QD	10 (15%)
Butt A.	NA	SOF + LDV + RBV (n = 25), SOF + LDV (n = 83)	NA	NA
Garcia Agudo R.	8 (73%)	SOF/LDV ± RBV (n = 4) SOF + RBV (n = 4), SOF + DCV + RBV (n = 3)	400 mg QD	3 (27%)
Surendra M.	19 (100%)	SOF/LDV	400 mg/48 h	0
Borgia S.	27 (46%)	SOF + VEL	400 mg QD	13 (22%)
Eletreby R.	NA	SOF + pegIFN + RBV (n = 7) SOF + RBV (n = 6), SOF + DCV (n = 347) SOF + DAC + RBV (n = 172) SOF + LDV (n = 1), SOF + SMV (n = 41) SOF + SMV + DAC + RBV (n = 5)	200 mg QD	NA
Wiegand J.	NA	SOF + RBV (n = 2), SOF + SMV + RBV (n = 3) SOF + DCV + RBV (n = 5), SOF/LDV + RBV (n = 18)	400 mg QD	21 (4%)
Butt N.	10 (32%)	SOF + DCV	400 mg QD	6 (19%)
Seo H.	0	SOF + RBV	400 mg QD	2 (22%)
Goel A.	17 (41%)	SOF + DCV	200 mg QD	0
Debnath P.	12 (67%)	SOF/LDV (n = 13), SOF + DCV (n = 5)	400 mg QD	0
Michels F.	NA	SOF + DCV (n = 25), SOF + SMV (n = 8) SOF + pegIFN ± RBV (n = 1)	400 mg QD	NA
Poustchi H.	53 (51.5%)	SOF + DCV	400 mg QD	27 (26.2%)

DCV = daclatasvir; LDV = ledipasvir; SOF = Sofosbuvir, SMV = simeprevir, VEL = velpatasvir.

quency of patients undergoing maintenance dialysis ranged from 0.7% to 100%. The gender distribution ranged from 22% to 100% male. Table 3 shows data on viral characteristics; it appears that the majority of patients had infection with HCV genotype 1. Information on the study design, and details on sofosbuvir-based regimens with DAAs (including sofosbuvir dose) are shown in Tables 2–3. We have not retrieved in the medical literature RCTs or simply controlled clinical

trials of a comparison between SOF-based versus SOF-free regimen of HCV treatment in patients with advanced CKD (4–5 stage).

SVR rate: primary and stratified analysis

As listed in Fig 2, the summary estimate for sustained viral response across the identified trials was 0.99 (95% CI, 0.99, 1.00;

Review: Sofosbuvir for treatment of Hepatitis C virus in advanced CKD
 Comparison: 01 Sofosbuvir for HCV infection in advanced CKD
 Outcome: 01 Sofosbuvir for HCV in 4-5 stage CKD (Primary analysis)

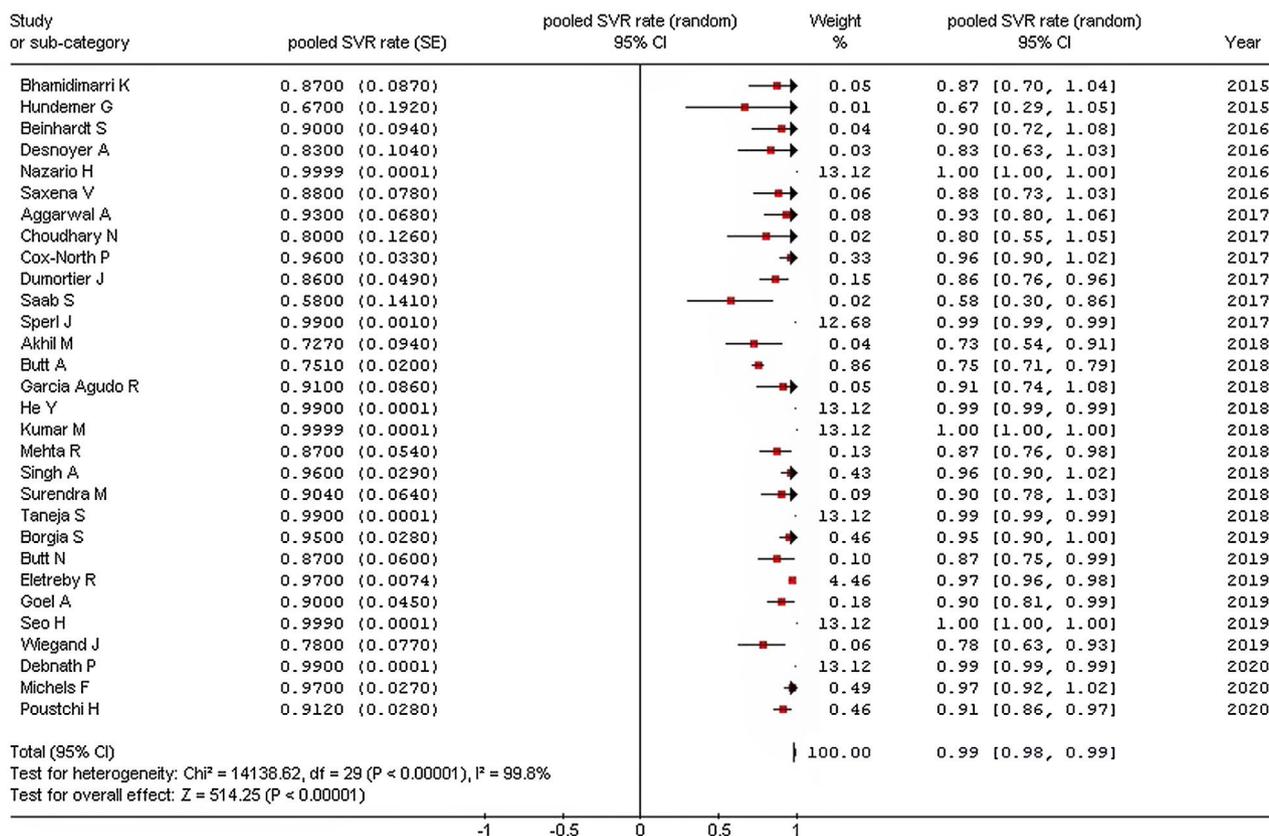


Fig. 2 – Forrest plot: summary estimate of sustained virological response (SVR) rate (random-effects model) (all studies).

$I^2 = 99.8\%$). Visual inspection of the funnel plot suggested no publication bias.

Stratified analyses were undertaken to explain the heterogeneity across studies (Table 4). The analysis by the fixed-effects model yielded very similar findings to the random-effects model (data not shown). The pooled SVR rate significantly changed in some comparisons; the pooled SVR rate in the subgroup of studies having high average HCV RNA levels ($\geq 6.5 \log_{10}$ IU/mL) (Fig. 3) and advanced age (≥ 60 years), respectively was lower ($P < 0.001$) (Table 4).

AE rate: primary and stratified analysis

The pooled estimate for drop-out rate due to AEs was 0.02 (95% confidence intervals, -0.01 ; 0.04 , $I^2 = 16.1\%$). The most frequent AEs requiring discontinuation of treatment were anemia ($n = 3$), and worsening kidney function ($n = 3$). The summary estimate of the rate of SAEs is shown in Fig. 4.

Table 5 shows the AEs reported in each study included in our meta-analysis. Common AEs were GI discomfort ($n = 51$), fatigue ($n = 39$), headache ($n = 38$), and anemia ($n = 35$).

Six studies (69 unique patients) reported eGFR levels at baseline- and post- antiviral therapy; no significant changes were found (Table 6). The frequency of serious or major AEs is reported in Table 7.

There was some difference regarding the frequency of SAEs in the subsets of studies adopting DAA therapies including RBV or not (Table 8).

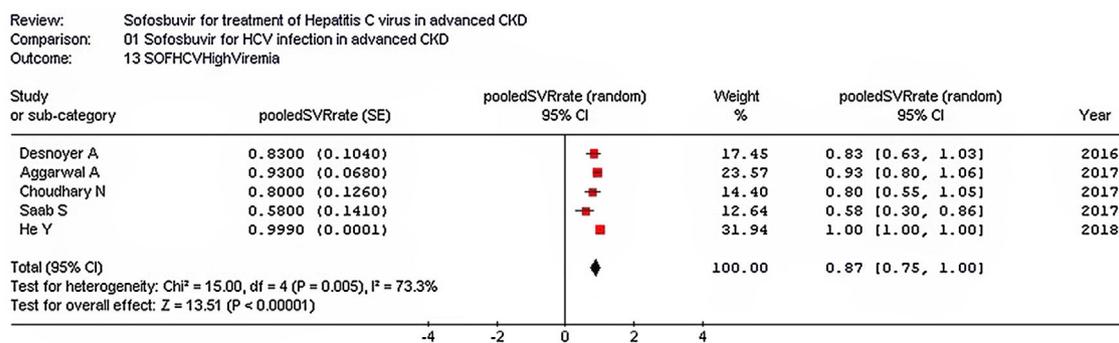
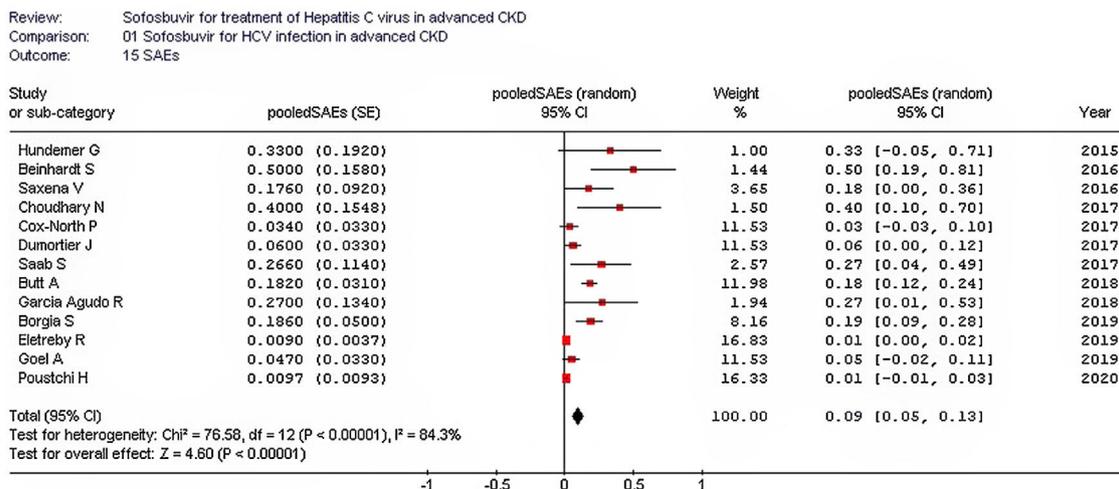
Discussion

Although the identification of hepatitis C virus was made three decades ago, the natural history of HCV has been recently characterized. HCV chronic infection is a hepatic disease which may lead to cirrhosis and/or hepatocellular carcinoma but also a systemic disease with extra-hepatic manifestations either associated with a cryoglobulinemic disease or chronic inflammation. Recent data support a relationship between anti-HCV positive serologic status and increased risk of liver or cardiovascular disease-related mortality even in the dialysis population. According to our meta-analysis, the summary estimate for adjusted death risk (all-cause mortality) with HCV was 1.26 (95% CI, 1.18; 1.34) ($P < 0.0001$). The overall estimate for adjusted death risk (cardiovascular mortality) was 1.8 (95% CI, 1.085; 1.29) ($P < 0.001$).³

HCV is the only chronic viral infection that is virologically cured. In contrast to HIV or hepatitis B, one can obtain with the treatments a virologic cure, the so-called SVR, defined by undetectable HCV RNA at 12 weeks after the end of antiviral treatment which corresponds to a true virological cure.

Table 4 – Summary estimates for sustained virological response (SVR) rate: primary and stratified analysis.

	Random-effects model SVR estimate (95% CI)	P-value (by χ^2 test)	I ²
All studies (n = 29)	0.99 (0.97; 1.0)	14,735.82 (0.0001)	99.8%
Studies from the US (n = 6)	0.95 (0.91; 1.00)	11.4 (0.04)	56.3%
Studies from Asia (n = 13)	0.95 (0.91; 0.98)	1,282,820.6 (0.00001)	100.0%
Dialysis pts (n = 15)	0.98 (0.9; 1.0)	102.96 (0.00001)	86.4%
Males (>80%) (n = 5)	0.98 (0.97; 1.0)	7.6 (0.11)	47.4%
Recent studies (n = 9)	0.99 (0.97; 1.0)	37.1 (0.00001)	81.1%
Prospective studies (n = 9)	0.99 (0.98; 1.0)	13.87 (0.03)	56.7%
Genotype 1 (n = 4)	0.87 (0.8; 0.94)	1.3 (0.70)	0%
Advanced age (n = 5)	0.87 (0.78; 0.97)	10.14 (0.04)	60.6%
Full-dose SOF (n = 13)	0.99 (0.85; 1.0)	33.29 (0.0009)	64%
RBV-free regimens (n = 14)	0.99 (0.99; 1.0)	7662.9 (0.0001)	99.8%
Study quality >5 (n = 11)	0.98 (0.92; 1.0)	26.4 (0.003)	62.1%
High viremia (n = 5)	0.87 (0.75; 1.0)	15.0 (0.005)	73.3%

**Fig. 3 – Forrest plot: summary estimate of sustained virological response (SVR) rate (random-effects model) (studies with high HCV RNA levels).****Fig. 4 – Forrest plot: summary estimate of pooled SAEs rate.**

Solid organ transplantation of infected individuals who have obtained SVR does not lead to any infection, despite deep immunosuppression.

Up to November 2019, two DAA regimens (grazoprevir/elbasvir and glecaprevir/pibrentasvir) have been approved by the FDA to treat HCV infection in patients with stage 4–5 CKD including those on dialysis. These combinations may not be available in some countries or regions and sofosbuvir-based combinations may be all that is available. Both these

combinations include NS3/NS4A protease inhibitors, which are not recommended for advanced liver disease. Sofosbuvir usually undergoes intracellular metabolism in the liver and the most important circulating metabolite of sofosbuvir (GS-331007) is mostly cleared by kidneys and achieves up to 456% increase in AUC in patients with creatinine clearance <30 mL/min compared with those having intact kidneys.

Despite these pharmacokinetic data, preliminary reports suggested acceptable efficacy and safety of SOF-based

Table 5 – Safety outcomes (Adverse Events, AEs).

Author	AEs, type
Bhamidimarri K.	Fatigue (n = 3), Itching (n = 2), Anemia (n = 2), Diarrhea (n = 1)
Hundemer G.	Anemia (n = 1), Leukopenia (n = 1)
Beinhardt S.	Fatigue, Nausea, Cephalgia, Photosensitivity, Anemia, Myalgia, Ascites
Saxena V.	Fatigue (n = 3), Headache (n = 1), Nausea (n = 3), Worsening renal function (n = 5), Anemia (n = 6)
Nazario H.	Insomnia (n = 2), Nausea (n = 1), Headache (n = 1), Anemia (n = 1)
Desnoyer A.	Anemia (n = 3), Headache (n = 2), Itching (n = 1), Muscle weakness (n = 1), Cough (n = 1), Anxiety (n = 1)
Dumortier J.	Headache (n = 16), Asthenia (n = 14), Digestive discomfort (n = 10), Insomnia (n = 8)
Aggarwal A.	Headache (n = 1), Fatigue (n = 3), Acid reflux (n = 1), Anemia (n = 2)
Choudhary N.	Fatigue (n = 4), Anemia (n = 2)
Sperl J.	Diarrhea
Cox-North P.	Anemia (n = 4)
Saab S.	Sepsis (n = 3), Neurologic event (n = 1)
Kumar M.	Fatigue, Headache, Insomnia, Nausea, Diarrhea, Anemia
Singh A.	Nausea (n = 5), Insomnia (n = 5), Headache (n = 2), Pruritus (n = 1)
Mehta R.	Headache, Joint pain, Muscle weakness, Itching
Akhil M.	Anemia (n = 9)
He Y.	Nausea (n = 13), Fatigue (n = 13), Hyperkalemia (n = 10), HBV reactivation (n = 6), Anorexia (n = 6), Constipation (n = 3), Increased appetite (n = 2), Hair loss (n = 2), Joint pain (n = 2), Hypoglycaemia (n = 1), Dizziness (n = 3), Elevated blood pressure (n = 2), Insomnia (n = 1), Blurred vision (n = 1), Hematuria (n = 1), Cough (n = 1)
Taneja S.	Nausea (n = 5), Insomnia (n = 4), Headache (n = 4), Pruritus (n = 1)
Butt A.	Thrombocytopenia, Neutropenia
Garcia Agudo R.	Anemia, Fatigue, Headache
Surendra M.	Headache (n = 1), Dizziness (n = 1), AST/ALT elevation (n = 8)
Borgia S.	Headache (n = 10), Fatigue (n = 8), Nausea (n = 8), Vomiting (n = 8), Insomnia (n = 6)
Eletreby R.	NA
Wiegand J.	Fatigue, Headache, Nausea, Insomnia, Pruritus, Abdominal discomfort, Skin disorder, Diarrhea, Depressed mood, Anemia, Dyspnea, Restlessness, Alopecia
Butt N.	NA
Seo H.	Anemia (n = 5), Insomnia (n = 1), Fatigue (n = 2), Itching (n = 2), Nausea (n = 1)
Goel A.	NA
Debnath P.	Headache (n = 1), Dyspepsia (n = 4), Fatigue (n = 2)
Michels F.	Asthenia, Itching, Headache, Irritability, flu-like symptoms, dizziness, insomnia, low visual activity, nausea, anorexia, dysgeusia, depression, alopecia, diarrhea, exanthema
Poustchi H.	Headache (n = 3), Diarrhea (n = 4), Pruritus (n = 3), Nausea (n = 1)

NA = not available.

Table 6 – Safety outcomes (eGFR at baseline versus end of treatment or SVR12).

Authors	Patients, n	Baseline eGFR (mean or median) ^a	EOT or SVR12 eGFR (mean or median) ^a
Hundemer G. (2015)	4	27.7 (26–29)	34.7 (26–54)
Dumortier J. (2017)	15	29 (20–34)	27 (17–38)
Cox-North P. (2017)	20	22.2	20
Taneja S. (2018)	11	24.8 ± 3.9	24.4 ± 3.6
Singh A. (2018)	8	19.9 ± 9.4	17.9 ± 8.5
Kumar M. (2018)	11	34 (21–63)	35 (16–69)

^a eGFR mL/min/1.73 m².

combinations in HCV-infected patients with advanced CKD. Since then, two systematic reviews have been made⁴³⁻⁴⁴ but additional and large studies have been published. The efficacy and safety of SOF-based combinations in advanced CKD remains unclear.

According to our meta-analysis of observational studies (30 studies, n = 1537 patients), the pooled SVR12 rate (99%) was excellent and was similar to that observed with non-SOF-based therapies. Stratified analysis reported a lower efficacy in the subset of studies enrolling high levels of HCV RNA and elderly patients (average age, >60 years), respectively. Elderly individuals have a great number of comorbidities and this

could explain the low efficacy of SOF-based therapies in this group.

The current meta-analysis reported that the tolerance to SOF-based regimens in patients with stage 4–5 CKD was satisfactory. The aggregated rate of SAEs was 9%, the most common SAEs being anemia, and impaired eGFR. The incidence of SAEs was greater than that in patients with intact kidneys and this is in line with the safety risk factors typical of this population (advanced age, severe kidney impairment, cirrhosis, liver/kidney transplant recipient). SAEs were more common in the subset of studies adopting full dose sofosbuvir and RBV based therapies; we recommend caution when using

Table 7 – Safety outcomes (frequency of serious or major AEs).

Author	SAEs, n	SAEs, type
Bhamidimarri K.	0	
Hundemer G.	2	AKI (n = 1), Transfusion- dependent anemia (n = 1)
Beinhardt S.	5	Sepsis (n = 1), Peritonitis (n = 1), Ascites (n = 2), Pneumonia (n = 1)
Saxena V.	3	eGFR decline (n = 1), Cardiac disorder (n = 1), anemia (n = 1)
Nazario H.	0	
Desnoyer A.	0	
Dumortier J.	3	Transfusion-dependent anemia
Aggarwal A.	0	
Choudhary N.	4	Transfusion-dependent anemia (n = 3) Thrombocytopenia (n = 1)
Sperl J.	0	
Cox-North P.	1	Cardiac event
Saab S.	4	Sepsis (n = 3), Neurologic event (n = 1)
Kumar M.	0	
Singh A.	NA	
Mehta R.	0	
Akhil M.	0	
He Y.	0	
Taneja S.	0	
Butt A.	25	eGFR decline (>10%) (n = 8) ¾ Anemia (n = 13), ¾ neutropenia (n = 3), ¾ thrombocytopenia (n = 1)
Garcia Agudo R.	3	Transfusion-dependent anemia (n = 2) eGFR decline (>10%) (n = 1)
Surendra M.	0	
Borgia S.	11	Cardiac disorder (n = 2), Infection (n = 5), Depression (n = 2), Hemorrhage (n = 1), Neoplasia (n = 1)
Eletreby R.	5	eGFR decline (n = 2), Anemia (n = 2)
Wiegand J.	NA	Transfusion-dependent anemia, pneumonia, eGFR decline, liver failure
Butt N.	0	
Seo H.	0	
Goel A.	2	Pancreatitis (n = 1), Ascites (n = 1)
Debnath P.	0	
Michels F.	0	
Poustchi H.	1	Diarrhea

Table 8 – Summary estimates for severe adverse events (SAEs) rate: primary and stratified analysis.

	Random-effects model Pooled SAEs (95% CI)	P-value (by χ^2 test)	I ²
All studies (n = 13)	0.09 (0.05; 0.13)	76.6 (0.0001)	84.3%
Full-dose SOF (n = 8)	0.15 (0.06; 0.25)	35.2 (0.0001)	80.1%
Low-dose SOF (n = 4)	0.03 (–0.02; 0.08)	7.72 (0.05)	61.3%
RBV-free (n = 3)	0.07 (–0.01; 0.15)	13.22 (0.001)	84.9%
RBV-based (n = 10)	0.15 (0.07; 0.23)	63.6 (0.0001)	85.8%

DAA combinations containing RBV in advanced CKD. The frequency of drop-outs related to AEs was low (pooled drop-out rate due to adverse events, 2%).

A minority of the studies of our review gave detailed information on the relationship between sofosbuvir and progression of CKD. Six studies (n = 69 patients) reported eGFR levels at baseline- and post- antiviral therapy; no consistent deterioration of kidney function was noted. Data on urinary changes were incomplete. Kumar et al.²⁴ observed that the median (range) eGFR at baseline was 34 (21–63) mL/min/1.73 m². At 12 week after interrupting the treatment, median (range) eGFR was 34 (11–64) (n = 11 patients).

The data regarding the relationship between SOF-based therapies and progression of CKD remains controversial. Some studies, conducted in patients with moderate CKD, found a decline in kidney function with sofosbuvir therapy.⁴⁵ By contrast, HCV cure was associated with a 9.3 mL/min per 1.73 m²

improvement in eGFR during the 6-month post-treatment follow-up period.⁴⁶ Despite this controversial evidence, serum creatinine should be carefully monitored during therapy with SOF in patients with CKD.

The results from the current meta-analysis present many limitations. First, all the reports were observational studies without control group- from a theoretical point of view, a randomized controlled trial with placebo gives the best evidence on the efficacy and safety of an intervention. Large size studies and long follow-up would be needed; the current availability of safe and effective drugs (DAAs) for the treatment of HCV makes the randomization to placebo not ethically acceptable. Second, large between-study heterogeneity was found; the methodological quality of the studies was on average not ideal and was one of the factors responsible for this. Our stratified analysis partially captured the heterogeneity we found. RBV in patients with CKD should be used with caution,

as RBV accumulation can occur in CKD patients, who are already anemic at baseline. Thirdly, the large heterogeneity occurring in many comparisons suggested that all the studies of the current analysis are not functionally identical and this precluded the adoption of a fixed-effects model. Finally, individual data from each study ('meta-analysis of individual participant data') have been not retrieved, it is well known that this approach maximizes the power of the meta-analyses.

In conclusion, this meta-analysis shows an excellent efficacy of SOF-based combination therapy in patients with grade 4–5 CKD. Tolerance to SOF was satisfactory in this population – severe adverse events and treatment discontinuations were uncommon. Careful monitoring of kidney function should be performed during SOF-based therapy in CKD population.

Conflict of interests

All the authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.nefro.2021.01.008](https://doi.org/10.1016/j.nefro.2021.01.008).

REFERENCES

1. [Kidney Disease: Improving Global Outcomes \(KDIGO\) Hepatitis C Work Group. KDIGO 2018 clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl.* 2018;8:91–165.](#)
2. [Jadoul M, Bieber B, Martin P, Akiba T, Nwankwo C, Arduino J, et al. Prevalence, incidence, and risk factors for hepatitis C virus infection in hemodialysis patients. *Kidney Int.* 2019;95:939–47.](#)
3. [Fabrizi F, Dixit V, Messa P. Hepatitis C virus and mortality among patients on dialysis: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol.* 2019;43:244–54.](#)
4. [Chen Y, Li C, Tsai S, Chen Y. Anti-hepatitis C virus therapy in chronic kidney disease patients improve long-term renal and patient survivals. *World J Clin Cases.* 2019;7:1270–81.](#)
5. [AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C; 2019. <https://www.hcvguidelines.org/unique-populations/renal-impairment> \[Last update: 10.12.19\].](#)
6. [Moher D, Liberati A, Teztlaff J, Altman D, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097, <http://dx.doi.org/10.1371/journal.pmed.1000097>. Epub 2009 July 21.](#)
7. [Poynard T, Conn H. The retrieval of randomised clinical trials in liver disease from the medical literature. A comparison of MEDLARS and manual methods. *Control Clin Trials.* 1985;6:271–9.](#)
8. [Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale \(NOS\) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2000. Available from: \[http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp\]\(http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp\) \[accessed 17.02.14\].](#)
9. [Der Simonian R, Laird D. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–88.](#)
10. [Petitti D. Approaches to heterogeneity in meta-analysis. *Stat Med.* 2001;20:3625–33.](#)
11. [Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistencies in meta-analysis. *Br Med J.* 2003;327:557–60.](#)
12. [Bhamidimarri K, Czul F, Peyton A, Levy C, Hernandez M, Jeffers L, et al. Safety, and efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease. *J Hepatol.* 2015;63:763–73.](#)
13. [Hundemer G, Sise M, Wisocky J, Uferer N, Friedman L, Corey K, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. *Infect Dis \(Lond\).* 2015;47:924–9.](#)
14. [Beinhardt S, Al Zoairy R, Ferenci P, Kozbial K, Freissmuth C, Stern R, et al. DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and postkidney transplantation setting. *Transplant Int.* 2016;29:999–1007.](#)
15. [Saxena V, Koraishy F, Sise M, Lim J, Schmidt M, Chung T, et al., HCV-TARGET. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int.* 2016;36:807–16.](#)
16. [Nazario H, Ndungu M, Modi A. Sofosbuvir and simeprevir on hepatitis C genotype 1 – patients with end-stage renal disease on haemodialysis or GFR <30 ml/min. *Liver Int.* 2016;36:798–801.](#)
17. [Desnoyer A, Pospai D, Le M, Gervais A, Heurgue-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full-dose sofosbuvir-based regimen given daily in haemodialysis patients with chronic hepatitis C. *J Hepatol.* 2016;65:40–7.](#)
18. [Aggarwal A, Yoo E, Perumpail R, Cholankeril G, Kumari R, Daugherty T, et al. Sofosbuvir use in the setting of end-stage renal disease: a single center experience. *J Clin Transplant Hepatol.* 2017;5:23–6.](#)
19. [Choudhary N, Kumar A, Bodh V, Bansal S, Sharma R, Jain M, et al. Efficacy and safety of sofosbuvir-based regimens in chronic hepatitis C patients on dialysis. *Ind J Gastroenterol.* 2017;36:113–6.](#)
20. [Sperl J, Frankova S, Merta M, Tothova M, Spicak J. Combination of sofosbuvir and daclatasvir in the treatment of genotype 3 chronic hepatitis C virus infection in patients on maintenance haemodialysis. *Ther Clin Risk Man.* 2017;13:733–8.](#)
21. [Cox-North P, Hawkins K, Rossiter S, Hawley M, Bhattacharya R, Landis C. Sofosbuvir-based regimens for the treatment of chronic hepatitis C in severe renal dysfunction. *Hepatol Comm.* 2017;1:248–55.](#)
22. [Saab S, Jimenez M, Bau S, Choi G, Durazo A, El-kabany M, et al. Use of sofosbuvir-based treatment of chronic hepatitis C in liver transplant recipients on haemodialysis. *J Clin Gastroenterol.* 2017;51:167–73.](#)
23. [Dumortier J, Bailly F, Pageaux G, Vallet-Pichard A, Raadenne S, Habersetzer F, et al. Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure. *Nephrol Dial Transplant.* 2017;32:2065–71.](#)
24. [Kumar M, Nayak S, Gupta E, Kataria A, Sarin S. Generic sofosbuvir-based direct-acting antivirals in hepatitis C virus-infected patients with chronic kidney disease. *Liver Int.* 2018;38:2137–48.](#)

25. Singh A, Kumari S, Kumar P, De A, Singh V. Sofosbuvir with NS5A inhibitors in hepatitis C virus infection with severe renal insufficiency. *J Viral Hepat.* 2018;25, 1501–1056.
26. Mehta R, Desai K, Kabrawala M, Nandwani S, Shah J, Desai N, et al. Preliminary experience with sofosbuvir-based treatment regimens for patients dependent on haemodialysis. *Ind J Gastroenterol.* 2018;37:72–3.
27. Akhil M, Kirushnan B, Martin M, Arumugam K, Prasad N, Ravichandran R. Sofosbuvir-based treatment is safe and effective in Indian hepatitis C patients on maintenance haemodialysis: a retrospective study. *Nephrology.* 2018;23:446–52.
28. He Y, Yang S, Hu C, Dong J, Gao H, Yan T, et al. Safety and efficacy of sofosbuvir-based treatment of acute hepatitis C in end-stage renal disease patients undergoing haemodialysis. *Aliment Pharmacol Ther.* 2018;47:526–32.
29. Taneja S, Duseja A, De A, Mehta M, Ramachandran R, Kumar V, et al. Low-dose sofosbuvir is safe and effective in treating chronic hepatitis C in patients with severe renal impairment or end-stage renal diseases. *Dig Dis Sci.* 2018;63:1334–40.
30. Butt A, Ren Y, Puenpatom A, Arduino J, Kumar R, Abou-Samra A. Effectiveness, treatment completion and safety of sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir+dasabuvir in patients with chronic kidney disease: an ERCHIVES study. *Aliment Pharmacol Ther.* 2018;48:35–43.
31. Garcia-Agudo R, Aoufi-Rabih S, Salgueira-Lazo M, Gonzalez-Corvillo C, Fabrizi F. 'Real-life' experience with direct-acting antiviral agents for hepatitis C virus in end-stage renal disease. *Int J Artif Organs.* 2018;41:363–70.
32. Surendra M, Raju S, Sridhar N, Vijay Kiran B, Rajesh G, Anvesh G, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection in end stage renal patients: a retrospective observational study. *Hemodial Int.* 2018;22:217–21.
33. Borgia S, Dearden J, Yoshida E, Shafran S, Brown A, Ben-Ari Z, et al. Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis. *J Hepatol.* 2019;71:660–5.
34. Li M, Chen J, Fang Z, Li Y, Lin Q. Sofosbuvir-based regimen is safe and effective for hepatitis C infected patients with stage 4–5 chronic kidney disease: a systematic review and meta-analysis. *Virol J.* 2019;16:34.
35. Eleteby R, El-Serafy M, Anees M, Kasem G, Salama M, Elkhoully R, et al. Sofosbuvir-containing regimens are safe and effective in the treatment of HCV patients with moderate to severe renal impairment. *Liver Int.* 2019.
36. Wiegand J, Buggisch P, Mauss S, Boeker K, Klinker H, Muller T, et al. German Hepatitis C-Registry (Deutsches Hepatitis C-Register). *Eur J Gastroenterol Hepatol.* 2019;31:1424–31.
37. Butt N, Abbasi A, Khan M, Ali M, Mahesar G, Haleem F, et al. Treatment outcomes for patients undergoing hemodialysis with chronic hepatitis C on the sofosbuvir and daclatasvir regimen. *Cureus.* 2019;11:e5702.
38. Seo H, Seo M, Yoon S, Choi J, Ko S. Full-dose sofosbuvir plus low-dose ribavirin for hepatitis C virus genotype 2-infected patients on haemodialysis. *Korean J Intern Med.* 2019.
39. Goel A, Bhadauria D, Kaul A, Verma P, Mehrotra M, Gupta A, et al. Daclatasvir and reduced-dose sofosbuvir: an effective and pangenotypic treatment for hepatitis C in patients with estimated glomerular filtration rate <30 mL/min. *Nephrology.* 2019;24:316–21.
40. Debnath P, Chandnani S, Rathi P, Nair S, Pawar V, Contractor Q. Combined NS5A & NS5B nucleotide inhibitor therapy for patients with chronic hepatitis C with stage 5 chronic kidney disease on haemodialysis. *Arq Gastroenterol.* 2020-03-22.
41. Michels F, Amaral A, Carvalho-Filho R, Vieira G, Souza A, Ferraz M, et al. treatment of renal transplant and chronic kidney disease patients: efficacy and safety of direct-acting antiviral regimens containing sofosbuvir. *Arq Gastroenterol.* 2020.
42. Poutschi H, Jabbari S, Merat S, Sharifi A, Shayesteh A, Shayesteh E, et al. The combination of sofosbuvir and daclatasvir is effective and safe in treating patients with hepatitis C and severe renal impairment. *J Gastroenterol Hepatol.* 2020 Jan 29, <http://dx.doi.org/10.1111/jgh.14994>.
43. Li T, Qu Y, Guo Y, Wang Y, Wang L. Efficacy and safety of direct-acting antivirals- based antiviral therapies for hepatitis C virus patients with stage 4–5 chronic kidney disease: a meta-analysis. *Liver Int.* 2017;37:974–81.
44. Li M, Chen J, Gfang Z, Li Y, Lin Q. Sofosbuvir-based regimen is safe and effective for hepatitis C infected patients with stage 4–5 chronic kidney disease: a systematic review and meta-analysis. *Virol J.* 2019;16:34.
45. Rosenblatt R, Mehta A, Wagner M, Kumar S. Baseline creatinine clearance is a predictor of worsening renal function while on HCV treatment with sofosbuvir-ledipasvir. *J Hepatol.* 2016;64 Suppl.:S819.
46. Sise M, Backman E, Ortiz G, Hundemer G, Ufere N, Chute D, et al. Effect of sofosbuvir-based hepatitis C virus therapy on kidney function in patients with CKD. *Clin J Am Soc Nephrol.* 2017;12:1615–23.