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Review Article

Association between tumor necrosis factor-alpha (TNF-α) polymorphism (-308, G/A) and acute rejection of solid organ allograft: a meta-analysis

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Abstract: The association between gene polymorphisms of tumor necrosis factor-alpha (TNF-α) and risk of acute rejection (AR) of solid organ allograft was investigated in many published studies; however, the currently available results are inconclusive. Therefore, we performed a meta-analysis to provide a precise evidence for an association between the TNF-α polymorphism and risk of AR. A comprehensive electronic search of PUBMED, EMBASE, scholar of google, and Korean databases was performed until June 1, 2015. Meta-analysis was performed using the comprehensive meta-analysis software (Corporation, NJ, USA). The pooled *p* value, OR and 95% CI were used to measure the strength of the association with TNF-α. Forty five eligible studies were included in this meta-analysis. Our study revealed that combined genotype (A/A genotype +A/G genotype) was contributed to susceptibility of AR in solid organ recipients (OR = 1.424, 95% CI = 1.118-1.813, P = 0.004). Moreover, the Egger's test showed quantitative evidence for absence of publication bias (P = 0.149). This meta-analysis indicated the TNF-α polymorphism (-308, G/A) might be genetic risk factors for acute rejection. However, more studies with larger sample size were needed to provide more precise evidence.

Keywords: Tumor necrosis factor-α, polymorphism, acute rejection, meta-analysis

Introduction

Despite the use of potent immunosuppressive agents, acute allograft rejection remains a problem after solid organ transplantation. Acute rejection (AR) is the major predictor of the occurrence of chronic allograft rejection and long-term graft survival. Recently, there are increasing interests in the role of cytokines in the suscetibility of AR. Cytokines play an important role in the immunologic events after transplantation and they have an important bearing on graft rejection.

Tumor necrosis factor-alpha (TNF-α) is chiefly produced by activated macrophages and is a cell signaling protein involved in systemic inflammation [1]. TNF-α is one of the key enzymes in regulation of immunity. Also, it is closely associated with the pathogenesis of acute and chronic allograft rejection [2]. Many researchers have demonstrated an increased concentration of TNF-α in the plasma of recipients during AR of solid organ allografts [3-5]. It suggested that TNF-α may play a significant role in the development and progression of AR.

The TNF-α gene is localized in the HLA Class III region of the major histocompatibility complex (MHC) on chromosome 6p21.3 [6]. A G-to-A polymorphism at position -308 in the promoter region of the TNF-α gene increases transcriptional activity and elevates TNF-α production in vitro [7, 8]. The polymorphism (-308, G/A) of TNF-α has been reported to be associated with an increased risk of AR.

Up to now, several studies were to evaluate the association between TNF-α polymorphism (-308, G/A) and risk of acute allograft rejection in diverse populations. However, the results from the published studies remain conflicting rather than conclusive.

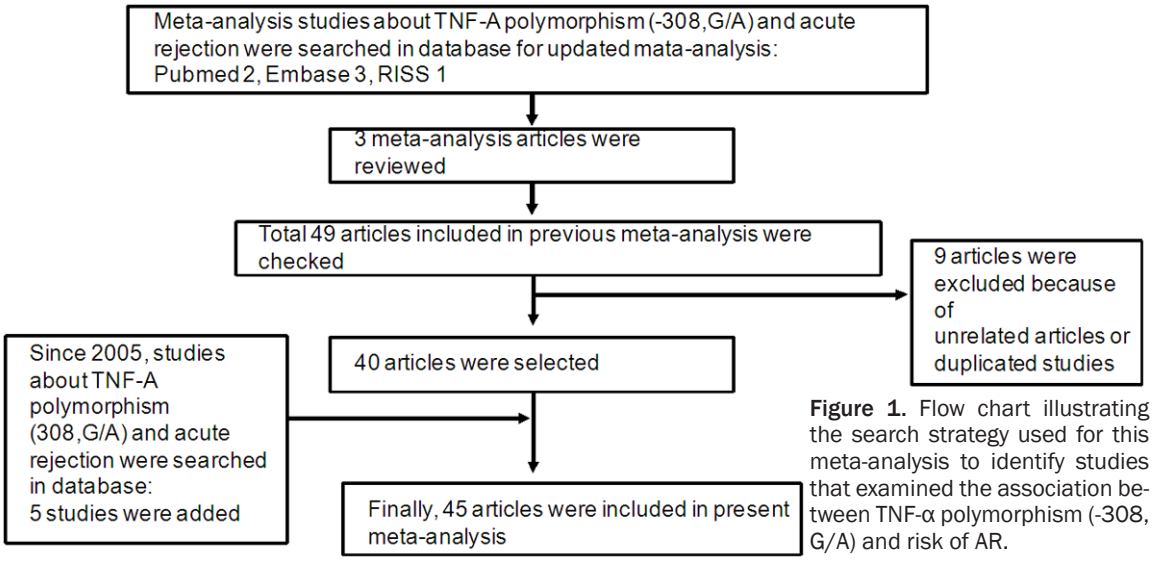

Figure 1. Flow chart illustrating the search strategy used for this meta-analysis to identify studies that examined the association between TNF-α polymorphism (-308, G/A) and risk of AR.

Therefore, we performed a meta-analysis on all eligible case-control studies to clarify the association between the TNF-α polymorphism (-308, G/A) and AR of solid organ allograft.

Materials and methods

Search strategy

In order to identify all eligible studies that were investigated the association between TNF-α polymorphism (-308, G/A) and susceptibility of AR in solid organ transplantation, a comprehensive electronic search including PUBMED, EMBASE, scholar of google, and Korean databases was performed until June 1, 2015. The keywords to find these studies were using following search terms: "tumor necrosis factor", "TNF-alpha", or "TNF-A", AND "polymorphism", "polymorphisms", or "variant" AND "rs1800-629", or "-308" AND "acute rejection", "AR", or "meta analysis". The previous meta-analysis studies about TNF-α (-308, G/A AR were considered as reference. Additional studies were identified by a hand search of the references of original studies.

Inclusion criteria

Studies were included if they met the following criteria: (1) evaluation the association between the TNF-α polymorphism (-308, G/A) and AR; (2) study was designed using the methodology of a case-control study; (3) contained sufficient distribution of TNF-α polymorphism (-308, G/A) in the AR group and the non-AR group for the estimation of an odds ratio (OR), 95% confidence interval (CI), and *p* value.

Data extraction

The investigators extracted data and reached consensus on all of the items. If the investigators generated different results, they would check the data again and had a discussion to come to an agreement. Data extracted from the selected articles including the first author's name, year of publication, population of subject, number of cases and controls, and genotype frequency of TNF-α polymorphism (-308, G/A).

Statistical analysis

Meta-analysis was performed using the comprehensive meta-analysis software (Biostat, Englewood, NJ, USA). The pooled *p* value, OR and 95% CI were used to evaluate association between risk of AR and TNF-α polymorphism (-308, G/A). We firstly calculated the heterogeneity within studies. The heterogeneity test was used for the null hypothesis that all studies evaluated the same effect. The chi-square-based Q test and I^2 test were applied. When *p* value of the Q test was less than 0.05 or I^2 statistic was >50%, heterogeneity was considered within studies. If there was significant heterogeneity, the random-effects Mantel-Haenszel method was adopted to evaluate the point estimates and 95% CI. Otherwise, the fixed-effects Mantel-Haenszel method was adopted.

Table 1. Information of eligible studies included in the meta-analysis

Author (year)	Population	Transplant organ	AR/ non-AR	AR			Non-AR		
				A/A	A/G	G/G	A/A	A/G	G/G
Bathgate et al. 2000 [9]	UK	Liver	68/76	15	25	28	4	30	42
Tambur et al. 2001 [10]	Israel	Liver	33/30	3 (A/A+A/G)		30	4 (A/A+A/G)		26
Jonsson et al. 2001 [11]	Australia	Liver	37/83	0	14	23	0	34	49
Cui et al. 2001 [12]	Australia	Liver	31/90	12 (A/A+A/G)		19	37 (A/A+A/G)		53
Warlé et al. 2002 [13]	Netherlands	Liver	41/48	1	16	24	2	20	26
Fernandes et al. 2002 [14]	USA	Liver	13/40	1	7	5	0	5	35
Jazrawi et al. 2003 [15]	USA	Liver	42/168	2	9	31	8	49	111
Mas et al. 2004 [16]	USA	Liver	19/55	9 (A/A+A/G)		10	11 (A/A+A/G)		44
Karasu et al. 2004 [17]	Turkey	Liver	26/17	8	0	18	0	0	17
Xie et al. 2008 [18]	China	Liver	41/145	0	6	35	0	15	130
Sankaran et al. 1999 [19]	UK	Renal	74/21	0	12	9	0	24	50
Pelletier et al. 2000 [20]	Mixed	Renal	33/68	12 (A/A+A/G)		21	21 (A/A+A/G)		47
Poli et al. 2000 [21]	Italy	Renal	92/77	31 (A/A+A/G)		61	17 (A/A+A/G)		60
Marshall et al. 2000 [22]	UK	Renal	114/95	7	34	73	7	30	58
Reviron et al. 2001 [23]	France	Renal	20/23	5 (A/A+A/G)		15	1 (A/A+A/G)		22
Cartwright et al. 2001 [24]	UK	Renal	25/24	4	6	15	2	8	14
Hahn et al. 2001 [25]	Mixed	Renal	32/88	14 (A/A+A/G)		18	22 (A/A+A/G)		66
Tian et al. 2001 [26]	China	Renal	19/72	3 (A/A+A/G)		16	6 (A/A+A/G)		66
Tian et al. 2002 [27]	China	Renal	26/89	7 (A/A+A/G)		19	6 (A/A+A/G)		83
Hutchings et al. 2002 [28]	UK	Renal	41/62	1	18	22	1	20	41
LV et al. 2002 [29]	China	Renal	39/87	18 (A/A+A/G)		21	11 (A/A+A/G)		76
McDaniel et al. 2003 [30]	Mixed	Renal	13/41	1	2	10	0	11	30
Yang et al. 2003 [31]	China	Renal	13/22	5 (A/A+A/G)		8	5 (A/A+A/G)		17
Wramner et al. 2004 [32]	Sweden	Renal	78/79	21 (A/A+A/G)		57	21 (A/A+A/G)		58
Park et al. 2004 [33]	Korea	Renal	151/13	0	5	8		14	137
Huang et al. 2004 [34]	China	Renal	33/69	17 (A/A+A/G)		16	15 (A/A+A/G)		54
Lee et al. 2004 [35]	USA	Renal	140/137	5	50	85	6	48	83
Ligeiro et al. 2004 [36]	Portugal	Renal	31/35	2 (A/A+A/G)		29	9 (A/A+A/G)		26
Pawlik et al. 2005 [37]	Poland	Renal	57/72	2	23	32	1	16	55
Guo et al. 2005 [38]	China	Renal	39/90	0	6	33	0	30	60
Dmitrienko et al. 2005 [39]	UK	Renal	50/50	3	11	36	6	8	36
Tajik et al. 2006 [40]	China	Renal	11/31	3 (A/A+A/G)		8	7 (A/A+A/G)		24
Gendzekhadze et al. 2006 [41]	Mixed	Renal	30/33	1	2	27	3	6	24
Canossi et al. 2007 [42]	Italy	Renal	25/61	0	3	22	1	8	52
Brabcova et al. 2007 [43]	Czech	Renal	190/246	2	50	138	3	62	181
Breulmann et al. 2007 [44]	Germany	Renal	115/109	34 (A/A+A/G)		81	40 (A/A+A/G)		69
Manchanda et al. 2008 [45]	India	Renal	18/82	7	9	2	25	26	31
Grinyo et al. 2008 [46]	Mix	Renal	62/160	20 (A/A+A/G)		42	32 (A/A+A/G)		128
Mendoza et al. 2008 [47]	Mexico	Renal	19/32	4 (A/A+A/G)		15	1 (A/A+A/G)		31
Azarpira et al. 2009 [48]	Iran	Renal	46/54	45 (A/A+A/G)		1	51 (A/A+A/G)		3
Dhaouadi et al. 2013 [49]	Tunisia	Renal	80/151	28 (A/A+A/G)		52	54 (A/A+A/G)		97
Mandegary et al. 2013 [50]	Iran	Renal	79/25	2 (A/A+A/G)		77	15 (A/A+A/G)		10
El-Gezawy et al. 2013 [51]	Egypt	Renal	37/47	15	0	22	9	0	38
Huijun et al. 2013 [52]	China	Lung	15/76	0	6	9	0	17	59
Mu et al. 2014 [53]	China	Lung	20/54	0	3	17	0	7	47

AR: acute rejection; non-AR: non acute rejection.

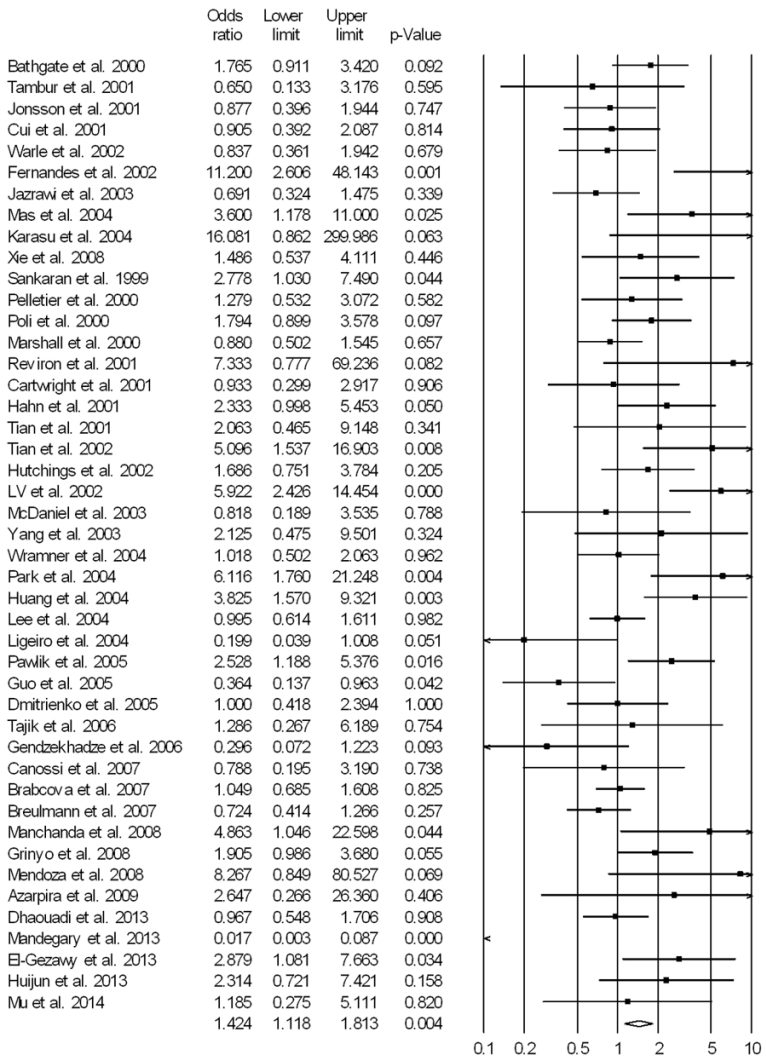

Figure 2. Overall analysis between TNF-α polymorphism (-308, G/A) between AR and non-AR in all solid organ allograft.

For meta-analysis of TNF-α polymorphism (-308, G/A), the pooled ORs, 95% CI, and *p* value were calculated using combination of genotype. We first estimated the risk of the A/A genotype and A/G genotype for AR compared with the G/G genotype as dominant model, respectively, and then evaluated the risk of "A allele vs. G allele", "A/A genotype +A/G genotype vs. G/G genotype", and "A/A genotype vs. A/G genotype +G/G genotype" on risk of AR, assuming dominant and recessive effects of the variant A allele, respectively. The P<0.05 was regarded as statistically significant association. Publication bias was evaluated using Begg's funnel plot and Egger's linear regression.

Results

Study characteristics

In order to evaluation between TNF-α polymorphism (-308, G/A) and susceptibility of AR, related studies were retrieved based on the search strategy. **Figure 1** shows flow chart illustrating the search strategy used for this meta-analysis to identify studies that examined the association between TNF-α polymorphism (-308, G/A) and risk of AR. Firstly, we searched the meta-analysis studies about TNF-α polymorphism (-308, G/A) and risk of AR. There were 3 meta-analysis articles. We checked the 49 articles included in previous meta-analysis. Then recent studies about TNF-α polymorphism (-308, G/A) and AR were searched since 2005 and we added the recent 5 studies in present meta-analysis. Finally, eligible 45 articles were selected [9-53]. The characteristics of eligible 45 studies were summarized in **Table 1**. There were 10 articles with AR of liver transplantation [9-18], 33 articles with AR of renal transplantation [19-51], and 2 articles with AR of lung transplantation [52, 53].

Quantitative synthesis

Among 45 articles, 22 articles were only including distribution of G/G genotype and distribution of combined A/G genotype +A/A genotype. 23 articles presented each distribution of A/A genotype, A/G genotype, and G/G genotype. Firstly, we analyzed whether combined genotype (A/A genotype +A/G genotype) of TNF-α polymorphism (-308, G/A) was associated with susceptibility of AR. There was significant heterogeneity among 45 studies [9-53]. The *p* value of Q test and value of I^2 statistic were P<0.001 and 64.951 (data not shown). Thus,

Table 2. Overall analysis between TNF-α polymorphism (-308, G/A) and susceptibility of AR

Organ	Comparison	Heterogeneity		Association test		
		P	I^2	Model	OR (95% CI)	P
All	A vs. G	<0.001	57.387	Random	1.379 (1.082-1.759)	0.009
Liver		0.002	71.975	Random	1.582 (0.874-2.864)	0.13
Renal		0.006	55.353	Random	1.322 (0.996-1.753)	0.05
Lung		0.551	<0.001	Fixed	1.651 (0.721-3.782)	0.24
All	AA+AG vs. GG	0.003	50.397	Random	1.413 (1.077-1.854)	0.013
Liver		0.010	64.159	Random	1.494 (0.807-2.767)	0.20
Renal		0.014	51.116	Random	1.390 (0.998-1.938)	0.05
Lung		0.483	<0.001	Fixed	1.784 (0.717-4.437)	0.21
All	AA vs. AG+GG	0.271	15.611	Fixed	1.516 (1.032-2.227)	0.034
Liver		0.187	35.161	Fixed	2.975 (1.322-6.693)	0.008
Renal		0.588	<0.001	Fixed	1.247 (0.805-1.930)	0.32
Lung		NA	NA	NA	NA	NA

AR: acute rejection; OR, odds ratio; CI, confidence interval.

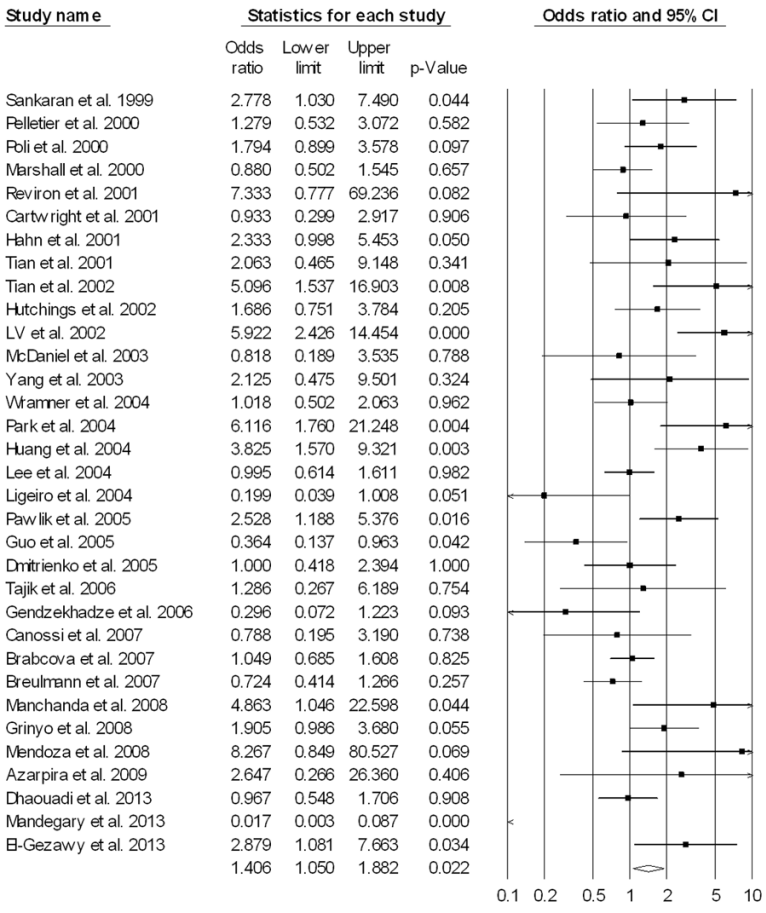

Figure 3. Overall analysis between TNF-α polymorphism (-308, G/A) between AR and non-AR in renal allograft.

the random-effects method was applied. **Figure 2** showed overall analysis between TNF-α polymorphism (-308, G/A) between AR and non-AR in eligible 45 studies. The result indicated that combined genotype (A/A genotype +A/G genotype) was contributed to susceptibility of AR in solid organ recipients (OR = 1.424, 95% CI = 1.118-1.813, P = 0.004, data not shown). To assess the publication bias, Begg's funnel plot was carried out and Egger's test was calculated. The funnel plot seemed symmetrical (data not shown). It is suggested that there were absence of publication bias. Additionally, the Egger's test showed quantitative evidence for absence of publication bias (P = 0.149).

Table 2 presents results of subgroup analysis by genotype and allele of TNF-α polymorphism (-308, G/A), and transplantation organ in 23 studies [9, 11, 13-15, 17-19, 22, 24, 28, 30, 33, 35, 37-39, 41-43, 45, 51-53]. We found that the A allele and genotypes included A allele were significantly associated with susceptibility of AR in solid organ recipients (A allele vs. G allele, random model, OR = 1.379, 95% CI = 1.082-1.759, P = 0.009; A/A+A/G genotypes vs. G/G genotype,

random model, OR = 1.413, 95% CI = 1.077-1.854, P = 0.013; A/A genotype vs. A/G+G/G genotypes, fixed model, OR = 1.516, 95% CI = 1.032-2.227, P = 0.034, respectively). According to transplantation organ, A/A genotype was associated with risk of AR in liver transplantation recipients (fixed model, OR = 2.975, 95% CI = 1.322-6.693, P = 0.008).

In previous meta-anslysis, Hu et al. 2011 investigated meta-analysis between TNF-α polymorphism (-308, G/A) and AR of renal allograft [54]. However, there was error in the study. Incorrect data about distribution of TNF-A polymorphism (-308, G/A) were included in meta-analysis. So, we analyzed relationship between polymorphism (-308, G/A) and AR of renal allograft. **Figure 3** shows overall analysis between TNF-α polymorphism (-308, G/A) between AR and non-AR in renal allograft. There was significant heterogeneity among 33 studies [19-51]. The *p* value of Q test and value of I^2 statistic were P<0.001 and 68.986 (data not shown). Thus, the random-effects method was applied. The result indicated that combined genotype (A/A genotype +A/G genotype) was contributed to susceptibility of AR in renal allograft (OR = 1.406, 95% CI = 1.050-1.882, P = 0.022, data not shown). To assess the publication bias, Begg's funnel plot was carried out and Egger's test was calculated. The funnel plot seemed symmetrical (data not shown). It is suggested that there were absence of publication bias. Additionally, the Egger's test showed quantitative evidence for absence of publication bias (P = 0.381).

Discussion

Acute allograft rejection has been regarded as a result of multiple immunological interactions between various cytokines. It is so important to identify the genetic role of cytokines that influence the incidence of AR in solid organ transplantation. Especially, the inter-individual differences of cytokine activity according to genetic polymorphism can influence on the various immune reaction in organ transplantation [7, 8, 55-58]. Many studies investigate the role of cytokine gene polymorphisms in solid organ allograft survival including acute and chronic rejection.

TNF-α encodes a multifunctional pro-inflammatory cytokine that belongs to the TNF superfamily [59] and -308 promoter polymorphism of TNF-α has been found. Kroeger et al. demonstrated that TNF-α polymorphism (-308, G/A) may play a role in the altered TNF-α gene expression observed in individuals with the major histocompatibility complex haplotype [60]. The correlations between TNF-α polymorphism (-308, G/A) and the risk of acute allograft rejection have been investigated in a broad range of studies with either a relatively small or larger sample of the different populations. However, because of the difference in the number of participants and genetic background, the evidence provided by each study is not sufficient enough to draw a convincing conclusion. A meta-analysis about renal allograft outcome reported that recipient TNF-α polymorphism (-308, G/A) was associated with incidence of AR of renal allograft. Also, it was associated with increased risk of recurrence of acute rejection [54]. However, another meta-analysis about liver allograft outcome demonstrated that this polymorphism may be not associated with acute rejection in liver transplant recipients among Caucasians [61]. Therefore, we conducted a meta-analysis including 45 case-control studies to evaluate the association between TNF-α polymorphism (-308, G/A) and the development of acute allograft rejection.

In our study, there was a significant correlation between TNF-α polymorphism (-308, G/A) and risk of acute allograft rejection under any genetic model in the total population. Some limitations remain in this meta-analysis and the results should be explained with caution. First, meta-analysis is a type of secondary and retrospective study, it is limited by the quality of primary studies, and our meta-analysis was so, too. Second, we could not perform the analysis of gene-gene and gene-environment interactions.

In conclusion, the present study investigated the relationship between TNF-α polymorphism (-308, G/A) and the susceptibility of acute allograft rejection. This study suggests that TNF-α polymorphism (-308, G/A) may play a major role in the pathogenesis of acute allograft rejection. Further lager studies considering gene-gene and gene-environment interactions are required to provide more precise evidence

of the association TNF-α polymorphism and the risk of acute allograft rejection.

Disclosure of conflict of interest

None.

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References

[1] Zakharova M and Ziegler HK. Paradoxical anti-inflammatory actions of TNF-alpha: inhibition of IL-12 and IL-23 via TNF receptor 1 in macrophages and dendritic cells. J Immunol 2005; 175: 5024-5033.

[2] Kamoun M. Cellular and molecular parameters in human renal allograft rejection. Clin Biochem 2001; 34: 29-34.

[3] Cunningham DA, Dunn MJ, Yacoub MH and Rose ML. Local production of cytokines in the human cardiac allograft. A sequential study. Transplantation 1994; 57: 1333-1337.

[4] Imagawa DK, Millis JM, Olthoff KM, Seu P, Dempsey RA, Hart J, Terasaki PI, Wasef EM and Busuttil RW. The role of tumor necrosis factor in allograft rejection. II. Evidence that antibody therapy against tumor necrosis factor-alpha and lymphotoxin enhances cardiac allograft survival in rats. Transplantation 1990; 50: 189-193.

[5] Maury CP and Teppo AM. Raised serum levels of cachectin/tumor necrosis factor alpha in renal allograft rejection. J Exp Med 1987; 166: 1132-1137.

[6] Hajeer AH and Hutchinson IV. TNF-alpha gene polymorphism: clinical and biological implications. Microsc Res Tech 2000; 50: 216-228.

[7] Bouma G, Crusius JB, Oudkerk Pool M, Kolkman JJ, von Blomberg BM, Kostense PJ, Giphart MJ, Schreuder GM, Meuwissen SG and Pena AS. Secretion of tumour necrosis factor alpha and lymphotoxin alpha in relation to polymorphisms in the TNF genes and HLA-DR alleles. Relevance for inflammatory bowel disease. Scand J Immunol 1996; 43: 456-463.

[8] Wilson AG, Symons JA, McDowell TL, McDevitt HO and Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A 1997; 94: 3195-3199.

[9] Bathgate AJ, Pravica V, Perrey C, Therapondos G, Plevris JN, Hayes PC and Hutchinson IV. The effect of polymorphisms in tumor necrosis factor-alpha, interleukin-10, and transforming growth factor-beta1 genes in acute hepatic allograft rejection. Transplantation 2000; 69: 1514-1517.

[10] Tambur AR, Ortegel JW, Ben-Ari Z, Shabtai E, Klein T, Michowiz R, Tur-Kaspa R and Mor E. Role of cytokine gene polymorphism in hepatitis C recurrence and allograft rejection among liver transplant recipients. Transplantation 2001; 71: 1475-1480.

[11] Jonsson JR, Hong C, Purdie DM, Hawley C, Isbel N, Butler M, Balderson GA, Clouston AD, Pandeya N, Stuart K, Edwards-Smith C, Crawford DH, Fawcett J and Powell EE. Role of cytokine gene polymorphisms in acute rejection and renal impairment after liver transplantation. Liver Transpl 2001; 7: 255-263.

[12] Cui H, RJ J, EX C and Elizabeth E. Relationship between TNF-α gene polymorphism and acute rejection after liver transplantation. Chin J Hepatobiliary Surg 2001; 7: 732-734.

[13] Warle MC, Farhan A, Metselaar HJ, Hop WC, Perrey C, Zondervan PE, Kap M, de Rave S, Kwekkeboom J, Ijzermans JN, Tilanus HW, Pravica V, Hutchinson IV and Bouma GJ. Cytokine gene polymorphisms and acute human liver graft rejection. Liver Transpl 2002; 8: 603-611.

[14] Fernandes H, Koneru B, Fernandes N, Hameed M, Cohen MC, Raveche E and Cohen S. Investigation of promoter polymorphisms in the tumor necrosis factor-alpha and interleukin-10 genes in liver transplant patients. Transplantation 2002; 73: 1886-1891.

[15] Jazrawi SF, Zaman A, Muhammad Z, Rabkin JM, Corless CL, Olyaei A, Biggs A, Ham J, Chou S and Rosen HR. Tumor necrosis factor-alpha promoter polymorphisms and the risk of rejection after liver transplantation: a case control analysis of 210 donor-recipient pairs. Liver Transpl 2003; 9: 377-382.

[16] Mas VR, Fisher RA, Maluf DG, Archer KJ, Contos MJ, Mills SA, Shiffman ML, Wilkinson DS, Oliveros L, Garrett CT and Ferreira-Gonzalez A. Polymorphisms in cytokines and growth factor genes and their association with acute rejection and recurrence of hepatitis C virus disease in liver transplantation. Clin Genet 2004; 65: 191-201.

[17] Karasu Z, Ulukaya S, Ayanoglu HO, Basturk B, Ulukaya E, Akyildiz M and Tokat Y. Cytokine gene polymorphism and early graft rejection in liver transplant recipients. Transplant Proc 2004; 36: 2791-2795.

[18] Xie HY, Wang WL, Yao MY, Yu SF, Feng XN, Jin J, Jiang ZJ, Wu LM and Zheng SS. Polymorphisms in cytokine genes and their association with acute rejection and recurrence of hepatitis B in Chinese liver transplant recipients. Arch Med Res 2008; 39: 420-428.

[19] Sankaran D, Asderakis A, Ashraf S, Roberts IS, Short CD, Dyer PA, Sinnott PJ and Hutchinson IV. Cytokine gene polymorphisms predict acute graft rejection following renal transplantation. Kidney Int 1999; 56: 281-288.
[20] Pelletier R, Pravica V, Perrey C, Xia D, Ferguson RM, Hutchinson I and Orosz C. Evidence for a genetic predisposition towards acute rejection after kidney and simultaneous kidney-pancreas transplantation. Transplantation 2000; 70: 674-680.
[21] Poli F, Boschiero L, Giannoni F, Tonini M, Scalamogna M, Ancona G and Sirchia G. Tumour necrosis factor-alpha gene polymorphism: implications in kidney transplantation. Cytokine 2000; 12: 1778-1783.
[22] Marshall SE, McLaren AJ, Haldar NA, Bunce M, Morris PJ and Welsh KI. The impact of recipient cytokine genotype on acute rejection after renal transplantation. Transplantation 2000; 70: 1485-1491.
[23] Reviron D, Dussol B, Andre M, Brunet P, Mercier P and Berland Y. TNF-alpha and IL-6 gene polymorphism and rejection in kidney transplantation recipients. Transplant Proc 2001; 33: 350-351.
[24] Cartwright NH, Keen LJ, Demaine AG, Hurlock NJ, McGonigle RJ, Rowe PA, Shaw JF, Szydlo RM and Kaminski ER. A study of cytokine gene polymorphisms and protein secretion in renal transplantation. Transpl Immunol 2001; 8: 237-244.
[25] Hahn AB, Kasten-Jolly JC, Constantino DM, Graffunder E, Singh TP, Shen GK and Conti DJ. TNF-alpha, IL-6, IFN-gamma, and IL-10 gene expression polymorphisms and the IL-4 receptor alpha-chain variant Q576R: effects on renal allograft outcome. Transplantation 2001; 72: 660-665.
[26] Tian Y, Ma W and Zhang Y. Influence of cytokine gene polymorphism on renal transplantation. Zhonghua Yi Xue Za Zhi 2001; 81: 719-721.
[27] Tian Y, Ma W and Zhang Y. Influence of cytokine gene polymorphism on renal transplantation. Zhonghua Wai Ke Za Zhi 2002; 40: 256-258.
[28] Hutchings A, Guay-Woodford L, Thomas JM, Young CJ, Purcell WM, Pravica V, Perrey C, Hutchinson IV and Benfield MR. Association of cytokine single nucleotide polymorphisms with B7 costimulatory molecules in kidney allograft recipients. Pediatr Transplant 2002; 6: 69-77.
[29] LV TM T and Ou L. TNF-α and IL-10 gene polymorphisms in prediction of kidney transplantation outcome. Acad J Sec Mil Med Univ 2002; 23: 656-658.
[30] McDaniel DO, Barber WH, Nguyan C, Rhodes SW, May WL, McDaniel LS, Vig PJ, Jemeson LL and Butkus DE. Combined analysis of cytokine genotype polymorphism and the level of expression with allograft function in African-American renal transplant patients. Transpl Immunol 2003; 11: 107-119.
[31] Yang LC and Liu Y. Correlation between tumor necrosis factor a gene promoter polymorphisms and acute rejection following renal transplantation. Chin J Urol 2003; 24: 166-168.
[32] Wramner LG, Norrby J, Hahn-Zoric M, Ahlmen J, Borjesson PA, Carlstrom J, Hytonen AM, Olausson M, Hanson LA and Padyukov L. Impaired kidney graft survival is associated with the TNF-alpha genotype. Transplantation 2004; 78: 117-121.
[33] Park JY, Park MH, Park H, Ha J, Kim SJ and Ahn C. TNF-alpha and TGF-beta1 gene polymorphisms and renal allograft rejection in Koreans. Tissue Antigens 2004; 64: 660-666.
[34] Huang XE, Fan LP, Li LY, Zhao M and Xia SS. [Risk factors of acute rejection in sensitized kidney transplant recipients]. Di Yi Jun Yi Da Xue Xue Bao 2004; 24: 1188-1191.
[35] Lee H, Clark B, Gooi HC, Stoves J and Newstead CG. Influence of recipient and donor IL-1alpha, IL-4, and TNFalpha genotypes on the incidence of acute renal allograft rejection. J Clin Pathol 2004; 57: 101-103.
[36] Ligeiro D, Sancho MR, Papoila A, Barradinhas AM, Almeida A, Calao S, Machado D, Nolasco F, Guerra J, Sampaio MJ and Trindade H. Impact of donor and recipient cytokine genotypes on renal allograft outcome. Transplant Proc 2004; 36: 827-829.
[37] Pawlik A, Domanski L, Rozanski J, Florczak M, Dabrowska-Zamojcin E, Dutkiewicz G and Gawronska-Szklarz B. IL-2 and TNF-alpha promoter polymorphisms in patients with acute kidney graft rejection. Transplant Proc 2005; 37: 2041-2043.
[38] Guo YF, Tan JM, Li RY, Liu SZ, Li Y, Ying K, Xie Y and Mao YM. Impacts of donor and recipient's SNP of cytokine and cytokine receptor on early acute renal allograft rejection. Zhonghua Yi Xue Za Zhi 2005; 85: 3126-3133.
[39] Dmitrienko S, Hoar DI, Balshaw R and Keown PA. Immune response gene polymorphisms in renal transplant recipients. Transplantation 2005; 80: 1773-1782.
[40] Tajik N, Kazemi T, Delbandi A, Ghods A and Salek Moghaddam A. The Predictive Value of HLA-DR Matching and Cytokine Gene Polymorphisms in Renal Allograft Acute Rejection: a Living-unrelated Donor (LURD) Study. Iran J Immunol 2006; 3: 150-156.
[41] Gendzekhadze K, Rivas-Vetencourt P and Montano RF. Risk of adverse post-transplant events after kidney allograft transplantation as

predicted by CTLA-4 +49 and TNF-alpha -308 single nucleotide polymorphisms: a preliminary study. Transpl Immunol 2006; 16: 194-199.
[42] Canossi A, Piazza A, Poggi E, Ozzella G, Di Rocco M, Papola F, Iaria G and Adorno D. Renal allograft immune response is influenced by patient and donor cytokine genotypes. Transplant Proc 2007; 39: 1805-1812.
[43] Brabcova I, Petrasek J, Hribova P, Hyklova K, Bartosova K, Lacha J and Viklicky O. Genetic variability of major inflammatory mediators has no impact on the outcome of kidney transplantation. Transplantation 2007; 84: 1037-1044.
[44] Breulmann B, Bantis C, Siekierka M, Blume C, Aker S, Kuhr N, Grabensee B and Ivens K. Influence of cytokine genes polymorphisms on long-term outcome in renal transplantation. Clin Transplant 2007; 21: 615-621.
[45] Manchanda PK and Mittal RD. Analysis of cytokine gene polymorphisms in recipient's matched with living donors on acute rejection after renal transplantation. Mol Cell Biochem 2008; 311: 57-65.
[46] Grinyo J, Vanrenterghem Y, Nashan B, Vincenti F, Ekberg H, Lindpaintner K, Rashford M, Nasmyth-Miller C, Voulgari A, Spleiss O, Truman M and Essioux L. Association of four DNA polymorphisms with acute rejection after kidney transplantation. Transpl Int 2008; 21: 879-891.
[47] Mendoza-Carrera F, Ojeda-Duran S, Angulo E, Rivas F, Macias-Lopez G, Buen EP and Leal C. Influence of cytokine and intercellular adhesion molecule-1 gene polymorphisms on acute rejection in pediatric renal transplantation. Pediatr Transplant 2008; 12: 755-761.
[48] Azarpira N, Aghdai MH, Raisjalali GA, Darai M and Tarahi MJ. Influence of recipient and donor IL-10, TNFA and INFG genotypes on the incidence of acute renal allograft rejection. Mol Biol Rep 2009; 36: 1621-1626.
[49] Dhaouadi T, Sfar I, Bardi R, Jendoubi-Ayed S, Abdallah TB, Ayed K and Gorgi Y. Cytokine gene polymorphisms in kidney transplantation. Transplant Proc 2013; 45: 2152-2157.
[50] Mandegary A, Azmandian J, Soleymani S, Pootari M, Habibzadeh SD, Ebadzadeh MR and Dehghani-Firouzabadi MH. Effect of donor tumor necrosis factor-alpha and interleukin-10 genotypes on delayed graft function and acute rejection in kidney transplantation. Iran J Kidney Dis 2013; 7: 135-141.
[51] El-Gezawy EM, Eldin EN, Mohamed WS, Mahmoud MS, Saied SA, Abd El-Latif HH and Ibrahim MA. Tumor necrosis factor-alfa and monocyte chemoattractant protein-1 gene polymorphisms in kidney transplant recipients. Saudi J Kidney Dis Transpl 2013; 24: 688-695.
[52] Huijun M, Ji Z, Ping X, Jingyu C and Bin Z. Linkage disequilibrium between TNF-alpha-308 G/A promoter and histocompatibility leukocyte antigen alleles in Han-nationality lung transplant recipients from Eastern China. Exp Clin Transplant 2012; 11: 264-269.
[53] Mu HJ, Xie P, Chen JY, Gao F, Zou J, Zhang J and Zhang B. Association of TNF-alpha, TGF-beta1, IL-10, IL-6, and IFN-gamma gene polymorphism with acute rejection and infection in lung transplant recipients. Clin Transplant 2014; 28: 1016-1024.
[54] Hu X, Bai Y, Li S, Zeng K, Xu L, Liu Z, Song X, Lu X, Wang L and Ying B. Donor or recipient TNF-A -308G/A polymorphism and acute rejection of renal allograft: A meta-analysis. Transpl Immunol 2011; 25: 61-71.
[55] Hutchinson IV, Turner DM, Sankaran D, Awad MR and Sinnott PJ. Influence of cytokine genotypes on allograft rejection. Transplant Proc 1998; 30: 862-863.
[56] McGuire W, Hill AV, Allsopp CE, Greenwood BM and Kwiatkowski D. Variation in the TNF-alpha promoter region associated with susceptibility to cerebral malaria. Nature 1994; 371: 508-510.
[57] Perrey C, Pravica V, Sinnott PJ and Hutchinson IV. Genotyping for polymorphisms in interferon-gamma, interleukin-10, transforming growth factor-beta 1 and tumour necrosis factor-alpha genes: a technical report. Transpl Immunol 1998; 6: 193-197.
[58] Turner D, Grant SC, Yonan N, Sheldon S, Dyer PA, Sinnott PJ and Hutchinson IV. Cytokine gene polymorphism and heart transplant rejection. Transplantation 1997; 64: 776-779.
[59] Kroeger KM, Carville KS and Abraham LJ. The -308 tumor necrosis factor-alpha promoter polymorphism effects transcription. Mol Immunol 1997; 34: 391-399.
[60] Liu F, Li B, Wei Y, Ma Y, Yan L and Wen T. Tumor necrosis factor-alpha-308 G/A polymorphism and acute liver graft rejection: a meta-analysis. Transpl Immunol 2010; 24: 45-49.
[61] Won J, Kim JE, Choi DH, Han MW, Lee DH, Kang SC and Song YJ. Effects of compounds isolated from a Litsea japonica fruit extract on the TNF-α signaling pathway and cell viability. Mol Cell Toxicol 2016; 12: 37-44.