Associations between polymorphisms in *IL-10* gene and the risk of viral hepatitis: a meta-analysis

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**Abstract**

**Background:** The relationships between polymorphisms in interleukin-10 (*IL-10*) gene and the risk of viral hepatitis remain inconclusive. Therefore, the authors conducted so far the very first meta-analysis to robustly assess the relationships between polymorphisms in *IL-10* gene and the risk of viral hepatitis by integrating the results of previous works.

**Methods:** Medline, Embase, Wanfang, VIP and CNKI were searched thoroughly for eligible studies, and 76 genetic association studies were finally included in this meta-analysis.

**Results:** We noticed that rs1800871 (−819 C/T), rs1800872 (−592 C/A) and rs1800896 (−1082 G/A) polymorphisms were all significantly associated with the risk of viral hepatitis in Asians, whereas only rs1800896 (−1082 G/A) polymorphism was significantly associated with the risk of viral hepatitis in Caucasians. In further analyses by disease subtypes, we noticed that the three investigated polymorphisms were all significantly associated with the risk of both HBV and HCV.

**Conclusions:** This meta-analysis demonstrates that rs1800871 (−819 C/T), rs1800872 (−592 C/A) and rs1800896 (−1082 G/A) polymorphisms may influence the risk of viral hepatitis in Asians, while only rs1800896 (−1082 G/A) polymorphism may influence the risk of viral hepatitis in Caucasians. In further analyses by disease subtypes, we noticed that the three investigated polymorphisms may influence the risk of both HBV and HCV.

**Keywords:** Viral hepatitis, Hepatitis B virus (HBV), Hepatitis C virus (HCV), Gene polymorphisms, Meta-analysis

**Background**

Viral hepatitis refers to a type of infectious disorder that is caused by hepatitis viruses which include HAV, HBV, HCV, HDV and HEV [1, 2]. In addition to acute liver injury, these hepatitis viruses may also lead to life-threatening conditions such as liver cirrhosis or hepatocellular carcinoma (HCC) [3, 4]. The clinical course of viral hepatitis is resulted from a complex interaction between pathogen, host and environmental factors, some patients may be asymptomatic the whole life, but some patients may eventually develop liver cirrhosis or even HCC [5, 6]. Therefore, there is no doubt that individual anti-viral immunity is vital for the onset and development of viral hepatitis.

Interleukin-10 (IL-10) serves as one of the most important anti-inflammatory and immunosuppressive factor, and it plays a crucial role in regulating anti-viral immune responses [7–9]. Considering the immune-regulatory effects of IL-10, over the last decade, investigators all over the world have repeatedly attempted to explore the relationships between polymorphisms in *IL-10* gene and the risk of viral hepatitis, yet the relationships between these polymorphisms and the risk of viral hepatitis are...
still inconclusive. So a meta-analysis was conducted to robustly analyze the relationships between polymorphisms in IL-10 gene and the risk of viral hepatitis by integrating the results of previous works.

Methods
The PRISMA guideline was strictly followed by the authors when designing and implementing this study [10].

Literature search and inclusion criteria
Medline, Embase, Wanfang, VIP and CNKI were thoroughly searched by the authors with the below terms: (Interleukin-10 OR IL-10 OR Interleukin 10 OR IL 10) AND (Polymorphism OR Polymorphic OR Variation OR Variant OR Mutant OR Mutation OR SNP OR Genotypic OR Genotype OR Allelic OR Allele) AND (Viral hepatitis OR Chronic hepatitis OR Acute hepatitis OR Hepatitis A OR Hepatitis B OR Hepatitis C OR Hepatitis D OR Hepatitis E OR HAV OR HBV OR HCV OR HDV OR HEV). Moreover, we also manually screened the reference lists of retrieved publications to make up for the potential incompleteness of electronic literature searching.

Selection criteria of this meta-analysis were listed below: (1) Studies without genotypic or allelic frequencies of IL-10 polymorphisms in cases with viral hepatitis and population-based controls; (2) The full manuscript with required genotypic or allelic frequencies of IL-10 polymorphisms is retrievable or buyable. Articles would be excluded if one of the following three criteria is satisfied: (1) Studies without complete data about genotypic or allelic frequencies of IL-10 polymorphisms in cases with viral hepatitis and population-based controls; (2) Narrative or systematic reviews, meta-analysis or comments; (3) Case series of subjects with viral hepatitis only. If duplicate publications were retrieved from literature search, we would only include the most complete one for integrated analyses.

Data extraction and quality assessment
The authors extracted the following data items from eligible studies: (1) Last name of the leading author; (2) Publication year; (3) Country and ethnicity of study population; (4) The number of cases with viral hepatitis and population-based controls; (5) Genotypic frequencies of IL-10 polymorphisms in cases with viral hepatitis and population-based controls. Hardy–Weinberg equilibrium was then tested by using genotypic frequencies of IL-10 polymorphisms, and the threshold of derivation from HWE was set at 0.05. The quality of eligible publications was assessed by the Newcastle–Ottawa scale (NOS) [11], and those with scores of 7–9 were considered to be publications of good quality. Two authors extracted data and assessed quality of eligible publications in parallel. A thorough discussion until a consensus is reached would be endorsed in case of any discrepancy between two authors.

Statistical analyses
All statistical analyses in this meta-analysis were performed by using the Cochrane Review Manager software. Relationships between IL-10 gene polymorphisms and the risk of viral hepatitis were explored by using odds ratio and its 95% confidence interval. The statistically significant p value was set at 0.05. The authors used I² statistics to evaluate heterogeneities among included studies. The authors would use DerSimonian–Laird method, which is also known as the random effect model, to integrate the results of eligible studies if I² is larger than 50%. Otherwise, the authors would use Mantel–Haenszel method, which is also known as the fixed effect model, to integrate the results of eligible studies. Meanwhile, the authors also conduct subgroup analyses by ethnic groups and disease subtypes. Stabilities of integrated results were tested by deleting one eligible study each time, and then integrating the results of the rest of eligible studies. Publication biases were evaluated by assessing symmetry of funnel plots.

Results
Characteristics of included studies
Three hundred and seventy-four literatures were retrieved by the authors by using our searching strategy. One hundred and thirty-nine literatures were then selected to screen for eligibility after omitting unrelated and repeated items. Six reviews and 48 case series were further excluded, and another nine literatures without all necessary genotypic or allelic data were further excluded by the authors. Totally 76 studies met the inclusion criteria, and were finally enrolled for integrated analyses (Fig. 1). Data extracted from eligible studies were summarized in Table 1 (Additional file 1).

Integrated analyses for rs1800871 polymorphism and the risk of viral hepatitis
Thirty-seven eligible literatures assess the relationship between rs1800871 polymorphism and the risk of viral hepatitis. The integrated analyses demonstrated that rs1800871 polymorphism was significantly associated with the risk of viral hepatitis in overall population (dominant comparison: OR=0.89, p=0.002; recessive comparison: OR=1.21, p=0.004; allele comparison: OR=0.90, p=0.0004) and Asians (dominant comparison: OR=0.84, p=0.0001; over-dominant comparison: OR=1.14, p=0.005; allele comparison: OR=0.88, p=0.0002), but not in Caucasians. Further
analyses by disease subtypes revealed similar positive results for rs1800871 polymorphism in both HBV and HCV subgroups (see Table 2).

**Integrated analyses for rs1800872 polymorphism and the risk of viral hepatitis**

Fifty-eight eligible literatures assessed the relationship between rs1800872 polymorphism and the risk of viral hepatitis. The integrated analyses demonstrated that rs1800872 polymorphism was significantly associated with the risk of viral hepatitis in overall population (dominant comparison: OR = 0.91, p = 0.003; allele comparison: OR = 0.93, p = 0.003) and Asians (dominant comparison: OR = 0.89, p = 0.0009; over-dominant comparison: OR = 1.10, p = 0.007; allele comparison: OR = 0.93, p = 0.004), but not in Caucasians. Further
| First author, year | Country | Ethnicity | Type of disease | Sample size | Genotypes (wt/wt/wt/m mt/m mt) | p-value for HWE | NOS score |
|--------------------|---------|-----------|-----------------|-------------|-------------------------------|----------------|-----------|
| Abbas 2009         | Egypt   | Mixed     | HCV             | 99/62       | 44/43/12                      | 0.752          | 7         |
| Afzal 2011         | Pakistan| Mixed     | HCV             | 89/99       | 16/66/7                       | <0.001         | 7         |
| Barrett 2003       | Ireland | Caucasian | HCV             | 92/66       | 49/38/5                       | 0.621          | 7         |
| Basturk 2008       | Turkey  | Caucasian | HBV             | 50/60       | 33/15/2                       | 0.175          | 7         |
| Chen 2007          | China   | Asian     | HCV             | 72/180      | 36/32/4                       | 0.819          | 7         |
| Cheong 2006        | Taiwan  | Asian     | HBV             | 261/72      | 133/110/18                    | 0.877          | 7         |
| Chuang 2009        | Taiwan  | Asian     | HCV             | 97/46       | 47/38/12                      | 0.491          | 7         |
| Constantini 2002   | UK      | Caucasian | HCV             | 546/354     | NA                            | NA             | NA        |
| Cunha 2018         | Brazil  | Mixed     | HCV             | 132/98      | 59/54/19                      | 0.685          | 7         |
| Khan 2014          | India   | Mixed     | HCV             | 150/150     | 48/79/23                      | 0.375          | 8         |
| Komatsu 2014       | Japan   | Asian     | HBV             | 52/57       | 24/18/10                      | 0.197          | 7         |
| Kusumoto 2006      | Japan   | Asian     | HCV             | 346/114     | 156/160/30                    | 0.994          | 7         |
| Li 2006            | China   | Asian     | HBV             | 122/63      | 55/52/15                      | 0.118          | 8         |
| Li 2015            | China   | Asian     | HCV             | 379/364     | 176/167/36                    | 0.383          | 8         |
| Maurya 2018        | India   | Mixed     | Viral hepatitis | 80/60       | 45/29/6                       | 0.138          | 7         |
| Miyazoe 2002       | Japan   | Asian     | HBV             | 213/52      | 153/56/4                      | 0.927          | 7         |
| Moudi 2016         | Iran    | Mixed     | HBV             | 221/200     | 40/163/18                     | <0.001         | 8         |
| Peng 2016          | China   | Asian     | HBV             | 173/181     | 74/77/22                      | 0.910          | 8         |
| Pereira 2008       | Brazil  | Mixed     | HCV             | 128/94      | 50/60/18                      | 0.305          | 8         |
| Persico 2006       | Italy   | Caucasian | HCV             | 120/110     | 60/54/6                       | 0.159          | 8         |
| Qiu 2011           | China   | Asian     | HBV             | 381/359     | 170/158/53                    | 0.389          | 7         |
| Ribeiro 2007       | Brazil  | Mixed     | HBV             | 30/41       | 17/12/1                       | 0.935          | 7         |
| Sepahi 2014        | Iran    | Mixed     | HCV             | 66/61       | 32/29/5                       | 0.099          | 7         |
| Sodsai 2013        | Thailand| Asian     | HCV             | 131/142     | 47/74/10                      | 0.584          | 8         |
| Sofian 2013        | Iran    | Mixed     | HBV             | 64/31       | 26/27/11                      | 0.358          | 7         |
| Srivastava 2014    | India   | Mixed     | HCV             | 232/76      | 111/75/46                     | 0.517          | 7         |
| Talaat 2014        | Egypt   | Mixed     | HBV             | 115/119     | 69/40/6                       | 0.143          | 7         |
| Tang 2012          | China   | Asian     | HCV             | 607/885     | 259/286/62                    | 0.653          | 8         |
| Tang 2015          | China   | Asian     | HBV             | 207/56      | 114/59/34                     | 0.006          | 7         |
| Vdigal 2002        | USA     | Mixed     | HCV             | 78/36       | 53/16/9                       | 0.672          | 7         |
| Wang 2012          | China   | Asian     | HBV             | 123/525     | 40/66/17                      | 0.567          | 7         |
| Xie 2008           | China   | Asian     | HCV             | 186/151     | 78/93/15                      | 0.266          | 7         |
| Yan 2009           | China   | Asian     | HBV             | 712/414     | 334/291/87                    | 0.219          | 8         |
| Yee 2001           | USA     | Mixed     | HCV             | 49/50       | 24/19/6                       | 0.250          | 7         |
| Zein 2004          | USA     | Mixed     | HCV             | 58/80       | 36/17/5                       | 0.279          | 7         |
| Zhang 2006         | China   | Asian     | HBV             | 231/135     | 103/103/25                    | 0.199          | 8         |
| Zhu 2015           | China   | Asian     | HCV             | 143/36      | 56/66/21                      | 0.616          | 7         |

rs1800871 — 819 C/T

| First author, year | Country | Ethnicity | Type of disease | Sample size | Genotypes (wt/wt/wt/m mt/m mt) | p-value for HWE | NOS score |
|--------------------|---------|-----------|-----------------|-------------|-------------------------------|----------------|-----------|
| Abbas 2009         | Egypt   | Mixed     | HCV             | 99/62       | 44/43/12                      | 0.752          | 7         |
| Afzal 2011         | Pakistan| Mixed     | HCV             | 89/99       | 16/66/7                       | <0.001         | 7         |
| Ahmadabadi 2012    | Iran    | Mixed     | HBV             | 57/100      | 31/24/2                       | 0.003          | 8         |
| Barkhash 2017      | Russia  | Caucasian | HCV             | 143/203     | 80/52/11                      | 0.032          | 7         |
| Barrett 2003       | Ireland | Caucasian | HCV             | 92/66       | 49/38/5                       | 0.621          | 7         |
| Basturk 2008       | Turkey  | Caucasian | HBV             | 50/60       | 33/15/2                       | 0.175          | 7         |
| Cao 2016           | China   | Asian     | HBV             | 241/254     | 88/104/49                     | 0.267          | 7         |
| Chen 2007          | China   | Asian     | HCV             | 72/180      | 36/32/4                       | 0.741          | 7         |

rs1800872 — 592 C/A
Table 1 (continued)

| First author, year | Country | Ethnicity | Type of disease | Sample size | Genotypes (wtwt/wtmt/mtmt) | p-value for HWE | NOS score |
|-------------------|---------|-----------|----------------|-------------|-----------------------------|----------------|-----------|
| Chen 2010         | China   | Asian     | HBV            | 304/361     | 150/124/30                 | 0.144          | 7         |
| Cheong 2006       | Taiwan  | Asian     | HBV            | 261/72      | 133/110/18                 | 0.877          | 7         |
| Chuang 2009       | Taiwan  | Asian     | HCV            | 143/134     | 73/56/14                   | 0.495          | 7         |
| Constantini 2002  | UK      | Caucasian | HCV            | 546/354     | NA                          | NA             | 7         |
| Falleti 2007      | Italy   | Caucasian | HCV            | 50/96       | 29/17/4                    | 0.980          | 7         |
| Gao 2009          | China   | Asian     | HBV            | 69/74       | 31/29/9                    | 0.641          | 7         |
| Gao 2009          | China   | Asian     | HCV            | 55/74       | 29/20/6                    | 0.641          | 7         |
| Gao 2016          | China   | Asian     | HBV            | 180/85      | 46/108/26                  | 0.029          | 8         |
| Jiang 2010        | China   | Asian     | HBV            | 169/119     | 75/74/20                   | 0.553          | 7         |
| Jiang 2013        | China   | Asian     | HBV            | 250/134     | 60/130/60                  | 0.409          | 7         |
| Jiang 2017        | China   | Asian     | HBV            | 136/289     | 68/54/14                   | 0.328          | 8         |
| Karatayli 2014    | Turkey  | Caucasian | HBV            | 116/53      | 63/41/12                   | 0.831          | 7         |
| Khalil 2017       | Egypt   | Mixed     | HCV            | 100/120     | 56/34/10                   | 0.089          | 7         |
| Komatsu 2014      | Japan   | Asian     | HBV            | 52/57       | 23/14/15                   | 0.131          | 7         |
| Kusumoto 2006     | Japan   | Asian     | HCV            | 346/114     | 156/160/30                 | 0.994          | 7         |
| Li 2003           | China   | Asian     | HBV            | 95/76       | 24/58/13                   | 0.218          | 7         |
| Li 2006           | China   | Asian     | HBV            | 122/63      | 55/52/15                   | 0.119          | 8         |
| Li 2015           | China   | Asian     | HBV            | 379/364     | 176/167/36                 | 0.345          | 8         |
| Mangia 2004       | Italy   | Caucasian | HCV            | 270/136     | 156/90/24                  | 0.003          | 7         |
| Maurya 2014       | India   | Mixed     | Viral hepatitis | 80/60       | 26/46/8                   | 0.534          | 7         |
| Miyazoe 2002      | Japan   | Asian     | HBV            | 213/52      | 95/91/27                   | 0.483          | 7         |
| Moudi 2016        | Iran    | Mixed     | HBV            | 221/200     | 36/168/17                  | <0.001         | 8         |
| Oleksyk 2005      | USA     | Mixed     | HCV            | 856/398     | NA                        | NA             | 7         |
| Peng 2006         | China   | Asian     | HBV            | 340/100     | 178/130/32                 | 0.519          | 7         |
| Peng 2016         | China   | Asian     | HBV            | 173/182     | 57/81/35                   | 0.860          | 8         |
| Pereira 2008      | Brazil  | Mixed     | HCV            | 128/94      | 50/60/18                   | 0.305          | 8         |
| Persico 2006      | Italy   | Caucasian | HCV            | 120/110     | 60/54/6                    | 0.159          | 8         |
| Qiu 2011          | China   | Asian     | HBV            | 721/359     | 354/282/85                 | 0.389          | 7         |
| Ramos 2012        | Brazil  | Mixed     | HCV            | 161/17      | 58/60/43                   | 0.120          | 7         |
| Ren 2017          | China   | Asian     | HBV            | 250/134     | 60/130/60                  | 0.409          | 7         |
| Ribeiro 2007      | Brazil  | Mixed     | HBV            | 30/41       | 17/12/1                    | 0.935          | 7         |
| Sepahi 2014       | Iran    | Mixed     | HCV            | 66/61       | 32/29/5                    | 0.099          | 7         |
| Shaker 2012       | Egypt   | Mixed     | HCV            | 100/80      | 35/33/32                   | 0.280          | 7         |
| Sheneef 2017      | Egypt   | Mixed     | HCV            | 100/50      | 58/23/19                   | 0.016          | 7         |
| Silva 2015        | Brazil  | Mixed     | HCV            | 245/230     | 106/110/29                 | 0.347          | 8         |
| Sodsai 2013       | Thailand| Asian     | HCV            | 131/142     | 47/74/10                   | 0.584          | 8         |
| Sofian 2013       | Iran    | Mixed     | HBV            | 86/31       | 31/42/13                   | 0.358          | 7         |
| Srivastava 2014   | India   | Mixed     | HBV            | 202/106     | 71/102/29                  | 0.033          | 7         |
| Tang 2012         | China   | Asian     | HCV            | 623/905     | 273/289/61                 | 0.058          | 8         |
| Tseng 2006        | Taiwan  | Asian     | HBV            | 344/184     | 169/148/27                 | 0.567          | 7         |
| Vidigal 2002      | USA     | Mixed     | HCV            | 78/36       | 53/16/9                    | 0.239          | 7         |
| Wang 2008         | China   | Asian     | HBV            | 335/165     | 132/169/34                 | 0.156          | 7         |
| Wang 2012         | China   | Asian     | HBV            | 123/525     | 43/63/17                   | 0.615          | 7         |
| Wu 2010           | China   | Asian     | HBV            | 175/153     | 82/67/26                   | 0.515          | 7         |
| Xiang 2014        | China   | Asian     | HBV            | 160/124     | 56/70/34                   | 0.203          | 7         |
| Xie 2008          | China   | Asian     | HBV            | 186/151     | 78/93/15                   | 0.266          | 7         |
| Yan 2009          | China   | Asian     | HBV            | 712/414     | 334/291/87                 | 0.219          | 8         |
Table 1 (continued)

| First author, year | Country   | Ethnicity | Type of disease | Sample size Case/control | Genotypes (wtwt/wtmt/mtmt) | p-value for HWE | NOS score |
|---------------------|-----------|-----------|-----------------|--------------------------|----------------------------|----------------|-----------|
| Yee 2001            | USA       | Mixed     | HCV             | 49/50                    | 24/19/6                    | 0.250          | 7         |
| Zein 2004            | USA       | Mixed     | HCV             | 52/80                    | 37/12/3                    | 0.111          | 7         |
| Zhang 2006           | China     | Asian     | HBV             | 396/135                  | 189/168/39                 | 0.199          | 8         |
| Zhu 2015             | China     | Asian     | HCV             | 179/705                  | 74/80/25                   | 0.142          | 7         |
|                      |           |           |                 |                          | rs1800896 — 1082 G/A       |                |           |
| Abbas 2009           | Egypt     | Mixed     | HCV             | 99/62                    | 41/41/17                   | 0.877          | 7         |
| Afzal 2011           | Pakistan  | Mixed     | HCV             | 89/99                    | 15/67/7                    | <0.001         | 7         |
| Barrett 2003         | Ireland   | Caucasian | HCV             | 92/66                    | 20/47/25                   | 0.344          | 7         |
| Basturk 2008         | Turkey    | Caucasian | HBV             | 50/60                    | 17/22/11                   | 0.049          | 7         |
| Bouzgarrou 2009      | Tunisia   | Mixed     | HCV             | 100/103                  | 38/43/19                   | 0.687          | 7         |
| Cao 2016             | China     | Asian     | HBV             | 241/254                  | 88/112/41                  | 0.954          | 7         |
| Chen 2007            | China     | Asian     | HCV             | 72/180                   | 70/2/0                     | 0.880          | 7         |
| Chen 2010            | China     | Asian     | HBV             | 304/361                  | 264/37/3                   | 0.544          | 7         |
| Cheong 2006          | Taiwan    | Asian     | HBV             | 261/204                  | 225/35/1                   | 0.531          | 7         |
| Chuang 2009          | Taiwan    | Asian     | HCV             | 143/133                  | 132/11/0                   | 0.686          | 7         |
| Conde 2013           | Brazil    | Mixed     | HBV             | 53/97                    | 27/20/6                    | 0.989          | 7         |
| Constantini 2002     | UK        | Caucasian | HCV             | 546/354                  | NA                         | NA             | 7         |
| Cunha 2018           | Brazil    | Mixed     | HCV             | 132/98                   | 56/54/22                   | 0.124          | 7         |
| Dogra 2011           | India     | Mixed     | HCV             | 70/70                    | 38/22/10                   | 0.764          | 7         |
| Falleti 2007         | Italy     | Caucasian | HCV             | 50/96                    | 17/25/8                    | 0.312          | 7         |
| Gao 2009             | China     | Asian     | HBV             | 69/74                    | 42/27/0                    | 0.918          | 7         |
| Gao 2009             | China     | Asian     | HCV             | 55/74                    | 32/21/2                    | 0.918          | 7         |
| Gao 2016             | China     | Asian     | HBV             | 190/81                   | 177/12/1                   | 0.261          | 8         |
| Gao 2017             | China     | Asian     | HBV+HCV         | 179/74                   | 109/68/2                   | 0.918          | 7         |
| Helal 2014           | Egypt     | Mixed     | HCV             | 50/50                    | 22/19/9                    | 1.000          | 7         |
| Jiang 2013           | China     | Asian     | HBV             | 250/134                  | 189/58/3                   | 0.019          | 7         |
| Karatayli 2014       | Turkey    | Caucasian | HBV             | 161/51                   | 48/86/27                   | 0.144          | 7         |
| Khan 2014            | India     | Mixed     | HCV             | 150/150                  | 64/67/19                   | 0.785          | 7         |
| Knapp 2003           | UK        | Caucasian | HCV             | 577/94                   | 183/250/144                | 0.090          | 7         |
| Kusumoto 2006        | Japan     | Asian     | HCV             | 346/114                  | 316/30/0                   | 0.588          | 7         |
| Li 2006              | China     | Asian     | HBV             | 62/63                    | 48/14/0                    | 0.448          | 8         |
| Li 2015              | China     | Asian     | HBV             | 379/364                  | 323/54/2                   | 0.577          | 7         |
| Lio 2003             | Italy     | Caucasian | HCV             | 60/135                   | 27/15/18                   | <0.0001        | 7         |
| Liu 2010             | China     | Asian     | HBV             | 513/187                  | 416/88/9                   | 0.075          | 7         |
| Mangia 2004          | Italy     | Caucasian | HCV             | 270/145                  | 120/110/40                 | 0.631          | 7         |
| Maurya 2018          | India     | Mixed     | Vral hepatitis  | 80/60                    | 65/13/2                    | 0.297          | 7         |
| Minton 2005          | UK        | Caucasian | HBV             | 284/54                   | 77/123/84                  | 0.669          | 7         |
| Miyazoe 2002         | Japan     | Asian     | HBV             | 213/200                  | 201/10/2                   | 0.773          | 7         |
| Moudi 2016           | Iran      | Mixed     | HBV             | 221/200                  | 72/118/31                  | 0.778          | 7         |
| Oleksy 2005          | USA       | Mixed     | HCV             | 856/398                  | NA                         | NA             | 7         |
| Pár 2014             | Hungary   | Mixed     | HCV             | 672/92                   | 214/333/125                | 0.087          | 8         |
| Pasha 2013           | Egypt     | Mixed     | HCV             | 440/220                  | 396/44/0                   | 0.332          | 8         |
| Peng 2006            | China     | Asian     | HBV             | 340/100                  | 314/23/3                   | 0.798          | 7         |
| Peng 2016            | China     | Asian     | HBV             | 173/182                  | 83/74/16                   | 0.653          | 7         |
| Pereira 2008         | Brazil    | Mixed     | HCV             | 128/94                   | 56/55/17                   | 0.881          | 8         |
| Persico 2006         | Italy     | Caucasian | HCV             | 120/110                  | 43/51/26                   | 0.628          | 8         |
| Ren 2017             | China     | Asian     | HBV             | 250/134                  | 189/58/3                   | 0.019          | 7         |
analyses by disease subtypes revealed similar positive results for rs1800871 polymorphism in both HBV and HCV subgroups (see Table 2).

**Integrated analyses for rs1800896 polymorphism and the risk of viral hepatitis**

Fifty-nine eligible literatures assessed the relationship between rs1800896 polymorphism and the risk of viral hepatitis. The integrated analyses demonstrated that rs1800896 polymorphism was significantly associated with the risk of viral hepatitis in overall population (dominant comparison: OR = 0.87, p = 0.02; recessive comparison: OR = 1.60, p < 0.0001; allele comparison: OR = 0.83, p < 0.0001), Asians (dominant comparison: OR = 0.88, p = 0.02) and Caucasians (recessive comparison: OR = 1.67, p = 0.009; allele comparison: OR = 0.78, p = 0.03). Further analyses by disease subtypes revealed similar positive results for rs1800871 polymorphism in both HBV and HCV subgroups (see Table 2).

**Sensitivity analyses**

The authors examined stabilities of integrated analyses results by deleting studies that violated HWE, and then integrating the results of the rest of studies. The trends of associations were not significantly altered in sensitivity analyses, which indicated that from statistical perspective, our integrated analyses results were reliable and stable.

**Publication biases**

The authors examined potential publication biases in this meta-analysis by assessing symmetry of funnel plots. Funnel plots were found to be overall symmetrical, which indicated that our integrated analyses results were not likely to be severely deteriorated by publication biases.

**Discussion**

This meta-analysis, for the first time, robustly assessed associations between polymorphisms in *IL-10* gene and the risk of viral hepatitis. The integrated analyses results demonstrated that rs1800871 (−819 C/T), rs1800872 (−592 C/A) and rs1800896 (−1082 G/A) polymorphisms were all significantly associated with the risk of viral hepatitis in Asians, whereas only rs1800896 (−1082 G/A) polymorphism was significantly associated with the risk of viral hepatitis in Caucasians. In further analyses by disease subtypes, we noticed that the three investigated polymorphisms were all significantly associated with the risk of both HBV and HCV.

The following three points should be considered when interpreting our integrated findings. First, based on the findings of previous observational studies, it is believed

### Table 1 (continued)

| First author, year | Country | Ethnicity | Type of disease | Sample size Case/control | Genotypes (wt/wt/wt/mt/mt) | p-value for HWE | NOS score |
|--------------------|---------|-----------|-----------------|--------------------------|-----------------------------|----------------|-----------|
| Ribeiro 2007       | HBV     | Mixed     | HBV             | 30/41                    | 12/16/2                     | 0.743           | 7         |
| Sepahi 2014        | Iran    | Mixed     | HCV             | 50/50                    | 20/15/15                    | <0.001          | 7         |
| Sheneef 2017       | Egypt   | Mixed     | HCV             | 100/50                   | 26/43/31                    | 0.003           | 7         |
| Silva 2015         | Brazil  | Mixed     | HCV             | 245/230                  | 106/10/29                   | 0.029           | 8         |
| Sodsai 2013        | Thailand| Asian     | HBV             | 130/142                  | 116/13/1                    | 0.448           | 8         |
| Sofian 2013        | Iran    | Mixed     | HBV             | 66/31                    | 32/27/7                     | 0.655           | 7         |
| Srivastava 2014    | India   | Mixed     | HBV             | 232/76                   | 96/73/63                    | 0.002           | 7         |
| Talaat 2014        | Egypt   | Mixed     | HBV             | 115/119                  | 32/53/30                    | 0.352           | 7         |
| Tang 2012          | China   | Asian     | HCV             | 626/914                  | 552/74/0                    | 0.029           | 8         |
| Truelove 2008      | USA     | Mixed     | HBV             | 45/76                    | 15/24/6                     | 0.837           | 7         |
| Vidigal 2002       | USA     | Mixed     | HCV             | 78/36                    | 29/22/27                    | 0.346           | 7         |
| Wu 2010            | China   | Asian     | HBV             | 175/153                  | 148/27/0                    | 0.567           | 7         |
| Xie 2008           | China   | Asian     | HBV             | 186/151                  | 164/22/0                    | 0.957           | 7         |
| Yan 2009           | China   | Asian     | HBV             | 732/414                  | 644/68/0                    | 0.526           | 8         |
| Yao 2015           | China   | Asian     | HBV             | 318/318                  | 125/141/52                  | 0.898           | 7         |
| Zein 2004          | USA     | Mixed     | HCV             | 52/80                    | 17/18/17                    | 0.087           | 7         |
| Zhang 2006         | China   | Asian     | HBV             | 396/135                  | 335/61/0                    | 0.464           | 8         |
| Zhu 2005           | China   | Asian     | HBV             | 167/123                  | 115/45/7                    | 0.766           | 7         |

*HBV* hepatitis B virus infection, *HCV* hepatitis C virus infection, *wt* wild type, *mt* mutant type, *HWE* Hardy–Weinberg equilibrium, *NOS* Newcastle–ottawa scale, *NA* not available
Table 2  Meta-analyses results of IL-10 gene polymorphisms and viral hepatitis

| Variables | Sample size | Dominant comparison | Recessive comparison | Over-dominant comparison | Allele comparison |
|-----------|-------------|---------------------|----------------------|-------------------------|------------------|
|           |             | p value | OR (95% CI) | I² statistic (%) | p value | OR (95% CI) | I² statistic (%) | p value | OR (95% CI) | I² statistic (%) |
| rs1800871 |             | 0.002   | 0.89 (0.82–0.96) | 28 | 0.004   | 1.21 (1.06–1.38) | 0 | 0.17   | 1.06 (0.98–1.14) | 24 | 0.0004 | 0.90 (0.85–0.95) | 27 |
| Overall   | 6835/5679   | 0.0001  | 0.84 (0.76–0.92) | 0 | 0.09    | 1.14 (0.98–1.33) | 0 | 0.005  | 1.14 (1.04–1.25) | 0 | 0.0002 | 0.88 (0.82–0.94) | 0 |
| Asian     | 4436/3832   | 0.63    | 1.13 (0.67–1.91) | 51 | 0.37    | 0.71 (0.33–1.51) | 39 | 0.93   | 1.02 (0.71–1.46) | 0 | 0.48   | 1.19 (0.73–1.93) | 62 |
| Caucasian | 808/590     | 0.05    | 0.90 (0.80–1.00) | 38 | 0.03    | 1.21 (1.02–1.45) | 9 | 0.51   | 1.04 (0.93–1.16) | 36 | 0.02   | 0.91 (0.84–0.98) | 37 |
| HBV       | 3504/2734   | 0.05    | 0.89 (0.80–1.00) | 0 | 0.07    | 1.20 (0.99–1.45) | 0 | 0.36   | 1.05 (0.94–1.18) | 0 | 0.03   | 0.91 (0.83–0.99) | 0 |
| HCV       | 3251/2885   | 0.05    | 0.89 (0.80–1.00) | 0 | 0.07    | 1.20 (0.99–1.45) | 0 | 0.36   | 1.05 (0.94–1.18) | 0 | 0.03   | 0.91 (0.83–0.99) | 0 |
| rs1800872 |             | 0.003   | 0.91 (0.86–0.97) | 25 | 0.06    | 1.09 (1.00–1.20) | 13 | 0.07   | 1.06 (0.99–1.12) | 30 | 0.003  | 0.93 (0.89–0.98) | 34 |
| Overall   | 12121/9873  | 0.0009  | 0.89 (0.83–0.95) | 9 | 0.20    | 1.07 (0.96–1.19) | 0 | 0.007  | 1.10 (1.03–1.18) | 29 | 0.004  | 0.93 (0.88–0.98) | 8 |
| Asian     | 7935/6880   | 0.70    | 0.96 (0.78–1.18) | 0 | 0.15    | 1.36 (0.89–2.08) | 34 | 0.39   | 0.91 (0.74–1.13) | 0 | 0.19   | 0.89 (0.76–1.06) | 41 |
| Caucasian | 1387/1078   | 0.008   | 0.90 (0.83–0.97) | 26 | 0.43    | 1.05 (0.93–1.18) | 19 | 0.02   | 1.10 (1.02–1.19) | 31 | 0.04   | 0.94 (0.89–1.00) | 39 |
| HBV       | 6900/4995   | 0.35    | 0.96 (0.87–1.05) | 1 | 0.05    | 1.17 (1.00–1.37) | 1 | 0.64   | 0.98 (0.89–1.08) | 12 | 0.08   | 0.94 (0.87–1.10) | 14 |
| HCV       | 5141/4818   | 0.35    | 0.96 (0.87–1.05) | 1 | 0.05    | 1.17 (1.00–1.37) | 1 | 0.64   | 0.98 (0.89–1.08) | 12 | 0.08   | 0.94 (0.87–1.10) | 14 |
| rs1800896  |             | 0.02    | 0.87 (0.78–0.98) | 57 | <0.0001 | 1.60 (1.41–1.82) | 26 | 0.56   | 0.96 (0.85–1.09) | 60 | <0.0001 | 0.83 (0.76–0.90) | 55 |
| Overall   | 13133/8862  | 0.02    | 0.88 (0.79–0.98) | 49 | 0.48    | 1.12 (0.82–1.53) | 0 | 0.11   | 1.09 (0.98–1.22) | 40 | 0.19   | 0.90 (0.77–1.05) | 54 |
| Asian     | 6452/4797   | 0.65    | 0.92 (0.64–1.32) | 69 | 0.009   | 1.67 (1.14–2.46) | 54 | 0.22   | 0.80 (0.55–1.15) | 72 | 0.03   | 0.78 (0.62–0.98) | 64 |
| Caucasian | 2210/1165   | 0.01    | 0.82 (0.70–0.96) | 51 | <0.0001 | 1.73 (1.42–2.10) | 27 | 0.61   | 1.04 (0.89–1.21) | 51 | 0.002  | 0.81 (0.71–0.93) | 57 |
| HBV       | 6227/4067   | 0.52    | 0.94 (0.79–1.13) | 60 | <0.0001 | 1.52 (1.29–1.80) | 33 | 0.14   | 0.87 (0.71–1.05) | 66 | 0.008  | 0.85 (0.75–0.96) | 51 |

The values in italic represent there is statistically significant differences between cases and controls.

HBV: Hepatitis B virus infection; HCV: Hepatitis C virus infection. OR: Odds ratio. CI: Confidence interval. NA Not available.
that the three investigated IL-10 polymorphisms may alter mRNA expression level of IL-10 gene, impact anti-viral immune responses, and then influence the risk of viral hepatitis [12, 13]. Nevertheless, it should be noted that future experimental studies are still required to reveal the exact molecular mechanisms underlying the observed positive findings of this meta-analysis. Second, we wish to study all polymorphic loci of IL-10 gene. However, our comprehensive literature searching did not reveal sufficient eligible literatures to warrant integrated analyses for other polymorphic loci of IL-10 gene, so we only assessed associations with the risk of viral hepatitis for the three most commonly investigated polymorphisms of IL-10 gene in this meta-analysis. Third, although we aimed to investigate all subtypes of viral hepatitis in this meta-analysis, it is worth noting that the majority of eligible studies were about HBV or HCV. So future studies should continue to explore associations between polymorphisms in IL-10 gene and the risk of other subtypes of viral hepatitis.

The three major limitations of our integrated analyses were listed below. Firstly, our integrated analyses results were only derived from unadjusted pooling of previous works. Without access to raw data of eligible studies, we can only estimate associations based on re-calculations of raw genotypic frequencies, but we have to admit that lack of further adjustment for baseline characteristics may certainly impact reliability of our findings [14]. Secondly, environmental factors may also affect relationships between polymorphisms in IL-10 gene and the risk of viral hepatitis. However, most of the authors only paid attention to genetic associations in their publications, so it is impossible for us to explore genetic-environmental interactions in a meta-analysis based on these previous publications [15]. Thirdly, we did not enroll grey literatures for integrated analyses because these literatures are always incomplete and it is impossible for us to extract all required data items from these literatures or assess their quality through the NOS scale. Nevertheless, considering that we did not include grey literatures for integrated analyses, despite that funnel plots were found to be overall symmetrical, it should be acknowledged that publication biases still may affect the robustness of our integrated analyses results [16].

Conclusion
In conclusion, this meta-analysis demonstrates that rs1800871 (−819 C/T), rs1800872 (−592 C/A) and rs1800896 (−1082 G/A) polymorphisms may influence the risk of both HBV and HCV. However, future studies should continue to investigate associations between polymorphisms in IL-10 gene and the risk of other subtypes of viral hepatitis.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s13099-020-00372-7.

Additional file 1. References of 76 eligible studies that were included in this meta-analysis

Abbreviations
HBV: Hepatitis B virus; HCV: Hepatitis C virus; IL-10: Interleukin-10; HWE: Hardy–Weinberg equilibrium; NOS: Newcastle–Ottawa scale; OR: Odds ratios; CI: Confidence intervals.

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Authors’ contributions
YZ and HC conceived and designed this meta-analysis. YZ and LC searched literatures. YZ and LC analyzed data. YZ and HC wrote the manuscript. All authors read and approved the final manuscript.

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