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META-ANALYSIS Open Access

The association between angiotensin II type 1 receptor A1166C gene polymorphism and the risk of essential hypertension: a meta-analysis

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Abstract

Background: Since first reported having the association with essential hypertension, angiotensin II type 1 receptor (AT1R) A1166C was globally investigated worldwide. However, controversy was found. Furthermore, previous meta-analyses did not adequate to clarify the precise correlation due to some limitations. Therefore, we aimed to perform a meta-analysis concerning the association between AT1R A1166C single-nucleotide polymorphism (SNP) and the risk of essential hypertension with eliminating the limitations of previous studies.

Methods: A meta-analysis was conducted from February to March 2019. Some information related to sample size of hypertension and control groups and genotype frequencies of hypertension and control groups were extracted from each study. Data were analyzed using fixed or random effect model to determine the overall correlation.

Results: A total of 45 papers consisting of 11911 cases and 1340 controls were enrolled for the study. Our overall analysis showed that C allele and AC genotype of AT1R A1166C was associated with 1.18-fold and 1.15-fold respectively increased risk of essential hypertension, while the decreased risk of essential hypertension was observed in A allele and AA genotype. In sub-group analysis, increased risk of essential hypertension was found in C allele, AC genotype, and CC genotype of both Asian population and PCR-RFLP sub-groups, while decreased risk was observed in A allele and AA genotype.

Conclusions: Our meta-analysis reveals that AT1R A1166C remains a valuable SNP having an association with the risk of essential hypertension.

Keywords: Angiotensin II type 1 receptor, A1166C, Hypertension, Single-nucleotide polymorphism

Background

Hypertension remains a serious health problem causing a high-cost expenditure because of its fatal complications, such as heart failure [1], stroke [2], and renal disease [3]. Recently, various genetic mapping studies including gene-gene, gene-disease, and gene-environment interaction are believed to have a promising prospect for maintaining future treatment and prevention of the disease. In the context of hypertension, studies have focused on the polymorphism of genes in renin-angiotensin-aldosterone system (RAAS), the main pathway playing a pivotal role in the development of hypertension. Briefly, angiotensinogen is cleaved by renin into angiotensin I, and angiotensin I is converted into angiotensin II by angiotensin-converting enzyme (ACE) [4]. Of those precursors, angiotensin II is defined as the most potent vasoconstrictor. To trigger the adverse effects in hypertension, angiotensin II is mediated by angiotensin II type I receptor (AT1R) [5].

During this time, several studies have identified some AT1R single-nucleotide polymorphisms (SNPs), such as

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G2228A, C1424G, C521T [6], C573T, and A1166C [7]. Of those, studies reporting G2228A, C1424G, C521T; and C573T were limited, while A1166C, the substitution of cytosine for adenosine at position 1166 in the 3′ untranslated region of the human AT1R gene [8], was extensively investigated and proven to have a close correlation with AT1R activity in circulation [9]. Since first reported in the Caucasian population that this SNP had a significant association with essential hypertension [10], A1166C was widely investigated worldwide. However, the results were inconclusive. The controversy was observed among the reports. Moreover, previous meta-analyses in this context were not adequate to determine the real correlation because of some limitations. Therefore, our present study aimed to perform a meta-analysis concerning the correlation between AT1R A1166C gene polymorphism and the risk of essential hypertension. Our present study might clarify the better association in this topic.

Methods

Study design

A meta-analysis was performed from February to March 2019 to clarify the association between AT1R A1166C gene polymorphism and the risk of hypertension in the general population. To achieve our purpose, papers published in PubMed, Embase, Cochrane, and Web of science were searched and identified in accordance with eligibility criteria, and they were analyzed to determine the pooled odds ratio (OR) and 95% confidence interval (95%CI) using fixed or random effect model. The design of our present study was adapted from our previous meta-analyses [11–15].

Eligibility criteria

Papers were included in our analysis if they met the following inclusion criteria, such as (1) papers with the following designs: retrospective; prospective; cross-sectional, and randomized controlled trials (RCTs); (2) English publication language; (3) available full text; (4) evaluating the correlation between AT1R A1166C gene polymorphism and the risk of essential hypertension (essential hypertension was assessed using standard criteria formulated by the Joint National Committee VII); and (5) having required data for calculation of OR95%CI, while articles were excluded if the following criteria were found: (1) obvious irrelevance title and or abstract, (2) review, (3) non-standard data presentation, (4) evaluating secondary hypertension; (5) unavailable full text, and (6) deviation from Hardy-Weinberg equilibrium ($\chi^2 < 3.84$ was considered in Hardy–Weinberg equilibrium) [16]. Newcastle-Ottawa scale was used to evaluate the quality of each study [17].

Search strategy and data extraction

A comprehensive searching with English publication language was performed in PubMed, Embase, Cochrane, and Web of science up to 10 March 2019 to collect the papers evaluating the association between AT1R A1166C gene polymorphism and the risk of essential hypertension. For searching the papers, we used the combination of the following keywords: (AT1R A1166C or angiotensin II type 1 receptor A1166C) and (essential hypertension). If we found studies using the same data, only studies with larger sample size were included in our analysis. Moreover, for data extraction, information related to (1) name of first author, (2) year of publication, (3) country of origin, (4) genotyping method, (5) sample size of hypertension and control groups, and (6) genotype frequencies and percents of hypertension and control groups were extracted from each study.

Statistical analysis

The association between AT1R A1166C gene polymorphism and the risk of hypertension was determined using Z test and the calculation of OR and 95%CI. This calculation model, whether using fixed or random effect model, was confirmed by a Q test. If the p value was less than 0.10, a random effect model was used, while a fixed effect model was used if the p value was more than 0.10. Moreover, to evaluate publication bias, we used an Egger's test ($p < 0.05$ was considered statistically significant). All data were analyzed using Review Manager (RevMan; Cochrane, London, UK) version 5.3 and Comprehensive Meta-Analysis (CMA, NJ, USA) version 2.1.

Results and discussion

Eligible studies

A total of 45 papers evaluating the association between AT1R A1166C gene polymorphism and the risk of essential hypertension was enrolled for our analysis. These papers were searched in PubMed, Embase, Cochrane, and Web of Science. In initial searching, totally, we found 579 papers. Of those, 484 papers were excluded because of irrelevance title and or abstract. Further exclusions were as follows: 12 papers were excluded because of review, six papers were excluded because data were not presented in standard format, 18 papers were excluded because full texts were not found, and 14 papers were excluded because they were not presented in Hardy-Weinberg equilibrium. Detail of exclusion process in our study is presented in Fig. 1, and baseline characteristics of our study are described in Table 1.

Data synthesis

A total of 45 papers consisting of 11,911 cases and 1340 controls was included in our analysis. The cumulative genotype percentage in case for AA, AC, and CC was

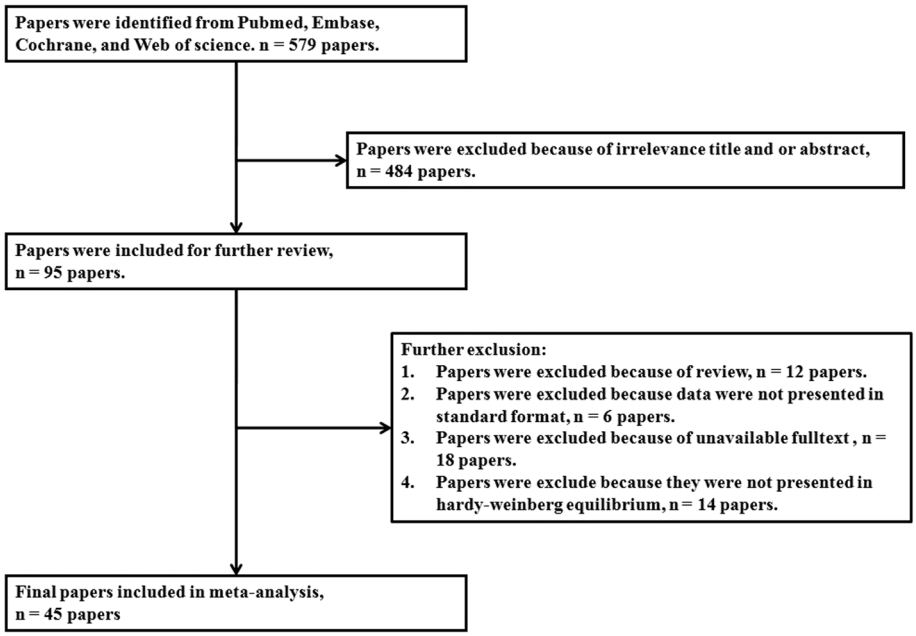

Fig. 1 Flowchart of eligibility pathway in our study

73.69%, 22.47%, and 3.85%, respectively, while in the control group, the percentage was 77.65%, 19.51%, and 2.84% for AA, AC, and CC, respectively. Overall, our analysis found that A allele (OR95%CI = 0.88 [0.75–0.97], $p = 0.0130$) and AA genotype (OR95%CI = 0.82 [0.71–0.94], $p = 0.0050$) were associated with decreased risk of essential hypertension, while C allele (OR95%CI = 1.18 [1.04–1.34], $p = 0.0130$) and AC genotype (OR95%CI = 1.15 [1.04– 1.28], $p = 0.0060$) were found to increase the odds of having essential hypertension (Figs. 2 and 3).

To establish a comprehensive analysis, we also performed a sub-group analysis according to the continent of origin and genotyping method. Continent sub-group analysis consisted of Europe, America, Asia, and Africa sub-groups, while genotyping method consisted of polymerase chain reaction (PCR) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) sub-groups. In the America continent sub-group analysis, the genotype percentage in patients with essential hypertension was 63.73%, 31.64%, and 4.63% for AA, AC, and CC, respectively. In the control group, the percentage was 67.39, 27.03, and 5.59% for AA, AC, and CC, respectively. In the Europe continent sub-group, the genotype percentage in patients with essential hypertension for AA, AC, and CC was 60.00%, 33.54%, and 6.46%, respectively, while the genotype percentage in the control group was 62.61%, 31.85%, and 5.54% for AA, AC, and CC, respectively. In the Asia sub-group analysis, the genotype percentage for AA, AC, and CC in patients with essential hypertension was 80.75%, 16.74%, and 2.51%, respectively, while in the control group, the percentage was 83.55%, 14.93%, and 1.52% for AA, AC, and CC, respectively. In the Africa continent sub-group, the percentage was 83.49%, 14.11%, and 2.40% for AA, AC, and CC, respectively, in patients with essential hypertension. In the control group, the genotype percentage for AA, AC, and CC was 84.33%, 13.18%, and 2.49%, respectively. Our results found no association between AT1R A1166C gene polymorphism and the risk of essential hypertension in the Europe, America, and Africa continent sub-groups, while in the Asia sub-group, the increased risk of essential hypertension was found in C allele (OR95%CI = 1.27 [1.04–1.55], $p = 0.0190$) (Fig. 4a), AC genotype (OR95%CI = 1.19 [1.01–1.41], $p = 0.0410$) (Fig. 4b), and CC genotype (OR95%CI = 1.81 [1.38–2.36], $p < 0.0001$) (Fig. 4c).

In genotyping method sub-group, the genotype percentage for the PCR sub-group was 72.24%, 24.32%, and 3.45% for AA, AC, and CC respectively in patients with essential hypertension, while in the control group, the percentage for AA, AC, and CC was 77.01%, 20.10%, and 2.89%, respectively. In the PCR-RFLP sub-group, the percentage in the essential hypertension group was 74.90%, 20.92%, and 4.18% for AA, AC, and CC, respectively. In the control group, the genotype percentage for AA, AC, and CC was 78.42%, 18.80%, and 2.78%, respectively. Our cumulative calculation found that the correlation was found in the PCR-RFLP sub-group. Our results found that A allele (OR95% CI = 0.77 [0.61–0.96], $p = 0.0190$) and AA genotype (OR95% CI = 0.74 [0.58–0.95], $p = 0.0160$) were associated with decreased risk of essential hypertension, while increased odds of having

Table 1 Baseline characteristics of studies included in our analysis

Author and year	Hypertension					Control					Country	Genotyping
	AA	AC	CC	N	χ^2 HWE	AA	AC	CC	N	χ^2 HWE		
Agachan et al. 2003 [18]	63	35	6	104	0.15	60	20	1	81	0.22	Turkey	PCR
Ashavaid et al. 2000 [19]	91	14	0	105	0.54	159	33	0	192	1.70	India	PCR-RFLP
Bautista et al. 2008 [20]	222	33	0	255	1.22	207	23	1	231	0.17	The USA	PCR
Bayramoglu et al. 2015 [21]	123	19	0	142	0.73	104	4	0	108	0.04	Turkey	PCR
Castellano et al. 1996 [22]	41	37	4	82	1.45	42	50	16	108	0.03	Italy	PCR
Chandra et al. 2014 [9]	101	114	35	250	0.1	155	83	12	250	0.04	India	PCR-RFLP
Dzida et al. 2001 [23]	131	95	24	250	1.21	96	48	6	150	0.00	Poland	PCR
El-banawy et al. 2015 [24]	45	22	5	72	0.97	22	7	1	30	0.22	Egypt	PCR-RFLP
Farrag et al. 2011 [25]	39	1	0	40	0.01	12	3	0	15	0.19	Egypt	PCR-RFLP
Filigheddu et al. 2008 [26]	290	262	61	613	0.03	88	93	18	199	0.88	Italy	PCR-RFLP
Freitas et al. 2007 [27]	60	29	1	90	1.52	58	45	12	115	0.54	Brazil	PCR-RFLP
Hannila-Handelberg et al. 2010 [28]	90	49	6	145	0.04	103	62	9	174	0.01	Finland	PCR
Jiang et al. 2009 [29]	201	19	0	220	0.45	212	23	0	235	0.62	China	PCR
Jinmin et al. 2013 [30]	83	20	1	104	0.03	129	19	2	150	1.66	China	PCR-RFLP
Kato et al. 2000 [31]	701	132	6	839	0.01	525	103	3	631	0.74	Japan	PCR-RFLP
Kim et al. 2015 [32]	489	48	1	538	0.02	167	27	1	195	0.01	Korea	PCR-RFLP
Kooffreh et al. 2013 [33]	605	7	0	612	0.02	606	6	0	612	0.01	Nigeria	PCR-RFLP
Kretowski et al. 2007 [34]	107	131	28	266	1.71	87	79	18	184	0.00	Colorado	PCR
Kurbanova and Eliseyeva 2010 [35]	122	48	2	172	1.32	41	19	0	60	2.12	Uzbekistan	PCR-RFLP
Lapierre et al. 2006 [36]	24	12	1	37	0.12	22	3	0	25	0.10	Argentina	PCR-RFLP
Lesage et al. 1997 [37]	35	36	3	74	2.87	64	47	9	120	0.01	France	PCR
Liu et al. 2002 [38]	420	26	0	446	0.4	277	25	0	302	0.56	China	PCR-RFLP
Lozinsky 2016 [39]	43	74	33	150	0.01	83	39	6	128	0.26	Ukraine	PCR-RFLP
Mehri et al. 2011 [40]	26	29	8	63	0	17	24	14	55	0.85	Tunisia	PCR
Morisawa et al. 2001 [41]	104	26	1	131	0.21	150	23	2	175	1.04	Japan	PCR-RFLP
Nie et al. 2010 [42]	445	64	1	510	0.69	452	56	2	510	0.04	China	PCR-RFLP
Onna et al. 2004 [43]	79	65	10	154	0.49	104	77	17	198	0.26	Netherlands	PCR
Ono et al. 2003 [44]	1259	224	9	1492	0.08	2071	335	17	2423	0.73	Japan	PCR
Parchwani et al. 2018 [45]	66	100	58	224	2.52	100	115	42	257	0.84	India	PCR-RFLP
Patnaik et al. 2014 [46]	200	36	4	240	2.36	157	13	0	170	0.27	India	PCR-RFLP
Saab et al. 2011 [47]	31	64	29	124	0.13	83	52	11	146	0.50	Lebanon	PCR-RFLP
Schmidt et al. 1997 [48]	215	168	31	414	0.05	81	76	15	172	0.23	Germany	PCR
Shahin et al. 2014 [49]	67	37	4	108	0.16	64	32	6	102	0.54	Jordan	PCR-RFLP
Shamaa et al. 2016 [50]	55	21	7	83	2.54	53	7	0	60	0.23	Egypt	PCR-RFLP
Soualmia et al. 2014 [51]	254	119	15	388	0.05	277	131	20	428	0.78	Tunisia	PCR-RFLP
Stankovic et al. 2003 [52]	52	40	8	100	0.01	109	74	15	198	0.24	Serbia	PCR
Szombathy et al. 1998 [53]	26	18	4	48	0.12	23	19	6	48	0.43	Hungary	PCR-RFLP
Takami et al. 1998 [54]	261	56	4	321	0.25	172	40	3	215	0.15	Japan	PCR
Tchelougou et al. 2015 [55]	195	7	0	202	0.06	197	7	0	204	0.06	Burkina Faso	PCR
Thomas et al. 2000 [56]	203	28	1	232	0	152	21	1	174	0.09	Hong Kong	PCR
Tiret et al. 1998 [57]	238	174	41	453	1.25	184	150	28	362	0.11	France	PCR
Tong et al. 2017 [58]	278	33	1	312	0	580	42	1	623	0.07	China	PCR

Table 1 Baseline characteristics of studies included in our analysis *(Continued)*

Author and year	Hypertension					Control					Country	Genotyping
	AA	AC	CC	N	χ^2 HWE	AA	AC	CC	N	χ^2 HWE		
Tsai et al. 2003 [59]	379	29	1	409	0.31	270	16	0	286	0.24	Taiwan	PCR-RFLP
van den Born et al. 2007 [60]	102	42	3	147	0.31	97	35	7	139	2.45	Netherlands	PCR
Zhu et al. 2006 [61]	116	33	1	150	0.68	94	6	0	100	0.10	China	PCR-RFLP

HWE Hardy-Weinberg equilibrium, *PCR* polymerase chain reaction, *RFLP* restriction fragment length polymorphism

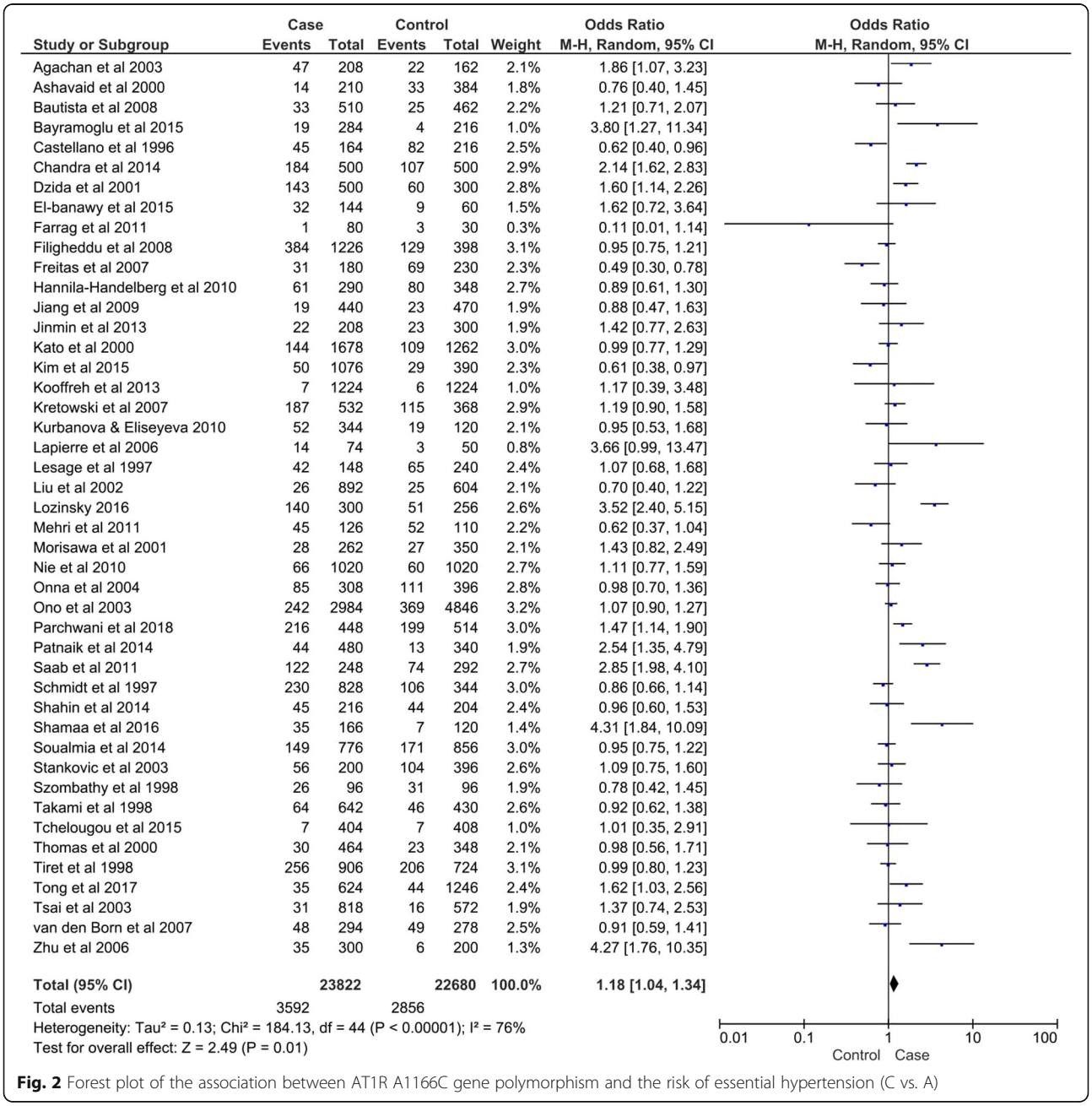

Fig. 2 Forest plot of the association between AT1R A1166C gene polymorphism and the risk of essential hypertension (C vs. A)

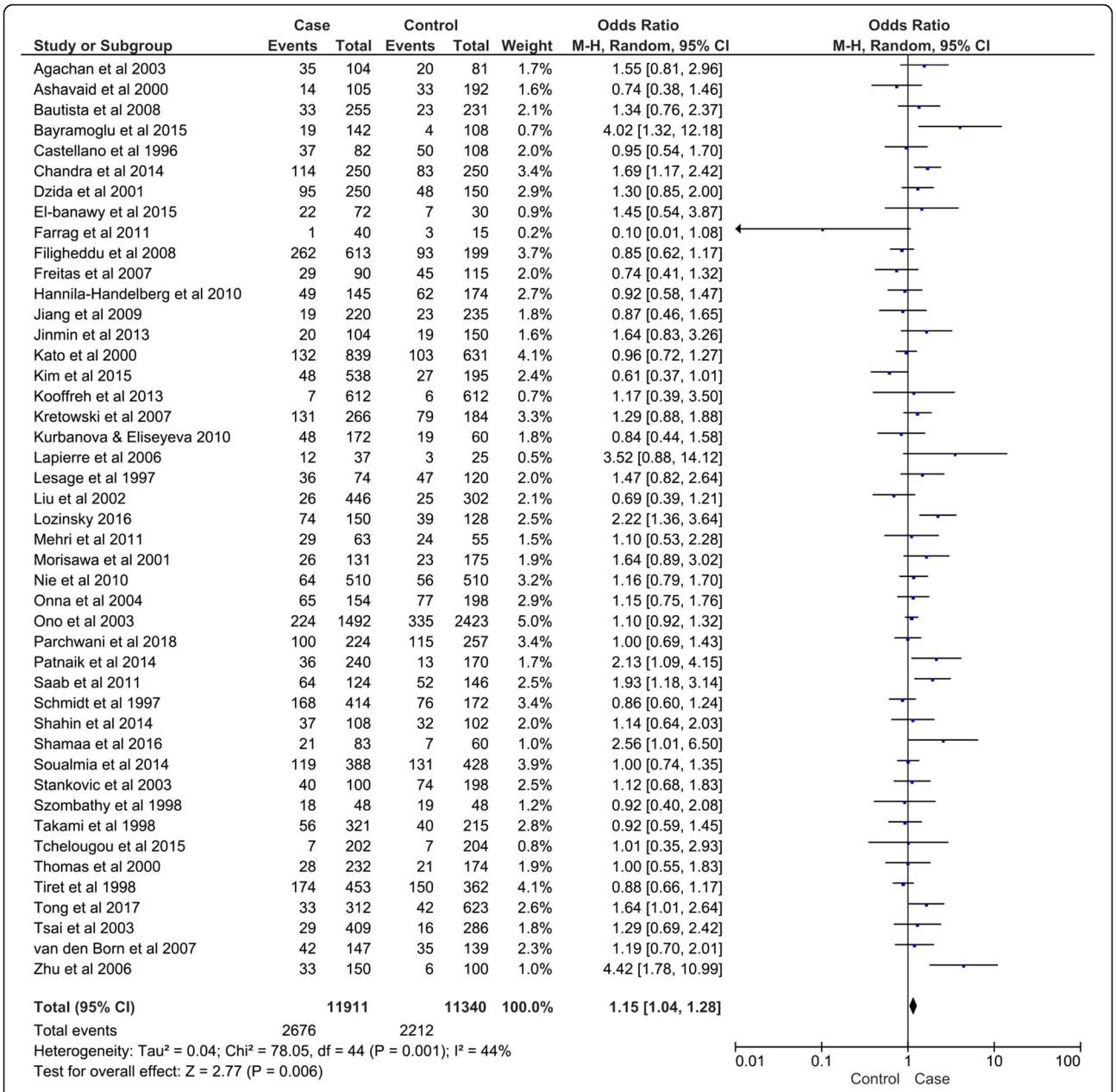

Fig. 3 The association between AT1R A1166C gene polymorphism and the risk of essential hypertension (AC vs. AA + CC)

essential hypertension was found in C allele (OR95% CI = 1.31 [1.05–1.63], $p = 0.0190$), AC genotype (OR95% CI = 1.20 [1.01–1.43], $p = 0.0430$), and CC genotype (OR95%CI = 1.53 [1.02–2.28], $p = 0.0390$) (Fig. 5a, b). We summarize the correlation between AT1R A1166C gene polymorphism and the risk of essential hypertension in Table 2.

Source of heterogeneity and publication bias

Overall, evidence for heterogeneity was observed in all alleles and genotypes of AT1R A1166C gene polymorphism ($p < 0.10$). Therefore, a random effect model was used to evaluate the correlation. In the continent subgroup, no heterogeneity ($p > 0.10$) was observed in AC genotype of the America and Africa sub-groups and CC genotype of the America, Asia, and Africa sub-groups. Therefore, data were assessed using fixed effect model, while other models were assessed using random effect model. In genotyping method sub-group, fixed effect model was used to evaluate AA, AC, and CC genotype of the PCR sub-group because we found no evidence of heterogeneity, while we found heterogeneity in other genetic models in the both PCR and PCR-RFLP subgroups, and therefore, we used random effect model. For publication bias, our Egger's test showed that the bias

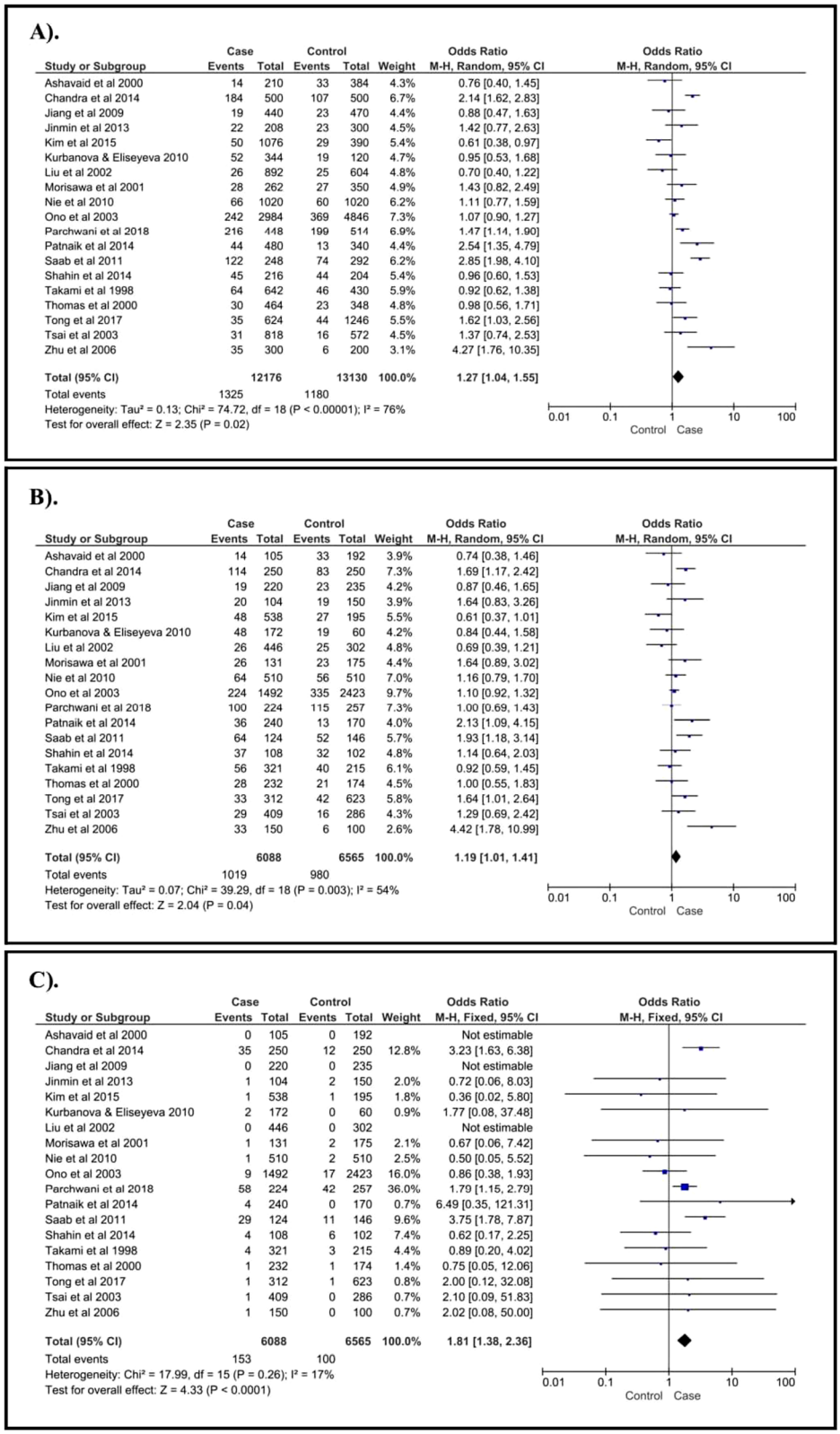

Fig. 4 The association between AT1R A1166C gene polymorphism and the risk of essential hypertension in the Asian sub-group. **a**. C vs. A, **b**) AC vs. AA + CC, and **c**) CC vs. AA + AC

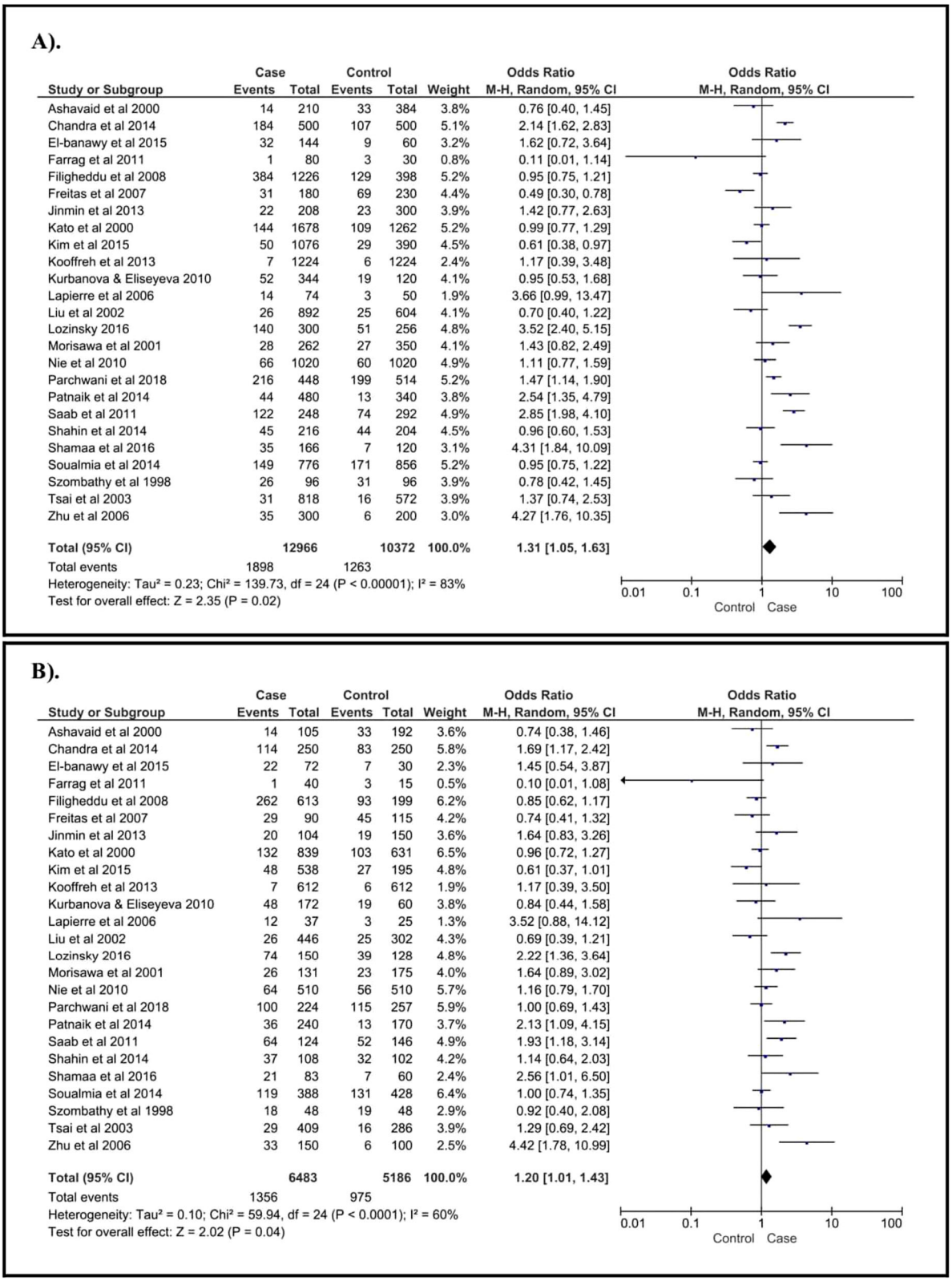

Fig. 5 The association between AT1R A1166C gene polymorphism and the risk of essential hypertension in the PCR-RFLP sub-group. **a**. C vs. A, **b**) AC vs. AA + CC

Table 2 Summary of analysis concerning the association between AT1R A1166C gene polymorphism and the risk of essential hypertension

No.	Allele and genotype	Parameters	Overall	Continent				Genotyping	
				Europe	America	Asia	Africa	PCR	PCR-RFLP
1	A vs. C	OR	0.84	0.88	0.94	0.78	0.89	0.95	0.77
		95%CI	0.75–0.97	0.72–1.08	0.52–1.67	0.64–0.96	0.54–1.48	0.85–1.07	0.61–0.96
		p	0.0130	0.2320	0.8190	0.0190	0.6620	0.4250	0.0190
		pH	< 0.0001	< 0.0001	0.0020	< 0.0001	0.0030	0.0200	< 0.0001
		pE	0.3580	0.3390	0.5000	0.3670	0.5150	0.1640	0.4820
2	C vs. A	OR	1.18	1.13	1.07	1.27	1.12	1.05	1.31
		95%CI	1.04–1.34	0.92–1.38	0.60–1.91	1.04–1.55	0.68–1.85	0.93–1.18	1.05–1.63
		p	0.0130	0.2320	0.8190	0.0190	0.6620	0.4250	0.0190
		pH	< 0.0001	< 0.0001	0.0020	< 0.0001	0.0030	0.0200	< 0.0001
		pE	0.3580	0.3390	0.5000	0.3670	0.5150	0.1640	0.4820
3	AA vs. AC + CC	OR	0.82	0.85	0.86	0.77	0.89	0.93	0.74
		95%CI	0.71–0.94	0.68–1.07	0.47–1.57	0.62–0.95	0.54–1.47	0.84–1.02	0.58–0.95
		p	0.0050	0.1710	0.6320	0.0160	0.6570	0.1060	0.0160
		pH	< 0.0001	< 0.0001	0.0090	< 0.0001	0.0250	0.1050	< 0.0001
		pE	0.3760	0.3700	0.5050	0.3980	0.4810	0.1440	0.5280
4	AC vs. AA + CC	OR	1.15	1.11	1.20	1.19	1.09	1.10	1.20
		95%CI	1.04–1.28	0.95–1.29	0.91–1.57	1.01–1.41	0.85–1.38	1.00–1.21	1.01–1.43
		p	0.0060	0.2030	0.1910	0.0410	0.5050	0.0490	0.0430
		pH	0.0010	0.0490	0.1520	0.0030	0.2550	0.5280	< 0.0001
		pE	0.2110	0.1860	0.2620	0.2570	0.2210	< 0.0001	0.3210
5	CC vs. AA + AC	OR	1.14	1.07	0.88	1.81	0.78	0.91	1.53
		95%CI	0.88–1.48	0.74–1.56	0.49–1.57	1.38–2.36	0.46–1.32	0.73–1.15	1.02–2.28
		p	0.3310	0.7190	0.6600	< 0.0001	0.3530	0.4410	0.0390
		pH	0.0010	0.0060	0.1350	0.2640	0.1210	0.3140	0.0060
		pE	0.4910	0.5030	0.9310	0.2770	0.6170	0.1810	0.5520

PCR polymerase chain reaction, *PCR-RFLP* PCR-restriction fragment length polymorphism, *OR* odds ratio, *CI* confidence interval, *pH p* heterogeneity, *pE p* Egger

was only found in AC genotype of the PCR sub-groups ($p < 0.0500$). The summary of heterogeneity and potential publication bias is provided in Table 2.

Discussion

The main pathway having crucial responsibility for the development of essential hypertension is RAAS [62]. One of the RAAS precursors, angiotensin II, plays a pivotal role to trigger adverse effects in hypertension through AT1R [63]. Until now, A1166C is one of AT1R genes widely reported. However, of the reports, inconsistency was found. Our present study aimed to perform a meta-analysis concerning the association between AT1R A1166C gene polymorphism and the risk of essential hypertension.

We collected 45 papers investigating the association between AT1R A1166C gene polymorphism and the risk of essential hypertension. Of those, 14 studies [9, 18, 21–23, 27, 32, 39, 45–47, 50, 58, 61] showed that AT1R A1166C gene polymorphism was associated with the risk of essential hypertension, while 31 other studies [19, 20, 24–26, 28–31, 33–38, 40–44, 48, 49, 51–57, 59, 60] failed to confirm the correlation. Our pooled calculation found that A allele and AA genotype of AT1R A1166C gene polymorphism were associated with a decreased risk of essential hypertension, while C allele and AC genotype were 1.18-fold and 1.15-fold, respectively, associated with increased odds of essential hypertension. During this time, there were three meta-analysis studies [64–66] evaluating the association between AT1R A1166C gene polymorphism and the risk of essential hypertension. Overall, our results were consistent with previous studies. However, some limitations of those previous studies were found, such as data discrepancy, unavailable full texts, and deviation from Hardy-Weinberg equilibrium (Table 3). Data discrepancy means that irrelevant data was found between data presented in the meta-analysis and the

Table 3 Summary of previous meta-analyses and the limitations

Author and year	Case setting	Searching strategy	NS	Limitations
Liu et al. 2015 [65]	Hypertension	PubMed, EMBASE, ISI Web of Science, Wanfang, and CNKI	56	5 studies had deviation from HWE 25 full texts were not found Data discrepancy was found
Wang et al. 2010 [64]	EHT	Chinese Biomedicine Database, CNKI, PubMed, and Medline	30	2 studies had deviation from HWE 21 full texts were not found
Yang et al. 2017 [66]	Hypertension	PubMed and Web of Knowledge	46	3 studies had deviation from HWE 3 full texts were not found

EHT essential hypertension, *CNKI* China National Knowledge Infrastructure, *NS* number of studies, *HWE* Hardy-Weinberg equilibrium

original papers. In previous studies [65, 66], we found irrelevant genotype frequency between data presented in meta-analyses and in original papers. This limitation often occurs in data collection without checking for validity, and it is considered as fatal analysis error having a crucial impact on study bias. Moreover, we also found unavailable full texts. Because of this limitation, data were not presented transparently. As a result, we could not confirm the validity of the data. Furthermore, papers with deviation from Hardy-Weinberg equilibrium were also found in the previous meta-analyses. Hardy-Weinberg equilibrium is defined as the basis of population genetics [67]. The distribution of genetics in population should not deviate from Hardy-Weinberg law. If the deviation has occurred, the distribution of gene in population will be misleading whatever method is used [68]. Therefore, these limitations might be considered as fatal limitations, and these fatal limitations might drive to false-positive findings. Because of these limitations, these previous studies might be considered having low evidence to confer the overall association. In our study, all full texts were available and data were presented transparently and in accordance with Hardy-Weinberg equilibrium. Therefore, our study might clarify better correlation between AT1R A1166C gene polymorphism and the risk of essential hypertension.

Theoretically, it has been globally known that RAAS is a group of pathways involving several precursors that act together to regulate blood pressure by maintaining the vascular tone and the balance of sodium and water [62]. Of all RAAS precursors, angiotensin II is considered as a potent vasoconstrictor [63]. Some literatures reveal that the effects of angiotensin II to cause vasoconstriction occur through its receptors, such as AT1R, AT2R, AT3R, and AT4R [63, 69, 70]. However, correlated to blood pressure maintaining, AT1R was reported to have more dominant role than other angiotensin receptors in governing the effects of angiotensin II. This receptor is expressed in a variety of organs and plays a crucial role in maintaining blood pressure homeostasis [71]. Some studies have reported AT1R gene polymorphism such as G2228A, C1424G, C521T [6], C573T, and A1166C [7]. However, A1166C was the widest of AT1R genes reported. A1166C is located at the 5′ end of the 3′ untranslated region of the gene [72]. This location is a non-coding region of AT1R, and it is linked to disequilibrium with a nearby mutation that may affect AT1R messenger ribonucleic acid (mRNA) stability [32]. In essential hypertension, the C allele of A1166C was revealed to have a pivotal role for influencing AT1R activities through affecting mRNA stability and transcription or alternatively be linked to other SNPs [65]. A study found that C allele of AT1R A1166C was associated with increased risk of hypertension through interrupting the ability of microRNA-155 to attenuate translation and resulting in augmented AT1R expression [73]. Another study also found that C allele of AT1R A1166C was associated with higher expression of AT1R gene and elevated plasma level of AT1R [9]. Moreover, a study found that C allele of A1166C was observed higher in subjects with increased AT1R protein expression and decreased miR-155 expression. Elevated blood pressure is positively correlated with increased AT1R protein expression and negatively related to miR-155 expression [74]. On other hand, gene-gene interaction study also supported our perspectives. They found that AT1R A1166C was linked to ACE I/D [75], and our previous study also revealed that ACE I/D gene polymorphism was correlated with hypertension [14]. In addition, AT1R A1166C gene polymorphism was also investigated in patients with hypertension-related condition, such as coronary artery disease and heart failure. In coronary artery disease, previous meta-analysis found that increased risk of coronary artery disease was observed in C allele [76], while in the case of heart failure, it was reported that the presence of C allele was associated with elevated levels of oxidative stress markers in heart failure patients such as protein carbonyl and myeloperoxidase [77]. This pathway might explain our results showing that C allele of AT1R A1166C gene polymorphism was associated with increased odds of having essential hypertension. However, further studies are required to clarify the precise mechanism how AT1R A1166C gene polymorphism affects essential hypertension.

Moreover, in the continent sub-group analysis, the correlation was observed only in the Asian population. We revealed that the increased risk of essential hypertension was observed in C allele, AC genotype, and CC genotype. Although it was difficult to explain the precise mechanism concerning A1166C gene polymorphism in the Asian population, however, our results might be supported by previous study. They found that this SNP was proven over-represented particularly in the Asian population [78]. However, they also failed to confirm the exact mechanism. Until now, it still becomes the paradigm that should be clarified whether the mechanism occurs through gene-gene interaction or gene-environment interaction or other genetic interaction models.

In the genotyping method, our results found the correlation in the PCR-RFLP sub-group. We showed that A allele and AA genotype were significantly associated with decreased risk of essential hypertension, while C allele, AC genotype, and CC genotype were associated with increased risk of essential hypertension. Since discovered, PCR-RFLP was widely used for genotyping in various SNPs. Although both genotyping methods were proven having the same efficacy [79], however, PCR-RFLP was reported providing an easy typing scheme of isolates [80]. In a study with larger sample size, this method may provide an easy method in data interpretation. Therefore, genotyping methods may govern the final results. This explanation may be a benchmark for the result of our study showing that the correlation was found only in the PCR-RFLP sub-group.

Although our results suggested that AT1R A1166C gene polymorphism was associated with the risk of essential hypertension, however, at present time, it is not possible to recommend this gene as a biomarker or as risk stratification in hypertensive patients. Moreover, although our study seemed having more complex design than previous meta-analyses, our study also had some crucial limitations that should be clarified in future studies. Therefore, further studies with more complex design involving gene-gene or gene-disease or gene-environment interaction may be required to clarify the better correlation.

Our study had several crucial limitations. First, some factors which might have a pivotal impact on essential hypertension such as age, physical inactivity, and body mass index [81] were not analyzed. Second, in the sub-group analysis, false-positive findings might occur because of the small sample size. Third, most of the studies included in our analysis were cross-sectional. Further analysis including only RCT studies may be required to reach a higher level of evidence. Fourth, the proportion of studies in each continent was not equal, and therefore, this might drive to analysis bias.

Conclusions

Our study reveals that A allele and AA genotype of AT1R A1166C gene polymorphism are associated with a protective effect against essential hypertension, while C allele and AC genotype of AT1R A1166C are correlated with the increased risk of essential hypertension. Our results may contribute to better understanding concerning gene-disease interaction between AT1R gene polymorphism and the risk of essential hypertension.

Abbreviations

95%CI: 95% confidence interval; A1166C: The substitution of cytosine for adenosine at position 1166; ACE: Angiotensin-converting enzyme; AT1R: Angiotensin II type I receptor; CMA: Comprehensive meta-analysis; mRNA: Messenger ribonucleic acid; OR: Odds ratio; PCR: Polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; RAAS: Renin-angiotensin-aldosterone system; RCT: Randomized controlled trial; RevMan: Review manager; SNP: Single-nucleotide polymorphism

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Authors' contributions

Idea/concept was contributed by BSP, JKF, and MS. Design was contributed by BSP, JKF, and MS. Control/supervision was done by BSP and TH. Data collection/processing was done by MS, BSP, JKF, EPS, PNBS, RRA, and FT. Analysis/interpretation was done by JKF and FT. The literature review was done by MS, EPS, PNBS, RRA, and FT. Writing the article was done by JKF. The critical review was done by BSP and TH. Revision of the article was done by JKF, BSP, SAH, AG, and TH. All authors have read and approved the final manuscript.

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Availability of data and materials

The data and material will be available with the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethics approval and informed consent were not required in our study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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