IL-6 and IL-10 gene polymorphisms and cirrhosis of liver risk from a comprehensive analysis

Minghui Zheng1,2†, Weizhen Fang1,2†, Menglei Yu2,3†, Rui Ding1,2, Hua Zeng1,2, Yan Huang4,5*, Yuanyang Mi6* and Chaohui Duan1,2*

Abstract

Background: Different inflammatory and immune cytokines play a key role in the development of cirrhosis of liver (CL). To investigate the association between interleukin-6,10 (IL-6,10) genes polymorphisms and CL risk through comparison of the allele and genotype distribution frequencies by meta-analysis.

Methods: A literature search covered with the PubMed, Embase, Cochrane Library, Web of Science, Google Scholar, SinoMed (CNKI and Wanfang) through 20th April, 2021. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the strength of associations.

Results: After a comprehensive search, three common polymorphisms (rs1800872, rs1800871, rs1800896) in IL-10 gene were selected, and three common polymorphisms (rs1800795, rs1800796, rs1800797) in IL-6 gene were also identified. The important finding was that IL-10 rs1800872 was a risk factor for CL development. For example, there has a significantly increased relationship between rs1800872 polymorphism and CL both in the whole group (OR: 1.30, 95%CI: 1.01–1.67 in heterozygote model), Asian population (OR: 1.40, 95%CI: 1.03–1.88 in heterozygote model) and hospital-based source of control (OR: 1.40, 95%CI: 1.01–1.96 in dominant model). In addition, significant association was found between rs1800896 and primary biliary cirrhosis subtype disease (OR: 1.30, 95%CI: 1.01–1.68 in allelic contrast model). No association was observed in all three polymorphisms in IL-6 gene.

Conclusion: Our present study suggests that the IL-10 rs1800872 and rs1800896 polymorphisms is potentially associated with the risk of CL susceptibility.

Keywords: Interleukin-10, Interleukin-6, Cirrhosis of liver, Polymorphism, meta-analysis, Risk
Background
Cirrhosis is characterized by extreme liver scarring (fibrosis), loss of organ function and serious complications related to portal hypertension (high blood pressure in the hepatic portal vein and its branches) [1].

Cirrhosis is the 11th leading cause of death worldwide, with a total burden of about 123 million deaths, of which about one tenth is decompensated [2, 3]. Liver cirrhosis (LC) is a severe public health problem worldwide, which is correlated with higher morbidity and mortality [4, 5]. The most common causes were chronic viral hepatitis [including infectious Hepatitis B virus (HBV, 39.64 million), and infectious Hepatitis C virus (HCV, 30.36 million)], alcoholic liver disease (26.04 million) and nonalcoholic fatty liver disease (NAFLD, 10.26 million), and other causes (16.62 million) [6]. With the implementation of HBV vaccination program and the application of effective anti HBV and HCV drugs in high endemic areas, the rate of liver cirrhosis caused by hepatitis gradually decreased, and the number of cases caused by NAFLD gradually increased [7]. NAFLD is now the commonest etiology worldwide, affecting 1 in 4 adults [8], and the progressive form that leads to patient with NAFLD, is predicted to increase by 63% between 2015 and 2030, representing a global cohort of at least 100 million individuals [9].

In the absence of effective intervention, cirrhosis can progress to decompensation, with ascites, gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, and liver cancer [7]. Liver transplantation is the most effective therapeutic option for end-stage liver disease but is a scarce resource [1]. Moreover, although antifibrotic or proregenerative drug therapies for cirrhosis have been approved, they have been in clinical trials and the effect has not been determined [1].

Cytokines, such as interleukins, play an integral role in the host immune response and may be a critical factor in determining the duration and severity of virus infection, fibrosis formation [10, 11]. Interleukin-10 (IL-10) is an important anti-inflammatory cytokine secreted by different cells such as liver cells, T regulatory lymphocytes, activated macrophages, and T helper (Th) 2 cells [12]. It inhibits macrophage-dependent antigen presentation, proliferation of T-lymphocytes, and Th1 cytokine secretion and acts as an inhibitor of Th1 effectors mechanism [12]. Three common polymorphisms -1082G/A (rs1800896), –819C/T (rs1800871), and –592 C/A (rs1800872) related to cirrhosis of liver (CL) have been wildly reported [13]. IL-6, a primary immunomodulatory cytokine, has been documented to play a pivotal role in regulating the biological processes of many cells including hepatocytes [14]. Three common polymorphisms -174G/C (rs1800795), –572G/C (rs1800796), and –597G/A (rs1800797) related to CL have been wildly reported [15].

In order to overcome the factors of sample size, regional and ethnic differences, our study summarized all published literatures related to the relationship between IL-6 and IL-10 genes polymorphisms and CL by meta-analysis, to comprehensively evaluate the relationship between several polymorphisms and CL, and to provide evidence-based medical research basis for the etiology of CL.

Materials and methods

Literature search strategy
A computerized literature search was performed for relevant studies from PubMed, Embase, Cochrane Library, Web of Science, Google Scholar, SinoMed (CNKI and Wanfang) before 20th April, 2021. The following keywords were jointly used “interleukin 10 or interleukin 6 or IL-10 or IL-6”, “polymorphism or variation or mutation”, “rs1800795 or rs1800796 or rs1800797 or rs1800896 or rs1800871 or rs1800872” and “live cirrhosis or primary biliary cirrhosis or non-alcoholic fatty liver disease”. If studies applied the same case clinic information, only the largest sample size was selected [16].

Inclusion criteria
The included studies met the following criteria: (a) there were clear criteria for the diagnosis of CL, such as B-ultrasound, CT, MRI, endoscopic retrograde choangiopancreatography, liver biopsy, and so on, (b) the correlation between CL risk and IL-10 and IL-6 genes polymorphisms (rs1800795 or rs1800796 or rs1800797 or rs1800896 or rs1800871 or rs1800872), (c) case-control or cohort design, (d) provided sufficient data for calculating odds ratio (OR) with 95% confidence interval (95%CI), and (e) duplicated studies with the same cases [17].

Data extraction
The following information was extracted from each included study: name of the first author, publication year, country of origin, ethnicity, numbers of cases and controls, HWE of control group, genotype method and sub-type of CL. The data were selected independently by 2 investigators who reached a consensus on all items [18].

Statistical analysis
The associations of the IL-10 and IL-6 genes polymorphisms and risk of CL were estimated by calculating the OR and 95%CI. The statistical significance of the OR was determined with the Z test [19]. The significance of the effect for correlation was determined by the Z test [18]. The heterogeneity among studies was evaluated using a Q test and I² test as described in other studies.
As a guide, $I^2$ values of <25% may be considered 'low', value of ~ 50% may be considered 'moderate' and values of >75% may be considered 'high' [22]. The Mantel-Haenszel (fixed effect) model was chosen, otherwise, if $P_{heterogeneity} < 0.1$, the random effects (DerSimonian-Laird) model was applied [23, 24]. Sensitivity analysis was undertaken by removing each study once to assess whether any single study could influence the stability of results [25]. The departure of frequencies of six polymorphisms from expectation under HWE was assessed by the Pearson’s $\chi^2$ test, $P < 0.05$ was considered significant [26]. Begg’s funnel plots and Egger’s regression test were performed to estimate the potential publication bias [27]. All statistical tests for this meta-analysis were performed using version 10.0 Stata software (StataCorp LP, College Station, TX, USA) [18].

Fig. 1 Flowchart illustrating the search strategy used to identify association studies for IL-10 and IL-6 polymorphisms and CL risk
### Table 1 Characteristics of included studies about polymorphisms in IL-6 and IL-10 genes and cirrhosis of liver risk

| Author       | Year | Country | Ethnicity | Case | Control | SOC  | HWE   | Genotype      | Sub-type     |
|--------------|------|---------|-----------|------|---------|------|-------|---------------|--------------|
| Chen         | 2004 | China   | Asian     | 77   | 54      | HB   | 0.633 | PCR-RFLP     | PBC          |
| Zappala      | 1998 | UK      | Caucasian | 171  | 141     | HB   | 0.071 | PCR           | PBC          |
| Matsushita   | 2002 | USA     | Caucasian | 94   | 72      | PB   | 0.501 | PCR-RFLP     | PBC          |
| Matsushita   | 2002 | USA     | Caucasian | 65   | 71      | PB   | < 0.01 | PCR-RFLP     | PBC          |
| Marcos       | 2008 | Spain   | Caucasian | 96   | 100     | HB   | 0.093 | PCR-RFLP     | ALC          |
| Yao          | 2015 | China   | Asian     | 318  | 318     | PB   | < 0.01 | PCR-RFLP     | LC           |
| Barooah      | 2020 | India   | Asian     | 96   | 110     | HB   | 0.009 | PCR-RFLP     | HCV-LC       |
| Liu          | 2015 | China   | Asian     | 192  | 192     | HB   | < 0.01 | PCR-RFLP     | Mixed        |
| Cao          | 2016 | China   | Asian     | 9    | 102     | PB   | 0.664 | PCR-RFLP     | HBV-LC       |
| Cheong       | 2005 | South Korea | Asian | 79   | 261     | HB   | < 0.01 | PCR           | HBV-LC       |
| Sheneef      | 2017 | Egypt   | African   | 50   | 50      | PB   | 0.889 | ARMS-PCR      | HCV-LC       |
| Corchado     | 2013 | Korea   | Asian     | 39   | 49      | HB   | 0.187 | PCR           | HCV-LC       |
| Fan          | 2004 | China   | Asian     | 77   | 160     | HB   | < 0.01 | PCR-RFLP     | PBC          |
| Khalifa      | 2016 | Saudi Arabia | Asian | 109  | 110     | HB   | 0.525 | PCR-RFLP     | HBV-LC       |
| Moreira      | 2016 | Brazil  | Mixed     | 37   | 102     | HB   | 0.316 | PCR-SSP       | HCV-LC       |
| Wang         | 2010 | China   | Asian     | 50   | 42      | HB   | < 0.01 | PCR           | HBV-LC       |
| Jiang        | 2009 | China   | Asian     | 169  | 119     | HB   | 0.552 | PCR-RFLP     | HBV-LC       |
| Wu           | 2010 | China   | Asian     | 50   | 96      | HB   | 0.125 | PCR-RFLP     | HBV-LC       |

---819 rs1800871

| Author       | Year | Country | Ethnicity | Case | Control | SOC  | HWE   | Genotype      | Sub-type     |
|--------------|------|---------|-----------|------|---------|------|-------|---------------|--------------|
| Chen         | 2004 | China   | Asian     | 77   | 54      | HB   | 1     | PCR-RFLP     | PBC          |
| Matsushita   | 2002 | USA     | Caucasian | 94   | 72      | PB   | 0.501 | PCR-RFLP     | PBC          |
| Matsushita   | 2002 | USA     | Caucasian | 65   | 71      | PB   | 0.049 | PCR-RFLP     | PBC          |
| Yao          | 2015 | China   | Asian     | 318  | 318     | PB   | 0.227 | PCR-RFLP     | LC           |
| Barooah      | 2020 | India   | Asian     | 9    | 102     | PB   | 0.359 | PCR-RFLP     | HBV-LC       |
| Cheong       | 2005 | South Korea | Asian | 79   | 261     | HB   | 0.458 | PCR           | HBV-LC       |
| Yang         | 2013 | China   | Asian     | 40   | 64      | PB   | 0.821 | ARMS-PCR      | ALC          |
| Fan          | 2004 | China   | Asian     | 77   | 160     | HB   | 0.455 | PCR-RFLP     | PBC          |
| Moreira      | 2016 | Brazil  | Mixed     | 37   | 102     | HB   | 0.316 | PCR-SSP       | HCV-LC       |
| Wang         | 2010 | China   | Asian     | 50   | 43      | HB   | 0.017 | PCR           | HBV-LC       |

---1082 rs1800896

| Author       | Year | Country | Ethnicity | Case | Control | SOC  | HWE   | Genotype      | Sub-type     |
|--------------|------|---------|-----------|------|---------|------|-------|---------------|--------------|
| Chen         | 2004 | China   | Asian     | 77   | 54      | HB   | 0.611 | PCR-RFLP     | PBC          |
| Bathgate     | 2000 | UK      | Caucasian | 61   | 330     | HB   | 0.003 | sequence      | PBC          |
| Matsushita   | 2002 | USA     | Caucasian | 94   | 72      | PB   | 0.859 | PCR-RFLP     | PBC          |
| Matsushita   | 2002 | USA     | Caucasian | 65   | 71      | PB   | 0.568 | PCR-RFLP     | PBC          |
| Abd El-Baky  | 2020 | Egypt   | African   | 22   | 48      | PB   | < 0.01 | TaqMan real-time PCR | HCV-LC       |
| Yao          | 2015 | China   | Asian     | 318  | 318     | PB   | 0.898 | PCR-RFLP     | LC           |
| Barooah      | 2020 | India   | Asian     | 96   | 110     | HB   | 0.054 | PCR-RFLP     | HCV-LC       |
| Liu          | 2015 | China   | Asian     | 266  | 532     | HB   | < 0.01 | PCR-RFLP     | Mixed        |
| Cao          | 2016 | China   | Asian     | 241  | 254     | PB   | 0.953 | PCR-RFLP     | LC           |
| Baghi        | 2015 | Iran    | Asian     | 9    | 102     | PB   | 0.047 | PCR-RFLP     | HBV-LC       |
Network of protein-interaction of IL-6 and IL-10 gene
To more complete understanding of the role of IL-6 and IL-10 in CL, the network of gene-gene interactions for IL-6 and IL-10 was predicted through online String database (http://string-db.org/) [28].

Results
Study searching and their basic information
As depicted in Fig. 1, 602 articles were garnered by PubMed, Embase, Cochrane Library, Web of Science, Google Scholar, SinoMed (CNKI and Wanfang (337 titles about IL-10 gene polymorphisms and 265 titles for IL-6 gene polymorphisms) database. 496 obviously irrelevant articles were excluded after screening the titles and abstract sections. The full texts were then evaluated, and 79 additional articles were further excluded as they were duplication (22), meta-analysis systematic analysis or review (42), other polymorphisms (5), clinical trial (8) and randomized controlled trial (2). Finally, 27 different articles [15, 29–55] met the inclusion criteria and were included in our meta-analysis. Among these included studies, 19 studies were performed about IL-10 three polymorphisms (19 case-control studies for rs1800872, 12 for rs1800871, 18 for rs1800896), and 9 studies was related to IL-6 three polymorphisms (6 for rs1800795, 4 for 1,800,796 and 2 for rs1800797). All the included studies used blood samples for DNA extraction (Table 1).

Quantitative synthesis
IL-10 − 592 polymorphism
In whole analysis, increased associations were observed in two genetic models (heterozygote comparison: OR: 1.30, 95%CI:1.01–1.67, \( P = 0.006 \) for heterogeneity, \( P = 0.039, I^2 = 50.9\% \), Fig. 3A; dominant
model: OR: 1.34, 95% CI: 1.04–1.72, \( P = 0.001 \) for heterogeneity, \( P = 0.021, I^2 = 57.5\% \). In subgroup analysis by ethnicity, based on different frequency of races, there also had increased associations between this polymorphism and CL in Asians not Caucasians in all models (allelic contrast: OR: 1.25, 95% CI: 1.01–1.55, \( P = 0.000 \) for heterogeneity, \( P = 0.042, I^2 = 72.3\% \); heterozygote comparison: OR: 1.40, 95% CI: 1.03–1.88, \( P = 0.001 \) for heterogeneity, \( P = 0.029, I^2 = 63.1\% \), Fig. 3A; dominant model: OR: 1.47, 95% CI: 1.09–1.99, \( P = 0.000 \) for heterogeneity, \( P = 0.013, I^2 = 68.3\% \)). In addition, regular analysis by source of control, also significantly trend was found for this SNP in HB rather than PB studies (dominant model: OR: 1.40, 95% CI: 1.01–1.96, \( P = 0.000 \) for heterogeneity, \( P = 0.046, I^2 = 68.2\% \), Fig. 3B). Finally, many causes may result in cirrhosis, such as primary biliary cirrhosis (PBC), alcoholics with liver cirrhosis, HCV-LC, HBV-LC and immune

![Fig. 2 The MAF of minor-allele (mutant-allele) for IL-10 and IL-6 polymorphisms from the 1000 Genomes online database and present analysis](image_url)

![Fig. 3 Forest plot of CL risk associated with IL-10 gene –592 polymorphism A: heterozygote comparison model in total analysis and in ethnicity subgroup; B: dominant model in source of control](image_url)
### Table 2: Stratified analyses of IL-6 and IL-10 genes’ common polymorphisms on cirrhosis of liver risk

| Variables | N    | Case/Control | OR(95%CI) | Heterozygote comparison OR(95%CI) | Dominant model OR(95%CI) |
|-----------|------|--------------|-----------|----------------------------------|--------------------------|
| **IL-10 -592** |      |              |           |                                  |                          |
| Total     | 19   | 2019/2403    | 1.15 (0.98–1.37) | 0.93 (0.75–1.17) | 1.10 (0.94–1.27) |
| Ethnicity |      |              |           |                                  |                          |
| Asian     | 13   | 1506/1867    | 1.25 (1.01–1.55) | 1.04 (0.87–1.24) | 1.12 (0.95–1.31) |
| Caucasian | 4    | 426/384      | 0.98 (0.78–1.22) | 0.84 (0.66–1.06) | 0.90 (0.71–1.12) |
| SOC       |      |              |           |                                  |                          |
| HB        | 14   | 1483/1790    | 1.19 (0.95–1.48) | 0.12 (0.09–1.53) | 1.07 (0.85–1.33) |
| PB        | 5    | 536/613      | 1.11 (0.93–1.33) | 0.24 (0.13–0.45) | 1.15 (0.92–1.44) |
| **Ethnicity** |      |              |           |                                  |                          |
| PBC       | 5    | 484/498      | 1.11 (0.91–1.35) | 0.31 (0.16–0.60) | 1.16 (0.85–1.59) |
| HBV-LC    | 6    | 466/730      | 1.46 (0.86–2.49) | 0.16 (0.08–0.34) | 1.46 (0.82–2.60) |
| HCV-LC    | 4    | 222/311      | 0.98 (0.75–1.28) | 0.41 (0.24–0.70) | 0.92 (0.56–1.52) |
| **Disease type** |      |              |           |                                  |                          |
| -819      | 12   | 1134/1549    | 1.07 (0.88–1.30) | 0.45 (0.27–0.74) | 1.01 (0.78–1.31) |
| Ethnicity |      |              |           |                                  |                          |
| Asian     | 9    | 938/1304     | 1.05 (0.82–1.34) | 0.89 (0.70–1.12) | 1.07 (0.84–1.34) |
| Caucasian | 2    | 159/143      | 1.28 (0.90–1.83) | 0.73 (0.46–1.18) | 1.22 (0.83–1.78) |
| SOC       |      |              |           |                                  |                          |
| HB        | 7    | 608/922      | 1.14 (0.88–1.47) | 0.32 (0.20–0.53) | 1.07 (0.83–1.38) |
| PB        | 5    | 526/627      | 0.96 (0.68–1.36) | 0.32 (0.19–0.55) | 0.93 (0.66–1.31) |
| **Disease type** |      |              |           |                                  |                          |
| PBC       | 4    | 313/357      | 1.24 (0.97–1.57) | 0.82 (0.57–1.18) | 1.10 (0.81–1.46) |
| HBV-LC    | 3    | 138/406      | 1.55 (0.55–4.43) | 0.40 (0.13–1.25) | 1.26 (0.59–2.70) |
| HCV-LC    | 2    | 133/212      | 0.92 (0.66–1.27) | 0.59 (0.36–0.95) | 0.88 (0.54–1.44) |
| **1082**  |      |              |           |                                  |                          |
| Total     | 18   | 1741/2776    | 1.01 (0.85–1.20) | 0.82 (0.66–1.01) | 1.03 (0.84–1.25) |
| Ethnicity |      |              |           |                                  |                          |
| Asian     | 12   | 1412/2103    | 0.94 (0.76–1.17) | 0.57 (0.37–0.88) | 0.97 (0.75–1.26) |
| Caucasian | 3    | 220/473      | 1.25 (0.94–1.65) | 0.12 (0.06–0.24) | 1.12 (0.77–1.61) |
| African   | 2    | 72/98        | 1.27 (0.82–1.97) | 0.28 (0.16–0.50) | 1.24 (0.80–1.94) |
| SOC       |      |              |           |                                  |                          |
| HB        | 10   | 902/1797     | 1.04 (0.89–1.21) | 0.61 (0.41–0.90) | 1.06 (0.80–1.40) |
| PB        | 8    | 839/979      | 0.99 (0.72–1.36) | 0.68 (0.47–0.99) | 0.96 (0.70–1.34) |
| **Disease type** |      |              |           |                                  |                          |
| PBC       | 5    | 374/687      | 1.30 (1.01–1.68) | 0.43 (0.17–1.01) | 1.14 (0.83–1.57) |
| HBV-LC    | 5    | 297/611      | 0.97 (0.71–1.32) | 0.68 (0.51–0.91) | 1.03 (0.82–1.31) |
| HCV-LC    | 4    | 205/310      | 0.98 (0.76–1.28) | 0.39 (0.24–0.61) | 0.94 (0.72–1.23) |
| LC        | 2    | 559/572      | 0.72 (0.50–0.98) | 0.00 (0.00–0.00) | 0.80 (0.54–1.15) |
| **IL-6 -174** |      |              |           |                                  |                          |
| Total     | 6    | 590/861      | 1.17 (0.73–1.80) | 0.75 (0.52–1.09) | 1.25 (0.82–1.92) |
| Ethnicity |      |              |           |                                  |                          |
| Caucasian | 3    | 410/501      | 0.89 (0.73–1.09) | 0.24 (0.14–0.43) | 0.90 (0.70–1.15) |
| SOC       |      |              |           |                                  |                          |

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cirrhosis, to our regret, no significant association was found in all kinds of this subgroup (Table 2).

**IL-10−1082 polymorphism**

No association was detected in total, ethnicity, source of control subgroups, however, in the subgroup of disease type subgroup, increased relationship was observed in the allelic contrast model (OR: 1.30, 95%CI:1.01–1.68, \(P=0.568\) for heterogeneity, \(P=0.043\), \(I^2=0.0%\)) (Fig. 4A). In the sub-type of CL, we found decreased association was existed in LC risk and this polymorphism (such as OR: 0.64, 95%CI:0.44–0.93, \(P=0.865\) for heterogeneity, \(P=0.019\), \(I^2=0.0%\), Fig. 4B).

**IL-10-819, IL-6−174, −572 and −597 polymorphisms**

No association was found in above four kinds of polymorphisms (data not shown) (Table 2).

**Bias diagnosis for publication and sensitivity analysis**

The publication bias was evaluated by both Begg’s funnel plot and Egger’s test (such as −592 polymorphism). At beginning, the shape of the funnel plots seemed asymmetrical in allele comparison for −592 by Begg’s test, suggesting no publication bias was existed. Then, Egger’s test was applied to provide statistical evidence of funnel plot symmetry. As a result, no obvious evidence of publication bias was observed (such as allelic contrast: \(t=2.57\), \(P=0.024\) for Egger’s test; \(z=1.75\), \(P=0.08\) for Begg’s test (Fig. 5A, B) (Table 3).

To delete studies which may influence the power and stability of whole study, we applied the sensitive analysis (such as −592 SNP) in three models (Fig. 5C).

**Gene-gene network diagram and interaction of online website**

String online server indicated that IL-10 and IL-6 gene interacts with numerous genes. The network of gene-gene interaction has been illustrated in Fig. 6.

**Discussion**

Cirrhosis is the final stage of liver fibrosis, which itself results from a perpetuated wound-healing process after a liver injury that can lead to a wide range of chronic diseases.

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**Table 2** Stratified analyses of IL-6 and IL-10 genes’ common polymorphisms on cirrhosis of liver risk (Continued)

| Variables | N  | Case/Allelic contrast | Heterozygote comparison | Dominant model |
|-----------|----|-----------------------|-------------------------|---------------|
|           |    | Allelic contrast       | Heterozygote comparison | Dominant model |
|           |    | OR (95% CI)            | \(P_{h}\)                | \(P_{h}\)          |
|           |    | Weight                 |                         |               |
| HB        | 3  | 198/305                | 1.98 (0.55–7.05)0.001 0.294 86.8% | 2.79 (0.41–18.88)0.000 0.294 90.4% | 2.71 (0.47–15.57)0.0000.26589.6% |
| PB        | 3  | 320/556                | 0.99 (0.63–1.55)0.083 0.961 59.8% | 1.04 (0.76–1.42)0.130 0.800 50.9% | 0.98 (0.73–1.32)0.110 0.916 54.7% |
| −572      |    |                        |                         |               |
| Total     | 4  | 1131/864               | 1.15 (0.97–1.36)0.859 0.117 0.0% | 2.23 (0.80–6.21)0.000 0.127 89.2% | 1.60 (0.83–3.06)0.005 0.157 76.3% |
| −597      |    |                        |                         |               |
| Total     | 2  | 280/374                | 0.84 (0.66–1.08)0.453 0.168 0.0% | 0.88 (0.63–1.23)0.203 0.462 38.3% | 0.84 (0.61–1.15)0.278 0.283 15.0% |

\(P_h\): value of \(Q\)-test for heterogeneity test; \(P_{h}\): Z-test for the statistical significance of the OR.
diseases involving the liver [56, 57]. In addition, cirrhosis is a burden on the individual and on public health. To our knowledge, the most prevalent chronic liver diseases are chronic viral hepatitis (from hepatitis B or C infection), alcohol-related liver disease, and NAFLD [56]. Cirrhosis negatively impacts on patient reported outcomes and health-related quality of life [58–60]. The impact of cirrhosis on quality of life can add to the existing impairment of quality of life related to viraemia in patients with hepatitis C [61, 62]. Conversely, effective treatment of hepatitis C can lead to significant gains in patients’ quality of life, especially for patients with decompensated cirrhosis. In addition, there is evolving evidence indicating that quality of life is significantly impaired in patients with NAFLD in the form of non-alcoholic steatohepatitis [63]. Nowadays, the trends indicate that the contribution from NAFLD related cirrhosis is increasing within cirrhosis. Other risk factors, such as substantial regional variation, and substantial variation in time trends in the prevalence of these etiology, should also be paid attention.

We devoted to find some susceptible factors, finally, we focused on two cytokines (IL-6 and IL-10). So far, multiple genes have been shown to be associated with increased liver disease risk, such as CTLA-4, IL-18, transmembrane 6 superfamily member 2 and GSTM1 [64–66]. Besides, more and more studies have indicated IL-6 and IL-10 polymorphisms may be associated with CL risk. Due to the limited number of samples about each study, the conclusion for every study may not be credible. Yao et al. found that IL-10 rs1800896 polymorphism was

Table 3 Publication bias tests (Begg’s funnel plot and Egger’s test for publication bias test) for IL-10 -592 polymorphism

| Genetic type       | Coefficient | Standard error | t   | P value | 95%CI of intercept | z  | P value |
|--------------------|-------------|----------------|-----|---------|--------------------|----|---------|
| C-allele vs. A-allele | −0.181      | 1.211           | −0.15| 0.883   | (−2.736 to 2.374) | 1.26| 0.208   |
| CA vs. AA          | −0.047      | 0.447           | −0.11| 0.917   | (−0.992 to 0.897) | 0.35| 0.726   |
| CC + CA vs. AA     | −0.047      | 0.51            | −0.09| 0.927   | (−1.124 to 1.029) | 0.56| 0.576   |
correlated with an increased risk of CL, especially in individuals with chronic hepatitis B [46]. Falleti et al. polymorphisms of IL-6 were associated with hepatocellular carcinoma (HCC) occurrence among patients with CL [34]. It is necessary to combine all previous studies and increase the sample size, we wish to obtain comprehensive and convince conclusions between IL-6 or IL-10 polymorphism and CL susceptibility.

It is in time to analyze the association between IL-6 and IL-10 polymorphisms and CL risk using meta-analysis method. After our searching through main database, 19 different case-control studies were identified for IL-10 polymorphism, and 9 case-control studies were detected for IL-6 polymorphism. The main results about current study are that IL-10 -592 polymorphism was a risk factor for CL risk in the whole samples, especially in Asian population, moreover, IL-10 −1082 polymorphism had an increased association for PBC, which may offer references for early detection, prevention and treatment about CL. No positive results were observed in other polymorphisms, which due to the sample size and publication bias.

We all know the development and outcome about CL is complex and multi-factorial. Focusing on only each gene or each polymorphism is limited. Hence, we try our best to detect other potential genes related with CL based on online String server. Other nine most possible genes and current two related genes were shown in the network. Among them, six genes belong to cytokine family, and these scores were all in the front, the first related genes are IL-10RA, which is the receptor of IL-10 gene. Hennig et al. indicated IL-10RA gene polymorphisms may play a modulatory role in the outcome (including severity of fibrosis and overall inflammation) of hepatitis C infection [67]. Galal et al. confirmed that TNF family lymphotixin-alpha GG genotype and low platelet count were independent predictors for HCC
development in patients with HCV-LC [68]. Amirpour-Rostami et al. summarized the main correlation between the polymorphisms within IL-18 and IL-1B genes and chronic hepatitis B [69]. In a word, we should deep explore these partners of IL-10 and 6 genes, and gene-gene interactions in the development and treatment for CL in the next step.

There are some limitations should be paid attention. At the beginning, further studies should focus on Mixed and African populations, which was vacant in current analysis and need many more studies. Second, because CL is a multi-factors disease, gene-gene and gene-environment interactions should be considered and brought in. It is possible that specific environmental and lifestyle factors influence the associations between IL-10 and IL-6 polymorphism and CL, including age, sex, diet, smoking, familial history, parasite history, virus and immune factors. Third, whether the CL patients within other complications, such as abnormal liver function, HCC and hepatitis, all the included factors have not been reported. Further comprehensive studies should include above items. Fourth, the stage of CL is not distinguished, which should be analyzed separately (compensatory and decompensated period) and can be more accurate for prediction and treatment.

Conclusions
Our present meta-analysis suggests that IL-10 -592 and –1082 polymorphisms may be associated with CL risk, which may be proved in following larger and comprehensive studies.

Abbreviations
CL: cirrhosis of liver; LC: Liver cirrhosis; HWE: Hardy–Weinberg equilibrium; OR: Odds ratio; 95% CI: 95% Confidence interval; PBC: primary biliary cirrhosis; ALC: alcoholic liver cirrhosis

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Not applicable.

Availability of data and material
All data generated or analyzed in this study are included in this published article and its supplementary information files.

Authors’ contributions
MZ and WF conceived of the study, MY and RD prepared the data, HZ and YM were involved in the data analyses, YM drafted the original manuscript. CD prepared the figures. All the authors agreed to the submission of the present work.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors proclaim that they have no competing interests.

Author details
1Department of Clinical Laboratory, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou 510120, China. Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou 510120, China. Emergency Department, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, People’s Republic of China. 2Department of Parasitology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong 510080, People’s Republic of China. 3Department of Tropical Disease Control (Sun Yat-sen University), Chinese Ministry of Education, Guangzhou, Guangdong 510080, People’s Republic of China. 4Department of Urology, Affiliated Hospital of Jiangnan University, 1000 Hefeng Rd, Wuxi 214000, People’s Republic of China.

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References
1. Fallowfield JA, Jimenez-Ramos M, Robertson A. Emerging synthetic drugs for the treatment of liver cirrhosis. Expert Opin Emerg Drugs. 2021;1–16. https://doi.org/10.1080/17428121.2021.2009799.
2. Arsani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151–71. https://doi.org/10.1016/j.jhep.2018.09.014.
3. Sepanlou SG, Safiri S, Bisignano C, Collaborator GC. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study. Lancet Gastroenterol Hepatol. 2020. 2017;5(3):245-66.
4. Scaglione S, Kletterhesms S, Cao G, Shoham D, Durazo R, Luke A, et al. The epidemiology of cirrhosis in the United States: a population-based study. J Clin Gastroenterol. 2015;49(8):696–6. https://doi.org/10.1097/MCG.0000000000000208.
5. Hsiang JC, Bai WW, Raos Z, Stableforth W, Upton A, Selvaratnam S, et al. Epidemiology, disease burden and outcomes of cirrhosis in a large secondary care hospital in South Auckland, New Zealand. Intern Med J. 2015;45(2):160–9. https://doi.org/10.1111/imj.12624.
6. Collaborators. GDaIIaP: Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet (London, England) 2018, 392(10159):1789–1858.
7. Xu JH, Yu YY, Xu XY. [research progress and prospect of liver cirrhosis]. Zhonghua Gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chin J Digest Dis. 2018, 19(2):102-02. https://doi.org/10.3760/cma.j.cn501113-20201102-00002.
8. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 To 2017: the growing impact of NAFLD. Hepatol. (Baltimore, Md). 2021;29(2):108-19. https://doi.org/10.1002/heap.2000113-20210102-00002.
9. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatol. (Baltimore, Md). 2020;72(5):1605-16.
10. Motawa M, Safari S, Alavian SM. Interleukin 18 gene promoter polymorphisms and susceptibility to chronic hepatitis B infection: a review study. Hepat Mon. 2014;14(7):e19879.
Shao HB, Sakuragawa N, Kato M, et al. Human methionine adenosyltransferase 2B (MAT2B) polymorphism and gallstone disease risk based on a comprehensive analysis. Genes Environ Off J Japan Environ Mutagen Soc. 2021;43(1):17. https://doi.org/10.18632/genesenv.2021.00011.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. PLoS ONE. 2013;8(1):e54188. https://doi.org/10.1371/journal.pone.0054188.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719–25. https://doi.org/10.1093/jnci/22.4.719.

Hirshovitz S, Caras I, Hershkovitz E, et al. Association between interleukin-6 promoter polymorphisms and the risk of alcoholic liver disease in a meta-analysis. PLoS ONE. 2012;7(9):e46632. https://doi.org/10.1371/journal.pone.0046632.

Caffo B, Hoadley KA, Silliman RA, et al. Population-based breast cancer survival and the interaction between interleukin-10 (IL-10) and TGF-β1 promoter polymorphisms. Mediat Inflamm. 2015;2015:582192. https://doi.org/10.1155/2015/582192.

R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

Huang X, Wang SQ, Zhen X, et al. Interleukin-10 gene promoter polymorphism and gallstone disease risk based on a comprehensive analysis. Genes Environ Off J Japan Environ Mutagen Soc. 2021;43(1):17. https://doi.org/10.18632/genesenv.2021.00011.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719–25. https://doi.org/10.1093/jnci/22.4.719.

Fan LY, Zhu Y, Zhong RQ, Tu XQ, Ye WM, Chen QB, et al. Genetic analysis of interleukin-10 gene promoter polymorphisms and hepatocellular carcinoma occurrence in patients with hepatitis C virus infection from Northeast China. Viral Immunol. 2020;33(6):457–67. https://doi.org/10.1089/vim.2019.0170.

Bathgate AJ, Pravica V, Perrey C, Hayes PC, Hutchinson N. Polymorphisms in tumour necrosis factor alpha, interleukin-10 and transforming growth factor beta 1 genes and end-stage liver disease. Eur J Gastroenterol Hepatol. 2000;12(12):1293–300. https://doi.org/10.1097/00042737-200012120-00011.

Gao LN, Cheng SL, Liu W: IL10 rs1800896 polymorphism is associated with liver cirrhosis and chronic hepatitis B. Genet Mol Res GM R. 2016, 15(1), 1, 15. https://doi.org/10.4238/gmr.15017256.

Cheong JY, Cho SW, Hwang IL, Yoon SK, Lee JH, Park CS, et al. Association between chronic hepatitis B virus infection and interleukin-10: tumor necrosis factor-alpha gene promoter polymorphisms. J Gastroenterol Hepatol. 2006;21(7):1163–9. https://doi.org/10.1111/j.1440-1746.2006.04304.x.

Cochrado S, Marquez M, Montes de Oca M, Romero-cores P, Fernandez-Gutierrez C, Grin-Gonzalez JA: Influence of genetic polymorphisms of tumor necrosis factor alpha and interleukin 10 genes on the risk of liver cirrhosis in HIV-HCV Coinfected patients. PLoS ONE. 2013;8(5):e65619. https://doi.org/10.1007/sj.gene.63656.

Liu Y, Yu MC, Zhang AQ, Wang YB, Jiang K, Dong JH: Interleukin-10 gene promoter polymorphism and risk of liver cirrhosis. Genet Mol Res GM R. 2015;14(1):1229–34. https://doi.org/10.4238/2015.February.13.1.

Marcus M, Pastor I, Gonzalez-Sarmiento R, Lasa FJ: Interleukin-10 gene polymorphism is associated with alcoholism but not with alcoholic liver disease. Alcohol Alcohol (Oxford, Oxfordshire), 2008,43(5):523–8. https://doi.org/10.1093/alcalc/agw010.

Matsushita M, Tanaka A, Kikuchi K, Kitazawa E, Kawaguchi N, Kawashima Y, et al. Association of single nucleotide polymorphisms of the interleukin-10 promoter gene and susceptibility to primary biliary cirrhosis: immunogenetic differences in Italian and Japanese patients. Autoimmunity. 2002;35(8):531–6. https://doi.org/10.1080/089169302100056703.

Sheneef A, Esmaat WM, Mohammad AN, Mahmoud AA, Moghazy HM, Noureldin AK: Interleukin-10 and interferon gamma gene polymorphisms and hepatitis C virus-related liver cirrhosis risk. J Interferon & Cytokine Res Off J Int Soc Interferon Cytokine Res. 2017;37(4):175–80. https://doi.org/10.1089/jir.2016.0106.

Yang AM, Wen LL, Yang CS, Wang SC, Chen CS, Bar MI: Interleukin 10 promoter haplotype is associated with alcoholic liver cirrhosis in Taiwanese patients. Kaohsiung J Med Sci. 2014;30(6):291–8. https://doi.org/10.1016/j.kjms.2014.02.021.

Yao L, Xing S, Fu X, Song H, Wang Z, Tang J, et al. Association between interleukin-10 gene polymorphisms and susceptibility to liver cirrhosis. Int J Clin Exp Pathol. 2015;8(9):11680–4.

Zappala F, Grove J, Watt FE, Daly AK, Day CP, Bassendine MF, et al. Polymorphisms in interleukin-4, interleukin-6, interleukin-8, and interleukin-12 are not associated with alcoholic liver disease. Alcohol Alcohol (Oxford, Oxfordshire), 2008,43(5):523–8. https://doi.org/10.1093/alcalc/agw010.

Ghaleh Baghi S, Alavian SM, Mehrnoush L, Salimi S: Impact of the IL-10 promoter polymorphism in the severity of chronic hepatitis B infection. Hepat Mon. 2015;15(7):e28287. https://doi.org/10.5812/hepamon.28287v2.

Jiang ZL, Zhang W, Zhang H, Liu YB, Su SB: Relationship between TNF-α, TGF-β1 and IL-10 genetic polymorphisms and post-hepatitis B cirrhosis.
World Chin J Digestology. 2009;17(31):3263–8. https://doi.org/10.11569/wcjdv17i31.3263.

51. Khalifa AS, Jaiash DA, Shady AM, El-saeed GK, Ghonaim MM, Makled AA, et al. Interleukins-10 and 18 genes polymorphisms in hepatitis B virus infected Saudi patients. Res J Immunol. 2016;9(1):1–8.

52. Moreira ST, Silva GF, de Moraes CF, Grotto RM, de Moura Campos Pardini MI, Ricalho Mda G, Moltera RA: influence of cytokine and cytokine receptor gene polymorphisms on the degree of liver damage in patients with chronic hepatitis C. meta gene. 2016:9;799–805. https://doi.org/10.1016/j.mgene.2016.04.003.

53. Tang S, Liu Z, Zhang Y, He Y, Pan D, Liu Y, et al. Rather than Rs1800796 polymorphism, expression of interleukin-6 is associated with disease progression of chronic HBV infection in a Chinese Han population. Dis Markers. 2013;35(6):799–805. https://doi.org/10.1155/2013/508023.

54. Wang SY, Sun SL, Ma WM, Zheng Q, Liu HZ. Relationship between live cirrhosis and interleukin-10 promoter polymorphisms in chronic hepatitis B patients. Immunological J. 2010;26(8):694–7.

55. Wu JX, Jia YT. Association analysis of interleukin-10 gene promoter polymorphisms with hepatitis B virus infection consequence. Chin J Integr Tradit Western Med Liver Dis. 2010;20(5):262–6.

56. Jepsen P, Younossi ZM. The global burden of cirrhosis: a review of disability-adjusted life-years lost and unmet needs. J Hepatol. 2021;75(Suppl 1):S3–s13. https://doi.org/10.1016/j.jhep.2020.11.042.

57. Schuppan D, Afghal NH. Liver cirrhosis. Lancet (London, England). 2008;371(9615):838–51.

58. Younossi ZM. Gastroenterol Rep. 2013;15(1):301. https://doi.org/10.1007/s11894-012-0301-5.

59. Rabiee A, Ximenes RO, Nikayin S, Hickner A, Juthani P, Rosen RH, et al. Factors associated with health-related quality of life in patients with cirrhosis: a systematic review. Liver Int Off J Int Assoc Study Liver. 2021;41(1):6–15. https://doi.org/10.1111/liv.14680.

60. Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. Curr Gastroenterol Rep. 2013;15(1):301. https://doi.org/10.1007/s11894-012-0301-5.

61. Younossi ZM, Stepanova M, Afdhal NH. Liver cirrhosis. Lancet (London, England). 2008;371(9615):838–51.

62. Younossi ZM, Stepanova M, Lawitz EJ, Reddy KR, Wai-Sun Wong V, Mangia A, et al. Patients with nonalcoholic steatohepatitis experience severe impairment of health-related quality of life. Am J Gastroenterol. 2019;114(10):1636–41. https://doi.org/10.14309/ajg.0000000000000375.

63. Zhang S, Yang X, Wang W. Associations of genetic polymorphisms in CTLA-4 and IL-1β with chronic liver diseases: evidence from a meta-analysis. Genomics. 2020;112(2):1889–96. https://doi.org/10.1016/j.ygeno.2019.11.001.

64. Chen X, Zhou P, De L, Li B, Su S. The roles of transmembrane 6 superfamily member 2 rs58542926 polymorphism in chronic liver disease: a meta-analysis of 24,147 subjects. Mol Genet Genom Med. 2019;7(8):e824.

65. Hennig BJ, Frodsham AJ, Hellier S, Knapp S, Yee LJ, Wright M, et al. Influence of IL-10RA and IL-22 polymorphisms on outcome of hepatitis C virus infection. Liver Int Off J Int Assoc Study Liver. 2007;27(11):1334–43. https://doi.org/10.1111/j.1478-3231.2007.01518.x.

66. Galal G, Tammam H, Abdel Aal A, Fahmy N, Sheneea A, Ahmed N, et al. Role of Lymphotoxin-a gene polymorphism in hepatitis C virus-related chronic liver disorders. Infect drug Resist. 2021;14:1921–30. https://doi.org/10.2147/IDR.S306879.

67. Amirpour-Rostami S, Kazemi Arababadi M. IL-18 and IL-1β gene polymorphisms: the plausible risk factors for chronic hepatitis B. Viral Immunol. 2019;32(5):208–13. https://doi.org/10.1089/vim.2018.0155.

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