Associations between twelve common gene polymorphisms and susceptibility to hepatocellular carcinoma: evidence from a meta-analysis

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Abstract

Background: Associations between polymorphisms in vitamin D receptor (VDR)/vascular endothelial growth factor (VEGF)/interleukin-18 (IL-18)/mannose-binding lectin (MBL) and susceptibility to hepatocellular carcinoma (HCC) were already explored by many studies, yet the results of these studies were inconsistent. The aim of this meta-analysis was to better clarify associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC by combing the results of all relevant studies.

Methods: Eligible publications were searched from PubMed, Embase, WOS, and CNKI. We used Review Manager to combine the results of individual studies.

Results: Thirty studies were included in this study. Combined results revealed that VDR rs7975232, VDR rs2228570, VEGF rs699947, VEGF rs3025039, IL-18 rs1946518, and MBL rs7096206 polymorphisms were all significantly associated with HCC in the overall pooled population. We also obtained similar significant associations for VDR rs7975232, VDR rs2228570, IL-18 rs1946518, and MBL rs7096206 polymorphisms in Asians.

Conclusions: Collectively, this meta-analysis proved that VDR rs7975232, VDR rs2228570, VEGF rs699947, VEGF rs3025039, IL-18 rs1946518, and MBL rs7096206 polymorphisms may confer susceptibility to HCC in certain populations.

Keywords: Vitamin D receptor (VDR), Vascular endothelial growth factor (VEGF), Mannose-binding lectin (MBL), Interleukin-18 (IL-18), Hepatocellular carcinoma (HCC), Meta-analysis

Background

Hepatocellular carcinoma (HCC) is one of the leading causes of death all over the world [1, 2]. Although we still did not reveal the exact mechanism of its pathogenesis, it was evident that genetic components were essential in the development of HCC. Firstly, the incidences of HCC in different populations were quite different [3, 4], and genetic background was probably one of the reasons behind differences in disease prevalence across different populations. Secondly, numerous susceptible genetic loci of HCC were also identified and validated by existing genetic association studies [5, 6].

Mannose-binding lectin (MBL) and interleukin-18 (IL-18) are crucial modulators of immunological reactions, whereas vitamin D receptor (VDR) and vascular endothelial growth factor (VEGF) are vital for both immune-regulation and angiogenesis [7–10]. So, if a genetic polymorphism could alter the transcription activity of VDR/VEGF/IL-18/MBL or the protein structure of VDR/VEGF/IL-18/MBL, there is a possibility that this polymorphism may lead to the development of chronic inflammatory cellular injuries and also confer susceptibility to many types of malignancy including HCC.
In the past 20 years, many studies explored associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC, yet the conclusions of these studies were somehow inconsistent [11–40]. To better clarify associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC, we designed this study to get a more credible conclusion by combing the results of all relevant studies.

**Methods**

We wrote this meta-analysis in accordance with the requirements of the PRISMA guideline [41].

**Literature search and inclusion criteria**

To retrieve eligible articles, we searched PubMed, WOS, Embase, and CNKI with keywords listed below: (“vitamin D receptor” or “VDR” or “vascular endothelial growth factor” or “VEGF” or “interleukin 18” or “IL 18” or “mannose-binding lectin” or “Mannose-binding protein” or “MBL”) and (“polymorphism” or “variant” or “variation” or “mutation” or “SNP” or “genome-wide association study” or “genetic association study” or “genotype” or “allele”) and (“hepatocellular carcinoma” or “HCC”). We found 168 articles during literature searching. Forty-five articles were assessed for eligibility after excluding unrelated or duplicate articles. We further excluded eight reviews and six case series, and another one publication was excluded because of missing crucial data. Totally, 30 articles were ultimately found to be eligible for inclusion (Fig. 1). Extracted data of eligible articles were summarized in Table 1.

**Data extraction and quality assessment**

Two authors extracted the following essential information from eligible studies: (I) name of the leading author; (II) published year; (III) country of the leading author; (IV) ethnicity of involved participants; (V) number of patients with HCC and controls in each study; (VI) genotype distributions of polymorphisms in VDR/VEGF/IL-18/MBL among patients with HCC and controls. P values of Hardy-Weinberg equilibrium (HWE) were also calculated.

The authors used the Newcastle-Ottawa scale (NOS) to assess the quality of eligible publications [42]. The score range of NOS is between 0 and 9, when a study got a score of 7 or more, we considered that the methodology quality of this study was good.

Two authors extracted data and assessed the quality of eligible studies. The authors wrote to the leadings authors for additional information if essential information was found to be incomplete.

**Statistical analyses**

We used Review Manager to combine the results of individual studies. Z test was employed to assess associations between polymorphisms in VDR/VEGF/IL-18/MBL and susceptibility to HCC. The statistical significance threshold of P value was set at 0.05. We used I² statistics to assess between-study heterogeneities. We used Random-effect models (DerSimonian-Laird method) to combine the results if I² is larger than 50%. Otherwise, fixed-effect models (Mantel-Haenszel method) were used to combine the results [43, 44]. We further carried out subgroup analyses by ethnicity to get ethnic-specific results. We examined the stability of combined results by deleting one study each time and combining the results of the remaining studies. We used funnel plots to estimate whether our combined results may be influenced by publication biases.

**Results**

**Characteristics of included studies**

We found 168 articles during literature searching. Forty-five articles were assessed for eligibility after excluding unrelated or duplicate articles. We further excluded eight reviews and six case series, and another one publication was excluded because of missing crucial data. Totally, 30 articles were ultimately found to be eligible for inclusion (Fig. 1). Extracted data of eligible articles were summarized in Table 1.

**Meta-analyses results for polymorphisms in VDR and HCC**

Six studies were eligible for estimation of associations between polymorphisms in VDR and HCC. VDR rs7975232 (dominant comparison OR = 1.58, 95% CI 1.04–2.39; over-dominant comparison OR = 0.80, 95% CI 0.65–0.98) and rs2228570 (dominant comparison OR = 1.54, 95% CI 1.25–1.89; recessive comparison OR = 0.67, 95% CI 0.54–0.84; allele comparison OR = 1.34, 95% CI 1.06–1.68) polymorphisms were found to be significantly associated with HCC in overall combined analyses. Subgroup analyses showed similar positive findings for rs7975232 (dominant comparison) and rs2228570 (dominant, recessive, and allele comparisons) polymorphisms in East Asians (see Table 2 and Additional file 1: Supplementary Figure S1).

**Meta-analyses results for polymorphisms in VEGF and HCC**

Nine studies were eligible for the estimation of associations between polymorphisms in VEGF and HCC. VEGF rs699947 (recessive comparison OR = 0.63, 95% CI 0.41–0.98) and rs3025039 (allele comparison OR = 1.21,
95% CI 1.00–1.46) polymorphisms were found to be significantly associated with HCC in overall combined analyses. Nevertheless, we did not observe any positive associations in subgroup analyses (see Table 2 and Additional file 1: Supplementary Figure S1).

**Meta-analyses results for polymorphisms in IL-18 and HCC**

Ten studies were eligible for the estimation of associations between polymorphisms in *IL-18* and HCC. *IL-18* rs1946518 (dominant comparison OR = 0.79, 95% CI 0.68–0.92; recessive comparison OR = 1.26, 95% CI 1.08–1.48; allele comparison OR = 0.78, 95% CI 0.67–0.91) polymorphism was found to be significantly associated with HCC in overall combined analyses. Subgroup analyses showed similar positive findings for rs1946518 polymorphism in East Asians (allele comparison), South Asians (dominant, recessive, and allele comparisons), and those with hepatitis B virus (HBV) infection (dominant and allele comparisons) (see Table 2 and Additional file 1: Supplementary Figure S1).

**Meta-analyses results for polymorphisms in MBL and HCC**

Five studies were eligible for the estimation of associations between polymorphisms in *MBL* and HCC. *MBL* rs7096206 (dominant comparison OR = 0.59, 95% CI 0.48–0.73; over-dominant comparison OR = 1.59, 95% CI 1.28–1.97; allele comparison: OR = 0.63, 95% CI...
Table 1 The characteristics of included studies for this meta-analysis

| First author, year | Country | Ethnicity | Type of disease | Medical history of patients | Sample size Case/ control | Genotype distribution (wt/wtmt/mmtmt) | P value for HWE | NOS |
|--------------------|---------|-----------|-----------------|-----------------------------|--------------------------|--------------------------------------|----------------|-----|
| Barooah 2019 [11]  | India   | South Asian | HCC             | NA                          | 60/102                   | 49/11/0 59/35/8                      | 0.391          | 8   |
| Falleti 2010 [12]  | Italy   | Caucasian  | HCC             | Viral hepatitis 87%         | 80/160                   | 27/38/15 53/85/22                    | 0.189          | 8   |
| Hung 2014 [13]     | Taiwan  | East Asian | HCC             | NA                          | 92/100                   | 65/24/3 55/40/5                      | 0.505          | 8   |
| Yao 2013 [16]      | China   | East Asian | HCC             | HBV 100%, alcohol intake 34.9% | 436/532                  | 112/216/108 114/275/143              | 0.395          | 8   |
| VDR rs1544410      |         |            |                 |                             |                          |                                      |                |     |
| Barooah 2019 [11]  | India   | South Asian | HCC             | NA                          | 60/102                   | 52/8/0 80/16/6 < 0.001               | 8   |
| Falleti 2010 [12]  | Italy   | Caucasian  | HCC             | Viral hepatitis 87%         | 80/160                   | 33/35/12 45/87/28                    | 0.206          | 8   |
| Hung 2014 [13]     | Taiwan  | East Asian | HCC             | NA                          | 92/100                   | 85/7/0 89/11/0                       | 0.560          | 8   |
| Yao 2013 [16]      | China   | East Asian | HCC             | HBV 100%, alcohol intake 34.9% | 436/532                  | 112/217/107 142/259/131              | 0.550          | 8   |
| VDR rs2228570      |         |            |                 |                             |                          |                                      |                |     |
| Falleti 2010 [12]  | Italy   | Caucasian  | HCC             | Viral hepatitis 87%         | 80/160                   | 36/36/8 69/73/18                     | 0.843          | 8   |
| Liu 2015 [14]      | China   | East Asian | HCC             | NA                          | 105/100                  | 41/44/23 23/48/29                    | 0.715          | 8   |
| Peng 2014 [15]     | China   | East Asian | HCC             | HBV 100%, alcohol intake 90.2% | 184/296                  | 54/90/40 77/152/67                   | 0.628          | 8   |
| Yao 2013 [16]      | China   | East Asian | HCC             | HBV 100%, alcohol intake 34.9% | 436/532                  | 131/198/107 102/241/189              | 0.111          | 8   |
| VDR rs731236       |         |            |                 |                             |                          |                                      |                |     |
| Barooah 2019 [11]  | India   | South Asian | HCC             | NA                          | 60/102                   | 48/8/4 71/21/10 <0.001               | 8   |
| Falleti 2010 [12]  | Italy   | Caucasian  | HCC             | Viral hepatitis 87%         | 80/160                   | 32/38/10 44/88/28                    | 0.160          | 8   |
| Hung 2014 [13]     | Taiwan  | East Asian | HCC             | NA                          | 92/100                   | 86/6/0 86/14/0                       | 0.452          | 8   |
| Yao 2013 [16]      | China   | East Asian | HCC             | HBV 100%, alcohol intake 34.9% | 436/532                  | 115/212/109 137/252/143              | 0.226          | 8   |
| VEGF rs699947      |         |            |                 |                             |                          |                                      |                |     |
| Liu 2017 [19]      | China   | East Asian | HCC             | HBV 60.2%, alcohol intake 60.8% | 476/526                  | 301/157/18 290/202/34                 | 0.882          | 8   |
| Machado 2014 [20]  | Portugal | Caucasian  | HCC             | Alcohol intake 100%         | 26/101                   | 7/14/5 19/49/33                     | 0.914          | 7   |
| Ratnasari 2017 [22] | Indonesia | East Asian | HCC             | HBV58%, HCV 11%             | 44/59                    | 18/21/5 23/30/6                     | 0.402          | 7   |
| Wu 2009 [23]       | China   | East Asian | HCC             | NA                          | 92/90                    | 48/40/4 58/28/4                      | 0.792          | 8   |
| Wu 2013 [24]       | China   | East Asian | HCC             | HBV48.5%                    | 101/110                  | 79/21/1 91/17/2                      | 0.271          | 8   |
| VEGF rs1570360     |         |            |                 |                             |                          |                                      |                |     |
| Baitello 2016 [17] | Canada  | Mixed       | HCC             | HBV 50%, HCV 21%, alcohol intake 56% | 102/127                  | 61/35/6 73/47/7                      | 0.875          | 8   |
| Wu 2009 [23]       | China   | East Asian | HCC             | NA                          | 90/99                    | 66/24/0 72/27/0                     | 0.116          | 8   |
| Wu 2013 [24]       | China   | East Asian | HCC             | HBV48.5%                    | 101/110                  | 83/17/1 75/31/4                     | 0.723          | 8   |
| VEGF rs2010963     |         |            |                 |                             |                          |                                      |                |     |
| Liu 2017 [19]      | China   | East Asian | HCC             | HBV 60.2%, alcohol intake 60.8% | 476/526                  | 162/232/82 200/248/78                | 0.937          | 8   |
| Ratnasari 2016 [21] | Indonesia | East Asian | HCC             | HBV56.5%, HCV 10.8%       | 46/136                   | 16/29/1 26/105/5 <0.001              | 7   |
| Wu 2009 [23]       | China   | East Asian | HCC             | NA                          | 92/99                    | 34/40/18 34/52/13                    | 0.320          | 8   |
### Table 1  The characteristics of included studies for this meta-analysis (Continued)

| First author, year | Country | Ethnicity | Type of disease | Medical history of patients | Sample size | Genotype distribution | P value for HWE | NOS |
|---------------------|---------|-----------|-----------------|-----------------------------|-------------|-----------------------|----------------|-----|
| Wu 2013 [24]       | China   | East Asian | HCC             | HBV 48.5%                   | 101/110     | 28/52/21               | 0.506          | 8   |
| VEGF rs3025039     |         |           |                 |                             |             |                       |                |     |
| Baitello 2016 [17] | Canada  | Mixed     | HCC             | HBV 50%, HCV 21%, alcohol intake 56% | 102/127     | 72/30/0                | 0.055          | 8   |
| Giacalone 2011 [18] | Italy   | Caucasian | HCC             | NA                         | 96/162      | 81/14/1                | 0.636          | 8   |
| Liu 2017 [19]      | China   | East Asian | HCC             | HBV 60.2%, alcohol intake 60.8% | 476/526     | 359/112/5              | 0.536          | 8   |
| Wu 2009 [23]       | China   | East Asian | HCC             | NA                         | 92/99       | 63/26/3                | 0.239          | 8   |
| Yvamoto 2015 [25]  | Brazil  | Mixed     | HCC             | Alcohol intake 47.1%        | 228/56      | 164/64/0               | 0.326          | 7   |
| IL-18 rs187238     |         |           |                 |                             |             |                       |                |     |
| Bakr 2018 [26]     | Egypt   | South Asian | HCC             | HCV 100%                   | 90/90       | 66/22/2                | <0.001         | 8   |
| Bao 2015 [27]      | China   | East Asian | HCC             | HBV 100%                    | 153/165     | 122/28/3               | 0.548          | 8   |
| Chen 2012 [28]     | China   | East Asian | HCC             | NA                         | 228/300     | 159/59/10              | 0.183          | 7   |
| Dai 2017 [29]      | China   | East Asian | HCC             | HBV 100%, alcohol intake 42% | 245/250     | 187/49/9               | 0.142          | 8   |
| Karra 2015 [30]    | India   | South Asian | HCC             | HBV 100%                   | 271/280     | 123/134/14             | 0.320          | 7   |
| Kim 2009 [31]      | Korea   | East Asian | HCC             | HBV 100%                    | 56/558      | 37/17/2                | 0.031          | 7   |
| Lau 2016 [32]      | Taiwan  | East Asian | HCC             | Alcohol intake 63.5%        | 342/559     | 266/73/3               | 0.370          | 8   |
| Migita 2009 [33]   | Japan   | East Asian | HCC             | HBV 100%                   | 47/63       | 43/3/1                 | 0.531          | 7   |
| Teixeira 2009 [34] | Brazil  | Mixed     | HCC             | Viral hepatitis 67.8%, alcohol intake 63.4% | 112/202     | 57/48/7                | 0.952          | 7   |
| Zhang 2016 [35]    | China   | East Asian | HCC             | HBV 100%                   | 109/127     | 82/25/2                | 0.110          | 8   |
| IL18 rs1946518     |         |           |                 |                             |             |                       |                |     |
| Bakr 2018 [26]     | Egypt   | South Asian | HCC             | HCV 100%                   | 90/99       | 13/34/43               | 0.603          | 8   |
| Bao 2015 [27]      | China   | East Asian | HCC             | HBV 100%                    | 153/165     | 37/73/43               | 0.322          | 8   |
| Chen 2012 [28]     | China   | East Asian | HCC             | NA                         | 228/300     | 47/126/55              | 0.429          | 7   |
| Dai 2017 [29]      | China   | East Asian | HCC             | HBV 100%, alcohol intake 42% | 247/250     | 62/118/67              | 0.900          | 8   |
| Karra 2015 [30]    | India   | South Asian | HCC             | HBV 100%                   | 271/280     | 70/152/49              | 0.119          | 7   |
| Lau 2016 [32]      | Taiwan  | East Asian | HCC             | Alcohol intake 63.5%        | 342/559     | 88/167/87              | 0.777          | 8   |
| Migita 2009 [33]   | Japan   | East Asian | HCC             | HBV 100%                   | 47/63       | 13/26/8                | 0.777          | 7   |
| Teixeira 2009 [34] | Brazil  | Mixed     | HCC             | Viral hepatitis 67.8%, alcohol intake 63.4% | 112/202     | 38/56/18               | 0.202          | 7   |
| Zhang 2016 [35]    | China   | East Asian | HCC             | HBV 100%                   | 109/127     | 22/55/32               | 0.127          | 8   |
| MBL rs7096206     |         |           |                 |                             |             |                       |                |     |
| Eurich 2011 [36]   | Germany | Caucasian | HCC             | NA                         | 62/115      | 27/34/1                | 0.292          | 7   |
| Gu 2016 [37]       | China   | East Asian | HCC             | NA                         | 334/171     | 232/95/7               | 0.015          | 8   |
| Lin 2015 [38]      | China   | East Asian | HCC             | Alcohol intake 77.7%        | 220/220     | 125/86/9               | 0.082          | 8   |
| Su 2016 [40]       | China   | East Asian | HCC             | HBV 70.2%                  | 315/315     | 207/91/17              | 0.583          | 8   |
| MBL rs1800450     |         |           |                 |                             |             |                       |                |     |
| Gu 2016 [37]       | China   | East Asian | HCC             | NA                         | 334/171     | 234/89/11              | 0.020          | 8   |
| Segat 2008 [39]    | Italy   | Caucasian | HCC             | NA                         | 215/164     | 127/78/10              | 0.050          | 7   |
(Continued)

Table 1 The characteristics of included studies for this meta-analysis

| First author, year | Country | Ethnicity | Type of disease | Medical History of patients | Sample size | Genotype distribution (wt/wt/wtmt/mtmt) | Case/control | NOS score | P value for HWE |
|--------------------|---------|-----------|-----------------|-----------------------------|-------------|----------------------------------------|--------------|-----------|----------------|
| Su 2016 [40]       | China   | East Asian| HCC             | HBV 70.2%                   | 308/315     |                                        | 208/88/20    | 239/69/7  | 0.450          |

Abbreviations: HWE Hardy-Weinberg equilibrium, NOS Newcastle-Ottawa scale, NA not available, HBV hepatitis B virus infection, HCV hepatitis C virus infection

0.053–0.76) polymorphism was found to be significantly associated with HCC in overall combined analyses. Subgroup analyses showed similar positive findings for rs7096206 polymorphism in East Asians (dominant, over-dominant, and allele comparisons) (see Table 2 and Additional file 1: Supplementary Figure S1).

Sensitivity analyses
We examined the stability of combined results by deleting one study each time and combining the results of the remaining studies. The trends of associations remained consistent in sensitivity analyses, which indicated that the combined results were statistically stable.

Publication biases
Funnels plots were employed to estimate whether our combined results may be influenced by publication biases. Funnel plots of every comparison were symmetrical, which indicated that the combined results were unlikely to be seriously impacted by overt publication biases.

Discussion
The combined results of this meta-analysis revealed that VDR rs7975232, VDR rs2228570, VEGF rs699947, VEGF rs3025039, IL-18 rs1946518, and MBL rs7096206 polymorphisms were significantly associated with susceptibility to HCC in certain populations. The trends of associations remained consistent in sensitivity analyses, which indicated that the combined results were statistically stable.

To better understand the combined results of this meta-analysis, some points should be considered. First, past basic studies revealed that all investigated polymorphisms were either correlated with altered transcription activity or protein structure [45–48]. So, these variations may influence the biological function of VDR/VEGF/IL-18/MBL, result in immune dysfunction, cause chronic inflammatory hepatocellular injury, and ultimately confer susceptibility to HCC. Thus, our meta-analysis may be statistically insufficient to observe the real underlying associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC in certain subgroups. Therefore, future studies still need to confirm our findings. Second, we noticed that most eligible studies were from Asian countries, whereas studies in other countries were highly scarce, so scholars from European and African countries should also try to examine associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC. Besides, considering the functional importance of VDR/VEGF/IL-18/MBL in regulating inflammatory reactions and angiogenesis, future studies also need to test the relationship between polymorphisms in VDR/VEGF/IL-18/MBL and other types of malignancies. Third, the etiology of HCC is very complicated, so we highly recommend further genetic association studies to explore the effects of haplotypes and gene-gene interactions on disease susceptibility [49]. Fourth, we aimed to investigate associations between all polymorphisms in VDR/VEGF/IL-18/MBL and HCC in the very beginning. However, we did not find any study on other VDR/VEGF/IL-18/MBL polymorphisms, so we only focused on 12 polymorphisms in this meta-analysis. Fifth, it is worth noting that Zhu et al. [50] also performed a meta-analysis about IL-18 polymorphisms and HCC in 2016. Based on combined analyses of eight eligible studies with 3572 subjects, they did not find any positive results regarding IL-18 polymorphisms and HCC in general or subgroup analyses. Since our pooled analyses about IL-18 polymorphisms were based on more eligible studies and larger sample sizes, our results should be more statistically robust. Nevertheless, studies with larger sample sizes are still warranted to test the genetic associations between IL-18 polymorphisms and HCC in the future.

Some limitations of this meta-analysis should also be mentioned. Firstly, the results regarding associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC were based on combining unadjusted findings of eligible studies due to the lack of raw data [51]. Secondly, the relationship between polymorphisms in VDR/VEGF/IL-18/MBL and HCC may also be affected by environmental factors. Unfortunately, the majority of eligible studies only focused on associations between polymorphisms in VDR/VEGF/IL-18/MBL and HCC, so we could not explore genetic-environmental interactions in this meta-analysis [52]. Thirdly, grey literatures were not searched. So although funnel plots of every comparison were symmetrical, it is still possible that the combined results may be affected by publication biases [53].
Table 2 Meta-analyses results of the current study

| Variables | Sample size | Dominant comparison |  | Recessive comparison |  | Over-dominant comparison |  | Allele comparison |  |
|-----------|-------------|---------------------|---|----------------------|---|-------------------------|---|---------------------|---|
|           |  | p value OR (95% CI) |  | p value OR (95% CI) |  | p value OR (95% CI) |  | p value OR (95% CI) |  |
| VDR rs7975232 |  | statistic |  | statistic |  | statistic |  | statistic |  |
| Overall | 668/894 | 0.03 | 1.58 | 0.42 | 0.90 (0.69–1.17) | 0.03 | 0.80 | 0.09 | 1.41 |
| East Asian | 528/632 | 0.02 | 1.39 | 0.40 | 0.88 (0.67–1.17) | 0.28 | 0.75 | 0.17 | 1.30 |
| VDR rs1544410 |  |  |  |  |  |  |  |  |  |
| Overall | 668/894 | 0.26 | 1.15 | 0.62 | 0.93 (0.71–1.22) | 0.54 | 0.93 | 0.30 | 1.09 |
| East Asian | 528/632 | 0.98 | 1.00 | 0.91 | 0.98 (0.75–1.30) | 0.90 | 1.02 | 0.96 | 1.00 |
| VDR rs2228570 |  |  |  |  |  |  |  |  |  |
| Overall | 805/1088 | < 0.0001 | 1.54 | 0.0004 | 0.67 (0.54–0.84) | 0.58 | 0.95 | 0.01 | 1.34 |
| East Asian | 725/928 | < 0.0001 | 1.63 | 0.0003 | 0.66 (0.53–0.83) | 0.58 | 0.95 | 0.01 | 1.40 |
| VDR rs731236 |  |  |  |  |  |  |  |  |  |
| Overall | 668/894 | 0.06 | 1.25 | 0.26 | 0.86 (0.66–1.12) | 0.42 | 0.92 | 0.06 | 1.16 |
| East Asian | 528/632 | 0.44 | 1.34 | 0.51 | 0.91 (0.68–1.21) | 0.54 | 0.77 | 0.39 | 1.08 |
| VEGF rs699947 |  |  |  |  |  |  |  |  |  |
| Overall | 739/886 | 0.92 | 1.02 | 0.04 | 0.63 (0.47–0.88) | 0.61 | 0.95 | 0.61 | 1.08 |
| East Asian | 713/785 | 0.84 | 1.05 | 0.10 | 0.67 (0.41–1.08) | 0.70 | 1.08 | 0.99 | 1.00 |
| VEGF rs1570360 |  |  |  |  |  |  |  |  |  |
| Overall | 293/336 | 0.12 | 1.31 | 0.57 | 0.75 (0.29–1.98) | 0.17 | 0.78 | 0.13 | 1.26 |
| East Asian | 191/209 | 0.28 | 1.49 | 0.24 | 0.27 (0.03–2.41) | 0.15 | 0.71 | 0.28 | 1.46 |
| VEGF rs2010963 |  |  |  |  |  |  |  |  |  |
| Overall | 715/871 | 0.79 | 1.05 | 0.26 | 1.17 (0.89–1.55) | 0.80 | 0.97 | 0.32 | 0.93 |
| East Asian | 715/871 | 0.79 | 1.05 | 0.26 | 1.17 (0.89–1.55) | 0.80 | 0.97 | 0.32 | 0.93 |
| VEGF rs3025039 |  |  |  |  |  |  |  |  |  |
| Overall | 994/970 | 0.08 | 1.20 | 0.08 | 0.50 (0.23–1.09) | 0.21 | 0.87 | 0.05 | 1.21 |
| East Asian | 568/625 | 0.10 | 1.24 | 0.07 | 0.83 (0.09–7.41) | 0.25 | 0.86 | 0.06 | 1.24 |
| IL-18 rs187238 |  |  |  |  |  |  |  |  |  |
| Overall | 1653/2594 | 0.38 | 1.19 | 0.50 | 1.14 (0.78–1.66) | 0.26 | 0.77 | 0.56 | 1.09 |
| East Asian | 1180/2022 | 0.62 | 1.11 | 0.27 | 1.33 (0.80–2.22) | 0.49 | 0.86 | 0.76 | 1.06 |
| South Asian | 361/370 | 0.60 | 1.70 | 0.65 | 1.19 (0.57–2.47) | 0.53 | 0.45 | 0.69 | 1.25 |
| HBV 881/1443 | 0.90 | 0.23 | 0.38 (0.81–2.33) | 0.73 | 0.92 | 0.96 | 1.01 | 0.70–1.46 |
### Table 2 Meta-analyses results of the current study (Continued)

| Variables | Sample size | Dominant comparison | Recessive comparison | Over-dominant comparison | Allele comparison |
|-----------|-------------|---------------------|----------------------|--------------------------|------------------|
|           |             | $P$ value OR (95%CI) $I^2$ statistic | $P$ value OR (95%CI) $I^2$ statistic | $P$ value OR (95% CI) $I^2$ statistic | $P$ value OR (95% CI) $I^2$ statistic |
| Overall   | 1599/2045  | 0.002 0.79 (0.68–0.92) | 0.004 1.26 (1.08–1.48) | 0.75 1.02 (0.90–1.17) | 0.002 0.78 (0.67–0.91) |
| East      | 1126/1464  | 0.09 0.86 (0.71–1.02) | 0.15 1.14 (0.95–1.37) | 0.79 1.02 (0.87–1.19) | 0.04 0.80 (0.65–0.99) |
| Asian     | 589/679    | 0.001 0.66 (0.51–0.85) | 0.02 1.57 (1.09–2.27) | 0.98 0.99 (0.61–1.61) | 0.02 0.72 (0.59–0.89) |
| South     | 827/885    | 0.01 0.77 (0.62–0.95) | 0.06 1.25 (0.99–1.57) | 0.52 1.06 (0.88–1.29) | 0.03 0.73 (0.55–0.96) |
| HBV       |            |                     |                      |                           |                  |
| MBL rs7096206 |         |                     |                      |                           |                  |
| Overall   | 931/821    | $<0.0001$ 0.59 (0.48–0.73) | 0.37 1.81 (0.50–6.59) | $<0.0001$ 1.59 (1.28–1.97) | $<0.0001$ 0.63 (0.53–0.76) |
| East      | 869/706    | $<0.0001$ 0.62 (0.50–0.78) | 0.35 2.08 (0.44–9.80) | 0.0005 1.50 (1.19–1.88) | $<0.0001$ 0.65 (0.53–0.79) |
| Asian     |            |                     |                      |                           |                  |
| MBL rs1800450 |         |                     |                      |                           |                  |
| Overall   | 857/650    | 0.85 0.95 (0.58–1.55) | 0.91 1.06 (0.37–3.06) | 0.70 1.10 (0.69–1.74) | 0.95 0.99 (0.65–1.50) |
| East      | 642/486    | 0.99 0.99 (0.44–2.23) | 0.61 1.47 (0.34–6.30) | 0.99 1.00 (0.49–2.03) | 0.95 0.98 (0.48–1.99) |
| Asian     |            |                     |                      |                           |                  |

Abbreviations: OR odds ratio, CI confidence interval, NA not available, HBV hepatitis B virus infection

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

### Conclusion

In summary, this meta-analysis proved that VDR rs7975232, VDR rs2228570, VEGF rs699947, VEGF rs3025039, IL-18 rs1946518, and MBL rs7096206 polymorphisms may confer susceptibility to HCC in certain populations. These results also indicated that VDR, VEGF, IL-18, and MBL may involve in the development of HCC. However, the combined results of this meta-analysis should still be verified by studies with larger sample sizes.

### Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12957-019-1748-8.

### Additional file 1: Figure S1. Forest plots of investigated polymorphisms.

### Abbreviations

VDR: Vitamin D receptor; VEGF: Vascular endothelial growth factor; MBL: Mannose-binding lectin; IL-18: Interleukin-18; HCC: Hepatocellular carcinoma; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa scale; OR: Odds ratios; CI: Confidence intervals.

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### Ethical approval and consent to participate

Not applicable.

### Informed consent

For this type of study formal consent is not required.

### Authors’ contributions

YQ and YH conceived and designed the study. YQ and JY conducted the contributions. The authors declare that they have no competing interests.

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### Availability of data and materials

The current study was based on the results of relevant published studies.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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