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Tumor Necrosis Factor-α-863C/A and 1031 T/C Single nucleotide polymorphic sites (SNPs) may be putative markers of HBV disease prognosis among Caucasoids: Evidence from a systematic review with meta-analysis

Hussein Mukasa Kafeero [a,b,*], Dorothy Ndagire [c], Ponsiano Ocama [d], Abdul Walusansa [b], Hakim Sendagire [a,b]

[a] Department of Medical Microbiology, Makerere University, College of Health Sciences, P. O Box 7062, Kampala, Uganda
[b] Department of Medical Microbiology, Habib Medical School, Faculty of Health Sciences, Islamic University in Uganda, P. O Box 7689, Kampala, Uganda
[c] Department of Plant Sciences, Microbiology and Biotechnology, College of Natural Sciences, Makerere University, P. O Box 7062, Kampala, Uganda
[d] Department of medicine, College of Health Sciences, Makerere University, P. O Box 7062, Kampala, Uganda

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ABSTRACT

Background: The pathogenesis and prognosis of hepatitis B virus (HBV) infection have been correlated with genetic polymorphisms in the gene loci within the promoter region of the immune system modulator molecules such as the cytokines including the tumor necrosis factor (TNF)-alpha. Besides, these polymorphisms vary at population levels but it is not conclusive whether races are involved or not. We aimed at testing the hypothesis that the SNPs in the promoter region of the TNF-alpha gene may have different effects in the Caucasoid populations by pooling the odds of association with the clearance/increased risk of the HBV infection from a large sample size obtained from many primary studies. We searched Scopus, PubMed, EMBASE, Cochrane, Willy and Google scholar databases for the published studies between January 1998 to December 2020. Studies that investigated the association between the TNF-α-238G/A, -308G/A, -857C/T, -863C/A and -1031 T/C gene promoter polymorphisms with the resolution/increased risk of HBV infection published in English and in peer reviewed journals were included. The odds ratios were used to evaluate the association of the TNF-α-gene SNPs with the risk/resolution of the disease. This study is registered on PROSPERO, number CRD42021266944.

Results: A significant association was observed between the TNF-α-857 homozygous mutation TT and its allele T with reduced risk of infection or resolution of the disease among both the Caucasoids and the Mongoloids ($p < 0.05$, OR < 1.0). In contrast, the TNF-α-1031 wild type genotypes TT; $p = 0.001$, OR $= 0.634$, 95%CI $=$ [0.489 to 0.822%] and its allele T; $p = 0.001$, OR $= 0.701$, 95%CI $=$ [0.571 to 0.860%] were significantly associated with reduced risk of infection or increased chances of resolution of the disease among the Caucasoids only. However, the TNF-α-863 homozygous mutation AA or its allele A and the TNF-α-1031 heterozygous mutation CT or the allele C were significantly associated with unresolved HBV infection among the Caucasoids ($p < 0.05$, OR > 1.0) but not among the Mongoloids.

Conclusion: Tumor Necrosis Factor-α-863C/A and 1031 T/C polymorphic sites may be putative markers of HBV disease prognosis and pathogenesis among the Caucasoid populations but not among the Mongoloid populations. Future research therefore should focus on the role of these presumed TNF-α-polymorphisms in the clinical profile of the HBV infections targeting an African or Negroid population.

Abbreviations: TNF-α, Tumor Necrosis Factor alpha; HBV, Hepatitis B; MHC, Major Histocompatibility Complex; PROSPERO, Prospective Register of Systematic Reviews; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle–Ottawa scale; OR, Odds Ratios; CHB, Chronic Hepatitis B; PRISMA, Preferred Reporting System for Systematic Reviews and Meta-analyses.

* Corresponding author at: Department of Medical Microbiology, Makerere University, College of Health Sciences, P. O Box 7062, Kampala, Uganda
E-mail address: husseinmukasakafeero@gmail.com (H.M. Kafeero).

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1. Introduction

The profile of the HBV infection is variable and a genetic component is highly implicated in the susceptibility and the evolution of the disease (Manjita et al., 2014). Thus, the risk of infection following exposure to the virus, the clearance of the disease and the progression to chronic infection contrasts at personal level, ethnic level, and at the level of the entire race (Manjita et al., 2014; Ma et al., 2018). Accordingly, the transmission of the TNF-α HBV susceptible/resistant alleles or genotypes through generations appears to have an evolutionary trend. The TNF-α is an inflammatory cytokine that is important in the prognosis of the liver diseases following infection with hepatitis B virus (Dyah et al., 2020). The TNF-α cytokine storm after the HBV exposure has been implicated in causing liver cell damage which accelerates liver fibrosis, cirrhosis and cancer (Mathew et al., 2016; Ma, 2018). Besides, it also affects the expression levels of the Major Histocompatibility Complex (MHC) class II which ordinarily influences the HBV viral antigen presentation (Godkin et al., 2005). None the less, the TNF-α can potentially inhibit the activities involved in the transcription of the HBV core promoter gene as well as inhibiting the HBV replication in the liver inducing viral clearance (Chen et al., 2005). The TNF-α gene has several single nucleotide polymorphisms in the promoter region located, but not limited to the following positions upstream of the transcription initiation site; −163G/A, −238G/A, −244A/G, −308G/A, −376G/A, −575A/G, -857C/T, -863C/A, −1031 T/C, −1125G/C and -1196C/T (Gusatti, 2016; Kim et al., 2003; Khayrulla et al., 2021). The expression of the TNF-α is tightly regulated at both transcriptional and post-transcriptional levels and is under the control of the genes within the promoter region (Wilson et al., 1997). Any polymorphisms within this region will alter the levels of the cytokine which in turn affects its effector mechanism (Berchtold et al., 2008). Moreover, the inability to express sufficient amount of TNF-α has been observed to influence the process of the HBV chronicity in the experimental virus infected neonatal woodchucks (Nakamura et al., 2001). Several primary studies have investigated the role of the -238G/A, −308G/A, -857C/T and -863C/A polymorphic sites in the susceptibility/resolution of HBV infection among the Caucasoids but the results are inconclusive (Heidari et al., 2016; Fletcher et al., 2011; Panigrahi et al., 2014) probably because such studies are limited by geographical scope and sample size affecting their statistical power and hence generalizability. Besides, whereas there is a plenitude of information from data synthesis on the significance of these polymorphic sites in the pathogenesis of the HBV among the Mongoloids (Zheng et al., 2010; Xia et al., 2011; Zhang et al., 2013; Xiao et al., 2016), the evidence from related studies among the Caucasoids is scanty. In addition, the previous meta-analyses on the association of the TNF-α gene promoter polymorphisms with the spontaneous clearance of the HBV or the risk of infection among the Caucasoids have been either limited to only two polymorphic sites of TNF-α-238G/A and TNF-α-308G/A (Zheng et al., 2010; Mekinian et al., 2011) or, have used study subjects from mixed races (Zheng et al., 2010; Xia et al., 2011; Zhang et al., 2013; Shi et al., 2012) whose conclusions cannot be pinched onto the Caucasoids populations due to the genetic diversities between the races (Masatoshi and Roychoudhury, 1974). Likewise, the genetic evolutionary relationship between the three major races of the Mongoloids, the Caucasoids and the Negroids have shown that the Caucasoids and the Negroids are more closely related genetically than the Caucasoids and the Mongoloids (Masatoshi and Roychoudhury, 1974). Therefore, the findings from the studies on the TNF-α gene promoter polymorphisms with the spontaneous clearance of the HBV or the risk of infection among the Mongoloids, Asians or from mixed races cannot be generalized to the Caucasoid populations. Therefore, a meta-analysis from all eligible studies is categorically necessary to establish a more accurate and dependable estimate of the role the TNF-α-gene promoter polymorphic sites on the risk of the HBV infection/resolution of the infection among the Caucasoids. Here we report the updated findings from a comprehensive meta-analysis on the relationship between those TNF-α gene single nucleotide polymorphisms and the risk of the HBV infection/resolution of the infection among the Caucasoids and the Mongoloids.

2. Materials and methods

2.1. Systematic review protocol registration, information sources, and search strategies

Our study was designed to investigate the TNF-α promoter gene polymorphisms in susceptibility to HBV infection among the Caucasoid and the Mongoloid populations. We registered the protocol with the International Prospective Register of Systematic Reviews (PROSPERO), University of York Centre for Reviews and Dissemination (https://www.crd.york.ac.uk/PROSPERO), under the registration number CRD42021266944. The findings of the review were reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement checklist (Page et al., 2021).

2.2. Journal article search strategy

Primary studies that investigated the TNF-α promoter gene polymorphisms and their effect on resolution/chronicity of the HBV infection among the Caucasoids and the Mongoloids were identified by thorough searches in the following databases; Scopus, PubMed, EMBASE, Cochran library, Willy Library and the Google scholar published between January 1998 to December 2020. The search was done by the three researchers (HMK, DN and AW) between June to July 2021 using terms related to the TNF-α gene promoter polymorphism in relation to the HBV infection among the Caucasoids and the Mongoloids. The key terms used included; "HBV infection and the TNF-alpha polymorphisms", "TNF-alpha polymorphisms and the resolution of the HBV infection", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection among the Caucasoids", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection among the Mongoloids", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in Asia", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in USA", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in Europe", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in Africa", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in European countries", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in Arab countries", "TNF-alpha promoter gene polymorphisms and the risk of the HBV infection in Persian countries". Between June 16-20th 2021, HMK, AW and DN searched the PubMed database using the aforementioned terms. We also carried out a snowball search to identify additional studies by searching the references of the publications eligible for full text review using the Google scholar to identify and screen the studies citing them. From June 26-30th 2021, HMK and AW conducted a search of the Google scholar using the aforesaid terms. As with the search from the PubMed database, a snowball search to identify additional studies by searching the references of the publications eligible for full text review using the Google scholar to identify and screen studies citing them was done. On July 7th 2021, HMK, AW and DN searched in the Scopus database and, using the same strategy of snowball search, they also identified the studies from the references of the eligible studies. Similar searchers using the aforementioned strategies were conducted by HMK and AW in the EMBASE, the Cochrane and the Willy libraries on July 10th, 11th and 12th 2021 respectively. Finally, we updated the database search on July 13th 2021 and the snowball using the same search strategy but narrowing the search to only 2010 onwards (Table 1).

2.3. Screening, data extraction and quality assessment

Two authors (HMK and AW) reviewed the tittles and the abstracts of the first 120 records out of the 420 records that deserved screening for

Table 1
Databases consulted. Date of the search and period covered.

Data base	Date the search was done	Period covered
PubMed	June 16-20th 2021	1998 to 2020
Google scholar	June 26-30th 2021	1998 to 2020
Scopus	July 7th 2021	1998 to 2020
Embase	July 10th 2021	1998 to 2020
Cochrane	July 11th 2021	1998 to 2020
Willey	July 12th 2021	1998 to 2020
All databases	July 13th 2021	2010 to 2020

tittle and abstract independently and discussed the inconsistencies which were resolved by a consensus. Any haunting disagreements were resolved by two additional authors (HS and PO) overruling. The remaining 300 records were distributed among three researchers (HK, PO and ND) and each reviewed 100 records autonomously. In case of any disagreements regarding which articles merited screening for full text review, a consensus was reached by discussion and consultations with the two authors (HMK and AW).

Three authors (HMK, AW, DN) independently reviewed the 275 records which qualified for full text review and discussed inconsistencies until agreement was obtained. For any incongruities, a fourth reviewer (HS) was consulted. Finally, the four reviewers settled at 47 records which were eligible for inclusion in the meta-analysis. From these, 20 records were excluded with reasons during data extraction leaving only 27 records for data synthesis. Three authors (HMK, AW and DN) extracted the data from the primary studies.

The following data were extracted; First author, year of publication, country, race of the study population, the number of the cases with chronic HBV infection, and the controls (health/resolved the infection). Three authors (HMK, DN and AW) extracted data independently in duplicate from the primary studies then compared their records and any differences were resolved by a consensus among all the authors. Further still, the genotypic frequencies of TNF-α-gene promoter polymorphisms in cases chronically infected with HBV and the health/resolved population-based controls were extracted. Finally, the Newcastle–Ottawa scale (NOS) was used to assess the quality of the eligible publications (Stang, 2010) and those with scores of 6, 7, 8 and 9 were considered publications of satisfactory quality. The three reviewers (HMK, AW and DN) independently assessed the articles for overall methodological quality. Data from the articles or their abstracts were entered into the spreadsheet on a daily basis by the three authors (HMK, AW and DN) who compared their separate records on a weekly basis to remove the duplicates.

2.4. Eligibility criteria

The Systematic review and meta-analysis included primary studies with full text articles that were case-control or cohort studies, investigated the association of the risk of infection with HBV/resolution of the infection with the five SNPs (−238G/A, −308G/A, -857C/T, -863C/A and -1031 T/C) in the TNF-α gene, with sufficient data to calculate odds ratio and relative proportion of genotypes and alleles among the cases and the controls, conducted among the Caucasoids and the Mongoloids published in peer-reviewed journals between the period of January 1st 1998 to December 31th 2020 in English language. Case reports, reviews, abstracts of conferences, studies that never used case-control or cohort study design, studies with insufficient or inaccessible data in the full text, pre-prints, studies that investigated other SNPs other than those of TNF-α, among Negros as well as those that were published before 1998 or after 2020, in languages other than English were excluded.

2.5. Statistical analysis

The Odds Ratios (OR) with the 95% Confidence Intervals (CIs) were used to assess the strength of association of the TNF-α gene promoter polymorphisms with either the risk of chronic hepatitis B virus infection or the resolution of the disease. The counts from the primary studies of the numbers of study subjects with the wildtype genotype, heterozygous mutation genotype and the homozygous mutation genotypes among the cases and the controls were done from which the genotype frequencies and allele frequencies of the dominant and the recessive alleles determined. The pooled ORs for the risk associated with the various genotypes and their alleles were compared between the cases and the controls. The sensitivity analysis was done through meta-regression of overall sample size, cases and controls and year of publication. Heterogeneity was evaluated by calculating the heterogeneity (I^2) statistic and a value of 50% was used as the cutoff. For those pooled studies with $I^2 \geq 50\%$, random-effects model (DerSimonian and Laird method) was used to pool the proportions and the Odds Ratios among the cases and the controls. For those pooled studies with $I^2 < 50\%$, the fixed effect models (Mantel–Haenszel method) were used (Zintzaras, 2005). The significance of the pooled Odds Ratio was determined by the *Z*-test, and $p < 0.05$ was considered as statistically significant. An estimate of potential publication bias was carried out by funnel plot, in which the standard error of Odds Ratio of each study was plotted against its Odds Ratio. An asymmetric plot suggests a possible publication bias and was assessed by the method of Egger's and Begg's test (Egger et al., 1997; Begg, 1994). A $p < 0.05$ was considered representative of statistically significant publication bias. All analyses were performed by using the statistical software MedCalc version 20.010.

3. Results

3.1. Study selection

According to the PRISAM flow chat (Fig. 1), we initially obtained 3865 records through the primary database searching; 842 records from PubMed, 675 records from Scopus, 1528 records from Google Scholar, 142 from EMBASE, 112 from Cochrane library, 146 from Willey library. Of these, 420 records were screened for tittles and abstracts and 145 records were excluded for not being relevant to the Caucasoids and the Mongoloids leaving 275 articles for screening for the full-text review. From these, 228 articles were excluded because they analyzed the association between the risk of HBV infection/resolution of the infection with other cytokine gene promoter polymorphisms other than those of the TNF-α gene. Finally, 47 articles met the inclusion criteria from which the following studies were removed with reasons; 11 had inaccessible or insufficient data, 3 were not published in English language while 6 used participants from mixed races. In total, 27 studies (Kim et al., 2003; Heidari et al., 2016; Fletcher et al., 2011; Panigrahi et al., 2014; Hohler et al., 1998; Saxena and Kumar, 2014; Suneetha et al., 2013; Heidari et al., 2020; Azar et al., 2016; M. Somi, et al., "Tumor Necrosis Factor-alpha Gene Promoter Polymorphism in Iranian Patients With Chronic Hepatitis B," no. January, 2006; Ga et al., 2005; Rybicka et al., 2020; Sghaier et al., 2015; Börekçi et al., 2020; Basturk et al., 2008; Chen et al., 2010; Yang et al., 2012; Wang et al., 2010; Wang et al., 2012; Zhang et al., 2011; Du et al., 2006; Li et al., 2005; Li et al., 2006; Lu et al., 2004; Cheong et al., 2006; Jang et al., 2008; Kao et al., 2010; Kummee et al., 2007) with a total of 5847 cases and 5115 controls were included in our meta-analysis.

Of the 27 eligible studies included in our meta-analysis, 9(33.3%) were from China (Chen et al., 2010; Yang et al., 2012; Wang et al., 2010; Wang et al., 2012; Zhang et al., 2011; Du et al., 2006; Li et al., 2005; Li et al., 2006; Lu et al., 2004), 4(14.8%) from India (Fletcher et al., 2011; Panigrahi et al., 2014; Saxena and Kumar, 2014; Suneetha et al., 2013), 3(11.11%) from Iran (Heidari et al., 2016; Azar et al., 2016; M. Somi, et al., "Tumor Necrosis Factor-alpha Gene Promoter Polymorphism in Iranian Patients With Chronic Hepatitis B," no. January, 2006), 3 (11.11%) from Korea (Kim et al., 2003; Jang et al., 2008; Cheong et al., 2020) and 2 (7.4%) from Turkey (Börekçi et al., 2020; Basturk et al., 2008). The other contributing countries including German (Hohler

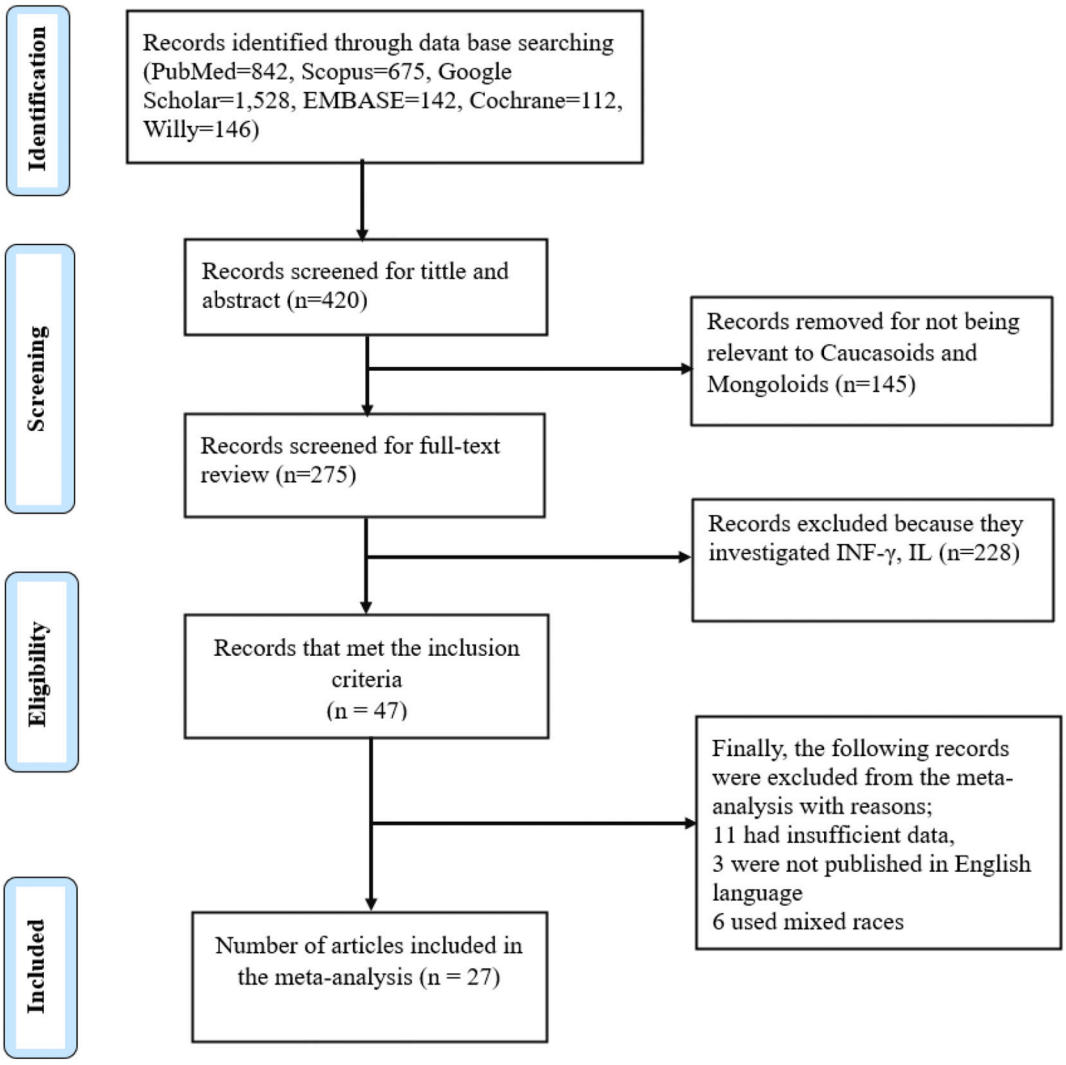

Fig. 1. The PRISMA flow chat summarizing the data base searched, screening procedure and the eligible studies for inclusion in data synthesis.

et al., 1998), Italy (Ga et al., 2005), Poland (Rybicka et al., 2020), Taiwan (Kao et al., 2010), Thailand (Kummee et al., 2007) and Tunisia (Sghaier et al., 2015) had 1(3.7%) record each (Fig. 2A). Overall, 14 (52%) records were retrieved for the Mongoloids and 13 (48%) for the Caucasoids. For the Caucasoids, the following records were included in the data synthesis; (Heidari et al., 2016; Fletcher et al., 2011; Panigrahi et al., 2014; Hohler et al., 1998; Saxena and Kumar, 2014; Suneetha et al., 2013; Azar et al., 2016; M. Somi, et al., "Tumor Necrosis Factor-

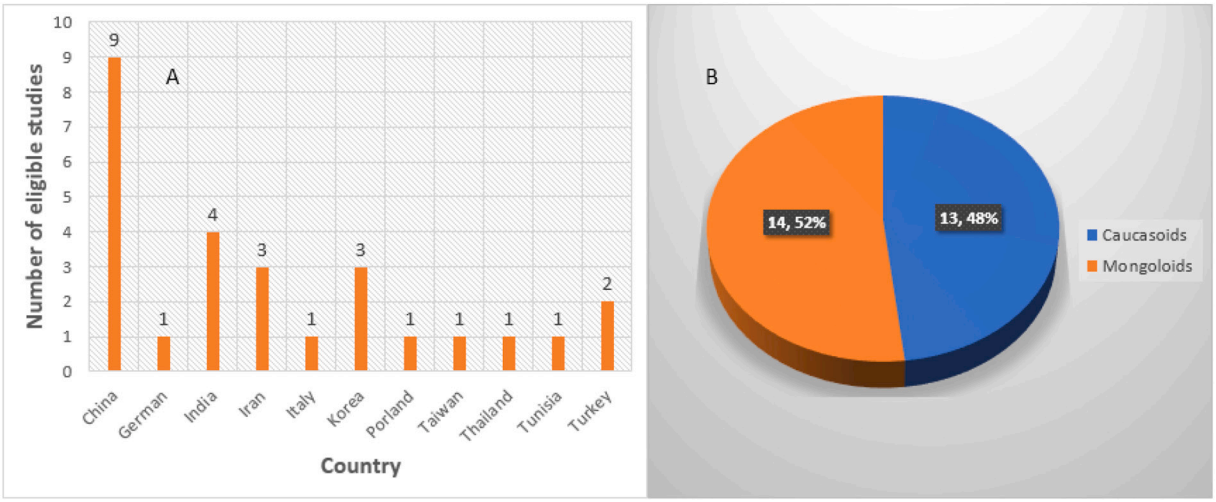

Fig. 2. Records eligible for inclusion in the systematic review and meta-analysis; A; – by country, B: - by race.

alpha Gene Promoter Polymorphism in Iranian Patients With Chronic Hepatitis B," no. January, 2006; Ga et al., 2005; Rybicka et al., 2020; Sghaier et al., 2015; Börekçi et al., 2020; Basturk et al., 2008) whereas for the Mongoloids, the records included were; (Kim et al., 2003; Zhang et al., 2013; Chen et al., 2010; Wang et al., 2010; Wang et al., 2012; Du et al., 2006; Li et al., 2005; Li et al., 2006; Lu et al., 2004; Cheong et al., 2006; Jang et al., 2008; Kao et al., 2010; Kummee et al., 2007) (Fig. 2B). Among the Caucasoids, 1918 were cases and 2082 were controls. In contrast, a total of 2929 cases and 3035 controls were obtained for the Mongoloids (Table 2).

Pertaining the number of cases and controls in the records included in the meta-analysis by country, China had the largest number of cases (1803) and controls (1953). This was followed by Korea with 1702 cases and 786 controls, Iran with 709 cases and 712 controls as well as India with 524 cases and 782 controls (Fig. 3).

The following data were extracted from each eligible record: single nucleotide polymorphism (SNP) investigated, the year of publication, country where the study was done, the race of the study participants, the definition of the cases/ control, the sample size of the cases/controls and the counts of the genotypes (wild type, mutant type or heterozygous). The results have been presented in Table 2.

Our results showed that the most characterized polymorphic sites within the promoter region of the tumor necrosis factor alpha gene as regards HBV risk to infection or resolution of the disease were 238G/A and 308G/A among both the Caucasoids and the Mongoloids. In contrast, the 1031 T/C, 857C/T and 863C/A single nucleotide polymorphisms were least studied for both races (Fig. 4).

3.2. Association of the TNF-α-238G/A polymorphism with the risk of HBV chronic disease or resolution of the infection

We included 15 records for the Mongoloids and 9 records for the Caucasoids in our meta-analysis of the association between the TNF-α-238G/A polymorphisms and clinical profile of HBV (Fig. 4). For most of the analyses, the heterogeneity remained high ($I^2 \geq 50\%$, $p < 0.05$) and hence the random effect model was used to pool the odds ratio. However, there was no heterogeneity for the analysis of the homozygous mutation TNF-α -238AA among both the Caucasoids ($I^2 = 0.00\%$, $p = 0.9829$) and the Mongoloids ($I^2 = 0.00\%$, $p = 0.9619$). Thus, the fixed effect model was used to pool the odds ratios. Regarding any sources of publication bias, both the Egger's and Begg's test found no evidence publication bias ($p > 0.05$). Our results showed that there was no significant association between the risk of infection with HBV or resolution of the infection with the genotypes and alleles of TNF-α-238G/A among both the Caucasoids and the Mongoloids ($p > 0.05$) (Table 3).

3.3. Association of the TNF-α-308G/A polymorphisms and the risk of chronic disease or resolution of the infection

Our analysis included 14 and 13 records for the Caucasoids and the Mongoloids respectively (Fig. 4). Similarly, the heterogeneity for both the TNF-α-308G/A genotypic and allelic models among the Caucasoids and the Mongoloids was high for most of the studies ($I^2 \geq 50\%$, $P < 0.05$). Consequently, a random effect model was adopted to pool the odds ratios. However, the heterogeneity was reduced for the wild type genotype TNF-α-308AA among the Mongoloids ($I^2 < 50\%, p > 0.05$) and the fixed effect model was instead used. Regarding the publication bias, both Egger's and Begg's test were used to assess the bias and, there was no any evidence of publication bias ($p > 0.05$). Our results indicated that both the genotypes and their alleles were not significantly associated with the HBV disease status and resolution among both the Caucasoids and the Mongoloids ($p > 0.05$) (Table 3).

Association of the TNF-α-857C/T polymorphisms and the risk of chronic disease or resolution of the infection.

We obtained 5 and 6 records for the Caucasoids and the Mongoloids respectively that merited inclusion in our meta-analysis analysis for the association of TNF-α-857C/T and HBV prognosis (Fig. 4). As with the aforementioned analyses, the heterogeneity remained high for TNF-α-857 CT and the allelic models TNF-α-857C and T among the Caucasoids ($I^2 \geq 50\%$, $p < 0.05$). Hence, the random effect model was used. However, the heterogeneity was reduced for TNF-α-857CC and TT ($I^2 < 50\%$, $p > 0.05$) and the fixed effects model was used to pool the odds ratio. Similarly, for the analysis among the Mongoloids, the heterogeneity remained high for most of the analyses ($I^2 \geq 50\%$, $p < 0.05$) and the random effect model was used to pool the odds ratios but it vanished for TNF-α-857TT ($I^2 = 0.00\%$, $p = 0.5912$) and its allele T ($I^2 = 0.00\%$, $p = 0.6309$). Hence, the fixed effect model was used to pool the odds of association of both the genotype and the allele with the HBV prognosis (Table 3).

A significant association was observed between the TNF-α-857 homozygous mutation TT and its allele T with the reduced risk or resolution of the disease among both the Caucasoids and the Mongoloids ($p < 0.05$, OR < 1) (Table 3, Figs. 5 and 6).

In contrast, the wild type genotype TNF-α-857CC, was significantly associated with increased risk of HBV infection and chronic development of the disease among the Caucasoids ($p = 0.03$, OR = 1.363, 95% CI = [1.03 to 1.804]) (Table 3, Fig. 7).

We also evaluated the likelihood of publication bias for the primary studies that investigated the association of the TNF-α-857C/T polymorphisms and disease prognosis among the Caucasoids and the Mongoloids using the Egger's and Begg's tests. There was no evidence of significant publication bias ($p > 0.05$). Similarly, the funnel plot, in which the standard error of odds ratio of each study was plotted against its odds ratio displayed a symmetrical spread of the plots suggesting little or no evidence of publication bias (Fig. 8).

3.4. Association of the TNF-α-863C/A polymorphisms and the risk of chronic disease or resolution of the infection

We further investigated TNF-α-863C/A and its association with the risk/resolution of HBV infection. Six studies had sufficient data for inclusion in the meta-analysis for each of the Caucasoids and the Mongoloids (Fig. 4). For all the included studies that were used to pool the odds ratio, the heterogeneity was high ($I^2 > 50\%$, $p < 0.05$) and hence the random effect model was used. However, it was reduced for the homozygous mutation TNF-α-863AA ($I^2 < 50\%$, $p > 0.05$) among the Caucasoids and the fixed effect model was used to pool the odds ratio (Table 3).

Our data synthesis established a statistically significant association of the TNF-α-863 homozygous mutation AA; $p < 0.001$, OR = 4.354, 95%CI = [2.45 to 7.735%] or its allele A; $p = 0.025$, OR = 1.464, 95%CI = [1.049 to 2.044%] with increased risk of the HBV infection or reduced chances of resolution of the infection among the Caucasoids (Table 3, Fig. 9). No significant association was observed between the TNF-α-863C/A genotypes and alleles with the HBV prognosis ($p > 0.05$). Again, for all the six studies for the Caucasoids included in our meta-analysis, there was no evidence of significant publication bias by both Egger's and Begg's tests ($p > 0.05$) (Table 3). This was in conformity with the symmetrical spread of studies from the funnel plot of the standard error of odds ratio against its odds ratio (Fig. 10). In contrast, bias was only detected among studies that investigated TNF-α-863C allele among the Mongoloids by Egger's test but not Begg's test (Table 3).

3.5. Association of the TNF-α-1031 T/C polymorphisms and the risk of chronic disease or resolution of the infection

We retrieved 4 studies for the Caucasoids and 3 studies for the Mongoloids that investigated the SNPs in the TNF-α-1031 T/C promoter gene with the risk of HBV infection or resolution of the infection. Because there was no heterogeneity ($I^2 = 0.00\%$, $p > 0.05$) for studies that pooled odds of association of the TNF-α-1031 T/C genotypes and allele with the risk/resolution of the infection among the Caucasoids, the

Table 2
The characteristics of eligible studies included in the meta-analysis.

First author, year	Country	Race	Case/Control	Sample size	Genotypes (wtwt/wtmt/mtmt)		NOS
				Case/control	Cases	Controls	
rs361525 TNF-α; Promoter -238A/G							
Woziwodzka, 2019 (Woziwodzka et al., 2019)	Poland	Caucasoid	CHB/Health	231/100	212/19/0	95/5/0	8
Sghaier, 2015 (Sghaier et al., 2015)	Tunisia	Caucasoid	CHB/Health	49/200	12/25.0/12	62/93/45	7
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Resolved	100/40	95/3/2	37/2/1	7
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Health	100/100	95/3/2	92/5/3	7
Niro, 2005 (Ga et al., 2005)	Italy	Caucasoid	CHB/Resolved	184/96	161/22/1	88/8/0	7
Hohler, 1998 (Hohler et al., 1998)	German	Caucasoid	CHB/Health	71/99	53/17/1	92/7/0	8
Hohler, 1998 (Hohler et al., 1998)	German	Caucasoid	CHB/Resolved	71/32	53/17/1	30/1/1	8
Panigrahi, 2014 (Panigrahi et al., 2014)	India	Caucasoid	CHB/Health	110/85	98/8/4	58/24/3	9
Fletcher, 2011 (Fletcher et al., 2011)	India	Caucasoid	CHB/Resolved	137/150	108/26/3	122/25/3	8
Kao, 2010 (Kao et al., 2010)	Taiwan	Mongoloid	CHB/Resolved	274/194	268/6/0	187/7/0	7
Kummee,2007 (Kummee et al., 2007)	Thailand	Mongoloid	CHB/Resolved	150/100	140/9/1	92/7/1	7
Kummee, 2007 (Kummee et al., 2007)	Thailand	Mongoloid	CHB/Health	150/150	140/9/1	140/10/0	7
Kim, 2003 (Kim et al., 2003)	Korea	Mongoloid	CHB/Resolved	1109/291	915/115/10	261/22/2	6
Cheong, 2006 (Cheong et al., 2006)	Korea	Mongoloid	CHB/Resolved	412/294	385/27/0	182/22/0	7
Jang, 2008 (Jang et al., 2008)	Korea	Mongoloid	CHB/Health	181/170	168/12/1	155/15/0	8
Jang, 2008 (Jang et al., 2008)	Korea	Mongoloid	CHB/Resolved	181/201	168/12/1	179/22/0	8
Lu, 2004 (Lu et al., 2004)	China	Mongoloid	CHB/Resolved	207/148	203/4/0	138/10/0	8
Li, 2006 (Li et al., 2006)	China	Mongoloid	CHB/Health	62/63	52/10/0	42/21/0	8
Du, 2006 (Du et al., 2006)	China	Mongoloid	CHB/Resolved	196/143	194/2/0	133/10/0	9
Li, 2005 (Li et al., 2005)	China	Mongoloid	CHB/Resolved	433/244	402/41/0	232/12/0	8
Zhang, 2011 (Zhang et al., 2011)	China	Mongoloid	CHB/Health	298/280	180/17/1	255/25/0	9
Wang, 2012 (Wang et al., 2012)	China	Mongoloid	CHB/Health	123/525	116/7/0	467/52/6	9
Chen, 2010 (Chen et al., 2010)	China	Mongoloid	CHB/Resolved	304/361	285/18/1	340/20/1	8
Wang, 2010 (Wang et al., 2010)	China	Mongoloid	CHB/Resolved	80/96	68/11/1	83/13/0	7
rs1800629 TNF-α; Promoter-308A/G							
Woziwodzka, 2019 (Woziwodzka et al., 2019)	Poland	Caucasoid	CHB/Health	231/100	165/63/3	73/26/1	8
Sghaier, 2015 (Sghaier et al., 2015)	Tunisia	Caucasoid	CHB/Health	49/200	13/25/11	80/72/48	7
Somi, 2014 (M. Somi, et al., "Tumor Necrosis Factor-alpha Gene Promoter Polymorphism in Iranian Patients With Chronic Hepatitis B," no. January, 2006)	Iran	Caucasoid	CHB/Health	100/89	78/20/2	75/13/1	7
Somi, 2014 (M. Somi, et al., "Tumor Necrosis Factor-alpha Gene Promoter Polymorphism in Iranian Patients With Chronic Hepatitis B," no. January, 2006)	Iran	Caucasoid	CHB/Resolved	100/91	78/20/2	70/20/1	7
Azar, 2016 (Azar et al., 2016)	Iran	Caucasoid	CHB/Health	409/483	114/215/80	228/233/22	8
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Resolved	100/40	92/6/2	25/10/5	7
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Health	100/100	92/6/2	64/29/7	7
Niro, 2005 (Ga et al., 2005)	Italy	Caucasoid	CHB/Resolved	184/96	154/28/2	75/21/0	7
Basturk, 2007 (Basturk et al., 2008)	Turkey	Caucasoid	CHB/Health	50/60	45/5/0	39/17/4	7
Hohler, 1998 (Hohler et al., 1998)	German	Caucasoid	CHB/Health	71/99	47/21/3	73/20/6	8
Hohler, 1998 (Hohler et al., 1998)	German	Caucasoid	CHB/Resolved	71/32	47/21/3	22/10/0	8
Suneetha, 2006 (Suneetha et al., 2013)	India	Caucasoid	CHB/Health	214/408	148/65/1	270/136/2	6
Fletcher, 2011 (Fletcher et al., 2011)	India	Caucasoid	CHB/Resolved	137/150	129/8/0	132/18/0	8
Saxena, 2014 (Saxena and Kumar, 2014)	India	Caucasoid	CHB/Health	63/139	56/7/0	128/11/0	8
Kao, 2010 (Kao et al., 2010)	Taiwan	Mongoloid	Chronic/Recovered	274/194	221/38/15	154/39/1	7
Kummee, 2007 (Kummee et al., 2007)	Thailand	Mongoloid	CHB/Resolved	150/100	128/22/0	82/18/0	7
Kummee, 2007 (Kummee et al., 2007)	Thailand	Mongoloid	CHB/Health	150/150	128/22/0	123/26/1	7
Kim, 2003 (Kim et al., 2003)	Korea	Mongoloid	CHB/Resolved	1109/291	971/68/1	251/32/0	6
Cheong, 2006 (Cheong et al., 2006)	Korea	Mongoloid	CHB/Resolved	412/294	366/45/1	175/28/1	7
Jang, 2008 (Jang et al., 2008)	Korea	Mongoloid	CHB/Health	181/170		145/22/3	8

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Table 2 (*continued*)

First author, year	Country	Race	Case/Control	Sample size	Genotypes (wtwt/wtmt/mtmt)		NOS
				Case/control	Cases	Controls	
Jang, 2008 (Jang et al., 2008)	Korea	Mongoloid	CHB/Resolved	181/201	158/20/3	172/28/1	8
Li, 2006 (Li et al., 2006)	China	Mongoloid	CHB/Health	62/63	158/20/3	44/19/0	8
Du, 2006 (Du et al., 2006)	China	Mongoloid	CHB/Resolved	196/143	44/18/0	128/10/5	9
Zhang, 2011 (Zhang et al., 2011)	China	Mongoloid	CHB/Health	298/280	179/15/2	251/28/1	9
Wang, 2012 (Qiu, 2012)	China	Mongoloid	CHB/Health	123/525	179/19/0	460/57/8	9
Chen, 2010 (Chen et al., 2010)	China	Mongoloid	CHB/Resolved	304/361	102/19/2	323/36/2	8
Wang, 2010 (Wang et al., 2010)	China	Mongoloid	CHB/Resolved	202/62	250/51/4	58/4/0	7
rs1799724 TNF-α; Promoter-857C/T							
Woziwodzka, 2019 (Woziwodzka et al., 2019)	Poland	Caucasoid	CHB/Health	231/100	175/48/8	67/37/4	8
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Resolved	100/40	80/12/8	25/4/11	7
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Health	100/100	80/12/8	72/7/21	7
Panigrahi, 2014 (Panigrahi et al., 2014)	India	Caucasoid	CHB/Health	110/85	79/27/4	67/14/4	9
Fletcher, 2011 (Fletcher et al., 2011)	India	Caucasoid	CHB/Resolved	137/150	116/18/1	120/27/2	8
Kao, 2010 (Kao et al., 2010)	Taiwan	Mongoloid	Chronic/Recovered	274/194	142/51/1	204/67/3	7
Kim, 2003 (Kim et al., 2003)	Korea	Mongoloid	CHB/Resolved	1109/291	719/298/23	208/66/6	6
Du, 2006 (Du et al., 2006)	China	Mongoloid	CHB/Resolved	196/143	156/22/18	112/6/25	9
Qiu, 2012 (Qiu, 2012)	China	Mongoloid	CHB/Resolved	180/189	115/55/10	100/70/19	8
Li, 2005 (Li et al., 2005)	China	Mongoloid	CHB/Resolved	433/244	345/69/19	173/60/11	8
Chen, 2010 (Chen et al., 2010)	China	Mongoloid	CHB/Resolved	304/361	210/79/15	234/105/22	8
rs1800630 TNF-α; Promoter-863A/C							
Woziwodzka, 2019 (Woziwodzka et al., 2019)	Poland	Caucasoid	chb/health	231/100	167/45/17	81/15/3	8
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Resolved	100/40	44/44/12	26/13/1	7
Heidari, 2016 (Heidari et al., 2016)	Iran	Caucasoid	CHB/Health	100/100	44/44/12	61/34/5	7
Niro, 2005 (Ga et al., 2005)	Italy	Caucasoid	CHB/Resolved	184/96	120/58/6	65/29/2	7
Panigrahi, 2014 (Panigrahi et al., 2014)	India	Caucasoid	CHB/Health	110/85	28/55/27	27/57/1	9
Fletcher, 2011 (Fletcher et al., 2011)	India	Caucasoid	CHB/Resolved	137/150	61/58/16	51/91/6	8
Kao, 2010 (Kao et al., 2010)	Taiwan	Mongoloid	CHB/Resolved	274/194	107/65/22	120/125/29	7
Kummee, 2007 (Kummee et al., 2007)	Thailand	Mongoloid	CHB/Resolved	150/100	85/58/7	70/28/2	7
Kummee, 2007 (Kummee et al., 2007)	Thailand	Mongoloid	CHB/Health	150/150	85/58/7	111/34/5	7
Kim, 2003 (Kim et al., 2003)	Korea	Mongoloid	CHB/Resolved	1109/291	684/317/37	209/65/5	6
Du, 2006 (Du et al., 2006)	China	Mongoloid	CHB/Resolved	196/143	122/50/24	93/23/27	9
Qiu, 2012 (Qiu, 2012)	China	Mongoloid	CHB/Resolved	180/189	111/55/14	137/48/4	8
Chen, 2010 (Chen et al., 2010)	China	Mongoloid	CHB/Resolved	304/361	192/92/20	220/116/25	8
rs1799964 TNF-α; Promoter-1031C/T							
Woziwodzka, 2019 (Woziwodzka et al., 2019)	Poland	Caucasoid	CHB/Health	231/100	148/74/9	76/23/1	8
Niro, 2005 (Ga et al., 2005)	Italy	Caucasoid	CHB/Resolved	184/96	107/64/13	59/34/3	7
Börekçi, 2020 (Börekçi et al., 2020)	Turkey	Caucasoid	CHB/Health	100/100	49/47/4	60/34/6	8
Fletcher et al., 2011	India	Caucasoid	CHB/Resolved	137/150	38/69/28	64/61/22	8
Kao, 2010 (Kao et al., 2010)	Taiwan	Mongoloid	Chronic/Recovered	274/194	128/60/6	184/75/15	7

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Table 2 (*continued*)

First author, year	Country	Race	Case/Control	Sample size	Genotypes (wtwt/ wtmt/mtmt)		NOS
				Case/ control	Cases	Controls	
Kim, 2003 (Kim et al., 2003)	Korea	Mongoloid	CHB/Resolved	1109/291	655/ 331/52	196/82/9	6
Du, 2006 (Du et al., 2006)	China	Mongoloid	CHB/Resolved	196/143	110/75/ 11	74/57/12	9

CHB: Chronic Hepatitis B, TNF-α: Tumor Necrosis Factor alpha, NOS: New Castle Ottawa Scale, wtwt: wild type-wildtype genotype, wtmt: wild type mutant type genotype, mtmt: mutant type, mutant type genotype.

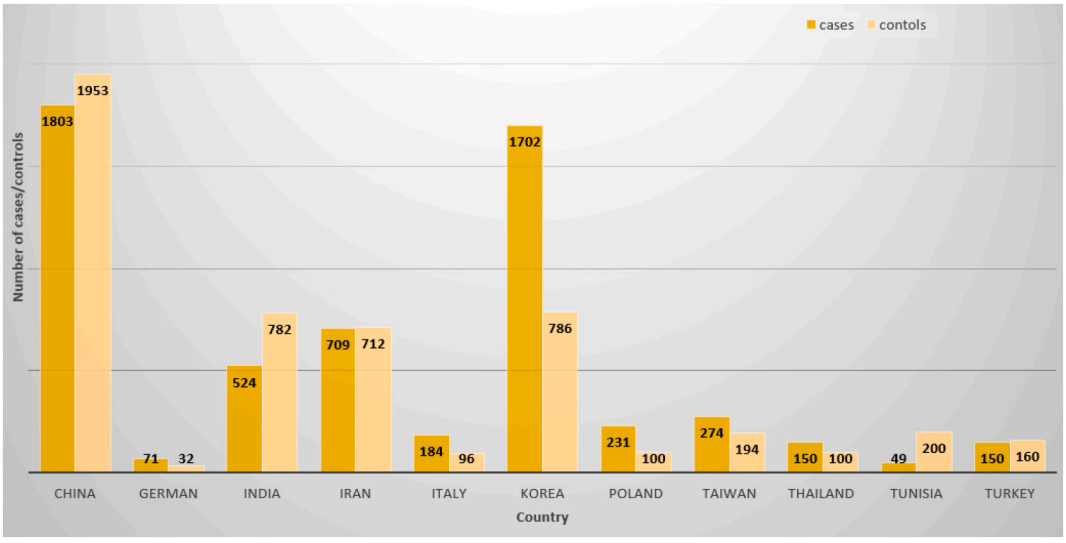

Fig. 3. Number of cases and controls in the records used for data-synthesis by country.

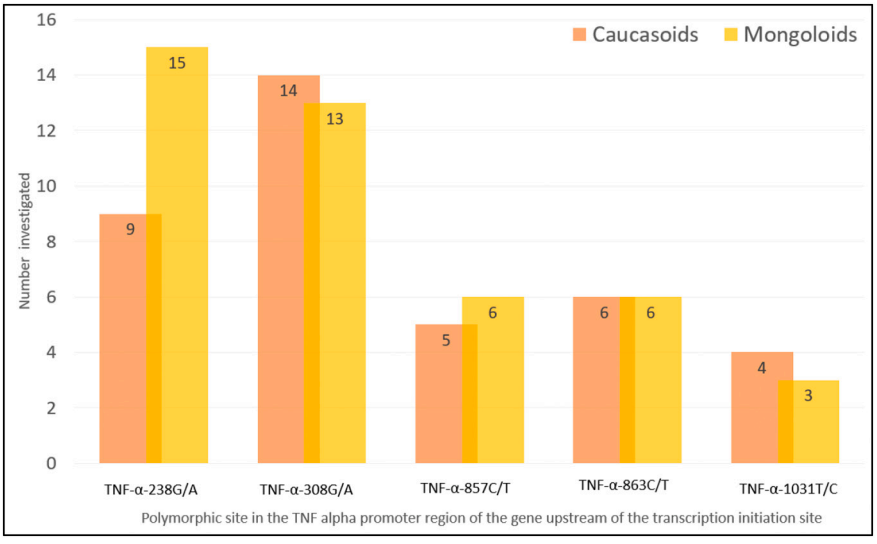

Fig. 4. Number of studies included in the meta-analysis on the risk of HBV infection/resolution of the disease for each of the TNF-α polymorphic site among the Caucasoids and the Mongoloids.

fixed effect model was used. However, for the studies that were used to pool the odds ratio among the Mongoloids, the heterogeneity remained high ($I^2 > 50\%$, $p < 0.05$) and the random effect model was used (Table 3).

Our results demonstrated that the TNF-α-1031 wild type genotypes TT; $p = 0.001$, OR = 0.634, 95%CI = [0.489 to 0.822%] and its allele T; p = 0.001, OR = 0.701, 95%CI = [0.571 to 0.860%] were significantly associated with reduced risk or resolution of the disease among the Caucasoids (Fig. 11).

In contrast, TNF-α-1031 heterozygous genotype TC; $p = 0.012$, OR = 1.395, 95%CI = [1.077 to 1.808%] and wild type allele C; $p < 0.001$, OR = 1.442, 95%CI = [1.174 to 1.770%] were significantly associated with

Table 3
Meta-analyses results of *TNF-α* gene polymorphisms and the risk of chronic infection/resolution of the infection.

			Statistical analysis		Heterogeneity analysis		Publication bias
Variable	No	Genotype/ Allele	*P* value	OR (95% CI)	I^2(95%)	P het	Egger's/Begg's P Value
TNF -α- genotype and allele frequency meta-analysis analysis among the Caucasoids for resolution/infection with HBV							
TNF-α-238G/A	9	GG	0.465	0.803(0.446 to 1.446)	72.95 (47.1 to 86.18)	0.0003**	0.5864/0.4042
	9	GA	0.569	1.199(0.643 to 2.237)	72.84 (46.8 to 86.13)	0.0003**	0.7578/0.5316
	9	AA	0.827	1.061(0.623 to 1.807)	0.00(0.00 to 0.00)	0.9829	0.9586/0.8046
	9	G	0.354	0.657(0.270 to 1.597)	95.1(86.13 to 94.8)	< 0.0001**	0.865/0.6767
	9	A	0.495	0.61(0.147 to 2.529)	97.04(95.78 to 97.93)	< 0.0001**	0.9562/0.8348
TNF-α-308G/A	14	GG	0.119	1.763(0.864 to 3.595)	95.34(93.57 to 96.63)	< 0.0001**	0.2584/0.8695
	14	GA	0.667	0.926(0.652 to 1.314)	77.10(61.83 to 86.26)	< 0.0001**	0.551/0.0554
	14	AA	0.711	1.154(0.541 to 2.464)	63.37(31.80 to 80.32)	0.0016**	0.1175/ 0.2365
	14	G	0.327	1.25(0.800 to 1.954)	90.42(85.70 to 93.58)	< 0.0001**	0.14/0.2983
	14	A	0.268	0.813(0.564 to 1.173)	85.37(77.01 to 90.69)	< 0.0001**	0.132/0.1711
TNF-α-857C/T	5	CC	0.03*	1.363(1.030 to 1.804)	37.23(0.00 to 76.62)	0.173	0.8388/ 1.0000
	5	CT	0.862	0.949(0.524 to 1.718)	67.23(15.04 to 87.36)	0.0159**	0.1397/0.3272
	5	TT	<0.001*	0.41(0.246 to 0.683)	0.00(0.00 to 79.18)	0.4393	0.3519/0.6242
	5	C	0.822	0.887(0.312 to 2.525)	95.12(26 to 97.27)	< 0.0001**	0.1751/0.3272
	5	T	0.045*	0.622(0.391 to 0.989)	72.79(31.81 to 89.14)	0.0054**	0.695/ 0.3272
TNF-α-863C/T	6	CC	0.135	0.741(0.500 to 1.098)	63.97(12.95 to 85.09)	0.0164**	0.0629/ 0.1885
	6	CA	0.814	0.946(0.597 to 1.500)	73.23(38.60 to 88.33)	0.0022**	0.168/ 0.1885
	6	AA	<0.001*	3.969(2.353 to 6.693)	17.83(0.00 to 62.63)	0.298	0.2775/0.5730
	6	C	0.554	0.848(0.491 to 1.463)	89.76(80.40 to 94.65)	< 0.0001**	0.2379/0.5730
	6	A	0.005*	1.541(1.137 to 2.088)	61.98(7.37 to 84.39)	0.022**	0.0955/0.1885
TNF-α-1031 T/C	4	TT	0.001*	0.634(0.489 to 0.822)	0.00(0.00 to 83.78)	0.496	0.9829/ 0.4969
	4	TC	0.012*	1.395 (1.077 to 1.808)	0.00(0.00 to 85.41)	0.4479	0.7437/0.1742
	4	CC	0.071	1.556(0.962 to 2.516)	0.00(0.00 to 86.83)	0.401	0.7571/ 0.4969
	4	T	0.001*	0.701(0.571 to 0.860)	0.00(0.00 to 74.52)	0.6776	0.9086/0.4969
	4	C	<0.001*	1.442(1.174 to 1.770)	0.00(0.00 to 76.52)	0.6481	0.8241/0.4969
TNF -α- genotype and allele frequency meta-analysis among the Mongoloids for resolution/infection with HBV							
TNF-α-238G/A	15	GG	0.337	1.381(0.714 to 2.670)	92.24(88.84 to 94.60)	< 0.0001**	0.3433/0.0260
	15	GA	0.064	0.838(0.695 to 1.010)	59.27(7.96 to 72.04)	0.0161**	0.146/0.200
	15	AA	0.397	1.419(0.632 to 3.186)	0.00(0.00 to 0.00)	0.9619	0.4364/0.218
	15	G	0.801	1.193(0.303 to 4.689)	98.55(98.21 to 98.83)	< 0.0001**	0.05/0.1250
	15	A	0.09	0.767(0.564 to 1.042)	60.27(30.06 to 77.43)	0.0014**	0.0112/0.0425
TNF-α-308G/A	13	GG	0.803	0.934(0.546 to 1.597)	91.94(88.03 to 94.58)	< 0.0001**	0.6592/0.7143
	13	GA	0.441	0.908(0.710 to 1.161)	53.63(13.11 to 75.26)	0.0112**	0.6890/0.2224
	13	AA	0.23	1.412(0.804 to 2.482)	14.02(0.00 to 55.31)	0.314	0.7323/0.4208
	13	G	0.89	0.953(0.481 to 1.886)	96.07(94.60 to 97.14)	< 0.0001**	0.7243/ 0.2224
	13	A	0.778	0.968(0.774 to 1.212)	53.96(13.80 to 75.41)	0.0105**	0.5104/0.3290
TNF-α-857C/T	6	CC	0.919	0.977(0.622 to 1.534)	89.06(78.81 to 94.35)	< 0.0001**	0.6139/ 0.5730
	6	CT	0.504	0.897(0.653 to 1.233)	71.41(33.62 to 87.68)	0.0037**	0.6193/ 0.8510
	6	TT	0.02*	0.682(0.493 to 0.951)	0.00(0.00 to 66.83)	0.5912	0.8041/0.5730
	6	C	0.361	0.741(0.390 to 1.409)	95.56(92.63 to 97.33)	< 0.0001**	0.5433/0.8510
	6	T	<0.001*	0.687(0.602 to 0.784)	0.00(0.00 to 64.29)	0.6309	0.245/0.3476
TNF-α-863C/A	6	CC	0.800	1.107(0.504 to 2.432)	94.72(90.98 to 96.91)	< 0.0001**	0.7178/0.5730
	6	CA	0.81	1.12(0.501 to 2.43)	95.01(91.0 to 97.01)	< 0.0001**	0.720/0.5710
	6	AA	0.554	1.229(0.621 to 2.431)	70.63(31.48 to 87.41)	0.0045**	0.231/0.1885
	6	C	0.557	1.41(0.45 to 4.496)	99.08(98.78 to 99.30)	< 0.0001**	0.002/0.0985
	6	A	0.101	1.7(0.902 to 3.204)	96.26(94.18 to 97.59)	< 0.0001**	0.9391/0.1765
TNF-α-1031 T/C	3	TT	0.159	0.352(0.0824 to 1.506)	97.04(94.04 to 98.52)	< 0.0001**	0.5182/0.6015
	3	TC	0.357	0.774(0.449 to 1.334)	84.21(52.75 to 94.72)	0.0018**	0.5879/0.6015
	3	CC	0.43	0.671(0.249 to 1.808)	76.05(21.29 to 92.71)	0.0154**	0.213/0.1172
	3	T	0.487	1.399(0.543 to 3.6)	96.03(91.49 to 98.15)	< 0.0001**	0.1600/0.1172
	3	C	0.522	0.9(0.653 to 1.242)	69.6(0.00 to 91.13)	0.0373**	0.1792/0.6015

increased risk of infection and progression to chronic disease in the same race (Fig. 12). Further still, no evidence of significant publication bias as shown by both the Egger's and Begg's test was revealed by the four eligible studies included in this analysis ($p > 0.05$). Moreover, the funnel plot of the standard error of odds ratio of each study against its odds ratio displayed a symmetrical spread of data confirming an insignificant evidence of publication bias (Fig. 13).

3.6. Meta-regression

We performed meta-regression analysis on the three continuous variables of overall sample size, number of cases and number of controls to assess how they varied with the year of publication. There was no statistical significance in either regression ($P > 0.05$) (Fig. 14), suggesting that the results are robust and the overall prevalence of the SNPs in the population is not directly influenced by the sample size or the year of publication.

4. Discussion

Over the years, studies have been conducted to investigate the effect of rs361525 TNF-α-238 G/A (Heidari et al., 2016; Fletcher et al., 2011; Hohler et al., 1998; Ga et al., 2005; Sghaier et al., 2015) and rs1800629 TNF-α-308G/A (Suneetha et al., 2013; Azar et al., 2016; M. Somi, et al., "Tumor Necrosis Factor-alpha Gene Promoter Polymorphism in Iranian Patients With Chronic Hepatitis B," no. January, 2006; Basturk et al., 2008; Cheong et al., 2020) single nucleotide polymorphisms on the risk of HBV infection and the clinical outcome of the disease. Unfortunately, the findings from many laboratories are inconclusive partly because of the limited sample sizes in these primary studies. Besides, there is a

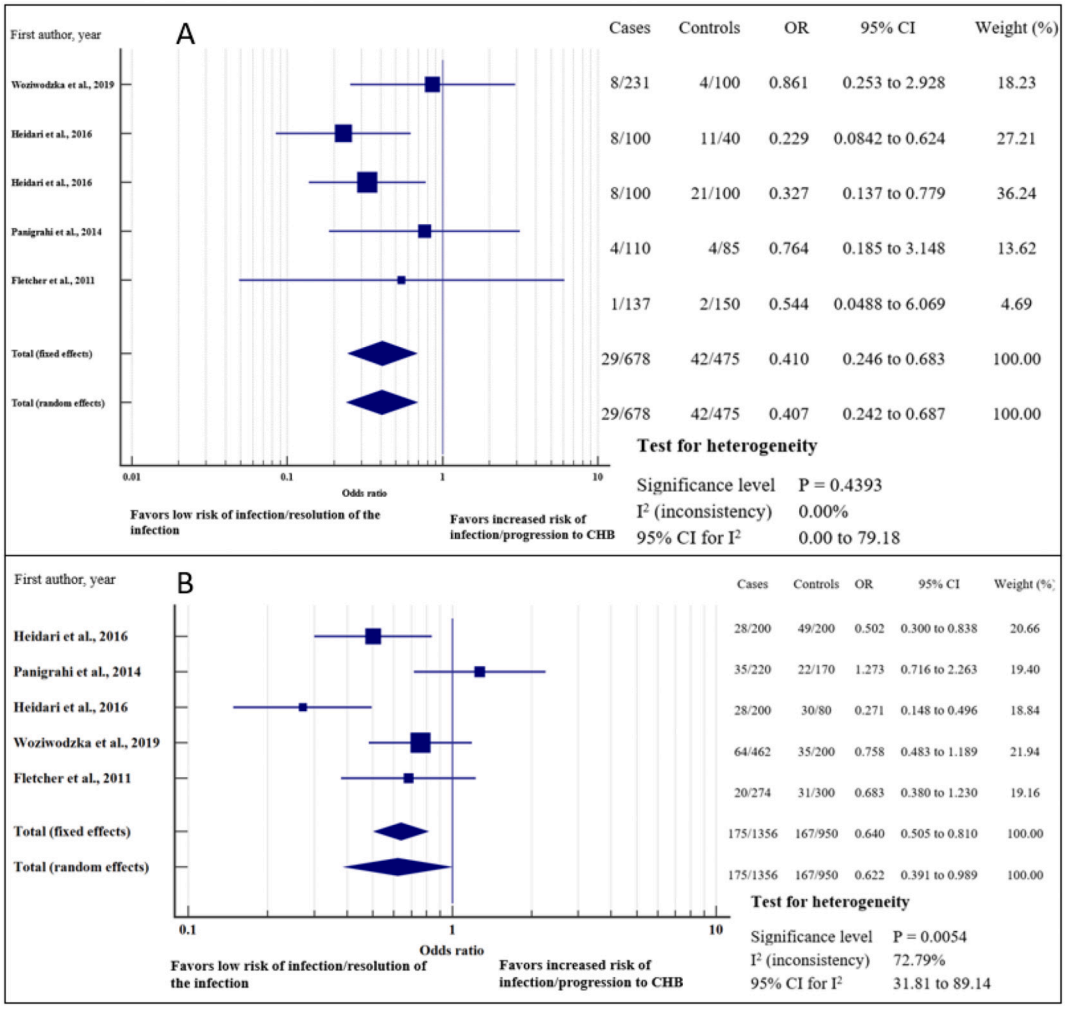

Fig. 5. A: - Genotypic model TT (Cases Vs Control) of SNP TNF-α 857C/T, B: - Allelic model; Wild type allele T (Cases Vs Control) of SNP TNF-α 857C/T on HBV reduced risk/resolution of the infection among Caucasoids. The association was indicated as odds ratio (OR) estimate with 95% CI. Odd. Ratio < 1 shows reduced risk of HBV infection and increased chances of HBV resolution among the health/resolved controls.

paucity of information on the relationship between TNF-α-857C/T (Heidari et al., 2016; Fletcher et al., 2011; Panigrahi et al., 2014), TNF-α-863A/C (Heidari et al., 2016; Fletcher et al., 2011; Panigrahi et al., 2014; Ga et al., 2005) and TNF-α-1031 T/C (Fletcher et al., 2011; Ga et al., 2005; Börekçi et al., 2020) single nucleotide polymorphisms and the risk of HBV infection/ resolution of the infection among specific races or ethnic groups. This meta-analysis has therefore given a comprehensive assessment of the association between the SNPs in the TNF-α gene and the risk of infection with HBV as well as resolution of the disease among Caucasoids. We pooled 4847 cases and 5117 controls to improve on the statistical power that usually limits the primary studies leading to biased findings.

No significant association between the TNF-α-238G/A polymorphism with the risk of HBV infection/resolution was observed in our study. However, Lu et al., (Lu et al., 2004) reported a higher frequency of TNF-α-238 allele G among the HBV chronically infected Mongoloids than among the self-limited suggesting that genotype GG could augment the risk of chronic HBV infection in this race. In contrast, Hohler et al., (Hohler et al., 1998) found a contradictory effect of genotype GG among the Caucasoids. The GG was more frequent in the controls than the chronically infected suggesting reduced risk of HBV infection/chronic disease consistent with the report from the meta-analysis by Xia et al., (Xia et al., 2011) among the European Caucasoids. The discrepancy observed in the results on the role of the TNF-α-238G/A polymorphism in the HBV disease profile in our meta-analysis and that of Xia et al., can largely be explained by the differences in the number of eligible studies included in each data synthesis. Xia et al., pooled the odds of association between TNF-α-238G/A with disease profile from only two studies (Hohler et al., 1998; Ga et al., 2005). Our meta-analysis pooled the odds ratio from nine studies for the Caucasoids and fifteen studies for the Mongoloids. Thus, the current study could have provided more robust and reliable results compared to the study by Xia and co-workers.

Likewise, no significant association between TNF-α-308G/A polymorphism with the risk of HBV infection/resolution was observed in our study in conformity with the findings from the meta-analyses of Zheng et al., (Zheng et al., 2010) and Mekinian et al., (Mekinian et al., 2011) among the Caucasoids and in the primary study of Jang et al., (Jang et al., 2008) among the Mongoloids. However, Basturk et al., (Basturk et al., 2008) reported a protective effect of TNF-α-308A allele (carries of GA and AA) against CHB among the Caucasoids. Similarly, the results from the meta-analysis by Zheng et al., (Zheng et al., 2010) reported TNF-α-308GA and AA genotypes to have a protective effect against chronic hepatitis B infection among the Mongoloids. In addition, findings from the primary studies by Xing et al., (Xing et al., 2007), Cheong et al., (Cheong et al., 2020), Kim et al., (Kim et al., 2003), Zhou et al., (Zhou et al., 2005) and Mao et al., (Mao et al., 2005) have reported a protective role of the TNF-α-308GA and AA genotypes among Mongoloids. On the contrary, Gusatti et al., (Gusatti, 2016) reported a moderately higher risk of development of chronic HBV among carriers of TNF-α-308A in Brazil most of whom were of European descent (Caucasoids).

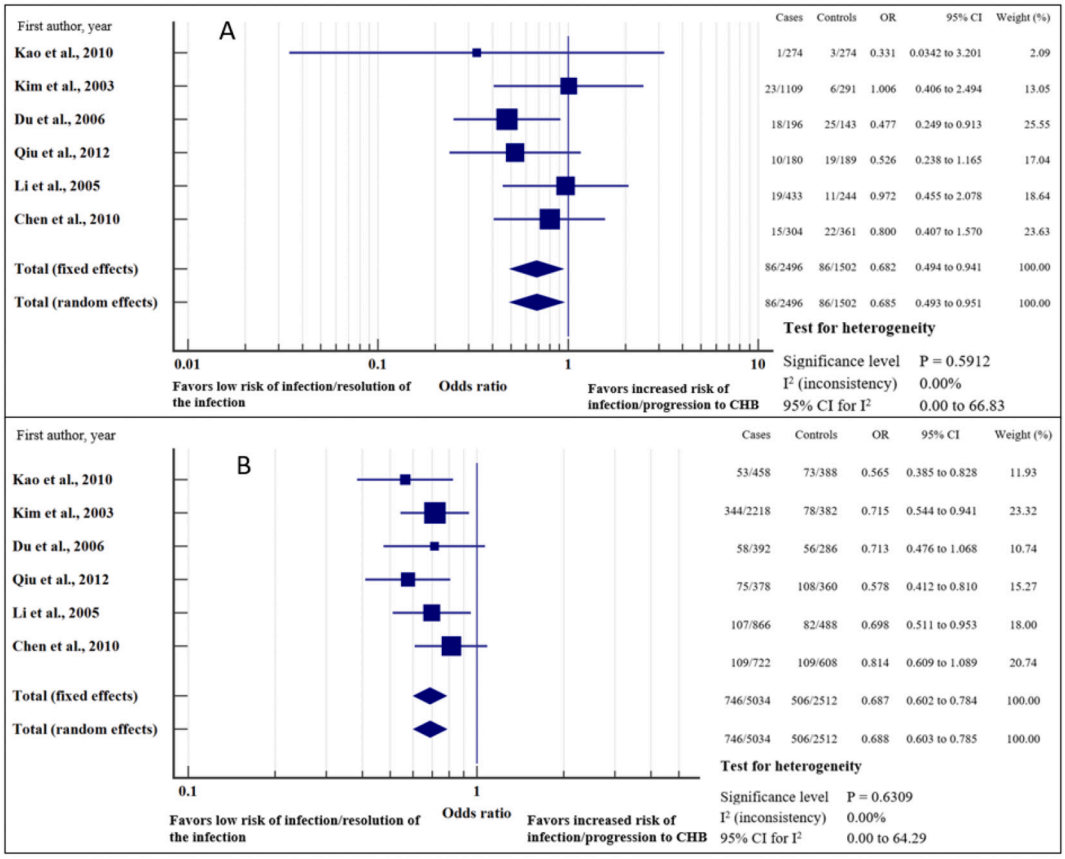

Fig. 6. A: - Genotypic model TT (Cases Vs Control) of SNP TNF-α 857C/T; B: - Allelic model; Wild type allele T (Cases Vs Control) of SNP TNF-α 857C/T on HBV reduced risk/resolution of the infection among Mongoloids. The association was indicated as odds ratio (OR) estimate with 95% CI. Odd. Ratio < 1 shows reduced risk of HBV infection and increased chances of HBV resolution among the health/resolved controls.

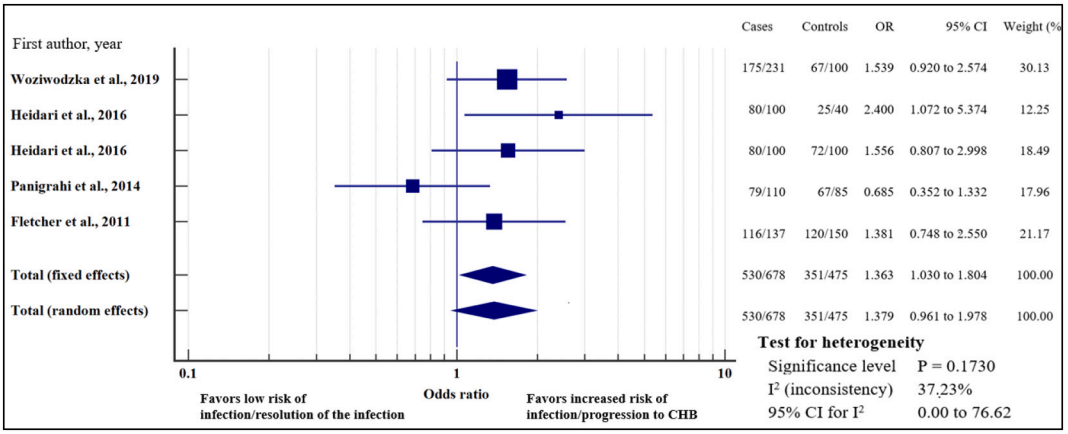

Fig. 7. Genotypic model CC (Cases Vs Control) of SNP TNF-α 857C/T on HBV reduced risk/resolution of the infection among the Caucasoids. The association was indicated as odds ratio (OR) estimate with 95% CI. Odd. Ratio < 1 shows reduced risk of HBV infection and increased chances of HBV resolution among the health/resolved controls.

The TNF-α-308G/A is associated with elevated production of TNF-α which is a focal mediator of the immune response and this effector mechanism seemingly appears to be more pronounced among the Mongoloids than the Caucasoids. However, this conclusion could be a working hypothesis but future research is needed for its validation because of the scanty data synthesis studies among the Caucasoids.

Overall, our results demonstrated that rs1799724 (TNF-α-857TT) homozygous mutation and its allele T were significantly associated with protection against HBV infection or resolution of the infection for both the Caucasoids and the Mongoloids. This result is contrary to the findings from the meta-analysis by Xia et al., (Xia et al., 2011) who did not observe any association between the TNF-α-857TT genotype with the risk of HBV infection/resolution of the infection. This could be attributed to the differences in the ethnicity between the study subjects in their study and our study. Their study used mixed races (Caucasoids, Negros and Mongoloids) but the current study disaggregated the data by two races; the Caucasoids and the Mongoloids. Interestingly, only one primary study (Heidari et al., 2016) in our data synthesis was in

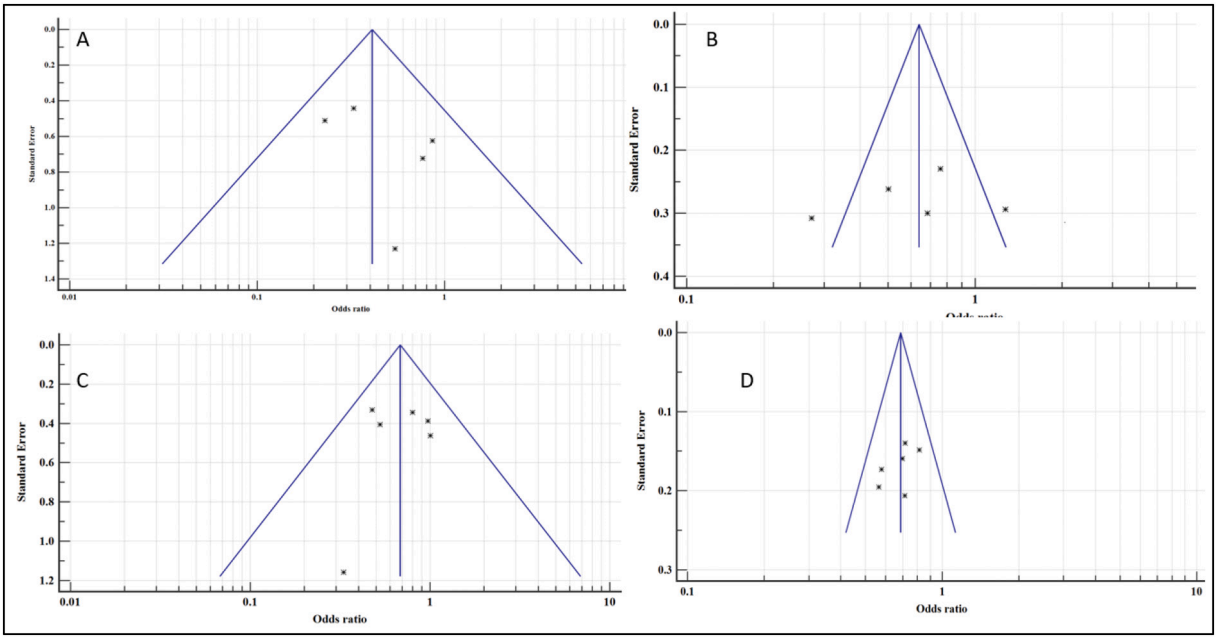

Fig. 8. Funnel plot to assess publication bias; A: - Genotypic model TT (Cases Vs Control) of SNP TNF-α 857C/T, B: - Allelic model; Wild type allele T (Cases Vs Control) of SNP TNF-α 857C/T for the Caucasoids, C: - Genotypic model TT (Cases Vs Control) of SNP TNF-α 857C/T; D: - Allelic model; Wild type allele T (Cases Vs Control) of SNP TNF-α 857C/T for the Mongoloids.

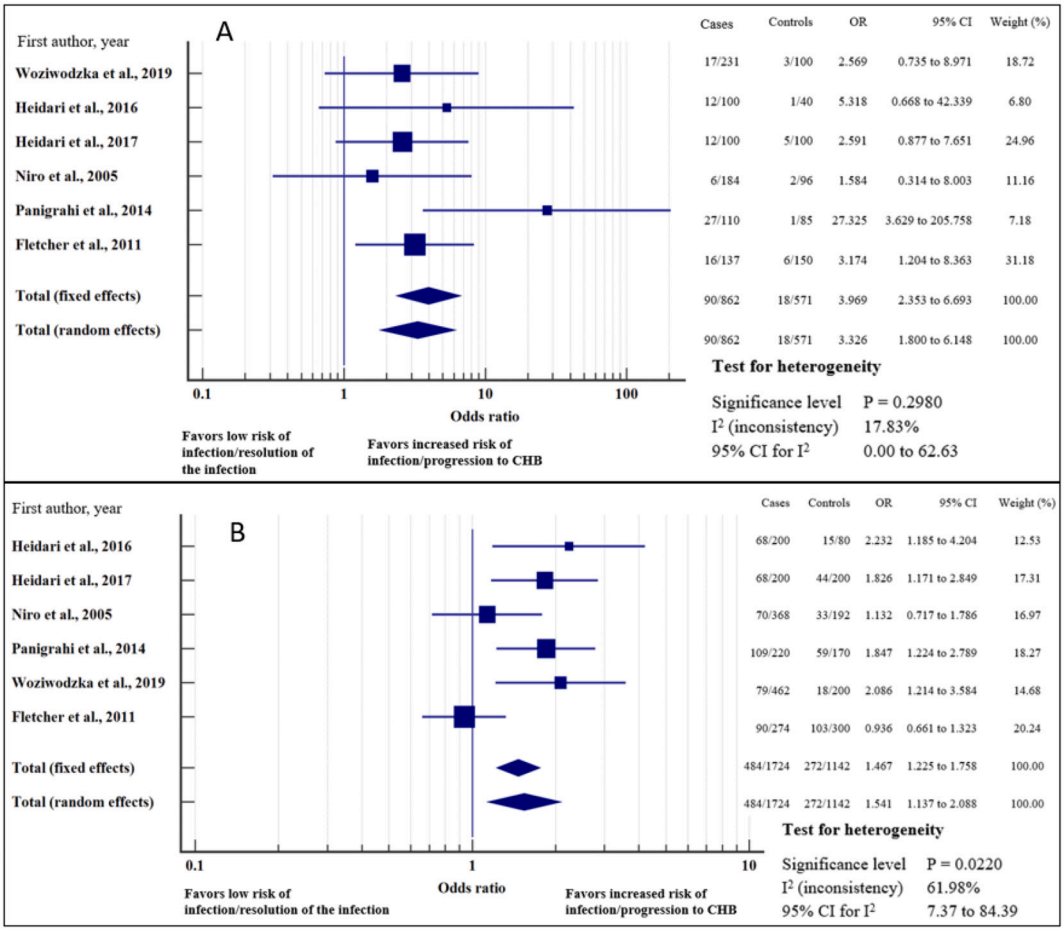

Fig. 9. A: Genotypic model AA (Cases Vs Control) of SNP TNF-α 863C/A; B: Allelic model; A allele (Cases Vs Control) of SNP TNF-α 863C/A on HBV increased risk/development of chronic infection among the Caucasoids. The association was indicated as odds ratio (OR) estimate with 95% CI. Odd. Ratio > 1 shows increased risk of HBV infection and reduced chances of HBV resolution following infection.

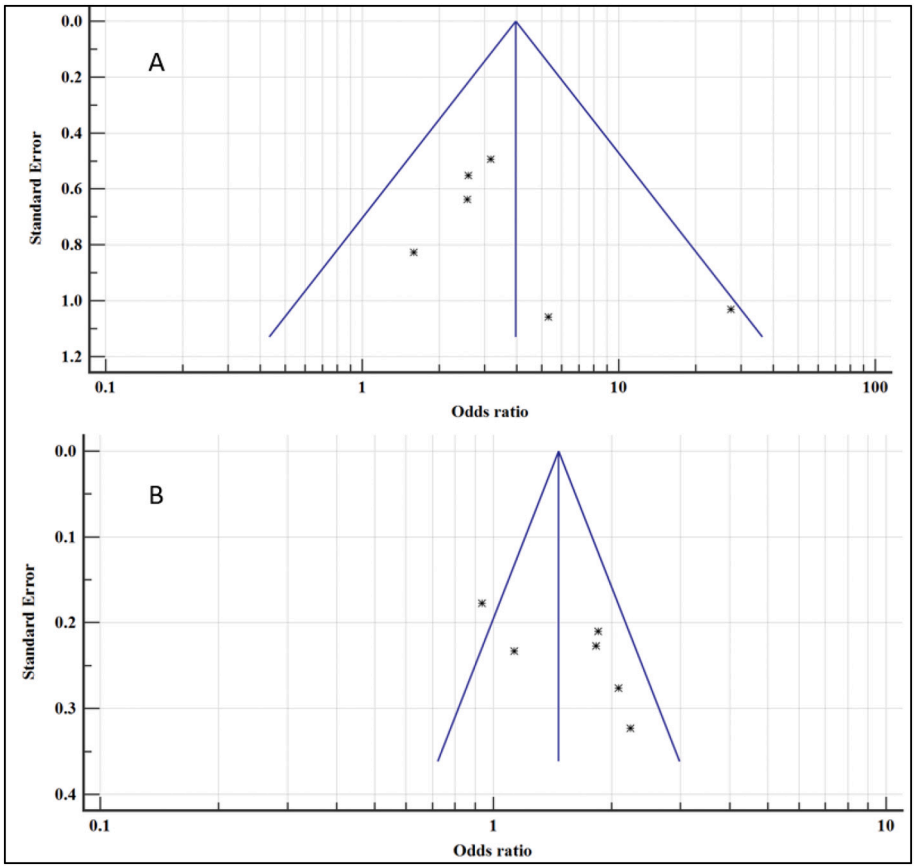

Fig. 10. Funnel plot to assess publication bias; A: - Genotypic model AA (Cases Vs Control) of SNP TNF-α 863C/A; B: - Allelic model; A allele (Cases Vs Control) of SNP TNF-α 863C/A among the Caucasoids.

conformity with this finding. Thus, individual studies which would otherwise lack statistical significance for a particular variable/intervention, when pooled together, the statistical power is raised to obtain statistically significant results. A similar association of the TNF-α-857 T allele with spontaneous clearance of the HBV infection has been prominent among the Mongoloids as reported in the meta-analyses by Zhang et al., (Zhang et al., 2013) and Shi et al., (Shi et al., 2012). Therefore, from our findings and from the earlier reports, similar disease profiles during the HBV infection are likely to manifest among both the Caucasoids and the Mongoloids though more laboratory-based studies are needed to justify this hypothesis using the Caucasoid subjects. On the other hand, the molecular basis for the interaction been TNF-α-857C/T SNPs has been explained by the Octamer transcription factor 1 (OCT1) binding to TNF-α-857 T but not TNF-α-857C and physiologically interacting with the NF-κB, which augments the TNF-α production (Zhang et al., 2013). However, this argument has been rejected by Mekinian et al., (Mekinian et al., 2011) who did not observe any association between the TNF-α mRNA transcript or protein expression levels and -857C/T polymorphisms in their meta-analysis. Therefore, future research should focus on the putative biochemical pathways that lead to different expression levels of the TNF-α-857C/T genes and their effects on the pathogenesis of HBV.

Regarding the TNF-α − 863C/A polymorphism and the prognosis of HBV among the Caucasoids and the Mongoloids, our meta-analysis reported interesting results. For the Caucasoids, the presence of the TNF-α-863 AA genotype and its allele A was significantly associated with unresolved HBV infection. In contrast, among the Mongoloids, there was no significant association between TNF-α-863C/A genotypes or their alleles with the HBV disease prognosis consistent with the results reported by Xia et al., (Xia et al., 2011) and Kao et al., (Kao et al., 2010). The role of the TNF-α − 863C/A gene polymorphisms in clinical out come during the HBV infection has been implicated on their potential to influence the expression levels in the TNF-α gene. The exact mechanism is not fully elucidated but Skoog et al., (Skoog et al., 1999) have implicated the TNF-α − 863C/A SNPs in influencing the binding of the nuclear proteins to the promoter region of the TNF-α gene. This ultimately affects gene expression causing variations in the plasma concentrations of the TNF-α. Besides, the race has also been highlighted as a confounder in the expression levels of the TNF-α gene with carriers of the A allele having significantly lower levels among the Caucasoid populations (Skoog et al., 1999; Ahmad et al., 2020) than among the Mongoloid populations (Higuchi et al., 1998; Soga et al., 2003). This therefore can provide a plausible explanation for the increased risk of HBV infection or reduced odds of resolution of the infection among the Caucasoid carries of the TNF-α-863AA genotype observed in our study but not the Mongoloids. Fortunately, the proportion of the TNF-α-863C/A single nucleotide polymorphisms has been reported to be low among the Caucasians than among the Mongoloids (Skoog et al., 1999; Higuchi et al., 1998; McGuire et al., 1994) and hence its role in the pathogenesis of HBV among the Caucasians may be limited.

Regarding the rs11799964 TNF-α-1031 T/C, the studies on the relationship between this polymorphism and the risk of HBV infection are still scanty in the databases. Accordingly, we pooled our odds ratio from only four studies among the Caucasoids and three studies among the Mongoloids. However, it has been associated with the risk of many diseases including polycystic ovary syndrome (Yun et al., 2011) and endometriosis (Abutorabi et al., 2015). Similarly, in the current study, the TNF-α-1031TT wild type genotype and its allele T were significantly associated with protection against the HBV infection or resolution of the infection among the Caucasoids. Besides, the TNF-α-1031TT has been associated with reduced odds of the clinical disease in the HEV infection as opposed to the TNF-α-1031CC among the Caucasoids (Mishra and

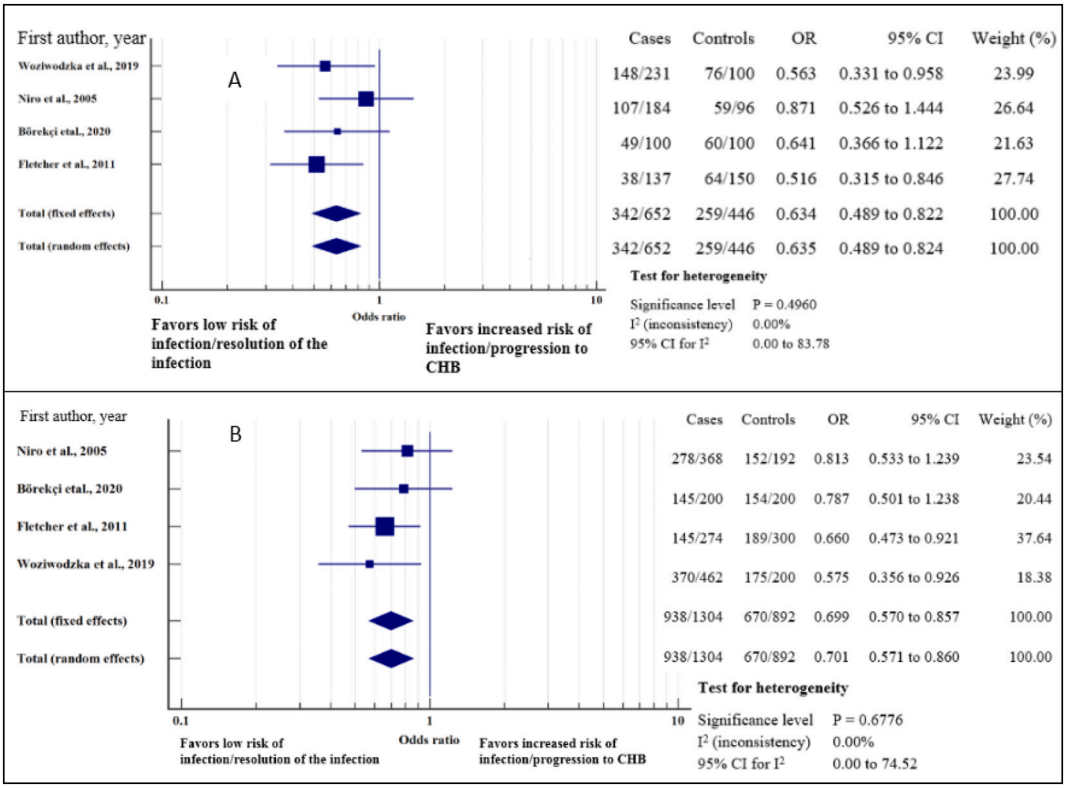

Fig. 11. A: -Genotypic model TT (Cases Vs Control) of SNP TNF-α-1031 T/C, B: - Allelic model; T allele (Cases Vs Control) of SNP TNF-α-1031 T/C on HBV reduced risk/resolution of the infection among Caucasoids. The association was indicated as odds ratio (OR) estimate with 95% CI. Odd. Ratio < 1 shows reduced risk of HBV infection and increased chances of HBV resolution among the health/resolved controls.

Vidya, 2011). On the other hand the findings from the meta-analysis of Xia et al., (Xia et al., 2011) did not observe any association between the TNF-α-1031TT genotype with the risk of HBV infection/resolution of the infection probably because they pooled studies from mixed races. However, as aforesaid, our understanding of the effect of the TNF-α-1031 T/C on the clinical profile during the HBV infection is still limited due to the inadequate peer reviewed published data on its effect on the resolution, risk of infection or progression to chronic disease during exposure to HBV by both the Caucasoids and the Mongoloids.

Finally, the following points regarding the role of the TNF-α in line with our findings should be noted. Firstly, the expression of TNF-α gene is tightly regulated at the transcriptional and post-transcriptional level (Kim et al., 2003) and any polymorphisms in the promoter region will alter the expression levels. Moreover, the polymorphisms are driven by the Darwinian natural selection under the influence of the different selection pressures imposed upon the individuals of the different races in their respective environments. Secondly, TNF-α participates in the HBV viral clearance by inhibiting transcription activity of hepatitis B virus core promoter (Skoog et al., 1999). Thus, this effector mechanism is liable to alterations depending on the polymorphisms in the promoter region of the gene. None the less, future laboratory-based studies to establish the putative immunological and molecular mechanisms behind the observed association of the various genotypes in the various polymorphic sites with the promoter region of the TNF-α gene observed in this meta-analysis are warranted. Thirdly, we wanted to study the association of several polymorphisms in the TNF-α gene (−163G/A, −238G/A, −244A/G, −308G/A, −376G/A, −575A/G, -857C/T, -863C/A, −1031 T/C, −1125G/C, and -1196C/T) with a wide range of clinical outcomes in HBV infection including hepatocellular carcinoma, liver cirrhosis, decompensation and fibrosis among the Caucasoids. However, our literature search could not disclose adequate eligible studies to justify our analysis, so we only assessed the association of five polymorphic sites (TNF-α-238G/A, −308G/A, -857C/T, -863C/A and -1031 T/C) with the risk of infection, protection against infection and resolution of the disease.

5. Conclusion

In conclusion, this meta-analysis has established the association between SNPs TNF-α − 238 G/A, − 308 G/A, − 857C/T, − 863C/A, − 1031 T/C and the risk of infection with HBV or resolution of the disease among the Caucasoids and the Mongoloids. The effects of the SNPs in the TNF-α − 238 G/A, − 308 G/A, and − 857C/T on the relative risk to the infection or resolution of the infection did not vary between the Caucasoids and the Mongoloids. Therefore, potential divergence during HBV prognosis between the two races appears to emanate from the TNF-α − 863C/A, and − 1031 T/C polymorphisms. Consequently, the novel findings from our meta-analysis are two. First, the significant association of the TNF-α − 863C/A recessive mutation AA or its allele A and the TNF-α − 1031 T/C heterozygous mutation CT or allele C and infection with unresolved HBV infection among the Caucasoids but not the Mongoloids. Second, the significant association of the TNF-α − 1031 T/C wild type genotype TT or its allele T reduced risk and resolution of the infection among the Caucasoids but not the Mongoloids. Therefore, at TNF-α- gene level and HBV disease profile, Mongoloid and Caucasoids appear to present alike for the following loci; TNF-α − 238 G/A, − 308 G/A and − 857C/T and hence, similar genotypes are implicated in the pathogenesis of HBV among both races. However, they appear to differ at the TNF-α − 863C/A and − 1031 T/C gene loci in the pathogenesis of HBV.

Finally, future laboratory based large scale studies are needed to verify our findings and critically analyze the role of these SNPs in the prognosis of HBV and the risk of infection among the Negros's. The key limitation of our study was the few published work on the aforementioned SNPs in the data base which could have limited our comprehensive assessment of their role in HBV disease profile.

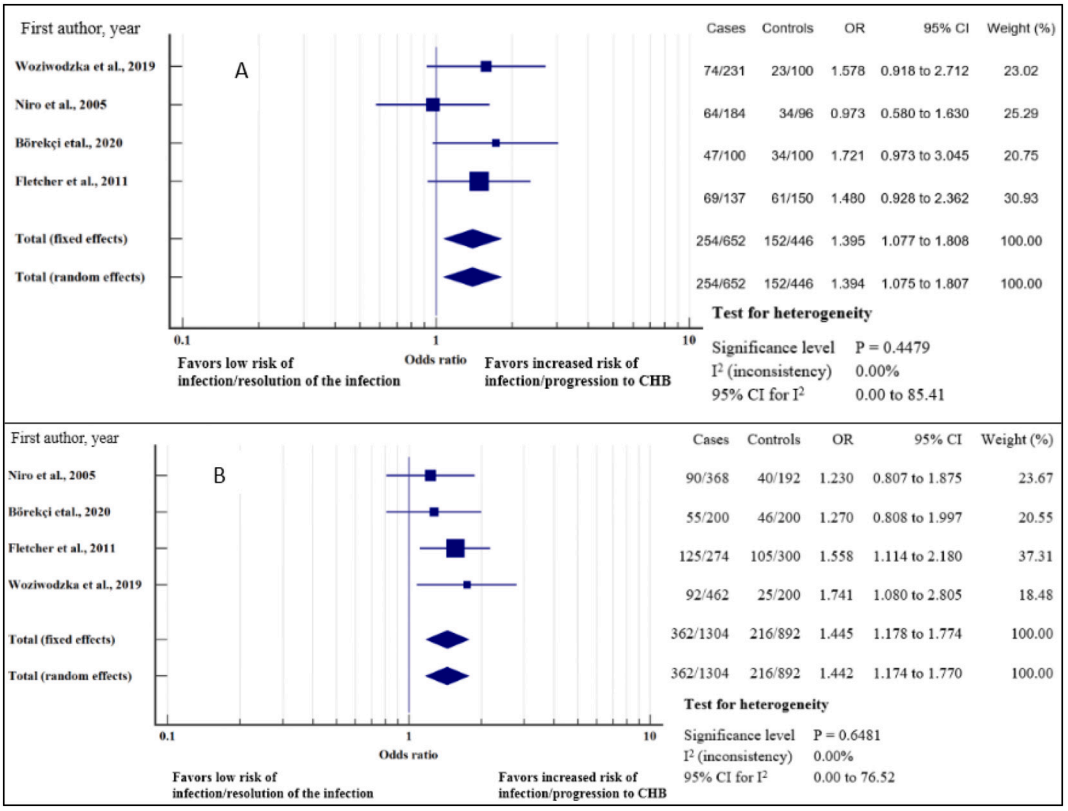

Fig. 12. A: -Genotypic model TC (Cases Vs Control) of SNP TNF-α-1031 T/C, B: - Allelic model; C allele (Cases Vs Control) of SNP TNF-α-1031 T/C on HBV reduced risk/resolution of the infection among Caucasoids. The association was indicated as odds ratio (OR) estimate with 95% CI. Odd. Ratio < 1 shows reduced risk of HBV infection and increased chances of HBV resolution among the health/resolved controls.

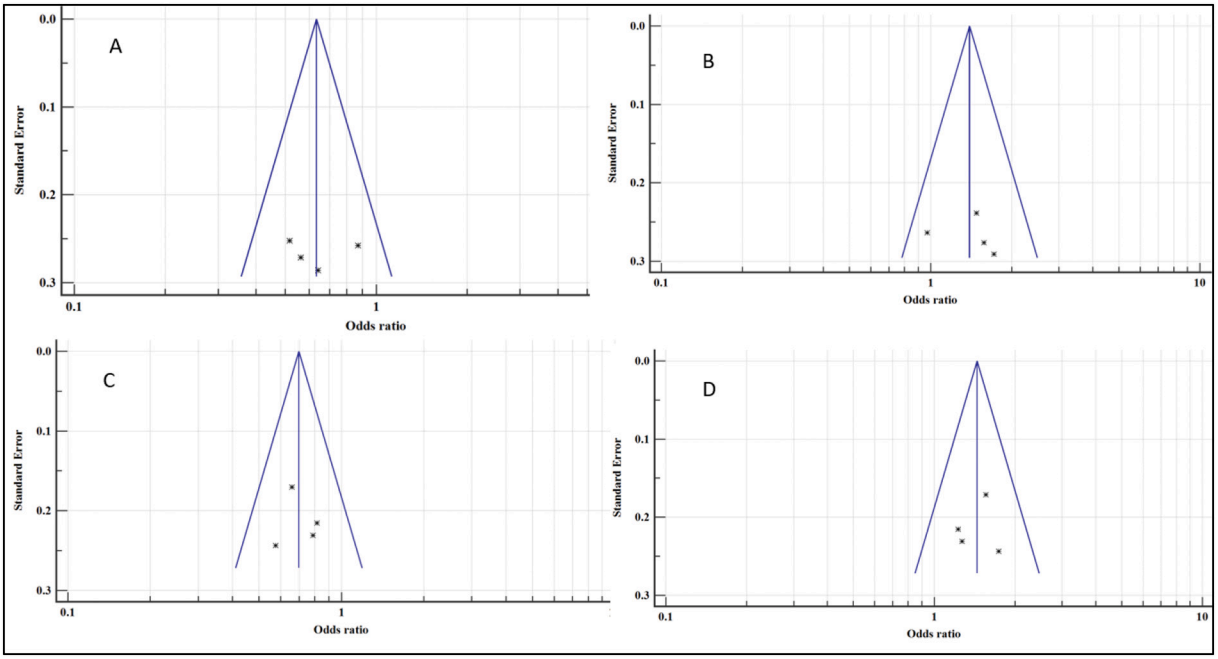

Fig. 13. Funnel plot to assess publication bias; A: - Genotypic model TT (Cases Vs Control) of SNP TNF-α-1031 T/C, B: - Allelic model; wild type allele T (Cases Vs Control), C: - Genotypic model TC (Cases Vs Control), D: - Allelic model; mutant allele C (Cases Vs Control).

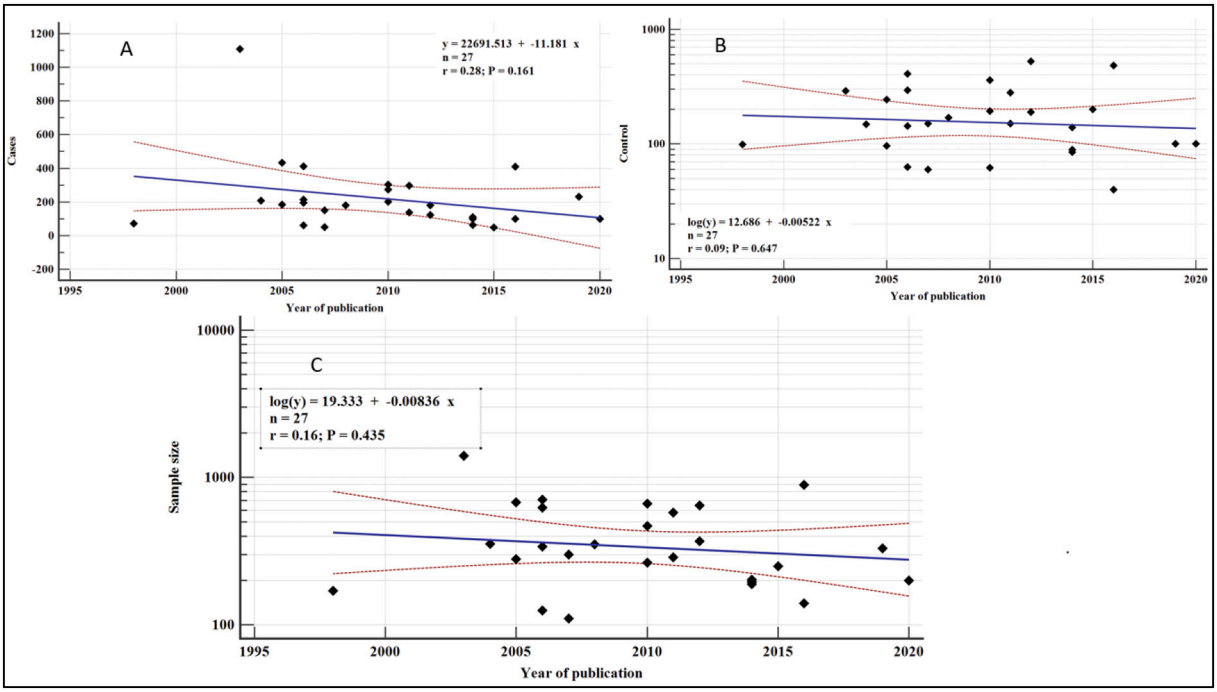

Fig. 14. Meta-regression analysis; A: - number of cases and year of publication, B: - number of controls and year of publication, C: - overall sample size and year of publication.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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CRediT authorship contribution statement

HMK and HS conceived the idea. HMK, AW and DN participated in the search for the articles from the databases. HMK and AW participated in the data presentation, analysis and discussion. HMK wrote the final manuscript draft. PO, ND, and HK reviewed the manuscript draft. All the authors read and approved the publication of the manuscript.

Declaration of competing interest

We declare that we do not have any financial and personal relationships with other people or organizations that could have inappropriately influenced (biased) our work.

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Authors' information

HMK is a molecular immunologist and virologist working on molecular immunology during hepatitis B virus infection targeting an African population. DN is an immunologist and biochemist with a PhD in Biochemistry and immunology working in the department of Plant Sciences, Microbiology and Biotechnology, College of Natural Sciences, Makerere University. HS holds a PhD in Biochemistry & is a physician in the Department of Microbiology Makerere University working on molecular markers of drug resistance in HIV and malaria infections. PO is a physician with a PhD in gastroenterology and is an associate professor of gastroenterology with a lot of expertise in liver diseases working in the department of Medicine College of Health Sciences, Makerere University. HK is a Microbiologist in the College of Health Sciences (CHS) Makerere University. HMK and AW are Ph.D. students at Makerere University in the colleges of Health Sciences and Natural Sciences employed at Islamic University in Uganda in the Departments of Medical Microbiology and Physiology as Doctoral fellows.

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