INTRODUCTION

An estimated 4.8 million new cases of gastrointestinal cancers and 3.4 million related deaths occurred worldwide in 2018. Gastrointestinal cancers account for 26% of the global cancer incidence and 35% of all cancer-related deaths. Gastrointestinal cancers mainly include oesophageal, gastric and colorectal cancers. Most of the gastrointestinal cancers were diagnosed at a middle or advanced stage. This situation is the major obstacle to the effective treatment of gastrointestinal cancers. Therefore, identifying early diagnosis markers for gastrointestinal cancers is of great significance to the treatment of gastrointestinal cancers.

Gastrointestinal cancers are multifactorial diseases caused by complex interactions between genetic and environmental factors. More than 50% of all gastrointestinal cancers are caused by environmental risk factors, including infection, alcohol consumption,
tobacco smoking and over obesity. Apart from the environmental factors, genetic variations are also implicated in the onset and outcome of gastrointestinal cancers.\textsuperscript{8–11} Single nucleotide polymorphisms (SNPs), the most common and effective variant type, are significantly associated with cancer susceptibility.\textsuperscript{12–14}

NF-κB, short for nuclear factor kappa B, is a pluripotent and critical dimer transcription factor. NF-κB orchestrates multiple physiological and pathological processes, particularly in cell survival, differentiation, inflammation and carcinogenesis.\textsuperscript{15–23} It was originally discovered by Sen and Baltimore in 1986.\textsuperscript{24} NF-κB family is consisted of 5 different protein subunits, including NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), c-Rel and RelB, in mammals.\textsuperscript{25} NF-κB expression is strictly regulated in normal cells, but it is generally overexpressed in many cancer cells.\textsuperscript{26} Upregulation of NF-κB has been observed in several types of cancer, including hepatocellular carcinogenesis,\textsuperscript{27,28} colon cancer,\textsuperscript{29} breast cancer,\textsuperscript{30} ovarian cancer\textsuperscript{31} and glioma cancer.\textsuperscript{32} Multiple number of NFKB1 gene SNPs were investigated in the implication of cancer. Among them, the rs28362491, namely the −94insertion/deletion ATTG polymorphism, ranks the most intensively investigated SNP.\textsuperscript{33,34} The deletion of ATTG bases prevents or reduces the binding to nuclear proteins and results in decreased transcript levels of the NFKB1 gene, thus influencing the stability of mRNA and efficiency of regulating translation. Research regarding NFKB1 gene −94insertion/deletion ATTG polymorphism on its association with gastrointestinal cancer risk was widely performed. However, the conclusions are still contradictory and inconsistent, partly attributed to the underpower and bias of independent studies, especially for small cohorts. Therefore, the exact association between NFKB1 −94insertion/deletion ATTG variant and risk of gastrointestinal cancer awaits to be determined. Here, a renewed meta-analysis with all potential studies performed before April 2021 was analysed to acquire a clearer impact of NFKB1 −94insertion/deletion ATTG polymorphism on gastrointestinal cancer susceptibility.

## MATERIALS AND METHODS

### 2.1 Search strategy

We reported this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.

### 2.2 Publication selection

We applied an all-sided literature retrieval using EMBASE, PubMed and MEDLINE up to April 2021. We used the following key words to carry out this procedure: (1) NFKB1 or NF-κB1 or nuclear factor kappa B1; (2) −94insertion/deletion ATTG or rs28362491 or SNPs or polymorphisms or polymorphism or variants; and (3) colorectal cancer or gastric cancer or gastrointestinal cancers or oesophageal cancer. To identify all the available studies, we also arranged two authors to screen eligible publications by hand-searching the references of included publications.

### 2.3 Eligibility criteria

Publications are required to meet the following criteria for inclusion: (1) evaluating the relationship between NFKB1 rs28362491 and gastrointestinal cancer risk; (2) case-control study; and (3)
### TABLE 1 Characteristics of studies included in the current meta-analysis

| Surname | Year | Cancer type | Country | Ethnicity | Control Source | Genotype method | Case Score | Control Score | HWE |
|---------|------|-------------|---------|-----------|----------------|-----------------|------------|---------------|------|
| Riemann | 2006 | Colorectal  | Germany | Caucasian | HB Pyrosequencing | 54 | 58 | 27 | 139 | 118 | 141 | 48 | 307 | 9 | 0.586 |
| Lewander | 2007 | Colorectal  | China   | Asian     | HB PCR-RFLP      | 50 | 101 | 42 | 193 | 113 | 266 | 79 | 458 | 9 | <0.001 |
| Lewander | 2007 | Colorectal  | Sweden  | Caucasian | HB PCR-RFLP      | 63 | 323 | 81 | 467 | 116 | 256 | 67 | 439 | 10 | <0.001 |
| Lo       | 2009 | Gastric     | China   | Asian     | HB PCR           | 62 | 89 | 31 | 182 | 20 | 62 | 34 | 116 | 7 | 0.361 |
| Vibeke   | 2010 | Colorectal  | Denmark | Caucasian | PB TaqMan        | 121 | 195 | 62 | 378 | 307 | 347 | 102 | 756 | 11 | 0.801 |
| Song     | 2011 | Colorectal  | China   | Asian     | HB PCR-RFLP      | 363 | 500 | 138 | 1,001 | 297 | 522 | 186 | 1,005 | 14 | 0.102 |
| Ungerback | 2012 | Colorectal  | Sweden  | Caucasian | HB TaqMan        | 114 | 187 | 43 | 344 | 256 | 270 | 96 | 622 | 8 | 0.079 |
| Arisawa  | 2013 | Gastric     | Japan   | Asian     | PB PCR-SSCP      | 172 | 239 | 68 | 479 | 342 | 435 | 103 | 880 | 11 | 0.046 |
| Umar     | 2013 | Oesophageal | India   | Asian     | HB PCR           | 131 | 132 | 27 | 290 | 160 | 129 | 22 | 311 | 10 | 0.561 |
| Mohd     | 2013 | Colorectal  | Malaysia| Asian     | HB PCR-RFLP      | 35 | 127 | 75 | 237 | 16 | 138 | 83 | 237 | 9 | <0.001 |
| Hua      | 2014 | Gastric     | China   | Asian     | HB MassARRAY     | 92 | 182 | 127 | 401 | 120 | 230 | 83 | 433 | 9 | 0.144 |
| Kopp     | 2015 | Colorectal  | Denmark | Caucasian | PB KASP          | 320 | 449 | 146 | 915 | 679 | 787 | 253 | 1,719 | 11 | 0.311 |
| Mohamed  | 2017 | Colorectal  | Egypt   | Caucasian | HB PCR-RFLP      | 30 | 56 | 14 | 100 | 4 | 58 | 23 | 85 | 9 | <0.001 |
| Giovanna | 2017 | Gastric     | Brazil  | Caucasian | HB PCR           | 15 | 71 | 34 | 120 | 110 | 246 | 117 | 473 | 10 | 0.379 |
| Giovanna | 2017 | Colorectal  | Brazil  | Caucasian | HB PCR           | 5 | 42 | 16 | 63 | 110 | 246 | 117 | 473 | 10 | 0.379 |
| Imene    | 2019 | Colorectal  | Algeria | Caucasian | PB TaqMan        | 54 | 56 | 17 | 127 | 68 | 57 | 24 | 149 | 9 | 0.048 |

Abbreviations: HB, hospital based; HWE, Hardy-Weinberg equilibrium; KASP, kompetitive allele specific PCR; PB, population based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction-single strand conformation polymorphism.
### TABLE 2 Meta-analysis of the association between NFKB1 -94Ins/Del (rs28362491) polymorphism and gastrointestinal cancer risk

| Variables          | No. of studies | Homozygous | Heterozygous | Recessive | Dominant | Allele |
|--------------------|----------------|------------|--------------|-----------|----------|--------|
|                    |                | II vs. DD  | ID vs. DD    | II vs. ID/DD | ID/II vs. DD | I vs. D |
|                    |                | OR (95% CI) | OR (95% CI)  | OR (95% CI) | OR (95% CI) | OR (95% CI) |
|                    |                | $p_{\text{het}}$ | $p_{\text{het}}$ | $p_{\text{het}}$ | $p_{\text{het}}$ | $p_{\text{het}}$ |
| All$^a$            | 16             | 0.94       | 0.99         | 0.92       | 0.97      | 0.96    |
|                    |                | (0.70–1.26) | (0.85–1.16)  | (0.74–1.14) | (0.81–1.16) | (0.84–1.09) |
| Cancer type        |                |            |              |           |           |        |
| Colorectal         | 11             | 1.01       | 1.07         | 0.94       | 1.00      | 0.98    |
|                    |                | (0.71–1.43) | (0.93–1.23)  | (0.71–1.25) | (0.87–1.23) | (0.85–1.14) |
| Gastric            | 4              | 0.85       | 0.87         | 0.93       | 0.88      | 0.94    |
|                    |                | (0.43–1.71) | (0.57–1.33)  | (0.58–1.45) | (0.54–1.43) | (0.68–1.30) |
| Oesophageal        | 1              | 0.67       | 0.83         | 0.78       | 0.74      | 0.82    |
|                    |                | (0.36–1.23) | (0.45–1.54)  | (0.56–1.07) | (0.41–1.33) | (0.64–1.05) |
| Ethnicity          |                |            |              |           |           |        |
| Caucasians         | 9              | 0.80       | 1.06         | 0.74       | 0.96      | 0.890   |
|                    |                | (0.56–1.13) | (0.93–1.22)  | (0.56–0.98) | (0.82–1.12) | (0.77–1.02) |
| Asians             | 7              | 1.13       | 0.90         | 1.16       | 0.95      | 1.03    |
|                    |                | (0.70–1.82) | (0.67–1.21)  | (0.88–1.53) | (0.67–1.35) | (0.84–1.28) |
| Source of control  |                |            |              |           |           |        |
| HB                 | 12             | 1.02       | 1.01         | 0.99       | 1.01      | 0.99    |
|                    |                | (0.67–1.55) | (0.82–1.26)  | (0.72–1.37) | (0.79–1.28) | (0.83–1.19) |
| PB                 | 4              | 0.78       | 0.95         | 0.81       | 0.87      | 0.87    |
|                    |                | (0.66–0.93) | (0.81–1.13)  | (0.72–0.91) | (0.75–1.02) | (0.80–0.94) |
| Score              |                |            |              |           |           |        |
| ≤9                 | 8              | 1.40       | 1.01         | 1.30       | 1.07      | 1.10    |
|                    |                | (0.82–2.38) | (0.72–1.41)  | (0.89–1.90) | (0.75–1.53) | (0.88–1.39) |
| >9                 | 8              | 0.70       | 1.03         | 0.72       | 0.97      | 0.86    |
|                    |                | (0.49–0.99) | (0.91–1.16)  | (0.55–0.94) | (0.81–1.15) | (0.74–1.00) |
| HWE                |                |            |              |           |           |        |
| >0.05              | 10             | 0.84       | 1.004        | 0.85       | 0.95      | 0.91    |
|                    |                | (0.60–1.18) | (0.81–1.25)  | (0.67–1.07) | (0.74–1.21) | (0.78–1.07) |
| ≤0.05              | 6              | 1.24       | 0.96         | 1.19       | 0.99      | 1.05    |
|                    |                | (0.67–2.31) | (0.80–1.16)  | (0.71–2.00) | (0.77–1.27) | (0.83–1.33) |

Note: The bold values indicate significant results.
Abbreviations: HB, hospital based; Het, heterogeneity; PB, population based.
$^a$ All the studies included.
enough data to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Editorials, meta-analyses, reviews, research on animals and repetitively published articles were excluded.

### 2.4 Data extraction

We arranged two researchers (Hanqiang Wu and Jianrong Liang) to acquire the data independently by adopting the unified data table. The authors acquired the following information from all the studies: surname of the first author, source of control, year of publication, type of cancers, ethnicity of the study subject, numbers of cases and controls, genotyping method, and genotype of SNPs. If the extracted information is disputable, the authors would re-check the references and make sure which extracted information is right. We assessed the methodologic quality of each study using the quality assessment criteria described by previous studies (Table S1). We judged the study quality to be high if the score was more than 9 points or otherwise to be low.

### 2.5 Statistical methods

We first test if the SNPs in the controls conformed to Hardy-Weinberg equilibrium (HWE) by goodness-of-fit test. The association between NFKB1 rs28362491 and gastrointestinal cancer risk was evaluated by identifying the genotype frequencies of all cases and controls. Odds ratio (OR) and 95% confidence interval (CI) were adopted to assess this relationship. The meta-analysis assessed association by using five different genetic models: homozygote model (II, homozygous insertion [ins/ins] or wild-type vs. DD, homozygous deletion [del/del]); heterozygote model (ID, heterozygous ins/del vs. DD); recessive model (II vs. ID/DD); dominant model (ID/II vs. DD); and allele contrast model (I vs. D). Stratification analyses were also performed by ethnicity, cancer type, source of control, score and HWE in controls, if applicable. We further analysed the heterogeneity among studies using Cochrane Q test. If $p < 0.10$ or $I^2 > 50\%$ for the Q test, the random effects model (DerSimonian-Laird method) was applied to conduct the analysis; if not, the fixed effects model (Mantel-Haenszel method) was applied. The included studies were deleted one by one, and then, the left studies were recalculated for ORs and 95% CIs to determine the influence of each study on the

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| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Riemann (2006) | 0.93 (0.70, 1.24) | 5.74 |
| Lewander (2007) | 0.94 (0.74, 1.19) | 6.36 |
| Lewander (2007) | 0.74 (0.61, 0.89) | 7.00 |
| Lo (2009) | 1.80 (1.29, 2.51) | 5.23 |
| Vibeke (2010) | 0.79 (0.66, 0.94) | 7.07 |
| Song (2012) | 1.27 (1.12, 1.44) | 7.62 |
| Ungerback (2012) | 0.90 (0.74, 1.09) | 6.93 |
| Arisawa (2013) | 0.89 (0.76, 1.05) | 7.25 |
| Umar (2013) | 0.82 (0.64, 1.05) | 6.25 |
| Mohd (2013) | 1.27 (0.98, 1.65) | 6.07 |
| Hua (2014) | 0.71 (0.58, 0.86) | 6.91 |
| Kopp (2015) | 0.89 (0.79, 0.99) | 7.71 |
| Mohamed (2017) | 2.18 (1.43, 3.30) | 4.32 |
| Giovanna (2017) | 0.75 (0.56, 1.00) | 5.78 |
| Giovanna (2017) | 0.72 (0.50, 1.06) | 4.74 |
| Imene (2019) | 0.99 (0.70, 1.41) | 5.03 |
| Overall (I-squared = 81.9%, p = 0.000) | 0.96 (0.84, 1.09) | 100.00 |

**FIGURE 2** Representative forest plots for the correlation between the NFKB1 −94ins/delATTG polymorphism and gastrointestinal cancer susceptibility. The horizontal lines represent the study-specific ORs and 95% CIs.
total combined effect size (sensitivity analysis). Publication bias for the included literature was determined using the funnel plot and Begg’s funnel plot. p value < 0.05 indicates significant finding. Trial sequential analysis (TSA) was performed as described by us previously. Briefly, after adopting a level of significance of 5% for type I error and of 30% for type II error, the required information size was calculated, and TSA monitoring boundaries were built. All statistical analysis was performed using STATA, version 11.0 (Stata Corporation, College Station, TX).

3 | RESULTS

3.1 | Literature retrieval results

The screening process of the current meta-analysis was shown in Figure 1. We first identified 22 articles with potential relevance from PubMed, MEDLINE and EMBASE. We then arranged two authors to identify whether there exist additional articles from the retrieved studies. Three articles were further identified. After careful review, we total identified 16 studies for final analysis.33,36-48

### FIGURE 3

Representative forest plots for the correlation between the NFKB1 -94ins/delATTG polymorphism and respective oesophageal, gastric and colorectal cancers susceptibility. The horizontal lines represent the study-specific ORs and 95% CIs.

3.2 | Studies characteristics

Among the 16 included studies (Table 1), 11 were reported on colorectal cancer, 4 on gastric cancer and 1 on oesophageal cancer. Nine were in Asian populations, 8 in Caucasian populations and 2 in Asian populations. For sources of control, 12 were hospital based and 4 were population based. For quality score, there were 8 publications of low quality and 8 studies of high quality. The SNPs in the control groups of 10 studies complied with HWE, while 6 deviated.
3.3 | Quantitative analysis

The detailed results of the meta-analysis were presented in Table 2 and Figures 2 and 3. The pooled analyses indicated that negative association was detected between the NFKB1 –94ins/delATTG polymorphism and overall gastrointestinal cancer susceptibility under all 5 genetic models (II vs. DD: OR = 0.94, 95% CI = 0.70–1.26; ID vs. DD: OR = 0.99, 95% CI = 0.85–1.16; II vs. ID/DD: OR = 0.92, 95% CI = 0.74–1.14; ID/II vs. DD: OR = 0.97, 95% CI = 0.81–1.16; and I vs. D: OR = 0.96, 95% CI = 0.84–1.09). In cancer type subgroup analysis, NFKB1 –94ins/delATTG polymorphism still failed to impact the susceptibility in subgroup of colorectal cancer, gastric cancer and oesophageal cancer. Subgroup analysis of ethnicity indicated that significant decreased cancer risk was detected in Caucasians (II vs. ID/DD: OR = 0.74, 95% CI = 0.56–0.98), but not in Asians. Further stratification analysis by source of control revealed that studies conducted as population base protect from cancer risk (II vs. DD: OR = 0.78, 95% CI = 0.66–0.93; II vs. ID/DD: OR = 0.81, 95% CI = 0.72–0.91; and I vs. D: OR = 0.87, 95% CI = 0.80–0.94). Moreover, score subgroup indicated that studies >9 were linked to decreased cancer risk (II vs. DD: OR = 0.70, 95% CI = 0.49–0.99; II vs. ID/DD: OR = 0.72, 95% CI = 0.55–0.94; and I vs. D: OR = 0.87, 95% CI = 0.74–1.00). Further stratification of HWE analysis in controls demonstrated that no significant association was detected in subgroup of both HWE ≤ 0.05 and HWE > 0.05.

3.4 | Sensitivity analysis

Here, we also carried out a sensitivity analysis by gradually deleting the included studies in a one-by-one manner. The no statistical
fluctuation of the pooled OR value suggested that the analytic results were reliable and stable (Figure 4).

### 3.5 | Publication bias

Begg's funnel plot did not have significant asymmetry (Figure 5). Statistical evidence of Egger’s test also could not identify obvious publication bias for all of the polymorphisms.

### 3.6 | Trial sequential analysis

To minimize random errors and strengthen the robustness of our conclusions, we performed TSA (Figure 6). This analysis showed that the cumulative z-curve did cross the trial sequential monitoring boundary, suggesting that further evidence is needed to verify the conclusions.

### 4 | DISCUSSION

In the current meta-analysis, we comprehensively extract information from available epidemiology studies to assess the association between NFKB1 gene −94ins/delATTG polymorphism and gastrointestinal cancer risk. Our findings indicate that NFKB1 gene −94ins/delATTG polymorphism could not modify gastrointestinal cancer susceptibility. Of note, this is the first meta-analysis performed by far on NFKB1 gene −94ins/delATTG polymorphism and gastrointestinal cancer susceptibility.

Growing evidence has pointed to the involvement of NFKB1 −94ins/delATTG polymorphism analysed here (rs28362491) in cancer susceptibility. Song et al. 40 observed that the NFKB1 −94ins/delATTG polymorphism could enhance the susceptibility of colorectal cancer in a Southern Chinese population. However, role of NFKB1 −94ins/delATTG polymorphism in specific cancer is contradictory, namely a decreased cancer susceptibility or a null association. To solve this controversy, several meta-analyses have been conducted. The first meta-analysis was carried out in 2011 by Zou et al. 49 Their study incorporated 2743 cases and 2195 controls by including eleven studies. They failed to detect any relationship between the −94ins/delATTG SNP and risk of overall cancer. However, subgroup analysis identified an ethno-specific association; the D allele could decrease the risk of cancer in Asians, but confer to a higher risk in Caucasians.

In a meta-analysis updated to July 2016 involving 18,299 cases and 23,484 controls from 50 case-control studies, Fu et al. 50 identified that the NFKB1 −94ins/delATTG polymorphism protects from getting overall cancer in the homozygote model; heterozygote model; dominant model; and allele contrast. Stratified and subgroup analyses indicated decreased susceptibility for prostate cancer, ovarian cancer, lung cancer, nasopharyngeal carcinoma and oral squamous cell carcinoma, and this association also is significant for Asians, especially Chinese subjects, in hospital-based studies, and in studies with quality score <9. Of note, by far, no available GWAS has identified the significant relationship between NFKB1 −94ins/delATTG polymorphisms and risk of gastrointestinal cancers.
Since then, several new relevant case-control studies on gastrointestinal cancers have emerged. Therefore, we set as a pioneer to determine whether NFKB1 -94ins/delATTG polymorphism impact risk of gastrointestinal cancers. However, NFKB1 -94ins/delATTG polymorphism under any five genetic models has not enough ability to influence susceptibility to overall gastrointestinal cancer. Several merits existed in the current meta-analysis. First, this is up to now the first and largest meta-analysis regarding NFKB1 gene -94ins/delATTG polymorphism and gastrointestinal cancers susceptibility. Second, in sensitivity analysis, relative stability and credibility of the results were achieved as no significant changes after deleting each study at a time. Third, there existed no obvious publication bias, indicating the reliability of conclusion. Some limitations in the current meta-analysis should be acknowledged. First, the number of subjects in the included studies is relatively small, especially in stratified analyses, which might result in a lack of statistical power and prevent a meaningful analysis of the results. Second, the association strength was only evaluated by unadjusted estimates. Adjustment analysis including gene-gene, gene-environment factors were not carried out because of the lack of original data. Third, in the included studies, the population sources were generally limited to Caucasians and Asians. Thus, the conclusion here should be interpreted in caution in Africans.

5 | CONCLUSION

In all, our finding has concluded that NFKB1 gene -94ins/delATTG polymorphism may not predispose to gastrointestinal cancers susceptibility. More attention should be paid to several research directions in future studies. First, more high-quality studies with expanded sample sizes are necessarily called to further identify the relationship of the NFKB1 gene -94ins/delATTG polymorphism and gastrointestinal cancer risk, especially in Caucasian and African populations. Second, functional studies are needed to clarify the underlying mechanisms of NFKB1 gene -94ins/delATTG in gastrointestinal cancers.

CONFLICT OF INTEREST

The authors declare that there are no competing interests associated with the manuscript.

AUTHOR CONTRIBUTIONS

Hanqiang Wu: Conceptualization (equal); Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal).

Jianrong Liang: Conceptualization (equal); Data curation (equal); Investigation (equal); Software (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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