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MAJOR ARTICLE

Hepatitis C Virus Coinfection in People With Human Immunodeficiency Virus in Iran: A Systematic Review and Meta-Analysis

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Background. Hepatitis C virus (HCV) coinfection is associated with higher mortality and morbidity in people with human immunodeficiency virus (PWH).

Methods. We aimed to characterize the epidemiology and factors associated with HCV coinfection among PWH in Iran. In this systematic review, we searched 3 English databases (MEDLINE, SCOPUS, Embase) and 2 Farsi databases (Scientific Information Database and Magiran) for studies that measured the prevalence of HCV coinfection among PWH, published between 2000 and January 1, 2021. We included studies with a minimum sample size of 5 PWH. Reviews, editorials, conference abstracts, theses, studies with no relevant data, and unclear serological assays were excluded.

Results. We summarized the HCV coinfection prevalence by random-effect meta-analysis and assessed the sources of heterogeneity by a meta-regression model. Of the 858 records identified, 69 eligible studies with 12 996 PWH were included. Overall, HCV coinfection prevalence was 64% (95% confidence interval [CI], 58–69). The prevalence was higher among older (mean age ≥35 years) PWH (69%; 95% CI, 64–74) and PWH who inject drugs (77%; 95% CI, 71–82). Furthermore, we found that coinfection was higher among studies conducted between 2000 and 2014 (67%; 95% CI, 59–75) versus 2015–2020 (57%; 95% CI, 50–64).

Conclusions. The prevalence of HCV coinfection is high in Iranian PWH, with significant geographical variations. Hepatitis C virus screening and treatment among PWH are warranted to avoid the future burden of HCV-related liver damage, cancer, and mortality.

Keywords. coinfection; hepatitis C; human immunodeficiency virus; Iran; people with HIV.

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) have emerged as 2 major public health issues, associated with substantial morbidity and mortality due to considerable complications [1]. Globally, there are 37.7 and 71 million people with HIV (PWH) and chronic HCV, respectively [2, 3]. There are regional diversities in the prevalence of HIV and HCV. It has been estimated that approximately 54 000 adults and children with HIV lived in Iran in 2020, and 2400 adults and children were newly infected with HIV [4, 5]. Moreover, approximately 15 000 PWH (29%) received antiretroviral therapy (ART). Based on the findings from Iran, the HIV prevalence rate in the young population was evaluated as less than 0.1 [5]. The prevalence of HCV in the general population is relatively low (0.6%) due to the prevention strategies, including screening HCV in all blood products in Iran [5–7] and nationwide harm reduction programs [8]. According to the Joint United Nations Programme on HIV/AIDS (UNAID), in 2019, the proportion of HCV infection in Iranian PWH who started HCV treatment was estimated at 36.1 [5].

Human immunodeficiency virus and HCV infections share similar routes of transmission, mainly through injection of drugs. People who inject drugs (PWID) are expected to be more vulnerable to HIV-HCV coinfection [9, 10]. Injection drug user (IDU) remains one of the crucial global health concerns for contracting bloodborne disorders, including HIV and HCV infections, particularly in developing countries [11, 12]. A global systematic review in 2016 reported the HCV coinfection among PWH as 82.4% among PWID [13]. In Iran, HCV prevalence in PWID was considerably high (46.5%) despite the implementation of HCV control standards since 2005 [14]. It is estimated that there are approximately 1 200 000 to 2 million substance users and approximately 170 000 to 224 000 injection drug users in Iran [15]. Furthermore, in Iran, approximately

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2.8% of injection drug users are diagnosed with HIV [16]. Specific harm reduction standards were applied in Iran from 2002 until now. These programs included education, opioid substitution treatment by methadone and buprenorphine, and providing access to sterile syringes, needles, and condoms [14]. High-risk participants with confirmed HIV infection were referred to a voluntary counseling and testing center that developed an opportunity to undergo HCV antibody (Ab) testing and care [17].

Human immunodeficiency virus-HCV coinfection is associated with a markedly high risk of developing cirrhosis, hepatoma, and liver fibrosis progression [18, 19]. In the natural history of chronic HCV, viral and host factors play a considerable role in the course of HCV. In the setting of HIV-HCV coinfection, disrupted immune reaction and low $CD4^+$ T-lymphocyte counts have consistently been shown to accelerate liver fibrosis progression [19, 20]. In addition, chronic HCV infection results in increased T-lymphocyte activation, thereby leading to increasing the possibility of sustained HIV infection. A multicenter, randomized clinical trial of 97 HIV-1 patients showed that HIV-HCV-coinfected patients seem to show a greater HIV-1 reservoir size compared to HIV monoinfected patients [21].

Although several national studies have estimated the prevalence of HIV-HCV coinfection, the exact size of coinfection is poorly evaluated. In Iran, several studies reported the prevalence of HIV-HCV coinfection with a wide range of 1.16% to 98% [11, 22–30]. Factors associated with such wide heterogeneity have not been studied. In previous studies, the impact of important factors including IDU, sex, age, and time of study on estimating the coinfection has been neglected [29, 30]. In this comprehensive systematic review and meta-analysis, we sought to estimate the prevalence of HIV-HCV coinfection in PWH in Iran and assessed the demographic and behavioral factors (IDU) associated with a heterogeneity of results.

METHODS

Search Strategy and Study Selection

This systematic review and meta-analysis were performed according to the Meta-analysis of Observational Studies in Epidemiology checklist [31] and PRISMA (preferred reporting items for systematic reviews and meta-analyses) standards [32]. We searched the literature for all studies published between 2000 and January 1, 2021 that evaluated the prevalence of HCV among PWH in Iran. Two experienced investigators (A.A. and S.-K.R.-A.) independently identified potentially relevant studies by electronic searches of MEDLINE (via PubMed), SCOPUS, Embase, Google Scholar, and 2 Persian databases, including Scientific Information Database and Magiran. Keywords for the search included "HIV"; "AIDS" OR "Acquired Immunodeficiency Syndrome"; AND "HCV"; "hepatitis C" OR "hepatitis C antibodies"; AND "Iran". No limitation regarding language was placed. To achieve all additional studies, manual searches were performed via the references section of eligible studies. We screened the article by first reading the title and abstract and then the full text. Conflicting results were resolved through joint discussion. In a joint discussion, each of the authors noticed convincing evidence regarding the strengths and weaknesses of the articles. All retrieved studies were collected in EndNote to identify duplication.

Eligible studies for our analysis met the following criteria: (1) studies with the cohort, clinical trials, cross-sectional, and case-control designs that assessed the prevalence of HCV in PWH in Iran; and (2) studies that diagnosed HIV and HCV with standard laboratory tests (enzyme-linked immunosorbent assay and molecular diagnostic assays). Exclusion criteria included the following: reviews, editorials, conference abstracts, theses, duplicates, studies with less than 5 PWH sample size, studies with no relevant data, and unclear serological assays.

Data Extraction

Data for the first author, year of study, setting of patients, city, type of HIV diagnostic test, HIV sample size, the median age of patients, male proportion, IDU proportion, type of HCV diagnostic test, and HCV/HIV coinfection size were separately extracted by 2 researchers (A.A. and S.-K.R.-A.). We reached out to the corresponding author of studies with unclear data or unavailable full text via E-mail.

The quality of eligible studies was independently evaluated by 2 authors (A.A. and S.-K.R.-A.) using the Joanna Briggs Institute (JBI) checklist [33]. The JBI critical appraisal checklist for systematic reviews assesses the quality of retrieved studies by examining 8 items to consider the risk of bias. A score less than 5 indicated insufficient study quality. Discrepancies were resolved through discussion.

Data Analysis

We used the Metaprop command using STATA version 14 (StataCorp, College Station, TX) for pooling the HCV coinfection among PWH. We estimated 95% confidence interval (CI) using the score statistic, the exact binomial method, and the Freeman-Tukey double arcsine transformation of proportions. Heterogeneity of the prevalence estimated between studies was assessed by Q statistic and I^2 Index, assuming that I^2 values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively. Q statistic is a measure of weighted squared deviation on a standardized scale and compared with the expected sum of squares (on the assumption that all studies share a common effect) to yield a test of null and estimate excess variance. I^2 is the proportion of observed dispersion that is real, rather than spurious, and not dependent on the scale [34]. We assessed the quality of each study using JBI. Forest plots were drawn displaying the variation of the HCV Ab test

positivity rate among all PWH (HIV/HCV coinfection proportion) together with the pooled measure and subgroup analysis.

Egger's weighted regression method was used to test for publication bias, with $P < .1$ indicative of statistically significant publication bias. In the case of publication bias, we will report estimates after adjusting for publication bias using the trim-and-fill method.

We assessed the heterogeneity effect of several characteristics (age, male proportion, IDU proportion, and HIV and HCV route diagnostic tests) using meta-regression.

The pooled prevalence of HCV coinfection in PWH was reported for 5 subregions: (1) North-Central region: Tehran, Qazvin, Mazandaran, Semnan, Golestan, Alborz, and Qom province; (2) South-Central region: Esfahan, Fars, Bandar Bushehr, Chaharmahal and Bakhtiari, Hormozgan, Kohgiluyeh, and Boyer-Ahamd province; (3) Northwest region: East Azerbaijan, West Azerbaijan, Ardabil, Zanjan, Gilan, and Kurdistan province; (4) Southwest region: Kermanshah, Ilam, Lorestan, Hamedan, Markazi, and Khuzestan province; (5) East region: Razavi Khorasan, South Khorasan, North Khorasan, Kerman, Yazd, Sistan, and Baluchestan province.

Patient Consent and Ethical Approval

The design of the work was approved by the Ethics Committee of Mazandaran University of Medical Science. All procedures performed in studies are in accordance with the ethical standards of the institutional and/or national research committee of Iran.

RESULTS

We identified 858 articles, 533 (62%) of which were duplicates and removed (Figure 1). We screened the title and abstract of 325 papers and read the full text of 84 articles. Of those, 16 articles were excluded for one of the following reasons: HIV-HCV coinfection was reported among HCV-positive individuals (5); the full text was not available (1); the sample size was less than 5 (4); insufficient statistics (6). Finally, we extracted data from 69 articles for analysis (Table 1). The 69 articles enrolled a total of 12 996 PWH, the majority from Tehran. As shown in Figure 2, the overall prevalence of HCV coinfection was 64.0% (95% CI, 58–69) among PWH. After the removal of 7 low-quality studies (total quality score below 5), pooling of these 62 studies (11 790 individuals) yielded an overall prevalence of HIV/HCV coinfection 64 (95% CI, .58–.71) per 100 PWH in Iran. Egger's test indicated no publication bias ($P = .19$).

Meta-Regression Analysis

Unadjusted meta-regression analysis showed that the prevalence of HCV coinfection increased by 1.4% (95% CI, .4–2.4; $P = .007$) with each year increase in age and increased by 0.4% (95% CI, .2–.6; $P < .001$) with each 1% increase in the prevalence of injecting drug use among the study sample. Table 2 showed that after adjustment of other variables, the prevalence of HCV coinfection was associated with older age ($P = .049$) and injecting drug use ($P = .03$). Furthermore, we noticed a reduction in HCV-HIV coinfection over time. From 2015 (a year when the annual number of PWH and related deaths remained relatively constant [5]) to 2020, the coinfection was 11% lower than from 2000 to 2014 ($P = .02$).

We observed that the prevalence of HCV coinfection was 61% and 69% among PWH with a mean age of less than 35 years and equal or more than 35 years (approximate combined mean), respectively (Table 3 and Figure 3).

The prevalence of HCV coinfection among PWH was 67% and 57% among PWH in the studies conducted in 2000–2014 and 2015–2020, respectively (Table 3 and Figure 4).

As shown in Table 3 and Figure 5, we found that the prevalence of HCV coinfection was 57% among PWH with IDU proportion of less than 75% and 77% among PWH with IDU proportion equal to or more than 75%.

Regarding the geographical disparities in HCV-HIV coinfection, the prevalence of HCV coinfection was 64% in North-Central, 75% in South-Central, 51% in Northwest, 61% in Southwest, and 59% in the East (Table 3 and Figure 6).

DISCUSSION

To our best knowledge, this is the first systematic review and meta-analysis of the prevalence of HCV coinfection in PWH by the conditional probability method in Iran. Few studies measured the effect of confounding factors on HCV coinfection among PWH in Iran [29]. Based on the findings of our meta-analysis, we found that 64% of PWH in Iran are coinfected with HCV. In other words, 1 in 1.56 PWH is coinfected with HCV. With an estimated 54 000 PWH in Iran, we could expect 34 560 of these people to be infected with HCV [4]. The preliminary studies that were included have been conducted in only 15 (of 31 provinces of Iran) provinces. However, from each of the 5 regions of Iran, which are divided by the Ministry of Interior of Iran based on the proximity, geography, and cultural commonalities, we have identified several studies and examined them in this study.

In the current review, we estimated that the greatest burden of this coinfection is in the South-Central region (including the provinces of Isfahan and Fars), followed by the North-Central region (including Tehran, the capital of Iran). The lowest prevalence of HIV-HCV coinfection was observed in the Northwestern regions of Iran (including the provinces of East Azerbaijan, West Azerbaijan, and Kurdistan), corresponding to a prevalence of 51%. There is no geographical variability in antinarcotic law in Iran. However, it is consistent with other studies in terms of resource limitations and deaths due to the consumption of these substances [94].

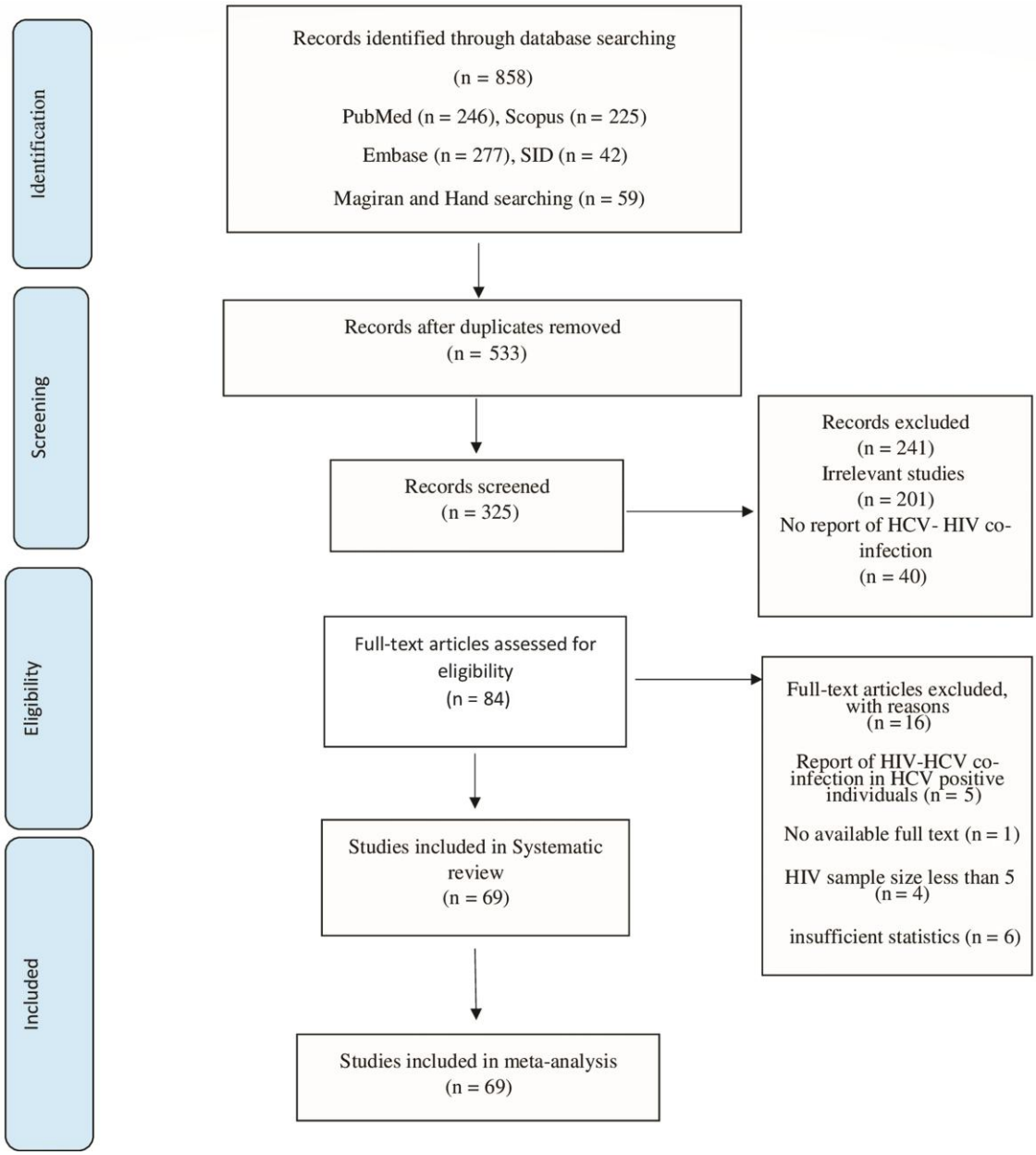

Figure 1. Flowchart of included studies. HCV, hepatitis C virus; HIV, human immunodeficiency virus; SID, Scientific Information Database.

Recent evidence indicated that during the years 2009–2017, the Central provinces of Iran always showed the highest incidence of HIV infection and the Western provinces (such as West Azerbaijan and Kurdistan) showed the lowest incidence of this infection [95]. Until 2015, the most important route of HIV infection in Iran was intravenous drug injection. Reports from the Ministry of Health of Iran showed that the transmission of infection by intravenous drug injection from 2000 to 2017 was evaluated at 67.6%, 67.3%, 70.4%, 69.6%, 78.1%, 84.5%, 75.4%, 77.3%, 74.9%, 71.1%, 66.6%, 62.6%, 57.8%, 50.4%, 47.7%, 43.4%, 43.4%, and 33.2%, respectively [4]. These numbers revealed that, until 2015, parenteral transmission remained the mainstay for contracting HIV infection in Iran, and simultaneously HCV infection could be considered probable.

In the current study, HIV/HCV coinfection was more common in older age. Numerous previous studies in Iran have shown that older individuals, especially older injecting drug users, are more vulnerable to being infected with HIV [4]. The higher prevalence of this coinfection in older PWH could result from the cumulative effects of HCV exposure in the elderly, the lack of coverage, and the impact of risk reduction

Table 1. Characteristics of Included Studies

Author	Year	City	District	HIV Sample Size (N)	Coinfection Sample Size (N)	Mean Age, Year	Male Proportion	IDU[a] %	HIV Test	HCV Test
Ramezani et al [35]	2012	Arak	Southwest	19	15	33.3	100	100	ELISA	Third-generation ELISA
Rahimi- movaghar et al [25]	2007	Tehran	North Central	52	37	33.87	95.77	100	ELISA	Third-generation ELISA
Rahimi- movaghar et al [25]	2007	Tehran	North Central	44	41	33.87	95.77	100	ELISA	Third-generation ELISA
Salem et al [36]	2009	Karaj	North Central	12	3	34.6	100	41/8	ELISA	Third-generation ELISA
SeyedAlinaghi et al [37]	2005	Tehran	North Central	201	135	36	85.57	33/3	ELISA	Third-generation ELISA
Sharif-Mood et al [38]	2005	Zahedan	East	47	19	37.5	89.36	12/77	ELISA and Western blot	Fourth-generation ELISA
Sofian et al [39]	2009	Arak	Southwest	9	8	30.7	100	100	ELISA and Western blot	Third-generation ELISA
Zahedi et al [40]	2011	Kerman	East	165	122	40.4	82.4	76.2	ELISA and Western blot	Third-generation ELISA
Afhami et al [41]	2005	Tehran	North Central	85	58	35/2	85.9	51/8	ELISA	Third-generation ELISA
Alavi et al [42]	2006	Ahwaz	Southwest	18	12	26/3	91.5	100	ELISA	Third-generation ELISA
Alavi et al [43]	2006	Ahwaz	Southwest	60	37	24/8	96.9	100	ELISA and Western blot	Third-generation ELISA
Rezaianzadeh et al [10]	2012	Shiraz	South Central	1338	1044	36	84.75	73/8	ELISA and Western blot	Third-generation ELISA
Alipour et al [44]	2013	Shiraz	South Central	1444	1132	38.4	82.2	74.1	ELISA and Western blot	Third-generation ELISA
Ataei et al [45]	2007	Isfahan	South Central	130	100	50.23	98.5	83.5	ELISA and Western blot	Third-generation ELISA
Babamahmoodi et al [46]	2010	Sari	North Central	80	47	37	82.5	81.5	ELISA and Western blot	Third-generation ELISA
Bagheri Amiri et al [29]	2012	Tehran	North Central	20	17	…	90	90	ELISA	Third-generation ELISA
Etminani-Esfahani et al [47]	2012	Tehran	North Central	98	54	40.25	74	55.7	ELISA	Third-generation ELISA
Honarvar et al [48]	2013	Shiraz	South Central	23	18	30.4	85.06	40.94	ELISA and Western blot	Third-generation ELISA
Hosseini et al [24]	2006	Tehran	North Central	112	100	…	100	100	ELISA and Western blot	Third-generation ELISA
Javadi et al [49]	2009	Isfahan	South Central	6	6	35.1	…	100	ELISA and Western blot	Third-generation ELISA
Keramat et al [50]	2007	Hamedan	Southwest	15	13	29.7	71.5	52.5	ELISA and Western blot	Third-generation ELISA
Khosravi et al [51]	2010	Shiraz	South Central	101	87	35	88.11	85.14	ELISA and Western blot	Third-generation ELISA
Mansoori et al [52]	2000	Tehran	North Central	44	39	38	91	75	ELISA and Western blot	Third-generation ELISA
MirNasseri et al [53]	2011	Tehran	North Central	70	61	35.24	89.5	88.8	ELISA and Western blot	Third-generation ELISA
Mohammadi et al [54]	2008	Lorestan	Southwest	391	282	40.5	91.6	51.6	ELISA and Western blot	Third-generation ELISA
Davarpanah et al [55]	2007	Shiraz	South Central	226	200	35.6	94.7	79.2	ELISA and Western blot	Third-generation ELISA
Majidpour et al [56]	2008	Tehran	North Central	12	9	33.52	91.5	100	ELISA and Western blot	Third-generation ELISA
Alavi et al [57]	2003	Ahwaz	Southwest	104	77	28	100	100	ELISA and Western blot	Third-generation ELISA
Ramezani et al [58]	2005	Tehran	North Central	95	65	33.8	83	55.33	ELISA	Third-generation ELISA
Moradmand Badie et al [59]	2009	Tehran	North Central	365	225	30.5	79.7	50.9	ELISA and Western blot	Third-generation ELISA

Table 1. Continued

Author	Year	City	District	HIV Sample Size (N)	Coinfection Sample Size (N)	Mean Age, Year	Male Proportion	IDU[a] %	HIV Test	HCV Test
Taeri et al [60]	2007	Isfahan	South Central	106	90	50.8	100	100	ELISA and Western blot	Third-generation ELISA
Aminzadeh et al [61]	2007	Tehran	North Central	21	14	34.4	100	100	ELISA	Third-generation ELISA
Azami et al [62]	2010	Tehran	North Central	200	118	36.5	76.5	56	ELISA and Western blot	Third-generation ELISA
Khorvash et al [63]	2005	Isfahan	South Central	9	9	31.7	98.91	100	ELISA and Western blot	Third-generation ELISA
Tabarsi et al [64]	2003	Tehran	North Central	15	12	36.9	87	87	ELISA and Western blot	Fourth-generation ELISA
Ramezani et al [65]	2005	Tehran	North Central	171	90	37	80.7	68.4	ELISA and Western blot	Third-generation ELISA
Ramezani et al [66]	…	Tehran	North Central	92	63	36.7	71.7	49	ELISA and Western blot	Third-generation ELISA
Mozhgani et al [67]	…	Tehran	North Central	50	27	31	74	70	ELISA	Third-generation ELISA
Afzali et al [68]	2014	Kashan	South Central	63	54	34.91	96.8	100	ELISA	Third-generation ELISA
Donyavi et al [11]	2018	Tehran	North Central	161	134	38.9	95	100	ELISA and Western blot	Third-generation ELISA
Jamshidi et al [26]	2017	Tehran	North Central	190	85	36.5	63.2	43.2	ELISA and Western blot	Third-generation ELISA
Dehghani-Dehej et al [69]	2015	Tehran	North Central	140	62	35.7	64.2	42.14	ELISA and Western blot	Fourth-generation ELISA
Teimoori et al [18]	2016	Ahwaz	Southwest	390	229	32	…	99.1	ELISA and Western blot	Third-generation ELISA
Bokharaei-Salim et al [70]	2014	Tehran	North Central	109	50	35.2	61.5	41.3	ELISA	Fourth-generation ELISA
Sabouri et al [71]	2009	Tehran	North Central	214	131	36.52	80.8	…	ELISA	ELISA
Zayedi et al [72]	2017	Ahwaz	Southwest	78	25	33.04	85.89	83.3	…	Fourth-generation ELISA
Moradi et al [12]	2017	8 provinces	North Central, Northwest, Southwest, South Central	38	17	36	84	13.4	ELISA and Western blot	Third-generation ELISA
Farhoudi et al [73]	2013	Tehran	North Central	85	50	…	…	…	ELISA	ELISA
Doosti-Irani et al [27]	2015	Khorramabad	Southwest	20	17	35.9	100	38.76	ELISA	Third-generation ELISA
Hashemi-Shahri et al [74]	2007	Zahedan	East	41	13	…	73.1	…	ELISA	Third-generation ELISA
Vaziri et al [75]	2007	Kermanshah	Southwest	888	60	30.7	97.9	…	ELISA	Third-generation ELISA
Saleh et al [76]	2013	Khorramabad	Southwest	50	26	…	49.5	…	ELISA	Third-generation ELISA
Haghgoo et al [77]	2012	East Azerbaijan	Northwest	371	168	30.8	91	59	ELISA	ELISA
Maracy et al [78]	2014	Isfahan	South Central	205	97	37.1	78	62	ELISA and Western blot	Third-generation ELISA
Hassanzadeh et al [79]	2011	Shiraz	South Central	180	47	…	66.7	…	ELISA	ELISA
Advay et al [80]	2015	Sanandaj	Northwest	165	121	38.3	83	100	ELISA and Western blot	Third-generation ELISA
Geibi et al [81]	2017	Shiraz	South Central	1216	794	34	74.2	67	…	…
Sani et al [82]	2017	Mashhad	East	64	53	…	95.3	90.6	ELISA and Western blot	Third-generation ELISA
Joulaei et al [83]	2013	Shiraz	South Central	101	76	39.1	70.9	17.1	ELISA	ELISA
Koochak et al [84]	2009	Tehran	North Central	200	121	…	72	…	ELISA and Western blot	ELISA
Khazaei et al [85]	2013	Aabadan, khoramshahr	Southwest	366	172	…	85.5	73.4	ELISA and Western blot	ELISA
Hajiabdolbaghi et al [86]	2010	Tehran	North Central	555	331	36.59	84.9	75.1	ELISA	ELISA

Table 1. Continued

Author	Year	City	District	HIV Sample Size (N)	Coinfection Sample Size (N)	Mean Age, Year	Male Proportion	IDU[a] %	HIV Test	HCV Test
Hosseini rad et al [87]	2014	Tehran	North Central	481	356	41.7	85	77.8	ELISA and Western blot	Third-generation ELISA
Pourahmad et al [88]	2003	Esfahan, Chaharmahal Bakhtiary, and Lorestan	South Central, Southwest	92	8	…	100	60.8	ELISA and Western blot	Third-generation ELISA
Khodadadi et al [89]	2010	Sanandaj	Northwest	97	30	34	100	100	ELISA and Western blot	Third-generation ELISA
Foroughi et al [90]	2013	Tehran	North Central	45	5	15.62	95.55	22.22	ELISA	Third-generation ELISA
Amini et al [91]	2016	Sanandaj	Northwest	185	99	39.26	76.1	61.4	ELISA and Western blot	Fourth-generation ELISA
Bakhti et al [92]	2016	Mazandaran	North Central	83	35	…	60.24	…	PCR	ELISA
Shadmand et al [93]	2015	Jahrom	South Central	73	45	…	72.6	…	ELISA	ELISA

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; PCR, polymerase chain reaction.

[a]The IDU refers to percentage of people with HIV who inject drugs.

strategies and other prevention programs in recent years in Iran [96]. In addition, we noticed that very low HCV coinfection in some studies was associated with a lower mean age of PWH [75, 88, 90].

Trends of shared injection and unprotected sexual contact have significantly increased in Iran. For 18 years from 2000 to 2017, the prevalence of sexual route of HIV infection in Iran has been estimated at 5%, 5.2%, 6.4%, 6.8%, 7.6%, 7.2%, 8.4%, 12.6%, 15.2%, 19.2%, 21.8%, 26.4%, 29.5%, 36.2%, 36.5%, 38.7%, 47.6%, and 46%, respectively [4]. We observed that coinfection prevalence has reduced to 11% among studies conducted after 2015 compared to those performed before 2015. Given the lower likelihood of transmitting HCV infection through sexual contact and the increasingly more effective coverage of national HIV programs implemented in Iran in recent years [14], we could expect a reduced prevalence of coinfection in studies conducted from 2015 onwards.

Based on the Iranian HIV Patient Registry System, at the end of 2019, of 22 054 cases, 14 311 (64.89%) and 6376 individuals (28.91%) were infected through intravenous injection and sexual contact, respectively [4, 97, 98]. Of special consideration, female partners of IDUs in Iran have always been considered one of the most high-risk groups for HIV in Iran. Previous studies have also shown a significantly higher risk of transmitting HCV infection within couples with at least 1 individual diagnosed with HIV [44, 99]. This information implies that we should ponder the likelihood of contracting these 2 infections simultaneously, either at the time of HIV infection or after its initial acquisition (individually or in dyads) as a crucial health issue. Because drug users are not prosecuted during the treatment period, according to the antinarcotics Law in Iran, there is a golden opportunity for these people for HIV and HCV infection screening.

In Iran, relatively good national programs for the prevention and management of HIV infection in 4 phases have been implemented since 2002. In the first phase (2002–2006), these programs focused on public awareness, risk reduction for injecting drug users, and mother-to-child transmission. Afterward, in the second (2007–2010) and third (2011–2015) phases, in addition to strengthening the first phase programs, the greatest concentration was placed on youth education. In the fourth phase (2016–2020), the main focus was on achieving the goals of UNAIDS and the 90-90-90 policy [4]. According to the 90-90-90 policy, by 2020, 90% of PWH will be aware of their HIV status, 90% of whom will receive ART, and 90% of PWH receiving antiretroviral therapy will have sustained viral suppression [100]. A recent study showed that 59 314 PWH live in Iran, 22 054 (37% of PWH) of whom were diagnosed with the infection. At the end of 2019, 25% of PWH received antiretroviral treatment. Furthermore, 11% of PWH achieved sustained viral load suppression by 2019. These reports clearly emphasized that further accurate programs are needed for prompt diagnosis of HIV infection in the general population and high-risk groups (especially PWID, their partners, and female sex worker groups) [101].

Our study had some limitations. First, we could not find a documented report to accurately estimate this coinfection in PWH from some provinces of Iran. However, the trim-and-fill analysis revealed that if reports were conducted in all Iran provinces, we would not have seen much change, and this simultaneous infection in PWH is approximately 58% (95% CI, 64–53). Second, different HIV and HCV diagnostic methods of

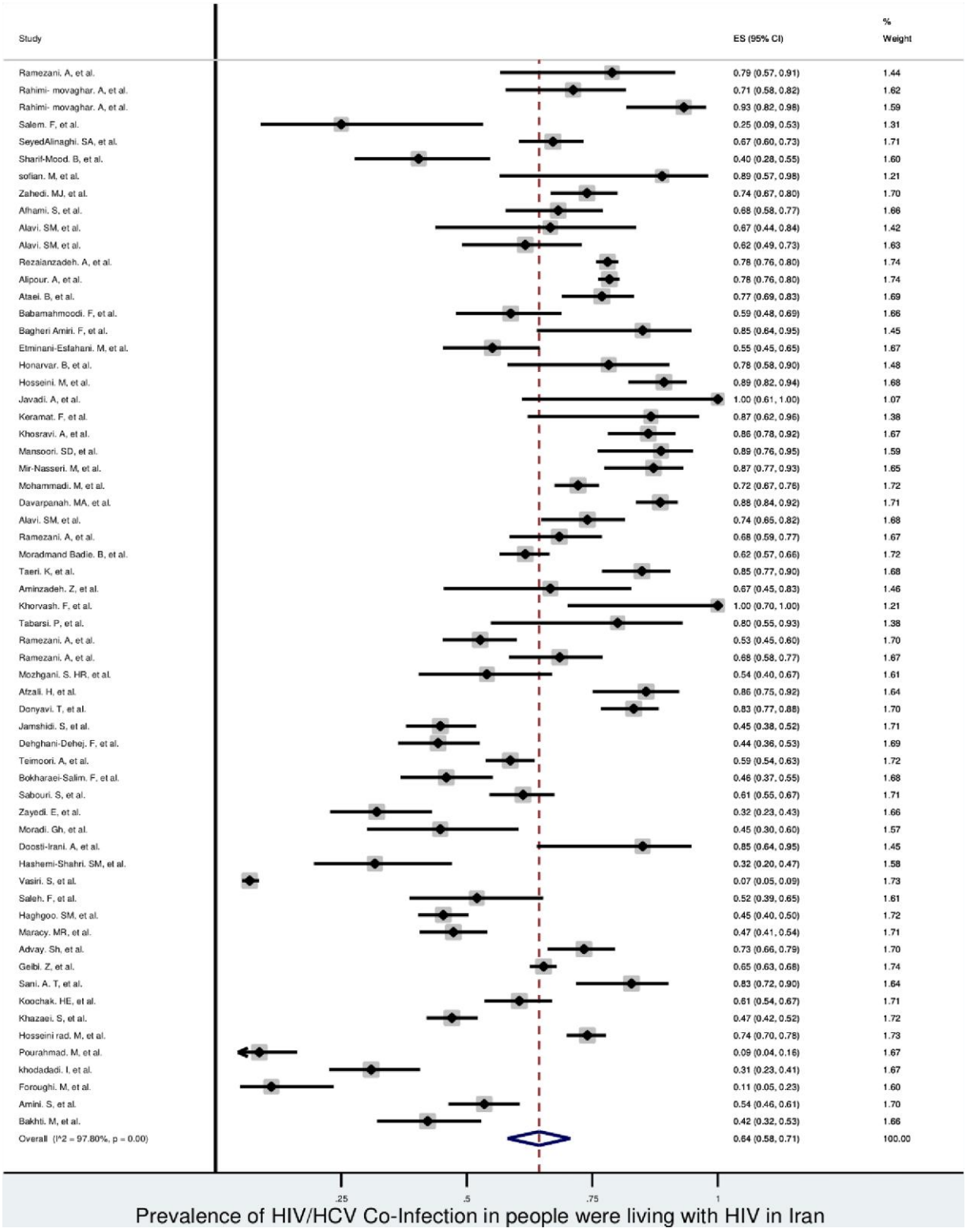

Figure 2. Prevalence of human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection in people with HIV in Iran. CI, confidence interval; ES, effect size.

preliminary studies may be another limitation of our research, which may be one of the reasons for the observed heterogeneity. We made our best effort to reduce heterogeneity effects by performing stratified analysis. The correlation between the anti-HCV level and HCV ribonucleic acid (RNA) is another issue. However, in the literature, a positive correlation

Table 2. Meta-Regression Results for Univariate and Multiple (Adjusted Effect) Models Assessing the Effect of Age, Male Proportion, and IDU Proportion, Year of Study, HIV and HCV Route Diagnostic Tests on the Prevalence of HIV/HCV Coinfection in Iranian People

Parameters	Unadjusted		Adjusted	
	β (95% CI)	*P* value	β (95% CI)	*P* Value
Age, year	0.014 (.001–.018)	.007	0.009 (.004– .024)	.049
Year (2015–2021 vs 2000–2014)	−0.07 (−.18 to .05)	.26	−0.11 (−.19 to −.02)	.02
Male proportion	0.004 (0–.009)	.12	0.002 (−.003 to .008)	.41
IDU proportion	0.004 (.002– .006)	<.001	0.003 (.002–.005)	.03
HIV route diagnostic test (ELISA vs ELISA and Western blot)	0.1 (0–.23)	.07	0.01 (−.11 to .13)	.83
HCV route diagnostic test (Third generation vs fourth generation ELISA test)	−0.15 (−.31 to .02)	.8	−0.08 (−.22 to .07)	.28

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; PCR, polymerase chain reaction.

Table 3. The Prevalence of HCV Coinfection in Different Subgroups of PWH

Parameter	Number of Studies	HIV Sample Size	I2, %	Overall Estimate (%) (95% CI)
Age, Year				
<35	20	3948	98.54	61 (47–75)
≥35	33	6814	93.39	69 (64–74)
Year of Studies				
2000–2014	47	8439	98.19	67 (59–75)
2015–2020	15	3351	93.18	57 (50–64)
IDU, Percentage				
<75	28	7448	96.38	57 (50–63)
≥75	28	2866	91.05	77 (71–82)
Geographic Areas				
North Central	27	3250	92.14	64 (58–70)
South Central	13	4959	96.94	75 (66–83)
Northwest	4	818	94.2	51 (36–66)
Southwest	13	2408	98.78	61 (41–80)
East	4	317	93.53	59 (35–80)

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; PWH, people with HIV.

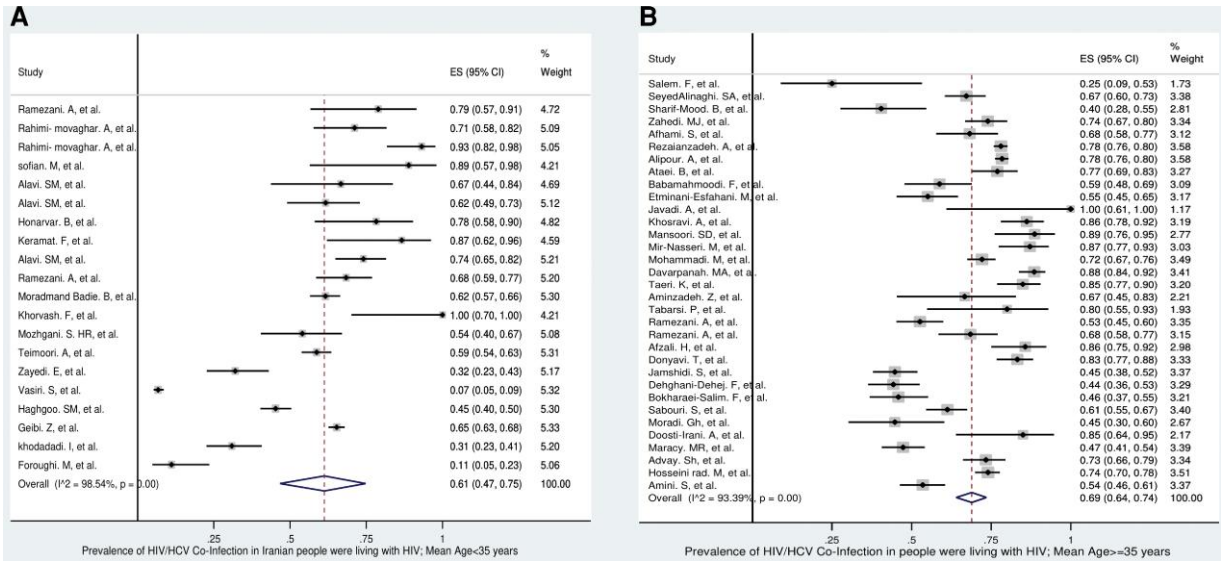

Figure 3. (*A*) Prevalence of human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection in people with HIV with mean age less than 35 years (*A*) and equal to or more than 35 years (*B*). CI, confidence interval; ES, effect size.

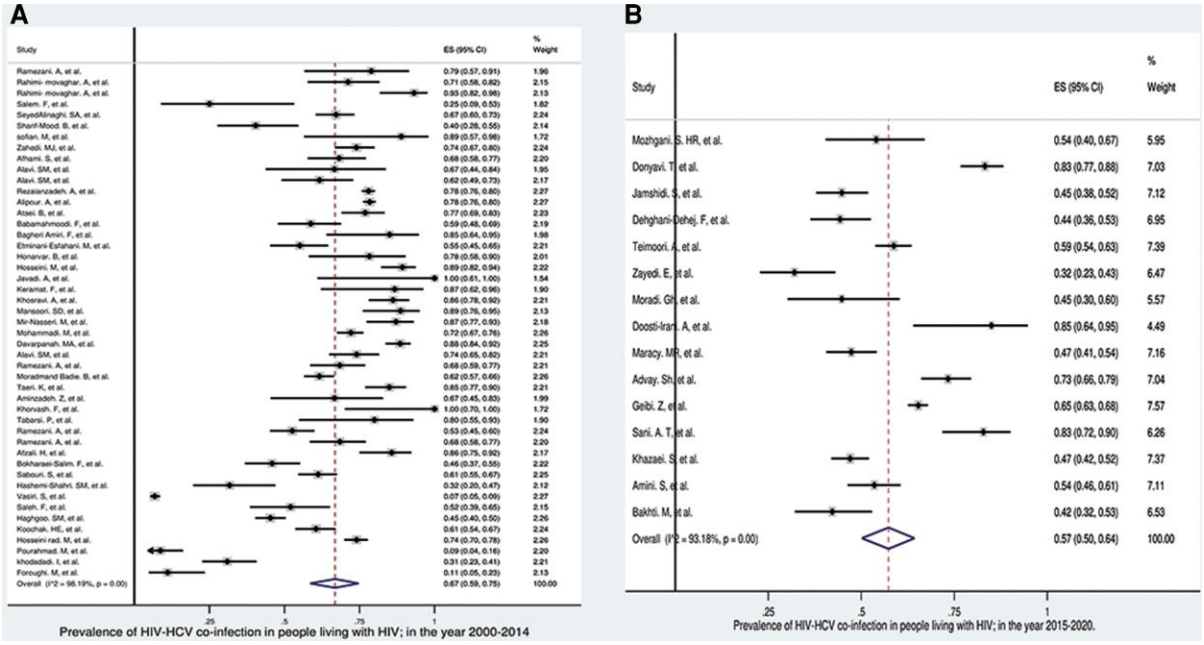

Figure 4. Prevalence of hepatitis C virus (HCV) coinfection in people with human immunodeficiency virus (HIV) in years 2000–2014 (*A*) and 2015–2020 (*B*). CI, confidence interval; ES, effect size.

between serum anti-HCV level and HCV RNA supported the hypothesis that the positivity of HCV RNA can be anticipated by the anti-HCV status [102]. Third, HCV infection was detected by anti-HCV assays, so our results showed past exposure and may not reflect the active HCV infection among PWH.

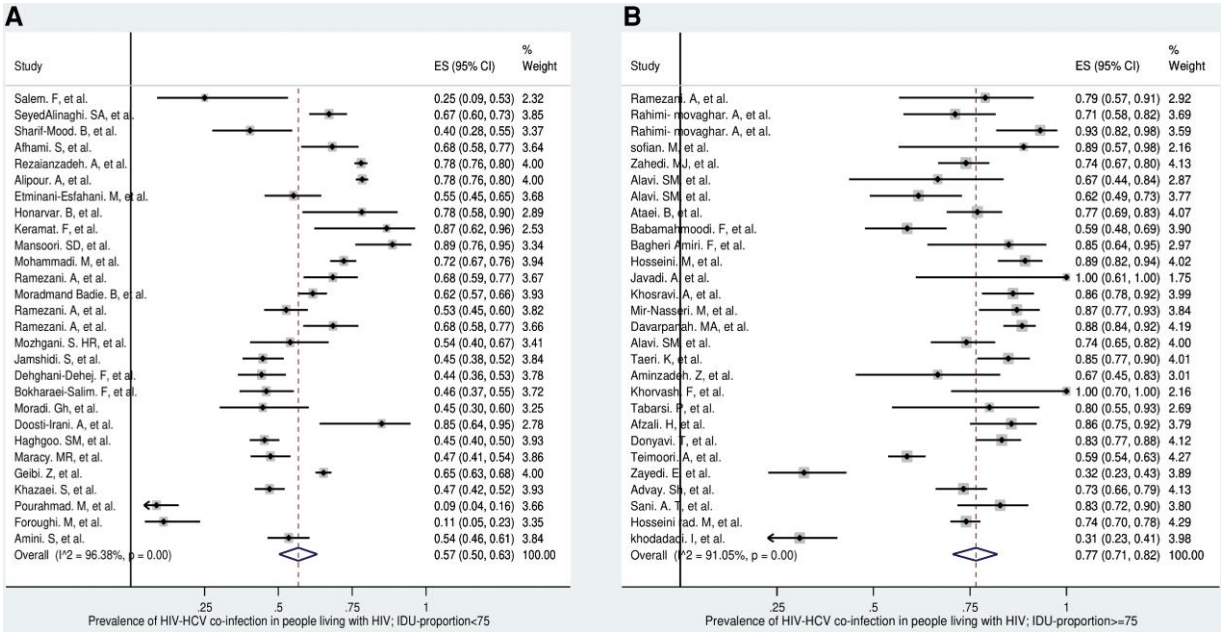

Figure 5. Prevalence of hepatitis C virus (HCV) coinfection among people with human immunodeficiency virus (HIV) with injection drug user (IDU) proportion less than 75% (*A*) and equal to or more than 75% (*B*). CI, confidence interval; ES, effect size.

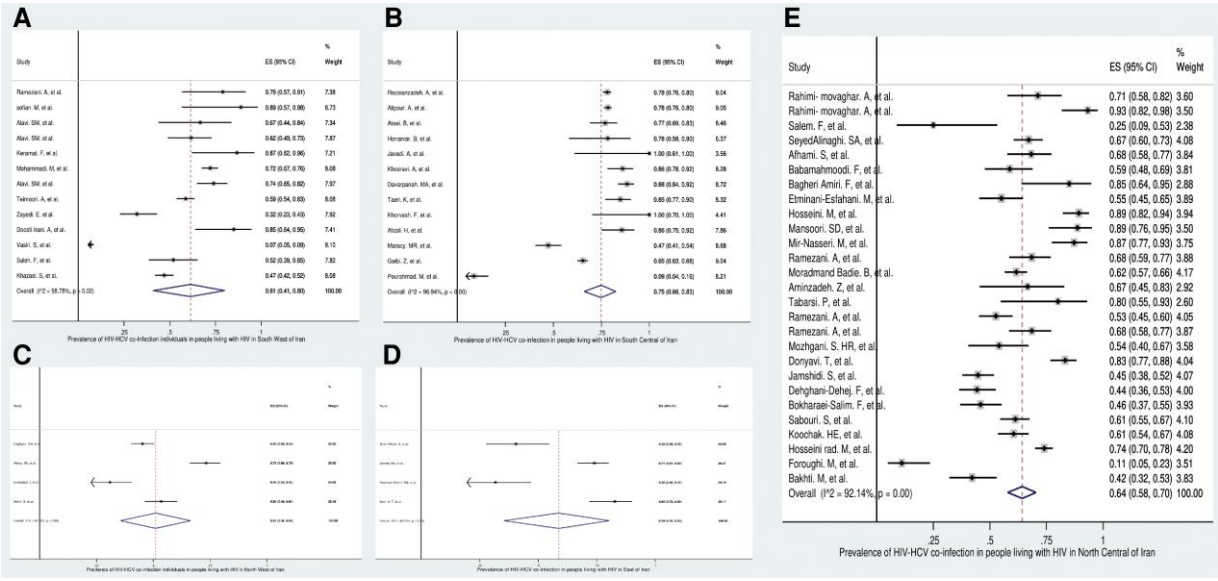

Figure 6. Prevalence of hepatitis C virus (HCV) coinfection in people with human immunodeficiency virus (HIV) in Southwest (*A*), South-Central (*B*), Northwest (*C*), East (*D*), and North-Cental Iran (*E*). CI, confidence interval; ES, effect size.

CONCLUSIONS

Our study showed that PWH continues to have a high prevalence of HCV coinfection. Screening for HCV and treatment among PWH is required to avoid the future burden of HCV-related liver damage, cancer, and mortality. Further national standards should be carefully developed for HCV screening in PWH, provision of appropriate HCV care, and access to direct-acting antiviral treatment for those with chronic active infection. For this purpose, it is essential to build HCV surveillance and treatment strategies in Iran.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. A. A. contributed to the study concept. A. A. and S.-K. R.-A. collected the data. A. A. performed the statistical analysis and data interpretation. S.-K. R.-A. and A. A. verified the data S.-K. R.-A. and A. A. drafted the manuscript and provided critical revision of the study. A. A. and S.-K. R.-A. revised the final version of the study.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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