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Review

# Gene Polymorphisms Increasing the Risk of Intracranial Aneurysms: Interleukin-6 -174G>C and -572G>C (Part II)

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**Abstract.** *Introduction:* The interleukin-6 (IL-6), a proinflammatory cytokine, supports the adaptive immune response and regulates inflammatory processes. The -174 G>C and -572 G>C promoter polymorphisms of the IL-6 gene take part in the pathogenesis of intracranial aneurysms (IAs) and influence the clinical presentation of subarachnoid hemorrhage. This meta-analysis purposes to evaluate whether and which IL-6 allelic variations are related to a risk of IAs formation. *Methods:* A PRISMA-based literature search was performed on the PubMed/Medline and Web of Science databases. The keywords used were "interleukin-6," "IL-6," "polymorphism," "interleukin-6 genotype," combined with "intracranial aneurysms" and "subarachnoid hemorrhage." Only human case-control studies, with a study (IAs) and a control group, written in English, and published in the last 15 years were selected. A meta-analysis was performed, estimating odds ratios and 95% confidence intervals in fixed- or random-effects models, as applicable. Statistical analysis was conducted with RevMan 5.0 software. *Results:* 9 studies were eligible. No associations were found between -174 G>C polymorphisms and IAs susceptibility. Notable results were reported by the analysis of -572G>C polymorphisms. -572GG/GC/CC genotypes were strongly related to IAs occurrence with a statistical significance of $p$=0.03, $p$=0.0009, and $p$=0.00001, respectively. *Conclusion:* A higher incidence of -572G>C promoter polymorphisms were demonstrated in the IAs group, highlighting the pivotal role of inflammatory genes in the natural history of brain aneurysms. Additional studies are required considering the racial heterogenicity and the need to widen the population sample. (www.actabiomedica.it)

**Key words:** Allele Variations; Gene Polymorphisms; IL-6; Inflammatory Cytokines; Interleukin-6; Intracranial Aneurysm; Subarachnoid Hemorrhage.

## Introduction

In their saccular type, intracranial aneurysms (IAs) turn out as focal bulges of the arterial wall. They have an overall incidence and prevalence of 4% and 2–5%, respectively (1-3). IAs are typified by specific histological features, including the loss of internal elastic lamina and destruction of tunica media (4). The sudden rupture of the thinned aneurysm layers causes subarachnoid hemorrhage (SAH), a life-threatening cerebrovascular disease accounting for 30% of strokes and resulting in high morbidity and mortality (5-12).

Despite the precise mechanisms underlying the natural history of IAs being still unclear, the inflammatory cascade proved to be critical in the genesis, growth, and rupture of IAs (13-15). The local recruitment of inflammatory mediators, macrophages, cytokines, along with endothelial dysfunction and phenotypic switching of smooth muscle cells, leads to the weakening of the arterial wall (16-18).

Amid the pro-inflammatory cytokines recruited, the interleukin-6 (IL-6) has an active role in the boosting of the immune pathways, immunoregulation, and maintenance of inflammatory processes (19, 20). The human IL-6 gene was mapped in the short arm of chromosome 7 (21). It displays two biallelic polymorphisms at positions -174G/C and -572G/C in its promoter region, both due to the replacement of a sole nucleotide (GG/GC/CC) (22-24). IL-6 promoter polymorphisms were revealed to be potential risk factors for many vascular diseases, mostly abdominal aortic, coronary, and brain aneurysms (20, 25-42).

Given the limited pieces of evidence reported in the literature, the present meta-analysis sought to clarify the associations between IL-6 gene promoter polymorphisms, with single nucleotide substitutions, and the incidence of IAs.

## Methods

### *Literature Search Strategy*

A comprehensive online literature review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov) and Web of Science (https://www.webofscience.com) electronic databases were used with the following keywords: "interleukin-6," "IL-6," "interleukin-6 polymorphism," "IL-6 polymorphism," "interleukin-6 genotype," "IL-6 genotype". The aforementioned terms were merged with further keywords as follows: "intracranial aneurysm," "cerebral aneurysm", and "subarachnoid hemorrhage." Only articles written in English or translated, published in the last 15 years, were chosen and filtered according to the best match and relevance. Inclusion criteria were human case-control studies, available data on GG/GC/CC allele frequencies. Reviews, editorials, comments, case reports, letters to editor, and animal studies, were excluded. The Newcastle-Ottawa quality assessment scale (NOS) was employed to assess the quality of the selected articles (NOS ≥6 high quality).

### *Statistical Analysis*

The meta-analysis was performed with the RevMan 5.0 software (Cochrane Informatics & Knowledge Management Department). Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were assessed using the Mantel-Haenszel method for fixed effects and the Der Simonian-Laird method for the random ones. The heterogeneity rate was estimated by the Cochrane's Q test and the consequent $p^q$ and $I^2$ (% of effect due to heterogeneity) values. $p^q$ <0.05 and $I^2$ >50% identify a high heterogeneity of the study samples. Fixed-effects models were applied if the results of the Q test were not significant. Otherwise, studies with significant heterogeneity were further analyzed through the random-effect model. Z-test for overall effect was performed in all cases and the *p*-value was set at < 0.05. ORs and CIs of each endpoint were showed as a Forest plot. The risk of publication bias was estimated by Begg's rank correlation method and Egger's regression asymmetry, and reported as a Funnel plot if needed.

## Results

### *Literature Volume*

The literature search returned a total of 141 articles. After duplicate removal, screening, and implementation of the exclusion criteria, a total of 37 studies were assessed for eligibility. Further refinements limited the search to 9 studies. Among them, articles on the association between IL-6 -174G>C and IL-6 -572G>C polymorphisms and IAs risk were 8 and 6, respectively. Figure 1 reports the PRISMA flow chart of the study (Figure 1).

All studies reported the genotypes of IL-6 polymorphisms, -174G>C and -572G>C, differentiating

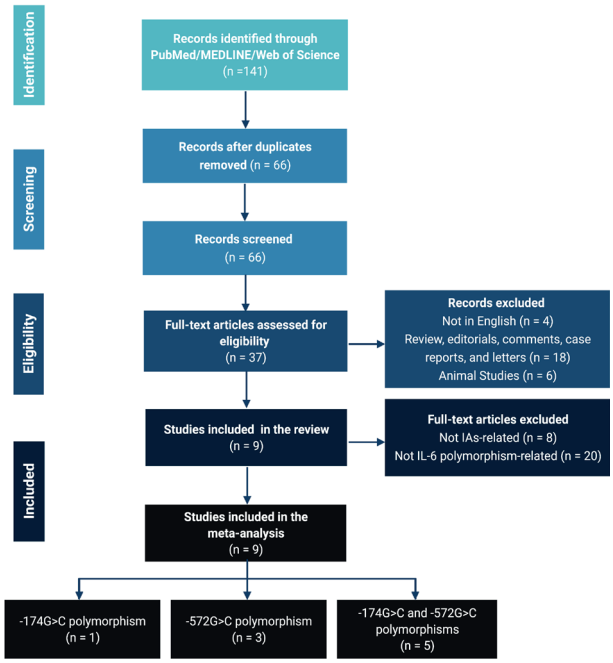



**Figure 1.** PRISMA flow diagram on the meta-analysis selection process

the frequency of alleles in GG/CG/CC. The study design was prospective for 6 articles, and retrospective for the remaining. 4 studies took place in China, 1 in the United Kingdom, 1 in Italy, 1 in Poland, and 1 in Turkey. The NOS score was higher than 6 for all the samples.

*Demographic and Genetic Data*

A total of 6765 patients belonging to 9 studies were involved in the meta-analysis. The IAs groups consisted of 1912 cerebral aneurysms, whereas the control ones accounted for 4853 healthy patients. The average patients' age was 45.5 and 48.3 years for the IAs and control groups, respectively. The mean percentage of the male was 43% and 51% in the study and control groups, respectively. Details of patients' demographics, genetic data, and studies' features are shown in Table 1.

*Quantitative Synthesis and Heterogeneity Analysis*

The associations between IL-6 -174G>C polymorphisms and risk of IAs were investigated

**Table 1. Overview of Data reported in the Literature about IL-6 Gene Polymorphisms and IAs**

| Author, Year | Study type | Country | Timeframe | N° of patients | | Age | | Gender | | Genotype | | | | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | IAs Group | Control Group | IAs Group (average y-o) | Control Group (average y-o) | IAs Group [N° of male (%)] | Control Group [N° of male (%)] | Polymorphism | Allele | IAs Group (N° of patients) | Control Group (N° of patients) | |
| Morgan et al., 2006 (26) | POS | UK | 2002-2003 | 91 | 2720 | 55 | 56 | 36 (40) | 2720 (100) | -174G>C | GG | 40 | 867 | 6 |
| | | | | | | | | | | | GC | 40 | 1358 | |
| | | | | | | | | | | | CC | 6 | 495 | |
| | | | | | | | | | | -572G>C | GG | 79 | 2359 | |
| | | | | | | | | | | | GC | 8 | 244 | |
| | | | | | | | | | | | CC | 4 | 9 | |
| Fontanella et al, 2008 (27) | POS | Italy | 2003-2006 | 179 | 156 | 53.7 | 53.7 | 58 (32) | 50 (32) | -174G>C | GG | 78 | 66 | 8 |
| | | | | | | | | | | | GC | 86 | 71 | |
| | | | | | | | | | | | CC | 15 | 19 | |
| | | | | | | | | | | -572G>C | GG | 149 | 131 | |
| | | | | | | | | | | | GC | 26 | 23 | |
| | | | | | | | | | | | CC | 4 | 2 | |

**Table 1. Overview of Data reported in the Literature about IL-6 Gene Polymorphisms and IAs**

| Author, Year | Study type | Country | Timeframe | N° of patients | | Age | | Gender | | Genotype | | | | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | IAs Group | Control Group | IAs Group (average y-o) | Control Group (average y-o) | IAs Group [N° of male (%)] | Control Group [N° of male (%)] | Polymorphism | Allele | IAs Group (N° of patients) | Control Group (N° of patients) | |
| Sun et al, 2008 (28) | ROS | China | 2005-2007 | 240 | 240 | 45.2 | 41.8 | 104 (43) | 116 (48) | -572G>C | GG | 59 | 9 | 6 |
| | | | | | | | | | | | GC | 130 | 82 | |
| | | | | | | | | | | | CC | 51 | 149 | |
| Zhang et al, 2011 (29) | POS | China | 2006-2008 | 182 | 182 | 36 | 33 | 103 (57) | 95 (52) | -572G>C | GG | 145 | 165 | 6 |
| | | | | | | | | | | | GC | 32 | 16 | |
| | | | | | | | | | | | CC | 5 | 1 | |
| Pera et al, 2012 (30) | POS | Poland | 2002-2009 | 276 | 581 | 50.5 | 56 | 120 (43) | 274 (47) | -174G>C | GG | 82 | 186 | 6 |
| | | | | | | | | | | | GC | 138 | 275 | |
| | | | | | | | | | | | CC | 56 | 120 | |
| Liu et al, 2012 (31) | ROS | China | 2012 | 220 | 220 | 47.4 | 45.6 | 95 (43) | 103 (47) | -572G>C | GG | 33 | 11 | 7 |
| | | | | | | | | | | | GC | 66 | 77 | |
| | | | | | | | | | | | CC | 121 | 132 | |
| Sathyan et al, 2015 (32) | ROS | India | 2014 | 220 | 250 | 51.2 | NA | 123 (56) | NA | -174G>C | GG | 144 | 153 | 6 |
| | | | | | | | | | | | GC | 63 | 80 | |
| | | | | | | | | | | | CC | 8 | 11 | |
| | | | | | | | | | | -572G>C | GG | 57 | 81 | |
| | | | | | | | | | | | GC | 126 | 111 | |
| | | | | | | | | | | | CC | 37 | 52 | |
| Bayri et al, 2015 (33) | POS | Turkey | 2015 | 120 | 120 | NA | NA | NA | NA | -174G>C | GG | 72 | 66 | 6 |
| | | | | | | | | | | | GC | 36 | 42 | |
| | | | | | | | | | | | CC | 12 | 12 | |
| | | | | | | | | | | -572G>C | GG | 94 | 83 | |
| | | | | | | | | | | | GC | 24 | 33 | |
| | | | | | | | | | | | CC | 2 | 4 | |
| Xu et al, 2021 (18) | POS | China | 2016-2020 | 384 | 384 | 57.1 | 66.5 | 117 (30) | 117 (30) | -174G>C | GG | 0 | 0 | 6 |
| | | | | | | | | | | | GC | 0 | 0 | |
| | | | | | | | | | | | CC | 384 | 384 | |
| | | | | | | | | | | -572G>C | GG | 17 | 18 | |
| | | | | | | | | | | | GC | 137 | 141 | |
| | | | | | | | | | | | CC | 230 | 225 | |

C: Cytosine; G: Guanine; IAs: Intracranial Aneurysms; N: Number; NA: Not Available; NOS: Newcastle-Ottawa quality assessment Scale; POS: Prospective Observational Study; ROS: Retrospective Observational Study

in 6 studies. Results of the analysis on -174GG, -174GC, and 174CC genotypes were OR= 1.13, 95% CI [0.95-1.35], p= 0.17; OR= 0.96, 95% CI [0.81-1.14], p=0.65; OR= 0.77, 95% CI [0.59-1.00], p= 0.05; respectively. Albeit revealing a clear correlation, the pooled results of each -174 genotype's examinations did not show differences. Regarding the heterogeneity, the $I^2$ value was less then 50% and $p^q$ >0.05 for all the -174G>C analyses (Figures 2-4).

IL-6 -572G>C polymorphisms and their rela-

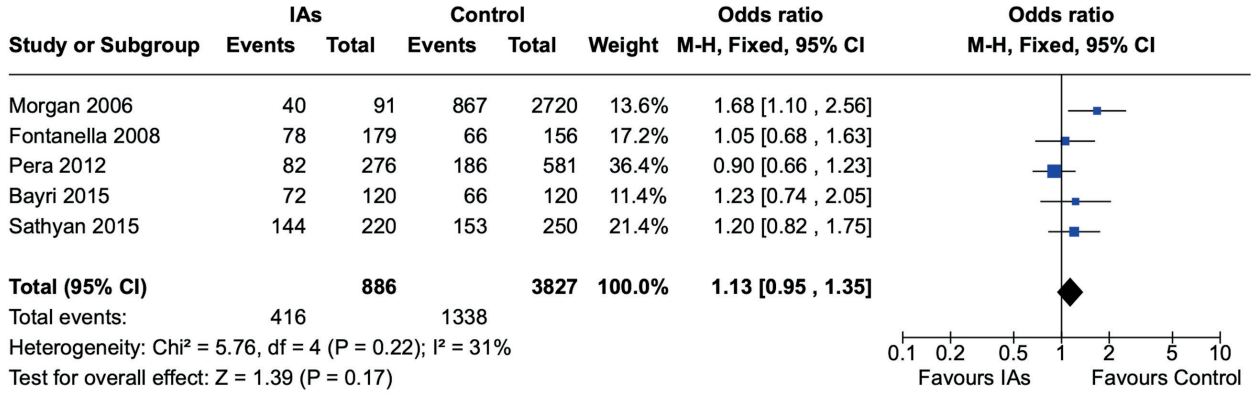



**Figure 2.** Forest plot for -174GG polymorphism

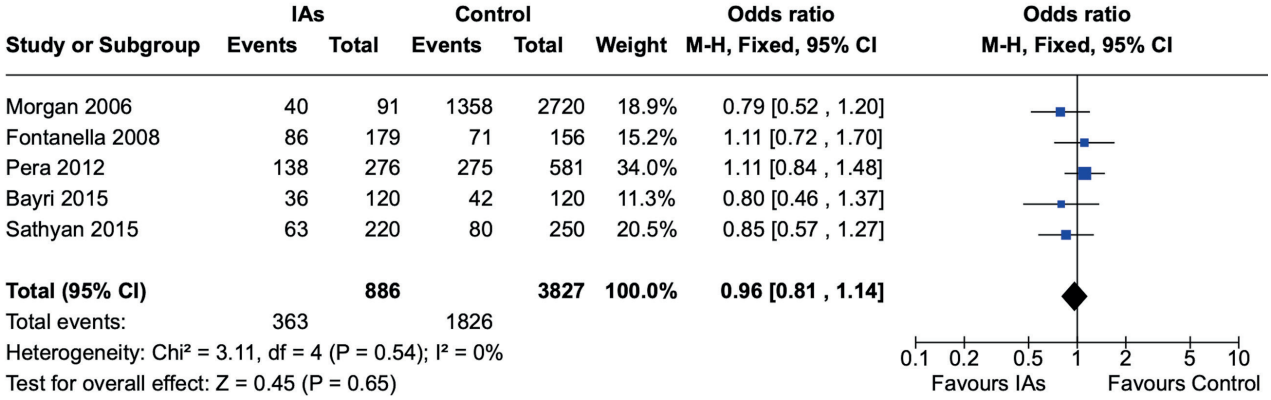



**Figure 3.** Forest plot for -174GC polymorphism

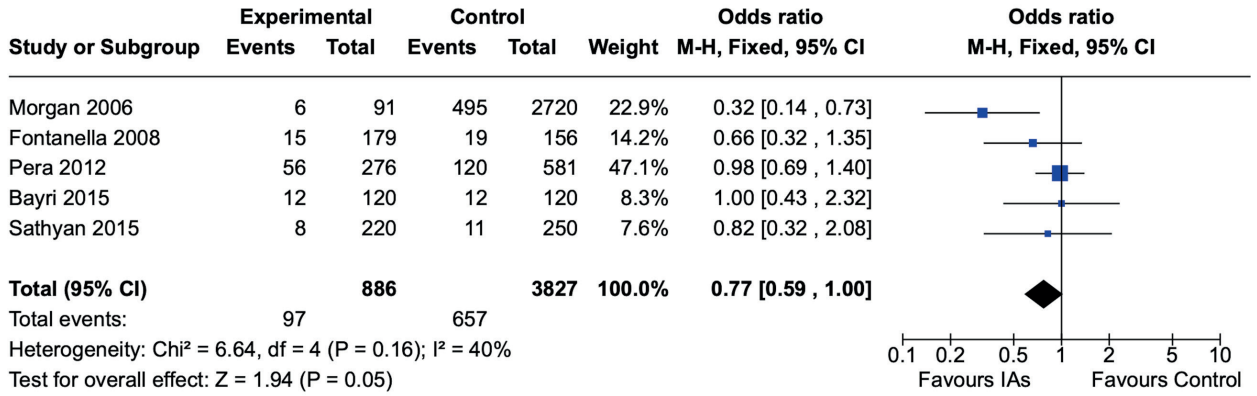



**Figure 4.** Forest plot for -174CC polymorphism

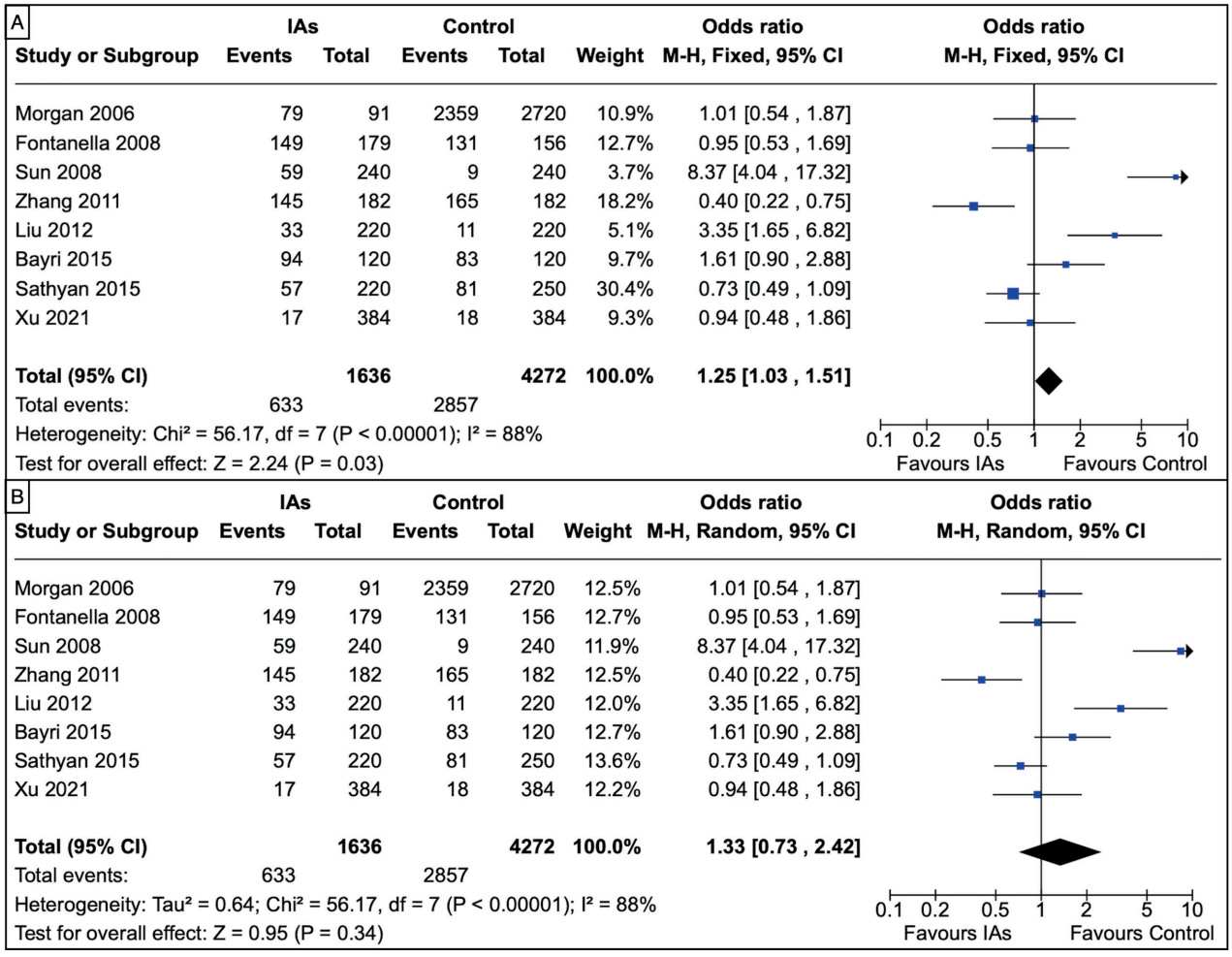



**Figure 5.** Forest plot for -572GG polymorphism. (A) Fixed and (B) random model.

tion to IAs was investigated in 8 case-control studies. About the -572GG genotype, the OR was 1.25, 95% CI [1.03 -1.51], and p=0.03. The analyses of -572GC and -572CC polymorphisms showed significant differences. Results were as follows: -572GC: OR=1.30, 95% CI [1.11-1.51], p= 0.0009; OR= 0.67, 95% CI [0.57-0.80], p= 0.00001 (Figures 5-7).

In the quantitative synthesis of the -572G>C genotype, the $I^2$ was found greater than 50% and the $p^q$ was <0.05. Consequently, the random-effect model was also applied, and the results were as follows: -572GG: OR= 1.33, 95% CI [0.73-2.42], p=0.34; -572GC: OR= 1.36, 95% CI [0.89-2.06], p= 0.15; -572CC: OR= 1.06, 95% CI [0.50-2.25], p= 0.88.

*Publication Bias*

Begg's rank and Egger's methods revealed no publication bias for the -174G>C genotype analysis (Figure 8).

Instead, increased risks of bias were found for the -572G>C polymorphism (Figure 9).

## Discussion

This meta-analysis aimed to explore the correlation between genotype variability of IL-6 -174G>C and -572G>C and susceptibility to IAs.

In the era of translational medicine, advances in

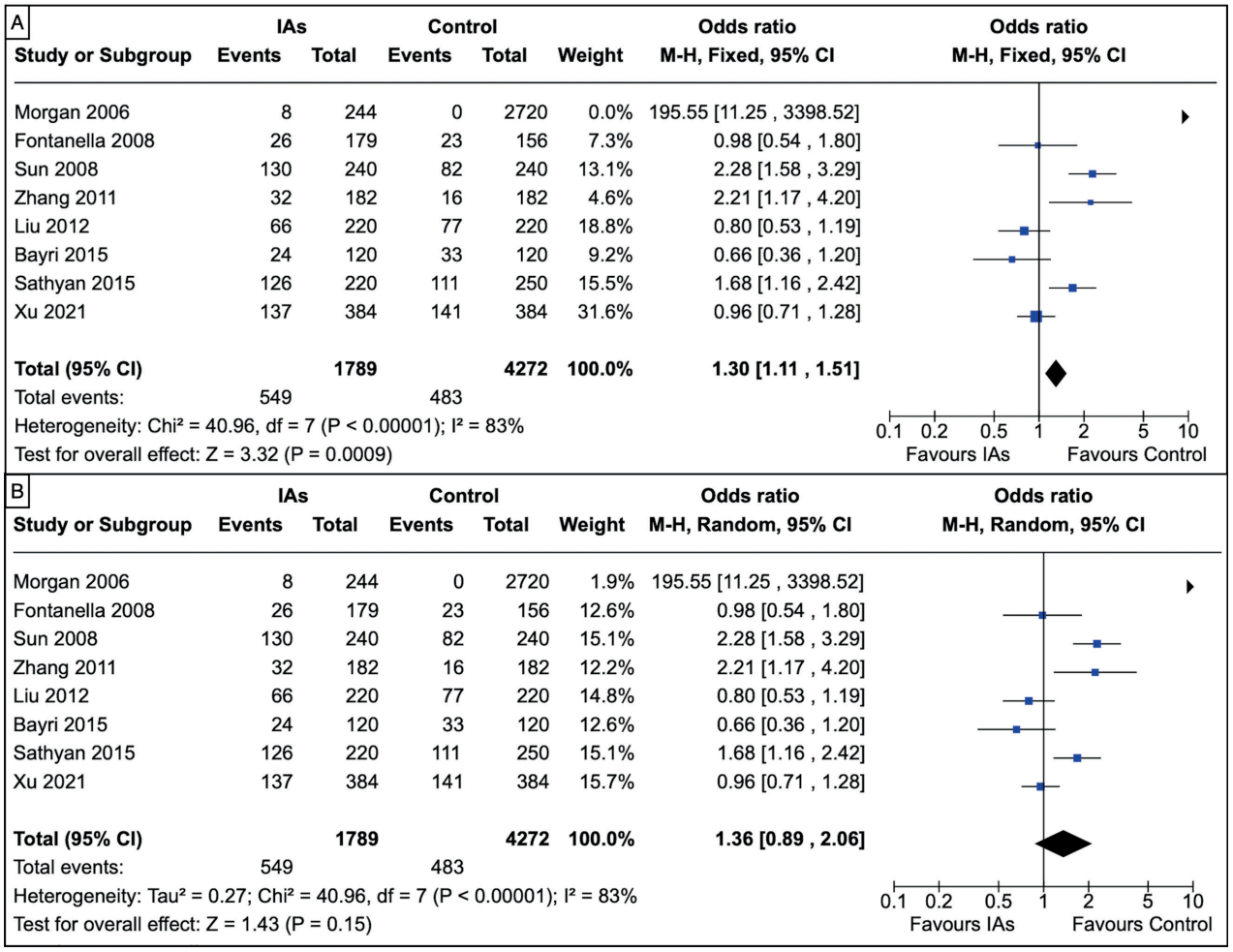



**Figure 6.** Forest plot for -572GC polymorphism. (A) Fixed and (B) random model..

molecular biotechnologies and haplotype-based genome-wide linkage analysis gave tremendous advantages in the identification of the inflammatory and genetic mechanisms underlying the pathogenesis of many neurovascular and neuro-oncological diseases (43-64).

The natural history of brain aneurysms is controversial, strongly influenced by individual immunogenetic stimuli. The primum movens was identified in the wall shear stress, which promotes endothelial dysfunction, vascular remodeling, and immune activation (13, 65-67). The recruited inflammatory cytokines and the endothelial oxidative stress progressively damage vessels, resulting in the thinning and bulging of the arterial wall (68-70). Genetic mutations of proinflammatory interleukin and the consequent imbalance in immunological response may affect the onset and progression of IAs (14, 71). IL-6 is secreted by macrophages, endothelial and lymphoid cells, and takes part in the adaptive immunity and tissue repair processes (72, 73).

Current pieces of evidence strongly support the correlation between the IL-6 -174G>C and -572G/C polymorphisms and SAH (74, 75). In 2006, Morgan et al. conducted the first population-based case-control study to test the relation of IL-6 genotypes with the intracranial aneurysmal disease, describing a reasonable association of the -572G>C polymorphism in Caucasian people (28). Studies on the Chinese population all reported a higher risk of IAs for patients harboring -572G>C genotype. The G allele variation was

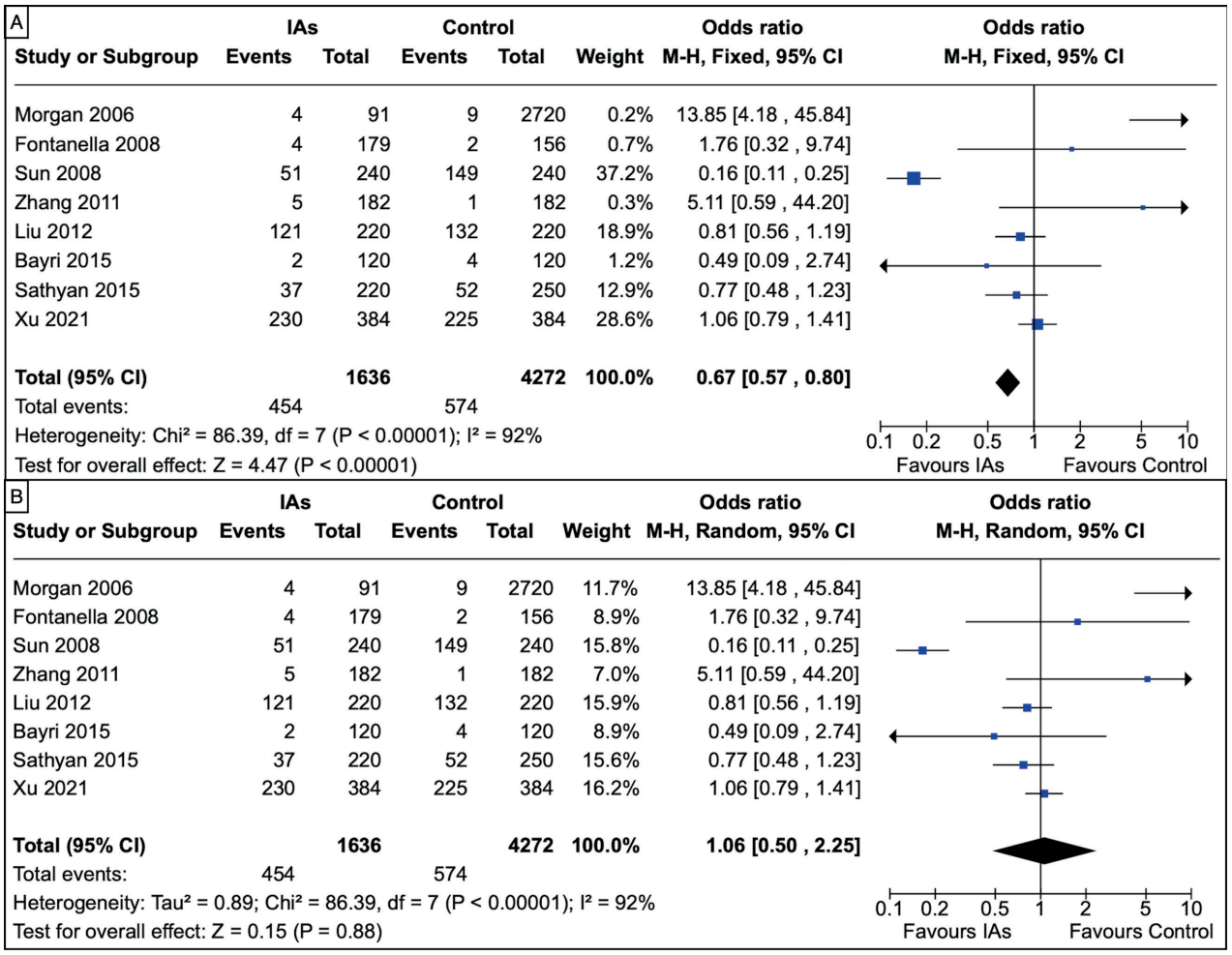


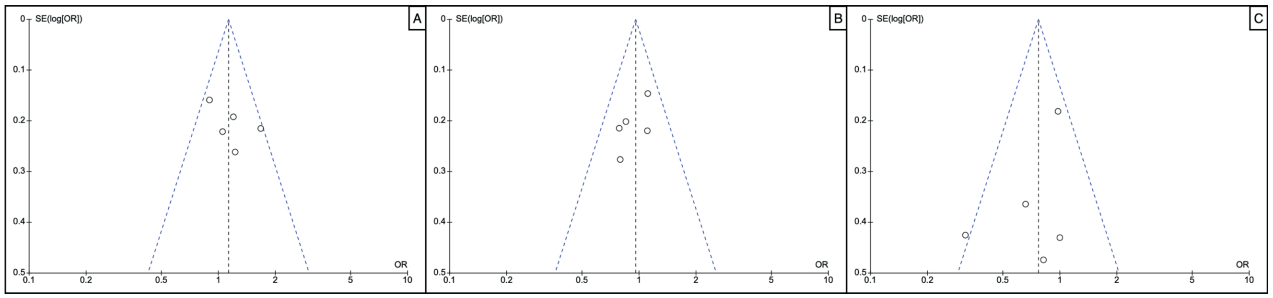

**Figure 7.** Forest plot for -572CC polymorphism. (A) Fixed and (B) random model

the most represented (30, 31, 33). Conversely, conflicting results were found in European populations. Neither Fontanella and colleagues, in 2008, nor Pera et al., in 2012, found any correlation between the IL-6 gene and IAs (29, 32). The most recent study by Xu et al. in 2021 demonstrated a close relation between proinflammatory cytokines polymorphisms and the genetic risk factors of IAs in Chinese people (20).

In accordance with the literature, our meta-analysis failed to find any connection between the -174G>C genotype and IAs. Moreover, we reported a statistical difference for -572GG/GC/CC genotypes distribution in the fixed-effects model (p=0.03, p= 0.0009; p= 0.00001), although limited by the high heterogeneity between the groups ($I^2$= 88%, $I^2$= 83%; $I^2$= 92%). By applying the random- model, the associations were no longer detected.

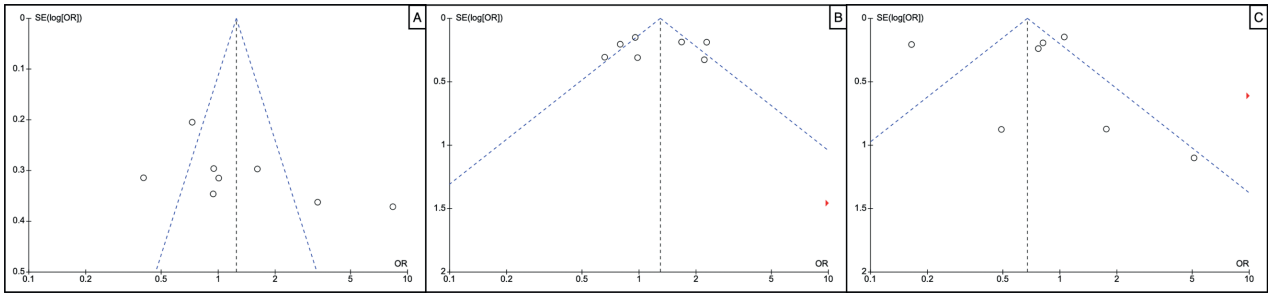
Our results highlight the importance of ethnic-specific differences in genetic polymorphisms expression and the racial influence, as reported by European vs Chinese studies, in IAs pathogenesis.

The increasing allele frequency of -572G>C raises the serum concentration of IL-6. It upregulates the inflammatory cascade, inhibits collagen production in the endothelial cells, and causes progressive damage fragility of the arterial wall (31). IL-6 modulates lipid metabolism, increases the risk of intracranial arteriosclerosis, and has a direct cytotoxic effect on oligodendrocytes (76-80). Furthermore, it acts as a strong vascular vasoconstrictor (81). The high level of IL-6




**(A) -174GG, (B) -174GC, and (C) -174CC polymorphisms**

**Figure 8.** Funnel plot for -174G>C polymorphisms




**(A) -572GG, (B) -572GC, and (C) -572CC polymorphisms**

**Figure 9.** Funnel plot for -572G>C polymorphisms

increases the incidence of vasospasm after SAH, worse cerebral ischemia, and indirectly affects the patient's outcome (81, 82).

## Limitations of the Study

The present study has some limitations. First, the selection bias cannot be avoided because of the relatively limited sample size and the high heterogeneity across ethnicities. Second, we did not include the acquired risk factors like smoking and hypertension. Third, the retrospective nature of studies included in the meta-analysis was a further limitation to be considered.

## Conclusion

Local recruitment of proinflammatory IL-6 at the arterial wall primes the endothelial dysfunction leading to the vessel damage and genesis of IAs.

IL-6 polymorphisms result in the upregulation of inflammatory pathways, thus affecting the natural history of IAs.

The present study reported a direct connection between IL-6 -572 GG/GC/CC polymorphisms and IAs, while no differences in -174 G>C polymorphisms were found.

Further genetic studies across different ethnicities are needed to confirm the association between IL6 gene polymorphisms and the risk of IAs.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

## References

1. Juvela S. Prevalence of and risk factors for intracranial aneurysms. Lancet Neurol. 2011;10(7):595-7.
2. Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29(1):251-6.
3. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence

of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol. 2011;10(7):626-36.
4. Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, et al. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. Stroke. 2004;35(10):2287-93.
5. Pritchard C, Foulkes L, Lang DA, Neil-Dwyer G. Psychosocial outcomes for patients and carers after aneurysmal subarachnoid haemorrhage. Br J Neurosurg. 2001;15(6):456-63.
6. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology. 1998;50(5):1413-8.
7. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103-10.
8. Serrone JC, Maekawa H, Tjahjadi M, Hernesniemi J. Aneurysmal subarachnoid hemorrhage: pathobiology, current treatment and future directions. Expert Rev Neurother. 2015;15(4):367-80.
9. Luzzi S, Gragnaniello C, Giotta Lucifero A, Del Maestro M, Galzio R. Surgical Management of Giant Intracranial Aneurysms: Overall Results of a Large Series. World Neurosurg. 2020;144:e119-e37.
10. Luzzi S, Gragnaniello C, Giotta Lucifero A, Del Maestro M, Galzio R. Microneurosurgical management of giant intracranial aneurysms: Datasets of a twenty-year experience. Data Brief. 2020;33:106537.
11. Luzzi S, Del Maestro M, Galzio R. Letter to the Editor. Preoperative embolization of brain arteriovenous malformations. J Neurosurg. 2019;132(6):2014-6.
12. Luzzi S, Del Maestro M, Elbabaa SK, Galzio R. Letter to the Editor Regarding "One and Done: Multimodal Treatment of Pediatric Cerebral Arteriovenous Malformations in a Single Anesthesia Event". World Neurosurg. 2020;134:660.
13. Cebral JR, Detmer F, Chung BJ, Choque-Velasquez J, Rezai B, Lehto H, et al. Local Hemodynamic Conditions Associated with Focal Changes in the Intracranial Aneurysm Wall. AJNR Am J Neuroradiol. 2019;40(3):510-6.
14. Tulamo R, Frösen J, Hernesniemi J, Niemelä M. Inflammatory changes in the aneurysm wall: a review. J Neurointerv Surg. 2010;2(2):120-30.
15. Giotta Lucifero A, Baldoncini M, Bruno N, Galzio R, Hernesniemi J, Luzzi S. Shedding the Light on the Natural History of Intracranial Aneurysms: An Updated Overview. Medicina (Kaunas). 2021;57(8).
16. Hasan D, Chalouhi N, Jabbour P, Hashimoto T. Macrophage imbalance (M1 vs. M2) and upregulation of mast cells in wall of ruptured human cerebral aneurysms: preliminary results. J Neuroinflammation. 2012;9:222.
17. Starke RM, Chalouhi N, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, et al. Critical role of TNF--in cerebral aneurysm formation and progression to rupture. J Neuroinflammation. 2014;11:77.
18. Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, et al. Biology of intracranial aneurysms: role of inflammation. J Cereb Blood Flow Metab. 2012;32(9):1659-76.
19. Niu PP, Wang X, Xu YM. Association of Interleukin-6 Signaling and C-Reactive Protein With Intracranial Aneurysm: A Mendelian Randomization and Genetic Correlation Study. Front Genet. 2021;12:679363.
20. Xu L, Hu L, Hu C, Liu J, Li B, Liao X, et al. Associations between Inflammatory Cytokine Gene Polymorphisms and Susceptibilities to Intracranial Aneurysm in Chinese Population. Biomed Res Int. 2021;2021:8865601.
21. Bowcock AM, Kidd JR, Lathrop GM, Daneshvar L, May LT, Ray A, et al. The human "interferon-beta 2/hepatocyte stimulating factor/interleukin-6" gene: DNA polymorphism studies and localization to chromosome 7p21. Genomics. 1988;3(1):8-16.
22. Rivera-Chavez FA, Peters-Hybki DL, Barber RC, O'Keefe GE. Interleukin-6 promoter haplotypes and interleukin-6 cytokine responses. Shock. 2003;20(3):218-23.
23. Brull DJ, Montgomery HE, Sanders J, Dhamrait S, Luong L, Rumley A, et al. Interleukin-6 gene -174g>c and -572g>c promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. Arterioscler Thromb Vasc Biol. 2001;21(9):1458-63.
24. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998;102(7):1369-76.
25. Bennermo M, Held C, Green F, Strandberg LE, Ericsson CG, Hansson LO, et al. Prognostic value of plasma interleukin-6 concentrations and the -174 G > C and -572 G > C promoter polymorphisms of the interleukin-6 gene in patients with acute myocardial infarction treated with thrombolysis. Atherosclerosis. 2004;174(1):157-63.
26. Smallwood L, Allcock R, van Bockxmeer F, Warrington N, Palmer LJ, Iacopetta B, et al. Polymorphisms of the interleukin-6 gene promoter and abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2008;35(1):31-6.
27. Greisenegger S, Endler G, Haering D, Schillinger M, Lang W, Lalouschek W, et al. The (-174) G/C polymorphism in the interleukin-6 gene is associated with the severity of acute cerebrovascular events. Thromb Res. 2003;110(4):181-6.
28. Morgan L, Cooper J, Montgomery H, Kitchen N, Humphries SE. The interleukin-6 gene -174G>C and -572G>C promoter polymorphisms are related to cerebral aneurysms. J Neurol Neurosurg Psychiatry. 2006;77(8):915-7.
29. Fontanella M, Rainero I, Gallone S, Rubino E, Fenoglio P, Valfrè W, et al. Interleukin 6 gene polymorphisms are not associated with aneurysmal subarachnoid haemorrhage in an Italian population. J Neurol Neurosurg Psychiatry. 2008;79(4):471-3.

30. Sun H, Zhang D, Zhao J. The interleukin-6 gene -572G>C promoter polymorphism is related to intracranial aneurysms in Chinese Han nationality. Neurosci Lett. 2008;440(1):1-3.
31. Zhang G, Tu Y, Feng W, Huang L, Li M, Qi S. Association of interleukin-6-572G/C gene polymorphisms in the Cantonese population with intracranial aneurysms. J Neurol Sci. 2011;306(1-2):94-7.
32. Pera J, Dziedzic T, Adamski M, Jagiella J, Krupa M, Moskala M, et al. Interleukin 6-174G>C polymorphism and risk of aneurysmal subarachnoid hemorrhage: case-control study and meta-analysis. Acta Neurol Scand. 2012;125(2):111-5.
33. Liu Y, Sun J, Wu C, Cao X, He M, You C. The interleukin-6-572G/C gene polymorphism and the risk of intracranial aneurysms in a Chinese population. Genet Test Mol Biomarkers. 2012;16(7):822-6.
34. Sathyan S, Koshy LV, Srinivas L, Easwer HV, Premkumar S, Nair S, et al. Pathogenesis of intracranial aneurysm is mediated by proinflammatory cytokine TNFA and IFNG and through stochastic regulation of IL10 and TGFB1 by comorbid factors. J Neuroinflammation. 2015;12:135.
35. Bayri Y, Ta-kin E, Ulus A, Bayrakli F, Altun A, Bagci H. Lack of Association Between Interleukin 6 Gene Promoter Polymorphisms and Aneurysmal Subarachnoid Hemorrhage in Turkish Population. Journal of Neurological Sciences. 2015;32:288-92.
36. Treska V, Topolcan O, Pecen L. Cytokines as plasma markers of abdominal aortic aneurysm. Clin Chem Lab Med. 2000;38(11):1161-4.
37. Lin CY, Lin CC, Hwang B, Chiang BN. Cytokines predict coronary aneurysm formation in Kawasaki disease patients. Eur J Pediatr. 1993;152(4):309-12.
38. Lindeman JH, Abdul-Hussien H, Schaapherder AF, Van Bockel JH, Von der Thüsen JH, Roelen DL, et al. Enhanced expression and activation of pro-inflammatory transcription factors distinguish aneurysmal from atherosclerotic aorta: IL-6- and IL-8-dominated inflammatory responses prevail in the human aneurysm. Clin Sci (Lond). 2008;114(11):687-97.
39. Fragoso J, Delgadillo H, Juárez-Cedillo T, Rodríguez-Pérez J, Vallejo M, Pérez-Méndez O, et al. The Interleukin 6 -572 G>C (rs1800796) Polymorphism Is Associated with the Risk of Developing Acute Coronary Syndrome. Genetic testing and molecular biomarkers. 2010;14:759-63.
40. Hua Y, Guo X, Huang Q, Kong Y, Lu X. Association between interleukin-6 -174G/C polymorphism and the risk of Alzheimer's disease: a meta-analysis. Int J Neurosci. 2013;123(9):626-35.
41. Zheng GH, Chen HY, Xiong SQ. Polymorphisms of -174G>C and -572G>C in the interleukin 6 (IL-6) gene and coronary heart disease risk: a meta-analysis of 27 research studies. PLoS One. 2012;7(4):e34839.
42. Yin YW, Hu AM, Sun QQ, Liu HL, Wang Q, Zeng YH, et al. Association between interleukin-6 gene -174 G/C polymorphism and the risk of coronary heart disease: a meta-analysis of 20 studies including 9619 cases and 10,919 controls. Gene. 2012;503(1):25-30.
43. Frösen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A, et al. Saccular intracranial aneurysm: pathology and mechanisms. Acta Neuropathol. 2012;123(6):773-86.
44. Tang G, Chiocca A. Gene transfer and delivery in central nervous system disease. Neurosurg Focus. 1997;3(3):e2.
45. Lim M, Weller M, Chiocca EA. Current State of Immune-Based Therapies for Glioblastoma. Am Soc Clin Oncol Educ Book. 2016;35:e132-9.
46. Reardon DA, Freeman G, Wu C, Chiocca EA, Wucherpfennig KW, Wen PY, et al. Immunotherapy advances for glioblastoma. Neuro Oncol. 2014;16(11):1441-58.
47. Samuel N, Radovanovic I. Genetic basis of intracranial aneurysm formation and rupture: clinical implications in the postgenomic era. Neurosurg Focus. 2019;47(1):E10.
48. Caranci F, Briganti F, Cirillo L, Leonardi M, Muto M. Epidemiology and genetics of intracranial aneurysms. Eur J Radiol. 2013;82(10):1598-605.
49. Giotta Lucifero A, Luzzi S, Brambilla I, Trabatti C, Mosconi M, Savasta S, et al. Innovative therapies for malignant brain tumors: the road to a tailored cure. Acta Biomed. 2020;91(7-s):5-17.
50. Luzzi S, Crovace AM, Del Maestro M, Giotta Lucifero A, Elbabaa SK, Cinque B, et al. The cell-based approach in neurosurgery: ongoing trends and future perspectives. Heliyon. 2019;5(11):e02818.
51. Luzzi S, Crovace AM, Lacitignola L, Valentini V, Francioso E, Rossi G, et al. Engraftment, neuroglial transdifferentiation and behavioral recovery after complete spinal cord transection in rats. Surg Neurol Int. 2018;9:19.
52. Palumbo P, Lombardi F, Augello FR, Giusti I, Luzzi S, Dolo V, et al. NOS2 inhibitor 1400W Induces Autophagic Flux and Influences Extracellular Vesicle Profile in Human Glioblastoma U87MG Cell Line. Int J Mol Sci. 2019;20(12).
53. Raysi Dehcordi S, Ricci A, Di Vitantonio H, De Paulis D, Luzzi S, Palumbo P, et al. Stemness Marker Detection in the Periphery of Glioblastoma and Ability of Glioblastoma to Generate Glioma Stem Cells: Clinical Correlations. World Neurosurg. 2017;105:895-905.
54. Savioli G, Ceresa IF, Macedonio S, Gerosa S, Belliato M, Iotti GA, et al. Trauma Coagulopathy and Its Outcomes. Medicina (Kaunas). 2020;56(4).
55. Giotta Lucifero A, Luzzi S. Against the Resilience of High-Grade Gliomas: The Immunotherapeutic Approach (Part I). Brain Sci. 2021;11(3).
56. Giotta Lucifero A, Luzzi S. Against the Resilience of High-Grade Gliomas: Gene Therapies (Part II). Brain Sci. 2021;11(8).
57. Garone G, Reale A, Vanacore N, Parisi P, Bondone C, Suppiej A, et al. Acute ataxia in paediatric emergency departments: a multicentre Italian study. Arch Dis Child. 2019;104(8):768-74.
58. Gastaldi M, Scaranzin S, Jarius S, Wildeman B, Zardini E, Mallucci G, et al. Cell-based assays for the detection of MOG antibodies: a comparative study. J Neurol. 2020;267(12):3555-64.

59. Foiadelli T, Piccorossi A, Sacchi L, De Amici M, Tucci M, Brambilla I, et al. Clinical characteristics of headache in Italian adolescents aged 11-16 years: a cross-sectional questionnaire school-based study. Ital J Pediatr. 2018;44(1):44.
60. Savasta S, Rossi A, Foiadelli T, Licari A, Elena Perini AM, Farello G, et al. Melkersson-Rosenthal Syndrome in Childhood: Report of Three Paediatric Cases and a Review of the Literature. Int J Environ Res Public Health. 2019;16(7).
61. Foiadelli T, Savasta S, Battistone A, Kota M, Passera C, Fiore S, et al. Nucleotide variation in Sabin type 3 poliovirus from an Albanian infant with agammaglobulinemia and vaccine associated poliomyelitis. BMC Infect Dis. 2016;16:277.
62. Savasta S, Rovida F, Foiadelli T, Campana AM, Percivalle E, Marseglia GL, et al. West-Nile virus encephalitis in an immunocompetent pediatric patient: successful recovery. Ital J Pediatr. 2018;44(1):140.
63. Michev A, Musso P, Foiadelli T, Trabatti C, Lozza A, Franciotta D, et al. Bickerstaff Brainstem Encephalitis and overlapping Guillain-Barré syndrome in children: Report of two cases and review of the literature. Eur J Paediatr Neurol. 2019;23(1):43-52.
64. Orsini A, Foiadelli T, Carli N, Costagliola G, Masini B, Bonuccelli A, et al. Rasmussen's encephalitis: From immune pathogenesis towards targeted-therapy. Seizure. 2020;81:76-83.
65. Katritsis D, Kaiktsis L, Chaniotis A, Pantos J, Efstathopoulos EP, Marmarelis V. Wall shear stress: theoretical considerations and methods of measurement. Prog Cardiovasc Dis. 2007;49(5):307-29.
66. Staarmann B, Smith M, Prestigiacomo CJ. Shear stress and aneurysms: a review. Neurosurg Focus. 2019;47(1):E2.
67. Sforza DM, Putman CM, Cebral JR. Hemodynamics of Cerebral Aneurysms. Annu Rev Fluid Mech. 2009;41:91-107.
68. Sakamoto N, Saito N, Han X, Ohashi T, Sato M. Effect of spatial gradient in fluid shear stress on morphological changes in endothelial cells in response to flow. Biochem Biophys Res Commun. 2010;395(2):264-9.
69. Turjman AS, Turjman F, Edelman ER. Role of fluid dynamics and inflammation in intracranial aneurysm formation. Circulation. 2014;129(3):373-82.
70. Frösen J. Smooth muscle cells and the formation, degeneration, and rupture of saccular intracranial aneurysm wall--a review of current pathophysiological knowledge. Transl Stroke Res. 2014;5(3):347-56.
71. Kataoka K, Taneda M, Asai T, Kinoshita A, Ito M, Kuroda R. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. Stroke. 1999;30(7):1396-401.
72. Le JM, Vilcek J. Interleukin 6: a multifunctional cytokine regulating immune reactions and the acute phase protein response. Lab Invest. 1989;61(6):588-602.
73. Song M, Kellum JA. Interleukin-6. Crit Care Med. 2005; 33(12 Suppl):S463-5.
74. Zheng S, Su A, Sun H, You C. The association between interleukin-6 gene polymorphisms and intracranial aneurysms: a meta-analysis. Hum Immunol. 2013;74(12):1679-83.
75. Hu L, Li B, Liao X, Yan J. Polymorphisms of Inflammatory Cytokine Genes and Risk for Intracranial Aneurysm: A Systematic Review and Meta-Analysis. Yonsei Med J. 2020;61(5):391-9.
76. Skirgaudas M, Awad IA, Kim J, Rothbart D, Criscuolo G. Expression of angiogenesis factors and selected vascular wall matrix proteins in intracranial saccular aneurysms. Neurosurgery. 1996;39(3):537-45; discussion 45-7.
77. Yoon BH, Jun JK, Romero R, Park KH, Gomez R, Choi JH, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy. Am J Obstet Gynecol. 1997;177(1):19-26.
78. Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. Semin Neonatol. 2000;5(1):3-16.
79. Giacomini T, Foiadelli T, Annovazzi P, Nosadini M, Gastaldi M, Franciotta D, et al. Pediatric optic neuritis and anti MOG antibodies: a cohort of Italian patients. Mult Scler Relat Disord. 2019;39:101917.
80. Foiadelli T, Gastaldi M, Scaranzin S, Franciotta D, Savasta S. Seizures and myelin oligodendrocyte glycoprotein (MOG) antibodies: Two paradigmatic cases and a review of the literature. Mult Scler Relat Disord. 2020;41:102011.
81. Osuka K, Suzuki Y, Tanazawa T, Hattori K, Yamamoto N, Takayasu M, et al. Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. Acta Neurochir (Wien). 1998;140(9):943-51.
82. Kwon KY, Jeon BC. Cytokine levels in cerebrospinal fluid and delayed ischemic deficits in patients with aneurysmal subarachnoid hemorrhage. J Korean Med Sci. 2001;16(6):774-80.

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