

SYSTEMATIC REVIEW

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Prevalence of occult HCV infection in hemodialysis and kidney-transplanted patients: a systematic review

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Aim: We performed a systematic review for determining the prevalence rate of occult HCV infection (OCI) among hemodialysis and kidney-transplanted (KT) patients. **Methods:** Electronic databases were searched with appropriate search strategies. We considered positive result for tests of HCV-RNA in peripheral blood mononuclear cell, ultracentrifuged serum or hepatocytes in the absence of HCV-RNA and anti-HCV antibody in patients' sera as the definition of OCI. **Results:** Two studies reported OCI prevalence rate of 0 and 2% among KT patients. Results of OCI prevalence rates among hemodialysis patients varied between 0 and 45% in ten different included studies showing a great heterogeneity. **Conclusion:** Although we still need more evidence to support our results, they suggest that checking OCI in hemodialysis or KT patients with unexplained signs of liver diseases may have some benefit.

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HCV infection is an important problem in dialysis and kidney transplantation centers. Hemodialysis patients are one of the high-risk groups for HCV infection. Also, HCV infection is proposed as a risk factor for graft loss and mortality among kidney-transplanted (KT) patients [1,2].

There is an occult type of HCV infection which is defined as detectable HCV-RNA in hepatocytes in the absence of HCV-RNA and anti-HCV antibody in the serum checked by usual laboratory tests [3]. This occult infection is different from an HCV seronegative status which is the condition of negative anti-HCV antibody and positive HCV-RNA in the patients' sera. While based on the aforementioned definition, diagnosis of occult HCV infection (OCI) requires a liver biopsy. Alternative approaches have been recommended for easier OCI diagnosis such as the detection of HCV-RNA in the peripheral blood mononuclear cells (PBMCs) and the ultracentrifuged sera of patients [4,5]. Liver fibrosis, cirrhosis and hepatocellular carcinoma are some of the reported OCI complications [6]. Data on the investigation of this form of HCV are available among several groups such as patients with cryptogenic liver disease [7], HBV infection [8], autoimmune hepatitis [9] and hemophilia [10].

Several studies which have investigated OCI among hemodialysis and KT patients have reported a significant effect of OCI on the status of patients in those settings. Important controversy exists regarding OCI prevalence among these populations [11,12]. Additionally, with a need to the special diagnostic method for OCI identification, the real prevalence of HCV among mentioned populations may be underestimated [13]. Here we performed a systematic review for determining the prevalence rate of OCI among hemodialysis and KT patients.

KEYWORDS

- kidney transplantation
- occult hepatitis C
- renal dialysis

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Evidence acquisition

• Data resources & search strategies

We performed a systematic and comprehensive search in electronic databases and resources including PubMed, Scopus, Science Direct and ISI web of science until 6 March 2016. Appropriate search strategies were developed for each database and with related keywords focusing on OCI, hemodialysis or KT patients (Appendix 1). We also evaluated references of all finally included studies for retrieving any possible missed paper. Furthermore, for investigation of gray literature, we searched Google Scholar and after finding the last related title, we continued our evaluation until identification of 50 unrelated serial titles. We did not limit our searches to the English language as long as the article included an English abstract. Finally, we updated our searches to find papers added to databases after our last search just before starting qualitative synthesis.

• Outcome definition

Prevalence of OCI among hemodialysis or KT patients was our investigated outcome in this project.

• Eligibility criteria

We considered positive result for test of HCV-RNA in PBMC, ultracentrifuged serum or hepatocytes in the absences of HCV-RNA and anti-HCV antibody in patients' sera as the definition of OCI. All publications were examined based on this definition and for inclusion in our project they needed to be a cross-sectional project with a clear report of OCI prevalence among patients with hemodialysis or kidney transplantation. We also tried to cover all related laboratory methods for OCI identification including PCR, real-time PCR, nested PCR and reverse transcriptase PCR (RT-PCR).

• Study selection, quality assessment & data extraction

All reviewing and screening processes in this project were according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline for reporting of systematic review [14]. Two investigators independently reviewed all papers identified through our searches in different levels of screening including title, abstract and full text of papers. After ending each level of screening, two authors resolved their discrepancies through a meeting. For any

remained discrepancies, mutual discussion with a third author was performed. Investigators were justified through a meeting for critical evaluation of studies with regard to OCI definition, appropriate sample size and considering any selection bias in studies. Then we extracted related data from selected and included studies to a predefined form. In some cases we did not have access to the full data of included articles which we required for analysis; therefore we emailed the corresponding author of them to get the related data. Extracted data related to studies were first author's name, year of publication, name of country and sample size; and those related to participants were mean age (standard deviation [SD]), percentage of male gender, mean (SD) duration of hemodialysis, history of blood transfusion, mean (SD) of aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transpeptidase, prevalence rate of hepatitis B surface antigen (HBs Ag), anti-HCV antibody, HCV-RNA, OCI and finally laboratory methods for OCI identification.

• Data analysis & synthesis

We needed to modify OCI prevalence in some studies to be compatible with our definition for OCI. For calculation of OCI prevalence rate, we only considered cases with negative HCV-RNA and anti-HCV antibody. 95% CI of studies' prevalence rates were calculated with STATA 10.0 according to Jeffrey's method. Because of the existence of large heterogeneity between results of studies regarding OCI prevalence in hemodialysis and KT patients, we just reported all related prevalence rates in a table and preferred not to pool them.

Results

• Study screening & critical evaluation

According to Figure 1, we identified 138 potentially eligible citations through database searching and after removing duplicates. We excluded 118 papers in the steps of title and abstract screening and then 20 full texts of articles were assessed for eligibility. In six studies [15–20], detectable HCV-RNA in the absence of anti-HCV antibody in the patients' sera had been considered as OCI definition and we excluded them. One study was excluded as it was related to HCV prevalence and not its occult type [21]. In another study [22], investigation of HCV-RNA in PBMCs had been performed only in patients with transitioning mode from HCV-RNA negative to HCV-RNA

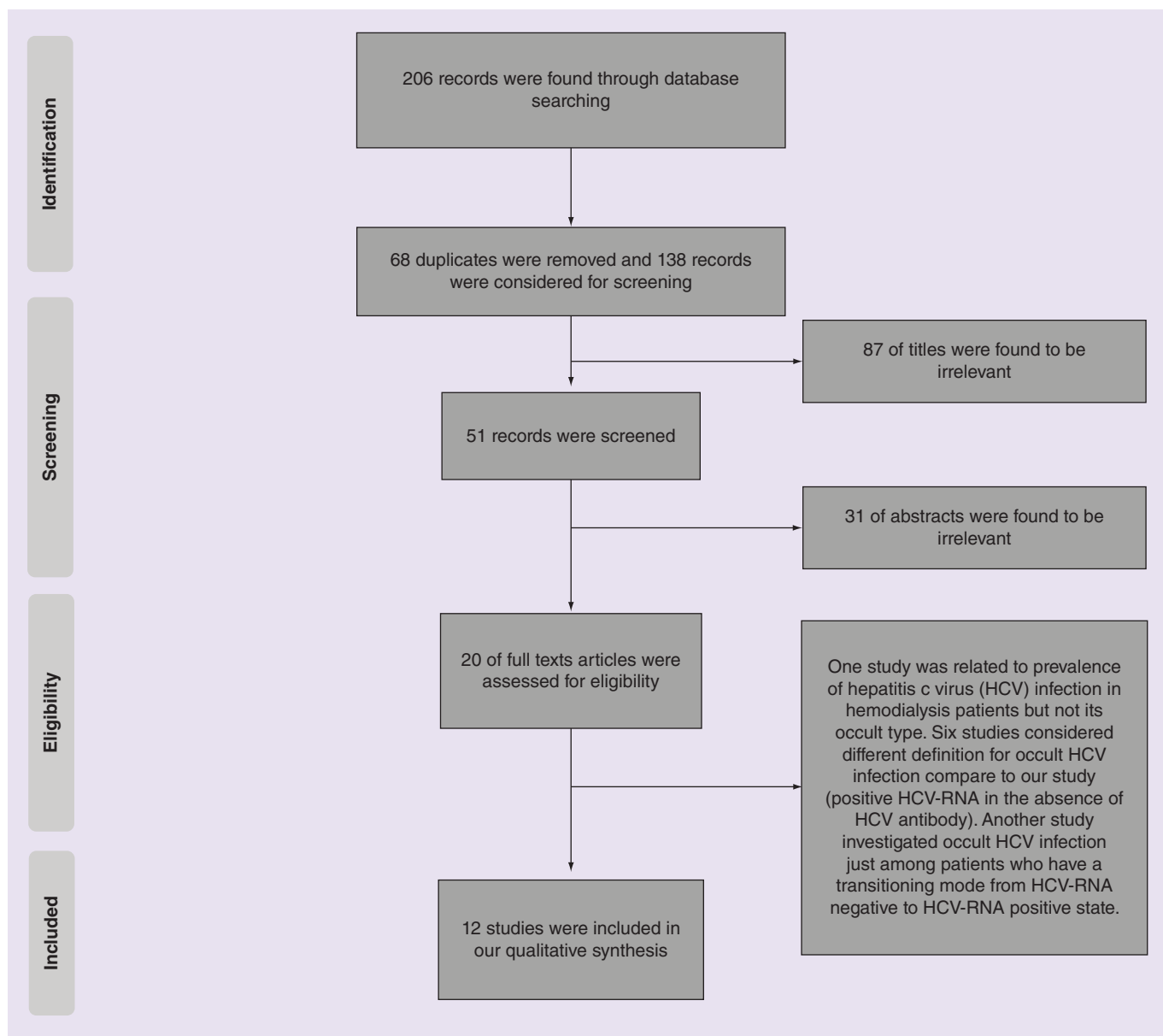


Figure 1. Screening of articles based on PRISMA statement.

positive type and therefore, we excluded it as the probability of the existence of selection bias could affect the reported OCI prevalence. Finally, after this step of assessment, we included 12 studies in our systematic review.

• Characteristics of included studies

Characteristics of all 12 included studies have been shown in **Table 1**. We found ten studies related to hemodialysis patients and two for KT patients. Egypt with three studies and Spain with two studies had the most number of projects related to this systematic review.

The mean age and duration of hemodialysis in participant ranged from 50 to 69 years and from 32 to 70.8 months, respectively.

• Outcome evaluation

Prevalence of OCI in hemodialysis patients

Ten studies with an overall sample size of 1275 participants were included. The oldest study was related to 1995. At that time, OCI had not been introduced but authors in that study have used method of OCI identification. These studies have major heterogeneity regarding OCI prevalence. In **Table 1**, all related OCI prevalence

Table 1. Characteristics of included studies (occult HCV infection has been defined as patients with negative test results for HCV antibody, serum HCV RNA and positive for HCV RNA in peripheral blood mononuclear cell).

Study characteristics	Hemodialysis										Kidney transplantation	
	Oester-reiche et al. [23]	Barril et al. [24] [†]	Choi et al. [25]	Barril et al. [26] [†]	Baid-Agrawal et al. [12]	Barril et al. [26] [†]	Bozkurt et al. [27]	El-Shishtawy et al. [28] [†]	Eslamifard et al. [29] [†]	Abdel-rahim et al. [30] [†]	Anbber et al. [31]	Baid-Agrawal et al. [12]
Publication year	1995	2008	2013	2014	2014	2014	2014	2015	2015	2016	2014	2010
Country name	Austria	Spain	Korea	Spain	Germany	Turkey	Egypt	Iran	Egypt	Egypt	Germany	France
Sample size (n)	67	109	77	210	417	100	51	70	81	93	417	26
Mean age, years (SD or range)	55 (16)	61.7 (14.9)	57.06 (10.6)	66.1 (14.9)	66.1 (14.9)	58.5 (13.9)	54.79 (13.03)	58.9 (14.7)	44.5 (13.8)	48.0 (10.5)	53.0 (12.8)	50 (31–66)
Male, n (%)	35 (52.23)	71 (65.13)	48 (62.3)	134 (63.9)	225 (54)	56 (56)	35 (66)	32 (45.7)	44 (54.3)	53 (57)	250 (60)	19 (73)
Mean duration of hemodialysis, months (SD or range)	44 (34)	51.5 (49.7)	39.2 (NA)	58.8 (62.4)	36 (6–264)	NA	45.24 (18–120)	70.8 (58.8)	32.7 (21.7)	33.5 (3.5)	78 (103.2) [†]	NA [†]
History of blood transfusion, n (%)	NA	59 (54)	NA	NA	57 (13.7)	NA	31 (58.5)	NA	46 (57)	NA	87 (20.8%)	NA
Prevalence of HBsAg, n (%)	0	NA	NA	0	2 (0.5)	4 (4)	NA	0	0	0	14 (3.4%)	4 (15)
HCV antibody positive, n (%)	10 (15)	0	0	0	15 (3.6)	10 (10)	0	0	0	48 (51.6)	20 (4.8%)	22 (84)
HCV RNA positive, n (%)	10 (15)	0	0	0	10 (2.4)	11 (11)	0	0	0	30 (32.3)	19 (4.6%)	0
Mean AST, IU/l (SD or range)	9 (9)	NA	NA	NA	25 (17)	16.1 (7.2)	NA	19.1 (8.1)	29 (16)	38.4 (2.4)	27 (24)	18 (7–63)
Mean ALT, IU/l (SD or range)	9 (8)	34 (21.2)	17.36 (11.6)	26 (26)	26 (26)	17 (1.1)	17.66 (11.31)	17.7 (9.5)	26 (12)	43.5 (3.4)	29 (62)	21 (9–84)
Mean GGTP, IU/l (SD or range)	48 (98)	99.3 (82)	NA	61 (82)	69 (10–160)	NA	44.38 (43.89)	NA	NA	NA	44 (87)	23 (11–85)
OCI prevalence, n (%) (95% CI)	1 (1.75) (0.18–7.90)	49 (45) (35.84–54.32)	3 (3.89) (1.10–10.03)	1 (0.24) (0.02–1.15)	49 (23.3) (18.00–29.32)	3 (3.37) (0.95–8.72)	8 (15.68) (7.70–27.42)	0 (0.00–3.51)	3 (3.70) (1.05–9.55)	9 (20.00) (10.38–33.33)	2 (0.50) (0.10–1.60)	0 (0.00–44.47)
Identification method	RT-PCR	Real-time PCR and <i>in situ</i> hybridization	Nested RT-PCR	TMA	Real-time PCR	Real-time PCR	RT-PCR	RT-PCR	Real-time PCR	Real-time PCR	TMA	Ultra-sensitive RT-PCR assay

[†]Only patients with negative serum HCV-RNA and anti-HCV antibody were included in these studies.
[‡]Time since last kidney transplantation.
[§]Five cases in this study evaluated for OCI through liver biopsy which showed negative results for all of them.
 ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGTP: Gamma-glutamyl transpeptidase; NA: Not available; OCI: Occult HCV infection; PBMC: Peripheral blood mononuclear cell; RT-PCR: Reverse transcriptase-PCR; SD: Standard deviation; TMA: Transcription-mediated amplification.

rates have been reported only based on PBMCs to reduce the mentioned heterogeneity as much as possible. Furthermore, we calculated OCI prevalence rate only based on the total cases with negative serum HCV-RNA and anti-HCV antibody. Five studies [24,26,28–30] included only patients with negative results for both serum HCV-RNA and anti-HCV antibody while others did not have this inclusion criterion. One of them [29] have found no OCI cases but four others have reported OCI prevalence (95% CI) as 45% (35.84–54.32) [24], 23.3% (18.00–29.32) [26], 15.68% (7.70–27.42) [28] and 3.70% (1.05–9.55) [30]. OCI has been investigated in three of these studies [24,26,30] with real-time PCR and in two others [28,29] with RT-PCR.

About the other five studies, except Anbber *et al.* [31], which reported 20.00% of OCI prevalence, the others [12,23,25,27] have reported the prevalence rate of OCI between 0.24 and 3.37%.

Prevalence of OCI in kidney transplant patients

We found two studies from France and Germany reported OCI prevalence among KT patients. In Baid-Agrawal *et al.*'s study [12], 417 KT patients with transcription mediated amplification method and in Nicot *et al.*'s study [32], 26 KT patients with RT-PCR method have been evaluated for OCI and prevalence rate (95%CI) has been reported as 2% (0.10–1.60) and 0% (0–44.47), respectively.

Conclusion

This project is the first systematic review investigating OCI prevalence among hemodialysis and KT patients. HCV infection is an important factor leading to morbidity and mortality in hemodialysis patients. There are various reports of HCV prevalence among hemodialysis patients in different countries ranging from 1.9 to 84.6% [31]. Occult type of this infection has special diagnosis method which is not routinely performed and it may worsen the situation especially in dialysis and transplantation centers [33,34].

Kidney transplantation has been recommended as a preferred treatment approach for HCV-infected patients with end-stage renal disease [1]. But nowadays, complete treatment of HCV infection can be considered in these patients [35]. OCI prevalence among KT patients was between 0 and 2% in two different studies. There is also a theoretical chance for reactivation of OCI in KT patients which

undergoing immunosuppressive treatment increasing risk of HCV replication [11].

The prevalence rate among hemodialysis patients had a wide range from 0 to 45%. Egypt which is the country with the highest prevalence rate of HCV infection in the world [36], had the most related studies. Middle East needs more attention regarding HCV infection, and epidemiological data, especially in some setting such as hemodialysis and transplantation center, are limited [2]. As we mentioned in the result parts of this project, there was a considerable heterogeneity between results of studies evaluating OCI prevalence in hemodialysis patients. The first point which should be considered is related to the location of performing studies. Those studies have been performed in different countries which certainly have a different prevalence rate of HCV infection and this consequently can influence on the OCI prevalence rate. Furthermore, it should be noted that control of HCV infection among dialysis and transplantation centers of those countries could be different [37,38]. Additionally, different laboratory methods used for OCI identification can be effective in the mentioned heterogeneity. We think that one of the important factors leading to this heterogeneity is related to the different eligibility criteria in those studies [13]. Accordingly, studies can be categorized into two groups such as those included patients with positive anti-HCV antibody and those excluded them. Our results showed that OCI prevalence in studies of the first category was relatively higher compared with studies in the second mentioned category. Correction of this issue was led to reduce the difference of OCI prevalence between these two categories of studies. However, after this correction the mentioned difference still remained high. Selection of participants and duration of dialysis are other important factors that could be responsible for the mentioned heterogeneity. OCI prevalence rate of 45% in Barril *et al.*'s study [24] is related to the subjects on long-term hemodialysis and with unexplained abnormalities in amino transferases. Lastly, history of blood transfusion and coinfection with HBV may play a role in causing the heterogeneity.

There is a conflicting data regarding severity of OCI. It is reported that OCI can independently influence mortality rate of hemodialysis patients (odds ratio: 3.84; 95% CI: 1.29–11.43) [24]. This association is very strong even comparing with classic HCV infection and survival rate of hemodialysis patients (adjusted relative risk: 1.34; CI: 1.13–1.59) [39].

Conversely, a comparative study demonstrated that OCI is less severe than classic HCV as OCI has significantly lower number of infected liver cells compared with the classic one [6].

Data regarding treatment of OCI patients are very limited [40]. Nowadays, new treatment strategies for HCV infection have provided opportunities for elimination of this infection [41]. Fortunately, some of these drugs can be safely used in hemodialysis and KT patients [35]. Effect of these regimens on OCI has not been fully addressed [42]. But there is a report of OCI detection in liver transplanted patients after achieving sustained virologic response with direct-acting antivirals [43].

OCI transmission in dialysis and transplantation centers may need more attention as OCI need special diagnostic approach and it may increase the risk of HCV transmission in these centers [11]. Although screening for OCI needs more investigation yet, it can be recommended in special conditions such as patients with unexplained signs or laboratory findings of liver disease such as abnormal aminotransferase.

Finally, based on our systematic review, OCI had various prevalence rates among hemodialysis and KT patients in different settings and

conditions which demonstrates that more attention is needed toward this issue. Considering major heterogeneity between results of included studies, we could not report pooled results of available literature and we believe that more original research may be needed regarding OCI prevalence in the mentioned populations.

Future perspective

Identification of OCI needs special diagnostic tests which can lead to underestimating of OCI prevalence in different settings such as hemodialysis or KT patients. Risk of transmission, clinical consequences and treatment of OCI in hemodialysis and kidney transplantation settings are important topics for further investigations.

Financial & competing interests disclosure

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EXECUTIVE SUMMARY

Occult HCV & patients with renal impairment

- Occult HCV infection (OCI) is defined as detectable HCV-RNA in hepatocytes in the absence of HCV-RNA and anti-HCV antibody in the serum checked by usual laboratory tests.
- OCI is diagnosed by a liver biopsy. Alternative approaches for easier OCI diagnosis are; detection of HCV-RNA in the peripheral blood mononuclear cells and ultracentrifugated sera of patients.
- Several studies which investigated OCI among hemodialysis and kidney-transplanted (KT) patients, reported a significant effect of OCI on the status of patients in those settings.
- Important controversy exists regarding OCI prevalence among hemodialysis or KT patients.

Determining prevalence rate of OCI among hemodialysis & KT patients

- We performed a systematic and comprehensive search in electronic databases and resources including PubMed, Scopus, Science Direct and ISI web of science to find related evidence.
- Two studies reported OCI prevalence rate of 0 and 2% among KT patients.
- Results of OCI prevalence rates among hemodialysis patients varied between 0 and 45% in ten different included studies showing a great heterogeneity.

Conclusion

- OCI transmission in dialysis and transplantation centers may need more attention as OCI needs a special diagnostic approach and it may increase the risk of HCV transmission in these centers.
- OCI screening can be recommended in special conditions such as hemodialysis or KT patients with unexplained signs or laboratory findings of liver disease.
- More original research is needed regarding OCI prevalence among hemodialysis and KT patients.

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