Interleukin-6 gene-174 G/C promoter polymorphism is not associated with multiple myeloma susceptibility: evidence from meta-analysis

A systematic review and meta-analysis

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Abstract

Purpose: Presently, whether interleukin-6 (IL-6) gene-174 G/C promoter polymorphism is correlated to the susceptibility of multiple myeloma (MM) remains controversial. For this reason, the method of meta-analysis was applied to exploring the association between IL-6 gene-174 G/C promoter polymorphism and MM.

Method: Two independent researchers systematically searched PubMed, EMBASE, Google academic, Cochrane Library and Chinese literature databases to screen case-control studies on IL-6 gene-174 G/C promoter polymorphism and MM susceptibility. The retrieval period was limited from the formation of the database to January 2020, and data analysis was conducted by employing Stata 11.0 software.

Result: Seven articles were ultimately included in the present study, including 594 MM patients and 681 controls. Integration analysis exhibited that compared with GC or CC genotype, GG genotype did not increase MM susceptibility (OR = 0.95, 95% CI 0.75–1.22; OR = 0.79, 95% CI 0.52–1.19, respectively). Further, in comparison with CC genotype, GC genotype also presented no effect on increasing MM susceptibility (OR = 0.79, 95% CI 0.53–1.16), while compared with GC+CC genotype, GG genotype had no significant relationship with MM susceptibility (OR = 0.94, 95% CI 0.75–1.19). In subsequent analysis, an observation was made that allele G or C was not related to MM susceptibility (OR = 0.92, 95% CI 0.76–1.12). Funnel chart and Begg test did not reveal publication bias in the included articles.

Conclusion: The results of the present study advocate that there is no testimony to support the relationship between IL-6 gene-174 G/C promoter polymorphism and MM susceptibility.

Abbreviations: CI = confidence interval, HO-1 = heme oxygenase-1, IL-6 = interleukin-6, MM = multiple myeloma, NF-KB = nuclear factor-kB, NOS = Newcastle-Ottawa Scale, OR = odds ratio, TNF-α = tumor necrosis factor-α.

Keywords: IL-6 promoter polymorphism, multiple myeloma, susceptibility

1. Introduction

Multiple myeloma[1,2,3,4] (MM) is a group of malignant plasma cell clonal diseases, with the cancer cells thereof being derived from the plasma cells, and plasma cells[5] being the cells in which B lymphocytes[6] grow to the ultimate functional stage. The primary feature of MM is abnormal proliferation of bone marrow plasma cells[7] with excessive production of monoclonal immunoglobulin[8] or light chain (M protein)[9,10] resulting in terminal organ damage. The evolution of MM is heterogeneous, and the survival time of patients with invasive manifestations is estimated to be less than 1 year.[11,12] Previous data highlighted that the incidence of MM accounts for about 1% of all system malignant tumors,[13,14] often occurring in middle-aged and elderly patients, with the clinical manifestations thereof being complex and diverse, potentially causing anemia, infection, bleeding, bone pain, and even fracture. Along with the aforementioned issues, MM could even lead to rare clinical symptoms, such as signs of nerve root irritation.[15] As reported by existing research, the incidence of multiple myeloma has progressively increased worldwide over the past few decades,[16–18] substantially affecting the quality of life of people and increasing the medical and health burden of society.
In addition to being a vital inflammatory factor, Interleukin-6 (IL-6) is also a risk factor for a series of diseases. The expression of IL-6 is regulated by a plurality of environmental factors inside and outside the body, namely tumor necrosis factor α (TNF-α) and IL-1 β. IL-6 level in healthy adults is generally low, while the elevated IL-6 level is strongly connected to the pathophysiology of autoimmune diseases, and other malignant tumors. IL-6 displays a critical function in the autocrine pathway by promoting the development of myeloma. A profusion of reports have determined that the IL-6 level in MM patients is significantly increased and is associated with clinical features and poor prognosis. In a study conducted by Wu, a hypothesis was made that IL-6 levels in the bone marrow microenvironment of MM patients could stimulate a high expression of heme oxygenase-1 (HO-1) in MM cells and the resistance thereof to lenalidomide. Human IL-6 DNA segment is positioned on chromosome 7p21. Transcription factors such as nuclear factor κB (NF-κB), Fos/Jun and glucocorticoid receptor can highly regulate the expression of IL-6 DNA segment at the transcriptional level by combining with the corresponding sequences of the promoter region of IL-6 gene. Thus, the polymorphism of the IL-6 gene promoter region will potentially lead to differences in gene transcription and expression among individuals, and subsequently affect individual susceptibility to IL-6-related diseases.

Currently, prior research has established the association between IL-6 gene-174 G/C promoter polymorphism and MM susceptibility. Most scholars have indicated that IL-6 gene-174 G/C promoter polymorphism is not connected with MM susceptibility. However, several scholars are of the belief that even though no notable difference was found in IL-6 gene-174 G/C promoter polymorphism between MM patients and control individuals, patients with GG genotype have higher IL-6 levels and poorer clinical prognosis compared with CC genotype. At the same time, the previous studies were all small sample studies and lack effective statistical efficiency. For the reasons stated above, a meta-analysis method was employed in the present study to comprehensively analyze the association between IL-6 gene-174 G/C promoter polymorphism and MM susceptibility.

2. Materials and methods

2.1. Literature search

In the present study, to screen case-control studies on IL-6 gene-174 G/C promoter polymorphism and MM, 2 independent researchers systematically searched PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (https://www.embase.com/), Google academic (https://scholar.google.com/), Cochrane Library (https://www.cochranelibrary.com/) and Chinese literature databases, including China national knowledge internet (https://www.cnki.net/), VIP database (http://www.cqvip.com), and Wanfang database (http://www.wanfangdata.com.cn/). Further, to avoid the omission of relevant literature, the references included in the literature were manually searched. The retrieval time was limited from the establishment of the database to January 2020, and the publication language was limited to Chinese and English. The keywords used in the retrieval process were as follows: (Multiple Myeloma or Multiple Myelomas or Myelomas, Multiple or Myeloma, Multiple or Myeloma, Plasma-Cell or Myeloma, Plasma Cell or Myelomas, Plasma-Cell or Plasma-Cell Myeloma or Plasma-Cell Myelomas or Myelomatosis or Myelomatoses or Plasma Cell Myeloma or Cell Myeloma, Plasma or Cell Myelomas, Plasma or Myelomas, Plasma Cell or Plasma Cell Myelomas or Kahler Disease or Disease, Kahler or Myeloma-Multiple or Myeloma Multiple or Myeloma-Multiples) and (Interleukin 6 or IL6 or B-Cell Stimulatory Factor 2 or B-Cell Stimulatory Factor-2 or Differentiation Factor-2, B-Cell or Differentiation Factor 2, B Cell or B-Cell Differentiation Factor-2 or B Cell Differentiation Factor 2 or B Cell Stimulatory Factor 2 or B-Cell Stimulatory Factor 2 or Differentiation Factor-2 or IFN-beta 2 or Plasmacytoma Growth Factor or Growth Factor, Plasmacytoma or Hepatocyte-Stimulating Factor or Hepatocyte Stimulating Factor or MGI-2 or Myeloid Differentiation-Inducing Protein or Differentiation-Inducing Protein, Myeloid or Myeloid Differentiation Inducing Protein or B-Cell Differentiation Factor or B Cell Differentiation Factor or Differentiation Factor, B-Cell or Differentiation Factor, B Cell or IL-6 or Interferon beta-2 or Interferon beta 2 or beta-2, Interferon or B Cell Stimulatory Factor-2 or B Cell Stimulatory Factor 2) and [(Polymorphism or Polymorphisms, Genetic or Genetic Polymorphisms or Genetic Polymorphism or Polymorphism (Genetics) or Polymorphisms (Genetics)]. This study has been approved by Huzhou Central Hospital Ethics Committee.

2.2. Inclusion criteria

Patients with clinically confirmed multiple myeloma; and IL-6 gene-174 G/C: promoter polymorphism was measured in MM patients and control individuals.

2.3. Exclusion criteria

Patients with idiopathic thrombocytopenic purpura, acute or chronic leukemia, myelodysplastic syndrome, hereditary spherocytosis, aplastic anemia or autoimmune hemolytic anemia; patients with pulmonary infection, urinary tract infection or shock; patients with acute myocardial infarction, acute stroke, acute pulmonary embolism or aortic dissection; patients with systemic sclerosis, rheumatoid arthritis or systemic lupus erythematosus; literature with incomplete data or data not available for analysis, including reviews or letters to the editor; and rat, pig or zebrafish experiments.

2.4. Data extraction and literature quality evaluation

Data were extracted from the literature ultimately included in our study by 2 independent researchers. The extracted data comprised the first author, time of publication, country, genotype, sample size of MM patients and control individuals, evaluating indicator and detection method. If a dispute occurred in the process of data extraction, advice was sought from another senior specialist to determine the correct way to proceed. In accordance with the risk assessment criteria of Newcastle-Ottawa Scale (NOS) bias, 2 evaluators comprehensively evaluated the quality of the included literature. For any disputes, the third evaluators negotiated for resolution.

2.5. Statistical analyses

Stata 11.0 software was employed in the present study for statistical analysis, with P < .05 revealing that there were differences among groups. Initially, the genotypes of the control individuals were tested through the Hardy-Weinberg equilibrium
test, if \( P < 0.05 \), this revealed that the control individuals’ genotypes did not conform to the Hardy–Weinberg equilibrium. Subsequently, the genotype distribution of different sites and different genetic models were calculated. Odds ratio (OR) and the 95% confidence interval (CI) thereof were operated as the effect amount of the merged analysis, and \( \alpha = 0.05 \) was adopted as the test level of statistical analysis. \( I^2 \) was utilized to test whether there was statistical heterogeneity among the included literature, and if \( I^2 < 50\% \), the suggestion was that there was no statistical heterogeneity among the included literature. Random effect model (M-H heterogeneity) was applied here to data analysis, while funnel plot and Begg test were adopted to evaluate publication bias, and sensitivity analysis was employed to assess the impact of individual reports on merger results.

3. Results

3.1. The flow chart of document retrieval and the basic characteristics of included literature

First, the Chinese and English literature databases were searched to select the literature, with literature not meeting the inclusion and exclusion criteria being eliminated according to the title and abstract. Further, the full text was read to determine whether the data of the literature were suitable for analysis. Finally, 7 articles\(^{[28,29,30,31,32,33,34]} \) were included in the present study, including 594 MM patients and 681 controls. The flow chart of literature retrieval is exhibited in Figure 1, and the basic characteristics of the included literature are displayed in Table 1.

3.2. GG vs GC genotype

Seven articles\(^{[28,29,30,31,32,33,34]} \) declared the association between GG and GC genotypes and MM susceptibility, including 594 MM patients and 681 controls. Integration analysis indicated that compared with GC genotype, GG genotype did not increase MM susceptibility (OR = 0.95, 95% CI 0.75–1.22; OR = 0.79) (Fig. 2a). Meanwhile, Funnel plot and Begg test (\( P = 0.475 \)) implied that there was no published bias between the included articles (Fig. 2b and d). Sensitivity analysis exhibited that gradually eliminating a study step by step would not significantly change the final result (Fig. 2c).

3.3. GG vs CC genotype

The relationship between GG and CC genotypes and MM susceptibility, including 594 MM patients and 681 controls, has been reported in 7 articles\(^{[28,29,30,31,32,33,34]} \). Meta-analysis displayed that compared with CC genotype, GG genotype did not increase MM susceptibility (OR = 0.79, 95% CI 0.52–1.19) (Fig. 3a). At the same time, funnel plot and Begg test (\( P = 0.422 \)) implied that there was no evidence to support the publication bias of the included articles (Fig. 3b and d). In parallel, sensitivity analysis demonstrated that gradually eliminating a study step by step would not significantly change the final result (Fig. 3c).

3.4. GC vs CC genotype

Seven articles\(^{[28,29,30,31,32,33,34]} \) highlighted the relationship between GG and CC genotypes and MM susceptibility, including 594 MM patients and 681 controls. The results of comprehensive analysis demonstrated that compared with CC genotype, GC genotype did not increase MM susceptibility (OR = 0.79, 95% CI 0.53–1.16) (Fig. 4a). While, funnel plot and Begg test (\( P = 0.955 \)) suggested that there was no evidence to support the publication bias of the included articles (Fig. 4b and d). Sensitivity analysis

| Authors              | Year | Country | MM (n) | Controls (n) | Evaluating indicator | Detection method | NOS score |
|----------------------|------|---------|--------|--------------|----------------------|-----------------|-----------|
| Aladžsity I          | 2009 | Hungary | 97     | 99           | IL-6–174 G/C        | PCR             | 7         |
| Mazur G              | 2005 | Poland  | 54     | 50           | IL-6–174 G/C        | PCR             | 7         |
| Cozen W              | 2006 | America | 146    | 125          | IL-6–174 G/C        | PCR             | 7         |
| Duch CR              | 2007 | Brazil  | 52     | 60           | IL-6–174 G/C        | PCR             | 8         |
| Chakraborty B        | 2017 | India   | 103    | 117          | IL-6–174 G/C        | PCR             | 8         |
| Zheng CY             | 2000 | Sweden  | 73     | 128          | IL-6–174 G/C        | PCR             | 7         |
| Iakupova EV          | 2003 | Russia  | 69     | 102          | IL-6–174 G/C        | PCR             | 7         |

MM = multiple myeloma, PCR = polymerase chain reaction.
similarly showed that gradually eliminating a study step by step would not significantly change the final result (Fig. 4c).

3.5. GG vs GC+CC genotype

The relationship between GG and CC genotypes and MM susceptibility, including 594 MM patients and 681 controls, was explored in 7 articles.\cite{28,29,30,31,32,33,34} Meta-analysis revealed that compared with GC+CC genotype, GG genotype had no significant relationship with MM susceptibility (OR = 0.94, 95% CI 0.75–1.19) (Fig. 5a). At the same time, funnel plot and Begg test ($P = .169$) highlighted that no evidence existed to support the publication bias of the included articles (Fig. 5b and d). In parallel, sensitivity analysis demonstrated that gradually eliminating a study step by step would not significantly change the final result (Fig. 5c).

3.6. Allele G vs allele C

Regarding the relationship between GG and CC genotypes and MM susceptibility, including 448 MM patients and 556 controls, this was reported in 6 articles.\cite{28,29,30,31,33,34} Comprehensive analysis exhibited that compared with allele C, allele G had no significant relationship with MM susceptibility (OR = 0.92, 95% CI 0.76–1.12) (Fig. 6a). Meanwhile, funnel plot and Begg test ($P = .073$) implied that no evidence existed to support the publication bias of the included articles (Fig. 6b and d). Sensitivity analysis also showed that gradually eliminating a study step by step would not significantly change the final result (Fig. 6c).

4. Discussion

A number of significant findings were made during the course of the present research. First, from the present understanding, the present study is the first to employ meta-analysis to analyze the relationship between IL-6 gene-174G/C promoter polymorphism and MM susceptibility. Second, no noteworthy association between IL-6 gene-174G/C promoter polymorphism and MM susceptibility was found after comparing patients and controls with different genotypes. Similarly, there was no significant relationship between different alleles and MM susceptibility. Third, sensitivity analysis indicated that the final results did not change majorly after a study was eliminated. Fourth, the funnel plot and Begg test advocate that there was no prominent publication bias, revealing that the consequence of comprehensive analysis was stable.

Amongst the background of more in-depth medical research being recently conducted, medical researchers have progressively recognized the correlation between inflammatory mediators,\cite{35} inflammation-related gene polymorphisms\cite{36} and malignant tumors. Along with chronic infection and inflammation being
two of the main risk factors for many cancers,[38] estimations have been made that potential infection and inflammation may be related to 15% of cancer patient mortality.[39] Previous data has demonstrated that long-lasting usage of anti-inflammatory treatments, such as aspirin or more selective COX-2 inhibitors, can delay the development of precancerous lesions, with these inhibitors also potentially reducing the occurrence of different forms of tumors.[40] This suggests that inhibition of inflammation can effectively reduce the incidence and mortality of tumors. Further, inflammatory cells and inflammatory mediators also exist in tumor microenvironments,[41] which have no relationship with inflammation or infection conditions. This is illustrated by leukocyte infiltration and the presence of soluble mediators, such as cytokines and chemokines, being evidence of cancer-related inflammation. The formation of inflammatory components in the tumor microenvironment could potentially be caused by conditions prone to cancer or by genetic events that lead to tumor transformation. Genetic changes of all oncogenes can, in actuality, increase the secretion of inflammatory mediators. For instance, previous results have clarified an internal inflammatory pathway and an external pathway caused by chronic inflammatory conditions,[41,42] which are generally considered to be critical factors leading to tumor progression. The expression level of IL-6 is determined by the polymorphism of the promoter site (IL-6-174G/C) and is an important inflammatory factor. IL-6 can regulate the secretion of other inflammatory molecules and maintain the inflammatory microenvironment needed for disease progression. Because NFκB and STAT3 pathways,[43] can regulate the secretion of cytokines in the body and the subsequent cellular response, several scholars have reported that said pathways are the main regulators of inflammatory pathways. Currently, the mechanism between IL-6-174G/C promoter gene polymorphism and susceptibility to MM is not well-defined. The variance in the distribution of IL-6-174G/C polymorphism between MM patients and control individuals was studied in this report, and a finding was made that there was no meaningful difference in IL-6-174G/C polymorphism between MM patients and control individuals. Further, the results of comprehensive analysis exhibited that the frequency of GC genotype was the highest in both MM patients and healthy controls, followed by GG genotype, with the lowest being CC genotype. Hence, the results of the present investigation align well with those of previous studies.[28,29,30,31,32,33,34]

This study has the following advantages. First, this study is the first time to find that there is no testimony to support the relationship between IL-6 gene-174G/C promoter polymorphism and MM susceptibility by means of meta-analysis, suggesting that there is not enough evidence to diagnose MM with IL-6 gene-174G/C promoter polymorphism. Second, the results of this study suggested that IL-6 gene-174G/C promoter polymorphism cannot be used for disease stratification of MM. The present research has the following limitations: Firstly, only Chinese and
Figure 4. GC vs CC genotype and multiple myeloma susceptibility. (a). GC vs CC genotype and multiple myeloma susceptibility (forest plots). (b). GC vs CC genotype and multiple myeloma susceptibility (funnel plot). (c). GC vs CC genotype and multiple myeloma susceptibility (sensitivity analysis). (d). GC vs CC genotype and multiple myeloma susceptibility (Begg test).

Figure 5. GG vs GC+CC genotype and multiple myeloma susceptibility. (a). GG vs GC+CC genotype and multiple myeloma susceptibility (forest plots). (b). GG vs GC+CC genotype and multiple myeloma susceptibility (funnel plot). (c). GG vs GC+CC genotype and multiple myeloma susceptibility (sensitivity analysis). (d). GG vs GC+CC genotype and multiple myeloma susceptibility (Begg test).
English studies were included in the present study. Owing to the language limitation, the present study cannot be included in the literature of other languages, which may lead to the existence of publication bias. Secondly, all the original data of the included studies could not be obtained, and there was no unified analysis standard for the included studies, which could affect the accuracy of the final results. Thirdly, the included studies were case-control studies, with a poor evidence level. These studies require further verification through a larger sample size and multi center trials, especially those trials based on mendelian randomization. Finally, there was not enough variety in the country/region of origin of the participants included in the present study, with participants only originating from a limited number of regions or countries. Further trials are necessary to verify whether the conclusions of the present study are applicable to other regions or populations.

In conclusion, the present results imply that there is no evidence to support the association between IL-6 gene-174G/C promoter polymorphism and MM susceptibility. Yet, multicenter and large sample trials are still required to further confirm this conclusion.

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