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The *GSTP1* A1578G polymorphism and the risk of childhood acute lymphoblastic leukemia: results from an updated meta-analysis

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ABSTRACT. Studies investigating the association between the glutathione S-transferase P1 (*GSTP1*) A1578G polymorphism and the risk of childhood acute lymphoblastic leukemia (ALL) report conflicting results. The aim of this study was to quantitatively summarize the evidence for such a relationship. Two investigators independently searched the Medline, Embase, China National Knowledge Infrastructure, and Wangfang databases for studies of the polymorphism and ALL. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the *GSTP1* polymorphism and childhood ALL were calculated in a fixed-effect model. Pooled ORs were calculated for a co-dominant model (GG *vs* AA, AG *vs* AA), a dominant model (GG + AG *vs* AA), and a recessive model (GG *vs* AA + AG). Analyses were also performed in subgroups stratified by race, study design, genotyping methods, and study sample size. This meta-analysis included 8 case-control studies with 1384 childhood ALL cases and 1755 controls. Overall, the variant genotypes (GG and AG) of A1578G were not associated with childhood

ALL risk, when compared with the wild-type homozygote AA genotype (GG *vs* AA, OR = 1.09, 95%CI = 0.84-1.43; AG *vs* AA, OR = 1.05, 95%CI = 0.91-1.23). Similarly, no associations were found in the dominant and recessive models (dominant model, OR = 1.06, 95%CI = 0.92-1.23; recessive model, OR = 1.09, 95%CI = 0.84-1.43). Stratified analyses did not detect significant association in any subgroup. No heterogeneity or publication bias was observed in the present study. This updated meta-analysis indicates that the *GSTP1* A1578G polymorphism is not associated with the risk of childhood ALL. In the future, additional studies in Asian and African-American patients should be performed to re-evaluate the association in these populations.

Key words: Acute lymphoblastic leukemia; Childhood; Meta-analysis; *GSTP1* polymorphism;

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and accounts for approximately 25-30% of all childhood malignancies. The occurrence of pediatric leukemia has been linked to several environmental, maternal, and paternal factors and to the exposure to various biological, physical, and chemical factors (Whyatt and Perera, 1995; Severson and Ross, 1999). Despite much investigation, the causes of ALL are not yet fully understood. Like many other cancers, acute leukemia is considered to be a complex disease caused by a combination of genetic and environmental factors (Arruda et al., 2001; Krajinovic et al., 2001). Children are particularly vulnerable to environmental toxins because of their greater relative exposure, immature metabolism, and higher levels of cell division and growth (Perera, 1997; Krajinovic et al., 2002a). Polymorphisms in genes encoding xenobiotic-metabolizing enzymes are largely responsible for inter-individual differences in the ability to activate and detoxify mutagenic/carcinogenic agents, and therefore may influence the susceptibility to cancer (Idle, 1991; Nebert, 1991).

Glutathione *S*-transferases (GSTs) are major phase II detoxifying enzymes that catalyze the conjugation of activated xenobiotics to an endogenous water soluble substrate, such as glutathione, uridine diphosphate glucuronic acid, or glycine (Millar et al., 1999). The GSTs are part of a complex and widespread enzyme superfamily that has been subdivided into 8 classes (Strange et al., 2001). Differences in the activities of some GSTs are determined by genetic polymorphisms. *GSTP1* encodes the enzyme glutathione S-transferase P1 and is located on chromosome 11q13. Polymorphisms in *GSTP1* were first reported by Board et al. (1989). They include an A→G transition at nucleotide 313 in exon 5 (*GSTP1*B*) and a G→T transversion at nucleotide 341 in exon 6 (*GSTP1*C*), resulting in the substitution of Ile→Val and Val→Ala, respectively, in the active site of the enzyme. These allele variants appear to reduce GSTP1 activity. A decrease in GST enzyme activity could result in the inefficient detoxification of various carcinogens, which could in turn lead to genetic damage and increase cancer risk (Harries et al., 1997; Ryberg et al., 1997).

Over the last 2 decades, a number of case-control studies have been conducted to investigate the association between the *GSTP1* A1578G polymorphism and the risk of childhood ALL. However, the results of these studies are conflicting. Recently, Vijayakrishnan and Houlston (2010) published a meta-analysis to assess the association between candidate gene polymorphisms

and the risk of childhood ALL and found that the *GSTP1* A1578G polymorphism was not associated with the risk of childhood ALL. However, Vijayakrishnan and Houlston's study had some limitations such as relatively small sample size, failure to include an important study, and some of the data (revealed in Vijayakrishnan and Houlston's Table S2, 2010), to our knowledge, were incorrect. In order to obtain a more comprehensive estimate of the association between the *GSTP1* A1578G polymorphism and the risk of childhood ALL, we conducted an updated meta-analysis to re-evaluate this association.

MATERIAL AND METHODS

Publication search

We searched the PubMed, Embase, China National Knowledge Infrastructure, and Wangfang databases for all articles on the association between *GSTP1* polymorphisms and childhood ALL risk (last search update August 15, 2012). The following key words were used: "acute lymphoblastic leukaemia" or "ALL," "GSTP1" or "glutathione s-transferase P1," and "polymorphism" or "variant". The search was not restricted by language and conducted on human subject studies. Simultaneously, the reference lists of previous reviews and meta-analyses were searched manually. If more than one article was published by the same author using the same case series, we selected the study where the most number of individuals were investigated.

Inclusion and exclusion criteria

We reviewed the abstracts of all citations and retrieved studies. The following criteria were used to include published studies: i) case-control studies were conducted to evaluate the association between the *GSTP1* A1578G polymorphism and the risk of childhood ALL; ii) sufficient genotype data were presented to calculate the odds ratios (ORs) and 95% confidence intervals (CIs); and iii) the paper clearly described the sources of cases and controls. Major reasons for the exclusion of studies were i) no control, ii) duplicated studies, and iii) sufficient data were not reported.

Data extraction

Two investigators (HG and SW) extracted information from all eligible publications independently according to the inclusion criteria listed above. Disagreements were resolved by discussion between the two investigators. The following characteristics were collected from each study: first author, year of publication, country of the first or corresponding author, ethnicity, number of cases and controls, study design [population-based case-control (PCC), hospital-based case-control (HCC)], genotyping methods, minor allele frequency in controls, and evidence of Hardy-Weinberg equilibrium (HWE) (Table 1).

Statistical analysis

We first assessed HWE in the controls for each study using the goodness-of-fit test (chi-square or Fisher exact test) and $P < 0.05$ was considered as significant disequilibrium. The strength of the association between childhood ALL and the *GSTP1* A1578G polymor-

phism was estimated using ORs, with the corresponding 95%CIs. Pooled ORs were calculated under a co-dominant model (GG *vs* AA, AG *vs* AA), a dominant model (GG + AG *vs* AA), and a recessive model (GG *vs* AG + AA). We also performed subgroup analyses by ethnicity, study sample size (>500/≤500 subjects), genotyping methods, and source of controls (HCC/PCC).

Both the Cochran's Q statistic (Cochran, 1954) to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity (Higgins et al., 2003) were calculated. A P value greater than the nominal level of 0.10 for the Q statistic indicated a lack of heterogeneity across studies, allowing for the use of a fixed-effect model (the Mantel-Haenszel method) (Mantel and Haenszel, 1959); otherwise, the random-effect model (the DerSimonian and Laird method) was used (DerSimonian and Laird, 1986). Sensitivity analysis was performed to assess the stability of the results.

Several methods were used to assess potential publication bias. Visual inspection of funnel plot asymmetry was conducted. The Begg's rank correlation method (Begg and Mazumdar, 1994) and the Egger's weighted regression method (Egger et al., 1997) were used to statistically assess publication bias ($P < 0.05$ was considered to be statistically significant). All analyses were done using the STATA software, version 11.0 (StataCorp, USA). All the P values were two-sided.

RESULTS

Characteristics of the studies

We identified 38 relevant studies by searching the databases. Ten publications described the association between the *GSTP1* polymorphism and childhood ALL. Their full texts were retrieved and carefully studied. Finally, a total of 8 eligible studies involving 1384 cases and 1755 controls were included in the pooled analyses (Krajinovic et al., 2002b; Balta et al., 2003; Barnette et al., 2004; Canalle et al., 2004; Clavel et al., 2005; Gatedee et al., 2007; Pigullo et al., 2007; Chan et al., 2011). The characteristics of the selected studies are summarized in Table 1. Ten studies were performed in Caucasian patients and 2 studies were performed in Asian patients. The studies were carried out in Canada, Turkey, USA, Brazil, France, Thailand, Italy, and Indonesia. Controls were mainly healthy children and were matched by age and/or gender. Six studies selected controls in a population-based manner whereas 2 used hospital-based controls. All studies extracted DNA from peripheral blood and a classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used in 5 of 8 studies. The distribution of genotypes in the controls of all studies was in agreement with HWE.

Quantitative synthesis

Table 2 lists the main results of this meta-analysis and Figure 1A-D show the association of childhood ALL risk with the *GSTP1* A1578G polymorphism. Overall, the variant genotypes (GG and AG) of the polymorphism were not associated with childhood ALL risk when compared with the wild-type AA homozygote (GG *vs* AA, OR = 1.09, 95%CI = 0.84-1.43; AG *vs* AA, OR = 1.05, 95%CI = 0.91-1.23), without any between-study heterogeneity. Similarly, no associations were observed in the dominant or recessive models (dominant model, OR = 1.06, 95%CI = 0.92-1.23; recessive model, OR = 1.09, 95%CI = 0.84-1.43).

Table 1. Characteristics of studies included in the meta-analysis.

First author	Year	Design	Country	Ethnicity	No. of case/control	AA		AG		GG		Genotyping methods	HWE
Reference						Case	Control	Case	Control	Case	Control		P
Krajinovic	2002b	PCC	Canada	Caucasian	278/302	116	143	137	127	25	32	ASO-PCR	0.632
Balta	2003	PCC	Turkey	Caucasian	136/185	76	103	55	73	5	9	PCR-RFLP	0.385
Barnette	2004	PCC	USA	Caucasian	83/288	37	122	36	132	10	34	AS-PCR	0.851
Canalle	2004	PCC	Brazil	Caucasian	113/221	50	100	53	103	10	18	PCR-RFLP	0.229
Clavel	2005	HCC	France	Caucasian	191/105	84	46	85	48	22	11	PCR-RFLP	0.769
Gatedee	2007	PCC	Thailand	Asian	100/100	59	61	36	37	5	2	PCR-RFLP	0.177
Pigullo	2007	HCC	Italy	Caucasian	323/384	162	203	130	148	31	33	AS-PCR	0.419
Chan	2011	PCC	Indonesia	Asian	160/170	97	99	50	61	13	10	PCR-RFLP	0.882

HWE = Hardy-Weinberg equilibrium of genotypes in controls. P, χ^2 test P value, if P > 0.05, frequencies of genotypes in the control group was in HWE; PCC = population-based case-control; HCC = hospital-based case-control; ASO-PCR = allele-specific oligonucleotide-polymerase chain reaction; PCR-RFLP = PCR-restriction fragment length polymorphism; AS-PCR = allele-specific PCR.

Table 2. Stratified analyses of the *GSTP1* A1578G polymorphism and risk of childhood acute lymphoblastic leukemia.

Variables	N	GG *vs* AA		AG *vs* AA		Dominant model		Recessive model	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Total	8	1.09 (0.84-1.43)	0.96	1.05 (0.91-1.23)	0.86	1.06 (0.92-1.23)	0.95	1.09 (0.84-1.43)	0.96
Ethnicity									
Asian	2	1.54 (0.72-3.32)	0.49	0.90 (0.62-1.29)	0.63	0.97 (0.69-1.37)	0.62	1.54 (0.72-3.32)	0.49
Caucasian	6	1.04 (0.78-1.39)	0.99	1.09 (0.92-1.29)	0.83	1.08 (0.92-1.27)	0.90	1.04 (0.78-1.39)	0.99
Study design									
HCC	2	1.15 (0.74-1.80)	0.88	1.06 (0.81-1.39)	0.68	1.08 (0.84-1.39)	0.69	1.15 (0.74-1.80)	0.88
PCC	6	1.06 (0.76-1.49)	0.87	1.05 (0.87-1.27)	0.68	1.05 (0.88-1.26)	0.85	1.06 (0.76-1.49)	0.86
Genotyping methods									
PCR-RFLP	5	1.16 (0.76-1.78)	0.82	0.97 (0.78-1.20)	0.97	0.99 (0.81-1.23)	0.99	1.16 (0.76-1.78)	0.82
Other	3	1.05 (0.74-1.49)	0.86	1.14 (0.93-1.41)	0.45	1.13 (0.92-1.38)	0.57	1.05 (0.74-1.49)	0.86
Study sample size									
>500	2	1.07 (0.73-1.59)	0.62	1.20 (0.95-1.51)	0.43	1.18 (0.94-1.47)	0.60	1.07 (0.73-1.59)	0.62
≤500	6	1.11 (0.77-1.62)	0.89	0.96 (0.78-1.17)	0.99	0.98 (0.81-1.19)	0.99	1.11 (0.77-1.62)	0.89

N = number of comparisons; P value of the Q-test for heterogeneity test. Random-effect model was used when P value for heterogeneity test <0.1; otherwise, fixed-effect model was used. HCC = hospital-based case-control studies; PCC = population-based case-control studies.

On the basis of the potential underestimation of the true effect of the polymorphism on ALL risk, we stratified these studies according to ethnicity, source of controls, genotyping methods, and study sample size. Different ethnicities were categorized as Asian and Caucasian. Different genotyping methods were defined as PCR-RFLP and other. In the stratified analyses, the variant genotypes (GG and AG) had no significant relationship with childhood ALL in all of the subgroups compared with the wild-type AA. Similar results were observed in the recessive and dominant models (Table 2).

Heterogeneity and sensitivity analyses

Significant heterogeneity between studies was not observed in overall comparisons and subgroup analyses. In the sensitivity analysis, the influence of each study on the pooled OR was examined by repeating the meta-analysis while omitting each study, one at a time. This procedure confirmed the stability of our overall results.

Publication bias

Funnel plot, Begg and Egger tests were used to evaluate publication bias of the literature on childhood ALL. Figure 2 displays the funnel plot that examines the *GSTP1* A1578G polymorphism and overall childhood ALL risk included in the meta-analysis in the homozygous comparison. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry. The statistical results did not show publication bias either (GG *vs* AA: Begg test, P = 0.39, Egger test, P = 0.41; AG *vs* AA: Begg test, P = 0.17, Egger test, P = 0.06; dominant model: Begg test, P = 0.71, Egger test, P = 0.08; recessive model: Begg test, P = 0.39, Egger test, P = 0.41).

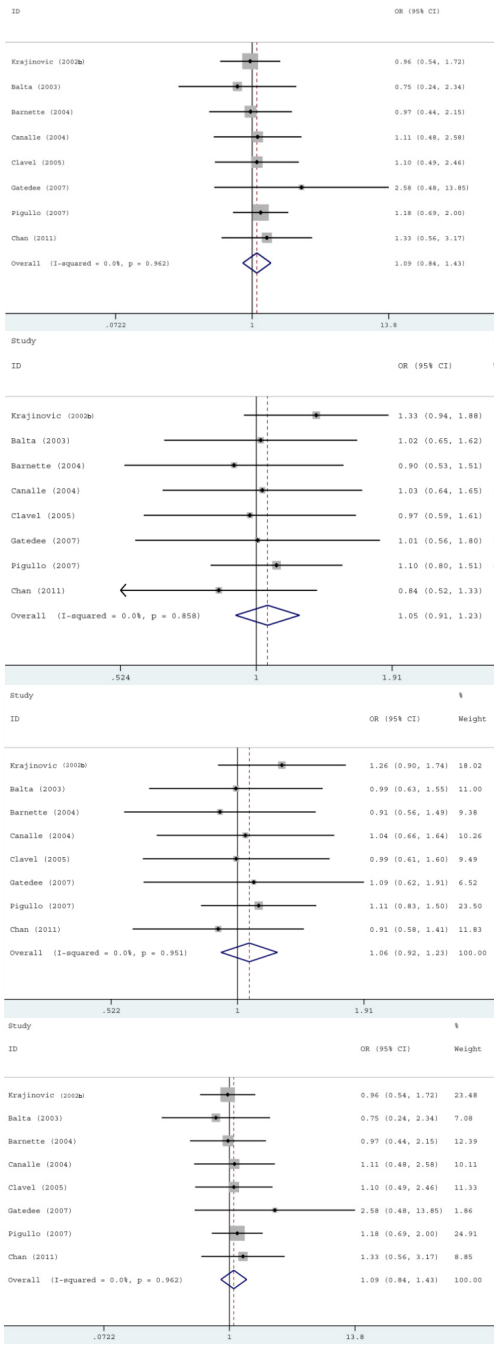

Figure 1. Forest plots of odds ratio (ORs) with 95% confidence intervals (CIs) for the *GSTP1* A1578G polymorphism and risk of childhood acute lymphoblastic leukemia. The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95%CI. **A.** GG *vs* AA. **B.** AG *vs* AA. **C.** GG + AG *vs* AA. **D.** GG *vs* AG + AA.

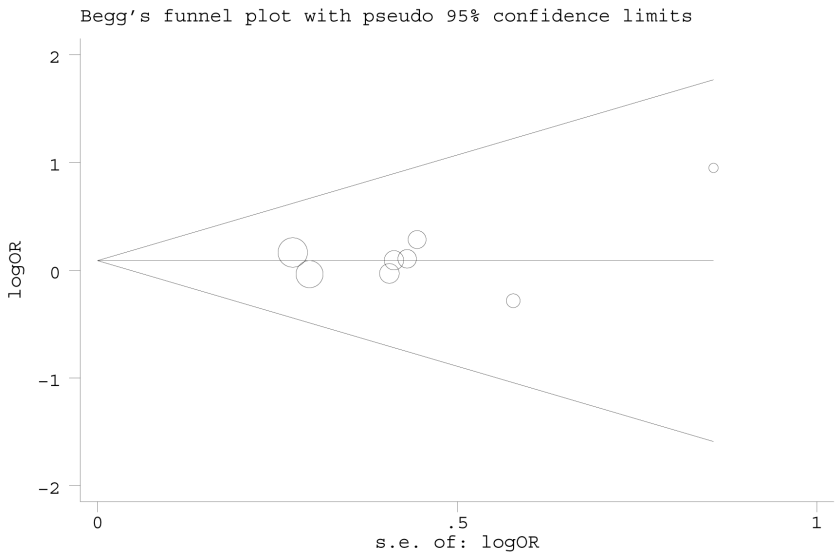

Figure 2. Funnel plot for publication bias test (GG *vs* AA). Each point represents a separate study for the indicated association.

DISCUSSION

ALL is the most frequent malignancy affecting children, accounting for 30% of all childhood cancers. Despite much investigation, the causes of this disease are not yet fully understood. Like many other cancers, ALL is considered to be a complex disease caused by a combination of genetic and environmental factors (Arruda et al., 2001; Krajinovic et al., 2001). In this context, understanding the interactions between the various predisposing genes and environmental factors in the pathogenesis of childhood leukemia is of considerable public health importance. Biological markers of individual susceptibility could prove useful for identifying persons at risk for developing leukemia and for targeting preventive strategies. The GSTs are a family of enzymes involved in the detoxification of a wide range of chemicals, including important environmental carcinogens [e.g., benzo(a)pyrene and other polycyclic aromatic hydrocarbons] (Perera, 1996; Hengstler et al., 1998). Human *GSTP1* has been shown to catalyze the isomerization of 13-cisretioic acid to all-transretioic acid (Fukai et al., 1992). As a result, GSTP1 is commonly studied for its effect on the susceptibility to acute myeloid leukemia (Allan et al., 2001). In recent years, a number of molecular epidemiologic studies have been conducted to evaluate the role of the A1578G polymorphism in the *GSTP1* gene on childhood ALL risk; however, the results remain conflicting rather than conclusive (Krajinovic et al., 2002b; Balta et al., 2003; Barnette et al., 2004; Canalle et al., 2004; Clavel et al., 2005; Gatedee et al., 2007; Pigullo et al., 2007; Chan et al., 2011). Meta-analysis is a powerful statistical method that can provide a quantitative approach for pooling the results of different studies on the same topic, and thus a systematic review and meta-analysis of the association between the *GSTP1* A1578G polymorphism and childhood ALL risk is of great value.

This updated analysis, based on 8 case-control studies with 1384 cases and 1755 controls explored the association between the *GSTP1* A1578G polymorphism and the risk of

childhood ALL. Consistent with the previous meta-analysis by Vijayakrishnan and Houlston (2010), our findings indicate that the *GSTP1* A1578G polymorphism is not associated with childhood ALL risk. Even after stratifying the studies by ethnicity, study sample size, genotyping methods, and source of controls, the results were similar. Moreover, our results are consistent with previous meta-analyses based on other cancers. For example, 3 previous meta-analyses confirmed that the *GSTP1* A1578G polymorphism is not associated with the risk for thyroid cancer (Li et al., 2012), colorectal cancer (Gao et al., 2009), or ovarian cancer (Economopoulos et al., 2010). However, Lu et al. (2011) concluded that the *GSTP1* A1578G polymorphism may increase the susceptibility to breast cancer in an Asian population. Similarly, Kellen et al. (2007) found that the *GSTP1* A1578G polymorphism was associated with a modest increase in the risk for bladder cancer, and Zhou et al. (2009) found that the *GSTP1* A1578G polymorphism may be associated with gastric cancer in Caucasians. Although the reasons for these apparent differences in risk for different tumors are as yet unknown, some possibilities should be considered. First, these genetic associations may vary in different types of cancer due to the different mechanisms of carcinogenesis in each cancer. Second, the use of different ethnic populations in the studies may contribute to the discrepancy. The inclusion of different studies performed in different populations may cause variability among meta-analyses results. Third, some methodological diversity, such as differences in inclusion criteria, the quality of the original studies included, selection bias, type I error, and small sample size may also contribute to the discrepancy.

Results of meta-analyses often depend on the procedures used for selecting the control population (Benhamou et al., 2002). Different sources of controls may be a confounding factor that may impact the conclusion of our study. For instance, some included studies used healthy children from the general population as the reference group, whereas others selected hospitalized children without ALL as the reference group. In order to eliminate interference from this confounding factor, we performed a subgroup analysis by stratifying studies based on the source of controls. Our results showed that there was no significant association between the *GSTP1* A1578G polymorphism and childhood ALL risk upon including only controls collected in hospitals or those collected only in the population, thus confirming the reliability of our overall results.

One of the major concerns in performing a sound meta-analysis is the degree of heterogeneity that exists between the component studies because non-homogeneous data are liable to result in misleading results. In the present study, the Q-test and I^2 statistics were used to test the significance of heterogeneity. Obvious heterogeneity between studies was not observed in overall comparisons and subgroup analyses. Another important issue for any meta-analysis is publication bias due to the selective publication of reports. In the current study, Funnel plot, Begg and Egger tests were performed to evaluate this problem. Both the shape of funnel plots and statistical results did not show publication bias.

However, there still exist some limitations in this meta-analysis: 1) only published studies were included in the meta-analysis; therefore, publication bias may have occurred, even though the use of a statistical test did not reveal it; 2) our meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs or when they did, the ORs were not adjusted by the same potential confounders, such as age, gender, ethnicity, and exposures; the lack of this information may cause serious bias; 3) meta-analysis is a retrospective approach that is subject to methodological limitations. In order to minimize bias, we developed a detailed protocol before initiating the study, and performed a meticulous

search for published studies using explicit methods for study selection, data extraction, and data analysis. Nevertheless, our results should still be interpreted with caution.

In conclusion, this updated meta-analysis indicates that the *GSTP1* A1578G polymorphism is not associated with altered susceptibility to childhood ALL. Since few studies were performed in non-Caucasian population, it is critical that larger and well-designed multicentric studies in Asian and African-American patients should be performed to re-evaluate this association.

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