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Research paper

Ethnic and age-specific acute lung injury/acute respiratory distress syndrome risk associated with *angiotensin-converting enzyme* insertion/deletion polymorphisms, implications for COVID-19: A meta-analysis

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ABSTRACT

Background: The reported association between an insertion/deletion (I/D) polymorphism in the *angiotensin-converting enzyme* (*ACE*) gene and the risk for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) remains controversial despite the publication of four meta-analyses on this topic. Here, we updated the meta-analysis with more studies and additional assessments that include adults and children within the context of the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Sixteen articles (22 studies) were included. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using three genetic models (allele, recessive and dominant), in which ARDS patients were compared with non-ARDS patients (A1) and healthy controls (A2). Mortality outcomes were also assessed (A3). The influence of covariates was examined by meta-regression. Bonferroni correction was performed for multiple pooled associations. Subgroup analyses based on ethnicity (Asians, Caucasians) and life stage (adults, children) were conducted. Heterogeneity was addressed with outlier treatment.

Results: This meta-analysis generated 68 comparisons, 21 of which were significant. Of the 21, four A1 and three A3 highly significant (P^a = 0.00001–0.0008) outcomes withstood Bonferroni correction. For A1, allele and recessive associations were found in overall (OR 0.49, 95% CI 0.39–0.61), Caucasians (OR 0.46, 95% CI 0.35–0.61) and children (ORs 0.49–0.66, 95% CI 0.33–0.84) analyses. For A3, associations were found in overall (dominant: OR 0.45, 95% CI 0.29–0.68) and Asian subgroup (allele/ dominant: ORs 0.31–0.39, 95% CIs 0.18–0.63) analyses. These outcomes were either robust, or statistically powered or both and uninfluenced by covariates.

Conclusions: Significant associations of the *ACE* I/D polymorphism with the risk of ALI/ARDS were indicated in Caucasians and children as well as in Asians in mortality analysis. These findings were underpinned by high significance, high statistical power and robustness. *ACE* genotypes may be useful for ALI/ARDS therapy for patients with COVID-19.

Abbreviations: ACE, angiotensin converting enzyme gene; ACE, angiotensin converting enzyme protein; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ASP, aggregate statistical power; CI, confidence interval; COVID-19, Corona virus-19 disease; DD, common homozygous genotype; F, female; HWE, Hardy Weinberg Equilibrium; I^2, measure of variability; I/D, insertion/deletion polymorphism; ID, heterozygous genotype; II, variant homozygous genotype; M, male; n, number of studies; OR, odds ratio; P^a, P-value for association; P_{het}, P-value for heterogeneity.

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1. Introduction

Acute respiratory distress syndrome (ARDS) is a consequence of impaired transport of pulmonary oxygen resulting from acute lung injury (ALI) (Piantadosi and Schwartz, 2004). A statistically high percentage of ARDS patients are in intensive care units (Hingorani et al., 2015). Moreover, approximately ~35% of ARDS mortality (Ware and Matthay, 2000) results from multiorgan failure (Montgomery et al., 1985), despite improvements in sepsis management and ventilatory support (Brower et al., 2000). This level of mortality can be attributed to several predisposing factors that include sepsis or infections by viral pathogens such as novel coronavirus disease 2019 (COVID-19) (Singhal, 2020). Indeed, up to 42% of patients hospitalized for COVID-19 develop ARDS (Gibson et al., 2020). ARDS prevalence and incidence vary greatly across countries (Villar et al., 2013) and ethnicities (Linko et al., 2009; Villar et al., 2011), which may be attributed to both nongenetic and genetic factors. Genetics have been implicated in the pathogenesis of ARDS (Ware and Matthay, 2000) whereby genes interact with the environment to result in various clinical manifestations, responses to treatment and outcomes among ARDS patients (Rahim et al., 2008). Examining these genetic factors might help to identify potential therapeutic targets and help lay a foundation to predict ALI/ARDS susceptibility and outcomes (Acosta-Herrera et al., 2014). Association studies have been widely used for detecting common, low-penetrant, gene variants that may contribute to the genetic architecture of ARDS (Flores et al., 2008). Studies on mouse and human models suggest that genetic variation plays a significant role in ARDS. One such genetic variation is the insertion/deletion (I/D) polymorphism in the *angiotensin converting enzyme* (*ACE*) gene located on chromosome 17q23, involving a restriction fragment length polymorphism defined by the presence (insertion, I) or absence (deletion, D) of a 287-bp alu repeat sequence in intron 16. *ACE* genotypes (ID heterozygote, DD and II homozygotes) account for substantial levels of and variation in expression (Gard, 2010), enzyme levels and plasma ACE activity (Rigat et al., 1990), suggesting a possible influence on the therapeutic response to ACE inhibitors (Haas et al., 1998). For example, DD homozygotes have been shown to account for 65% of the observed variance in ACE1 expression, and ID heterozygotes express 31% more ACE1 than II do homozygotes (Gard, 2010). In addition, high plasma and tissue ACE concentrations have been shown to be associated with the DD genotype (Tiret et al., 1992). DD homozygote carriers were found to have the highest serum ACE activity compared to carriers of the II homozygote and ID heterozygote genotypes, who exhibit low and intermediate ACE activity, respectively (Rigat et al., 1990; Suehiro et al., 2004). As the *ACE* I/D polymorphism is responsible for 20% variance in ACE levels and 50% variance in ACE activity (Rigat et al., 1990), the impact of this single polymorphism on endpoints such as sepsis and ARDS is considerable (Brugts and Den Uil, 2008). In sepsis, the DD genotype was found to be associated with a significantly higher mortality rate and worse disease severity (Harding et al., 2002), and ARDS patients were found to have increased DD genotype frequency and a higher mortality rate (Marshall et al., 2002b). In adults, higher mortality rates and ARDS prevalence in the intensive care unit population were significantly associated with the DD genotype (Jerng et al., 2006; Marshall et al., 2002a). In contrast, predominance of the II genotype was significant among premature infants (Sivasli et al., 2007). Between ethnicities, the DD genotype was prevalent among Asians compared to Caucasian and African populations (Sagnella et al., 1999). The value of *ACE* I/D as a genetic marker lies in its association with the risk of a wide range of clinical outcomes that include response to ACE inhibitor therapy (Scharplatz et al., 2004). Operating on the hypothesis that the *ACE* I/D polymorphisms is associated with ARDS, we performed the current meta-analysis (with an umbrella review) for four reasons: (i) to obtain less ambiguous, clearer estimates and to update the role of *ACE* I/D with in ARDS; (ii) to strengthen the evidence with the inclusion of more studies; (iii) to examine associations in adults and children; and (iv) to evaluate characteristics that might influence summary effects. This study aims to clarify the impact of *ACE* I/D in ARDS, which might lead to better prediction of ARDS risk and help manage therapies for COVID-19 patients (Essig et al., 2020). As recommended by (Matsuda et al., 2012), we replicated their meta-analysis with larger sample sizes, and/or samples from other populations.

2. Materials and methods

2.1. Literature search and study selection

Four databases (PubMed in MEDLINE, Google Scholar, Science Direct and Mednar) were searched for association studies as of April 28 2020. The terms used were "*ACE* I/D", "polymorphism", "ARDS", "*angiotensin converting enzyme* insertion-deletion" and "acute respiratory distress syndrome" as medical subject headings and text and restricted to the English language. The search strings used are summarized in Table S1. Additional eligible studies were identified from references cited in the retrieved articles.The inclusion criteria were as follows: (i) case–control study design evaluating the association between *ACE* I/D and ARDS and (ii) sufficient genotype or allele frequency data to allow calculation of odds ratios (ORs) and 95% confidence intervals (CIs). The exclusion criteria were as follows: (i) studies without controls or studies with genotype or allele frequencies that were unusable or absent; (ii) articles that did not cover the polymorphism or disease in question; (iii) reviews; and (iv) non-English articles.

2.2. Data extraction and data distribution

Two investigators (NP and PT) independently extracted the data that resulted in consensus. The data extracted from each article included the first author's name, publication year, country of origin, ethnicity, life stage, sex distribution, diagnosis, age of cases, other article features needed to tally Clark-Baudouin scores, sample sizes and genotype data. The use of the mean ± standard deviation indicated a normal data distribution ($P > 0.05$); otherwise, the choice was the median (with interquartile range). Data distribution was assessed with the Shapiro-Wilks test (Ghasemi and Zahediasl, 2012).

2.3. Study quality and Hardy-Weinberg Equilibrium (HWE)

The Clark-Baudouin scale was used to evaluate the methodological quality of the included studies (Clark and Baudouin, 2006). In this scale, low, moderate and high scores are <5, 5–6 and ≥ 7, respectively. The Hardy-Weinberg Equilibirum (HWE) was assessed using the application in https://ihg.gsf.de/cgi-bin/hw/hwa1.pl.

2.4. Data synthesis

Our study design followed that of a previous meta-analysis (Matsuda et al., 2012) which included three comparisons and three genetic models: The comparisons comprised ARDS patients versus non-ARDS patients (A1), ARDS patients versus healthy controls (A2) and mortality outcomes (A3). The genetic models compared the (i) I allele with the D allele (allelic model), (ii) II + ID versus DD (recessive) and (iii) II versus ID +DD (dominant) models. Raw data for genotype frequencies, without adjustment, were used for calculating study-specific estimates of the OR. To compare effects on the same baseline, we used raw data to calculate pooled ORs that were obtained using either fixed (Mantel and Haenszel, 1959) (in the absence of heterogeneity) or random (DerSimonian and Laird, 1986) (in its presence) effects models. Heterogeneity between studies was estimated using the χ2-based Q test (Lau et al., 1997), the significance of which was set at $P < 0.10$ (Higgins et al., 2003). The effect of heterogeneity was quantified with the I^2 statistic (Higgins and Thompson, 2002). I^2 values of 0%, up to 25% and above 25% indicate homogeneity, low-level heterogeneity and moderate to high heterogeneity, respectively. Meta-regression analysis was used to

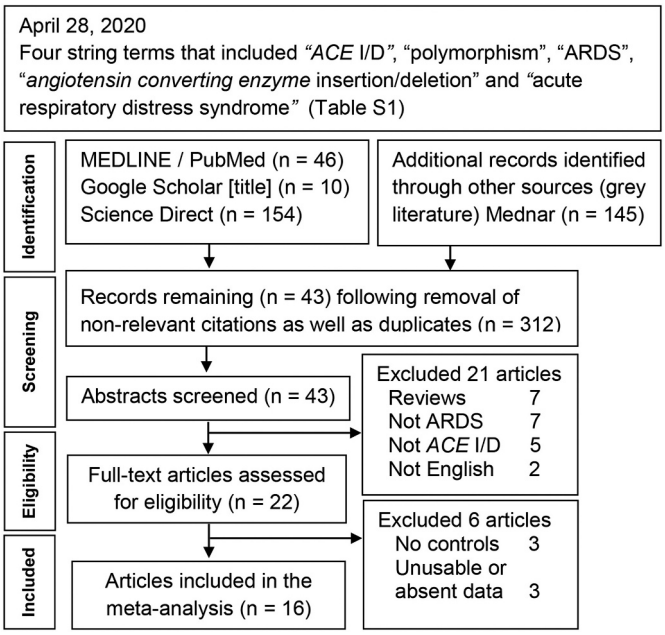

Fig. 1. Summary flowchart of literature search.
ACE: *angiotensin converting enzyme* gene; I/D: insertion/deletion polymorphism; ARDS: acute respiratory distress syndrome.

examine the potential influence of the study characteristics (covariates) on pooled outcomes. The Galbraith plot (Galbraith, 1988) was applied to identify potential outlier studies. Outlier treatment, directed at studies in the overall findings and subgroups, dichotomized the comparisons into preoutlier and postoutlier. Subgrouping was based on ethnicity (Caucasians and Asians) and life stage (adults and children). Pooled ORs were evaluated for statistical power with the G*Power program (Faul et al., 2007). Assuming an OR of 1.5 at a genotypic risk level of $\alpha = 0.05$ (two-sided), power was considered adequate at ≥80%. The robustness of the summary effects was assessed with sensitivity analysis, which we confined to significant outcomes. Multiple comparisons were corrected with the Bonferroni test. Publication bias was considered for comparisons that met two conditions: (i) ≥ 10 studies only (Ioannidis and Trikalinos, 2007) and (ii) significant outcomes. All *P* values were two-sided, the significance of which was set at <0.05 throughout except for heterogeneity estimation and publication bias. All analyses were performed using Review Manager (RevMan, v.4.2, Oxford, England), SigmaStat (v.2.03), and SigmaPlot (v.9.01).

3. Results

3.1. Search results and study characteristics

A flowchart of the study selection process is shown in Fig. 1; the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009), a checklist of which is detailed in Table S2 was followed for this study. The initial search resulted in 355 citations retrieved, followed by a series of omissions that eventually yielded 16 articles for inclusion (Adamzik et al., 2007; Cardinal-Fernandez et al., 2013; Çelik et al., 2010; Chan et al., 2005; Cruces et al., 2012; Jerng et al., 2006; Lu et al., 2016; Lu et al., 2011; Marshall et al., 2002a; Plunkett et al., 2008; Salnikova et al., 2013; Satar et al., 2012; Sivasli et al., 2007; Tsantes et al., 2013; Villar et al., 2008; Yimenicioglu et al., 2011). Eleven articles presented multiple datasets resulting in a total of 13, 7 and 9 studies for A1, A2 and A3, respectively (Table S3). Table 1 shows which articles were and were not included in the four previous meta-analyses (Deng et al., 2015; Hu et al., 2010; Matsuda et al., 2012; Tsantes et al., 2013). Six articles were included for the first-time in this meta-analysis. One article (Lu et al., 2011) examined ALI. Six articles involved pediatric subjects and the remaining 10 focused on adults, with baby-boomer demography (median: 60.1, interquartile range: 53.7–64.7). Most of the 16 Clark-Baudouin scores were in the moderate category (5–6, 56%) and less than half were in the high category (≥ 7: 44%). Non-normal distribution of the scores yielded a median of 6.0 and an interquartile range of 5.5–8.5. Based on these quantitative characteristics, the quality of the component studies was moderate. Control frequencies in four studies from three articles (Çelik et al., 2010; Lu et al., 2011; Yimenicioglu et al., 2011) deviated from HWE (Table S3).

3.2. Meta-analysis outcomes

Tables 2 and 3 show 36 and 32 pre- and postoutlier comparisons, of which two (6%) and 19 (59%) were significant, and two (6%) and 15 (47%) had zero to low-level heterogeneity (I^2 = 0%–9%), respectively. Between pre- and postoutlier analyses, the number of fixed-effect outcomes increased from four (11%) to 32 (100%). Overall and HWE-compliant outcomes were not materially different across the genetic models and between pre- and postoutlier analyses. None of the significant outcomes met both conditions for publication bias assessment. Table 4 summarizes the 21 significant pooled ORs, with sample sizes for cases and controls, aggregate statistical power (ASP) and sensitivity treatment outcomes as well as HWE and life stage outcomes. These features were not present in (Matsuda et al., 2012).

3.3. ALI/ARDS patients versus patients without ALI/ARDS (A1)

Table 2 shows 33 A1 comparisons, 10 of which were significant (P^a < 0.05). Of the 10, four highly significant (P^a = 0.00001–0.0008) pooled ORs survived Bonferroni-correction. Of the four, two involved child outcomes; that were statistically underpowered (74.9%). One in the allelic model (OR 0.66, 95% CIs 0.52–0.84) was robust and homogeneous (I^2 = 0%) and the other was nonhomogeneous (I^2 = 46%) and nonrobust in the recessive model (OR 0.49, 95% CI 0.33–0.72). The other two overall and Caucasian outcomes (ORs 0.46–0.49, 95% CIs 0.35–0.61) were robust, statistically powered (90.5%–99.4%) and nonhomogeneous (I^2 = 9%–24%) (Tables 2 and 4). Meta-regression revealed significant linear associations between study quality (P = 0.021) and sample size (P = 0.037) in the recessive Caucasian outcome (Table 5). However, the associations did not survive Bonferroni correction.

3.4. Mechanism of outlier treatment

The mechanism of outlier treatment is presented for the recessive model in the overall analysis of the A1 comparison (Figs. 2-4). Fig. 2 shows the preoutlier forest plot, with a pooled OR (0.75, 95% CI 0.49–1.15) that was nonsignificant (P^a = 0.19) and heterogeneous (P_{het} < 0.00001, I^2 = 75%). The Galbraith plot identified four outliers (Cardinal-Fernandez et al., 2013; Plunkett et al., 2008; Sivasli et al., 2007; Villar et al., 2008), found above the +2 confidence limit (Fig. 3). In Fig. 4, the postoutlier outcome (outlier omitted) showed reduced heterogeneity (P_{het} = 0.23, I^2 = 24%); and gained significance (OR 0.49, 95% CI 0.39–0.61, P^a < 0.00001). This operation is numerically summarized in Table 2.

3.5. ACE I/D-ALI/ARDS association analysis using healthy controls (A2)

Table 3 shows 12 A2 comparisons, three of which were significant in the recessive (OR 0.68, 95% CI 0.52–0.88, P^a = 0.003) and dominant models in overall (OR 1.39, 95% CI 1.04–1.87, P^a = 0.03) and HWE (OR 1.83, 95% CIs 1.22–2.72, P^a = 0.003) analyses. Both overall outcomes were statistically powered (85.3–90.1%) but without HWE (65.5%), none withstood Bonferroni correction, and they were not robust

Table 1
Characteristics of the included studies that examined *ACE* I/D polymorphism associations with ALI/ARDS.

	Included in previous meta-analyses				First author	Year	Country	Ethnicity	Life stage	Sex distribution cases (M/F)	Diagnosis	Age in cases mean ± standard deviation or median (range)	Clark-Baudouin score
	Hu et al., 2010	Matsuda et al., 2012	Deng et al., 2015	Tsantes et al., 2013									
1	Yes	Yes	Yes	No	Chan	2005	Hongkong	Asian	Adults	67/73	ARDS	59.1 (24–83) years	6
2	Yes	Yes	Yes	Yes	Jerng *	2006	Taiwan	Asian	Adults	68% M	ARDS	60.0 ± 21.0 years	6
3	No	No	No	No	Lu 2 *	2016	China	Asian	Adults	87/21	ARDS	60.2 ± 10.3 years	6
4	No	Yes	Yes	Yes	Lu 1*	2011	China	Asian	Adults	67.3% M	ALI	65 ± 16 years	5
5	No	No	No	No	Satar	2012	Turkey	Caucasian	Children	8/12	ARDS	30.2 ± 2.7 weeks	5
6	No	No	No	No	Yimenicioglu	2011	Turkey	Caucasian	Children	63/35	ARDS	31.1 ± 2.9 weeks	6
7	No	No	No	No	Sivasli	2007	Turkey	Caucasian	Children	25/16	ARDS	32.0 ± 3.7 weeks	7
8	No	No	No	No	Celik *	2010	Turkey	Caucasian	Children	No mention	ARDS	1.5–180 months	5
9	No	Yes	Yes	No	Plunkett	2008	United Kingdom	Caucasian	Children	7:6 ratio	ARDS	7.0 (1.55) months	9
10	No	No	Yes	No	Cruces	2012	Chile	Caucasian	Children	61% M	ARDS	7.5 (2–16) months	8
11	Yes	Yes	Yes	Yes	Adamzik *	2007	Germany	Caucasian	Adults	43/41	ARDS	43.0 ± 16.0 years	9
12	No	No	No	No	Salnikova	2013	Russia	Caucasian	Adults	81.1% M	ARDS	43.1 ± 1.2 years	9
13	Yes	Yes	Yes	Yes	Marshall *	2002	United Kingdom	Caucasian	Adults	61/35	ARDS	50.3 (17–91) years	8
14	No	No	Yes	No	Cardinal *	2013	Spain	Caucasian	Adults	71.4% M	ARDS	57.0 ± 17.0 years	9
15	No	No	Yes	Yes	Tsantes *	2013	Greece	Caucasian	Adults	62.3% M	ARDS	64.4 ± 17.9 years	5
16	Yes	Yes	Yes	Yes	Villar *	2008	Spain	Caucasian	Adults	63.2% M	ARDS	66 (52–75) years	6

ACE: *angiotensin converting enzyme* gene; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; M: male; F: female; I/D: insertion/deletion polymorphism; * included in the mortality analysis; the Clark-Baudouin scores range from 5 to 9, which places the scores in the moderate to high quality. However, there were more moderate scores (%) than high scores (44%) with the median (6.0) and interquartile range (5.5–8.5) indicating moderate quality of the studies.

(Table 4).

3.6. ACE I/D association with ALI/ARDS mortality outcomes (A3)

Table 3 shows 23 A3 comparisons, eight of which were significant, found in all genetic models. Of the eight, three survived Bonferroni correction. One of the three was significant in overall analysis of the dominant model (OR 0.45, 95% CI 0.29–0.68, $P^a = 0.0002$); it was robust and statistically powered (99%). Meta-regression of this low-level heterogeneous ($I^2 = 36\%$) outcome showed significant linear associations between the age of the subjects ($P = 0.028$) and the quality of the studies ($P = 0.032$) on this mortality outcome (Table 5) but did not survive Bonferroni correction. The other two comparisons were significant in the Asian subgroup analysis ($P^a = 0.0001$), with zero heterogeneity ($I^2 = 0\%$), and both were robust but underpowered (46.3–73.5%) (Table 4). One of the two was preoutlier in the dominant model (OR 0.31, 95% CI 0.18–0.54); the other was outlier derived in the allelic model (OR 0.39, 95% CI 0.24–0.63). However, the association of this postoutlier Asian outcome improved ($P_{INTERACTION} = 0.0004$) when tested for interaction with its Caucasian counterpart (OR 1.28, 95% CI 0.95–1.71, $P^a = 0.11$).

4. Discussion

4.1. Summary of findings

Our main findings indicate associations of *ACE* I/D with ALI/ARDS susceptibility and mortality; the findings are underpinned by high significance, high statistical power, zero to low-level heterogeneity and robustness. Overall, core outcomes were recessive in A1 but not in A3, involving the dominant model. Core subgroup outcomes were Caucasians and children in the allelic/recessive models for A1 and Asians in the allelic/dominant models for A3. The impacts of selection bias and population stratification on the results were likely minimal. Morover, the outlier-derived core outcomes were unlikely to have been influenced by the study characteristics. Outlier and meta-regression treatments as well as corrective procedures added stability and strength to the findings. These meta-analysis features were not present (by design) in the component single-study outcomes and were unclarified in previous meta-analyses.

The use of healthy controls (A2) is methodologically more powerful than using non-ARDS patients (A1) in associating *ACE* I/D genotypes with ALI/ARDS (Matsuda et al., 2012). Nonetheless, the power of A1 in yielding core outcomes was greater than that of A2. Similarity between

Table 2
Overall and subgroup outcomes of *ACE* I/D effects on ALI/ARDS with non-ALI/ARDS controls.

	Test of association				Test of heterogeneity			Test of association				Test of heterogeneity		
	n	OR	95% CI	P^a	P_{het}	I^2 (%)	Analysis model	n	OR	95% CI	P^a	P_{het}	I^2 (%)	Analysis model
	Preoutlier							Postoutlier						
Overall Non-ARDS controls (A1)														
Allele	13	0.91	0.70–1.19	0.50	0.00001	77	Random	9	**0.85**	**0.74–0.97**	**0.02**	0.10	40	Fixed
Recessive	13	0.75	0.49–1.15	0.19	0.00001	75	Random	9	**0.49**	**0.39–0.61**	**0.00001***	0.23	24	Fixed
Dominant	13	0.98	0.68–1.40	0.91	0.002	62	Random	10	1.19	0.96–1.47	0.11	0.10	38	Fixed
HWE														
Allele	11	0.98	0.73–1.32	0.91	0.00001	79	Random	8	0.92	0.79–1.06	0.23	0.16	33	Fixed
Recessive	11	0.88	0.55–1.40	0.59	0.0001	75	Random	7	**0.64**	**0.48–0.85**	**0.002**	0.12	41	Fixed
Dominant	11	0.96	0.66–1.41	0.84	0.001	66	Random	9	1.04	0.84–1.29	0.71	0.27	19	Fixed
Caucasian														
Allele	10	0.93	0.65–1.34	0.70	0.00001	81	Random	7	**0.81**	**0.68–0.97**	**0.02**	0.11	42	Fixed
Recessive	10	0.83	0.48–1.43	0.50	0.00001	79	Random	6	**0.46**	**0.35–0.61**	**0.00001***	0.36	9	Fixed
Dominant	10	0.92	0.54–1.58	0.77	0.001	67	Random	7	0.82	0.59–1.13	0.23	0.32	15	Fixed
Asian														
Allele	3	0.93	0.76–1.14	0.48	0.18	41	Fixed	–	–	–	–	–	–	–
Recessive	3	**0.54**	**0.37–0.78**	**0.001**	0.10	56	Fixed	–	–	–	–	–	–	–
Dominant	3	1.20	0.91–1.58	0.19	0.76	0	Fixed	–	–	–	–	–	–	–
Adults														
Allele	7	0.97	0.69–1.37	0.86	0.00001	81	Random	5	0.97	0.83–1.14	0.74	0.40	0	Fixed
Recessive	7	0.82	0.47–1.40	0.46	0.0001	80	Random	4	**0.61**	**0.44–0.83**	**0.002**	0.13	47	Fixed
Dominant	7	1.01	0.69–1.50	0.95	0.02	61	Random	6	1.22	0.96–1.54	0.11	0.94	0	Fixed
Children														
Allele	6	0.85	0.54–1.32	0.46	0.002	73	Random	5	**0.66**	**0.52–0.84**	**0.0008***	0.43	0	Fixed
Recessive	6	0.68	0.31–1.47	0.32	0.005	70	Random	5	**0.49**	**0.33–0.72**	**0.0003***	0.12	46	Fixed
Dominant	6	1.01	0.46–2.22	0.98	0.01	67	Random	5	**0.64**	**0.42–0.99**	**0.04**	0.38	5	Fixed

ALI: acute lung injury; *ACE*: *angiotensin converting enzyme* gene; I/D: insertion/deletion; ARDS: acute respiratory distress syndrome; n: number of studies; OR: odds ratio; CI: confidence interval; P^a: P-value for association; P_{het}: P-value for heterogeneity; I^2: measure of variability; values in bold indicate significant associations; *survived the Bonferroni correction.

Table 3
Summary *ACE* I/D effects on ALI/ARDS in analysis with healthy controls, mortality analysis in overall and subgroup outcomes.

	Test of association				Test of heterogeneity			Test of association				Test of heterogeneity		
	n	OR	95% CI	P^a	P_{het}	I^2 (%)	Analysis model	n	OR	95% CI	P^a	P_{het}	I^2 (%)	Analysis model
	Preoutlier							Postoutlier						
Overall healthy controls (A2)														
Allele	7	0.98	0.70–1.37	0.93	0.001	73	Random	6	1.09	0.90–1.31	0.38	0.61	0	Fixed
Recessive	7	0.98	0.55–1.74	0.94	0.0001	78	Random	6	**0.68**	**0.52–0.88**	**0.003**	0.12	43	Fixed
Dominant	7	1.23	0.73–2.10	0.44	0.003	69	Random	6	**1.39**	**1.04–1.87**	**0.03**	0.42	0	Fixed
HWE														
Allele	5	1.05	0.63–1.73	0.86	0.0002	82	Random	4	1.22	0.95–1.56	0.12	0.69	0	Fixed
Recessive	5	0.75	0.47–1.19	0.22	0.07	55	Random	4	0.96	0.66–1.39	0.84	0.98	0	Fixed
Dominant	5	1.35	0.60–3.06	0.47	0.0006	79	Random	4	**1.83**	**1.22–2.72**	**0.003**	0.73	0	Fixed
Mortality outcomes (A3)														
Overall														
Allele	9	1.08	0.61–1.93	0.78	0.00001	87	Random	4	1.28	0.95–1.71	0.11	0.38	2	Fixed
Recessive	9	1.02	0.50–2.08	0.95	0.00001	79	Random	6	**1.79**	**1.24–2.57**	**0.002**	0.13	42	Fixed
Dominant	9	0.57	0.29–1.12	0.10	0.003	65	Random	6	**0.45**	**0.29–0.68**	**0.0002***	0.17	36	Fixed
HWE														
Allele	7	1.20	0.62–2.33	0.58	0.00001	87	Random	3	1.17	0.82–1.65	0.38	0.34	6	Fixed
Recessive	7	1.14	0.56–2.32	0.72	0.0005	75	Random	5	**1.74**	**1.01–2.99**	**0.04**	0.10	48	Fixed
Dominant	7	0.49	0.22–1.09	0.08	0.009	65	Random	5	**0.47**	**0.29–0.75**	**0.002**	0.11	47	Fixed
Caucasian														
Allele	6	1.28	0.69–2.35	0.43	0.0001	82	Random	4	1.28 †	0.95–1.71	0.11	0.38	2	Fixed
Recessive	6	1.48	0.65–3.39	0.35	0.0002	79	Random	5	**1.96**	**1.31–2.95**	**0.001**	0.11	47	Fixed
Dominant	6	0.85	0.36–1.98	0.70	0.02	62	Random	5	1.18	0.73–1.93	0.50	0.25	25	Fixed
Asian														
Allele	3	0.77	0.18–3.24	0.72	0.00001	94	Random	2	**0.39** †	**0.24–0.63**	**0.0001***	0.68	0	Fixed
Recessive	3	0.44	0.11–1.74	0.24	0.02	75	Random	2	**0.22**	**0.08–0.58**	**0.003**	0.42	0	Fixed
Dominant	3	**0.31**	**0.18–0.54**	**0.0001***	0.62	0	Fixed	–	–	–	–	–	–	–

ALI: acute lung injury; *ACE*: *angiotensin converting enzyme* gene; I/D: insertion/deletion; ARDS: acute respiratory distress syndrome; n: number of studies; OR: odds ratio; CI: confidence interval; P^a: *P*-value for association; P_{het}: P-value for heterogeneity; I^2: meaure of variability; values in bold indicate significant associations; *survived the Bonferroni correction; † test for interaction between the significant Asian (OR 0.39, $P^a = 0.0001$) and the non-significant Caucasian (OR 1.28, $P^a = 0.11$) effects in the allelic model were significant ($P_{INTERACTION} = 0.0004$).

Table 4
Summary of significant outcomes and comparison of results with a previous meta-analysis.

		This study *										Matsuda et al. †					
			Test of association			Test of heterogeneity		Sample sizes					Test of association			Test of heterogeneity	
Comparison genetic model	Outlier status ‡	n	OR	95% CI	P[a]	P_{het}	I^2 (%)	Case	Control	ASP*	Sensitivity outcome	n	OR	95% CI	P[a]	P_{het}	I^2 (%)
Survived Bonferroni-correction ‡																	
Non-ARDS controls (A1)																	
Overall recessive	Post	9	0.49	0.39–0.61	**0.00001**	0.23	24	730	1607	**99.4**	Robust	6	0.81	0.48–1.37	0.43	0.03	61
Caucasian recessive	Post	6	0.46	0.35–0.61	**0.00001**	0.36	9	420	741	**90.5**	Robust	3	0.95	0.32–2.81	0.92	0.002	84
Children allele	Post	5	0.66	0.52–0.84	**0.0008**	0.43	0	282	451	74.9	Robust	–	–	–	–	–	–
Children recessive	Post	5	0.49	0.33–0.72	**0.0003**	0.12	46	282	451	74.9	Non-robust	–	–	–	–	–	–
Mortality outcomes (A3)																	
Overall dominant	Post	6	0.45	0.29–0.68	**0.0002**	0.17	36	628	1753	**99.0**	Robust	4	0.69	0.31–1.50	0.34	0.04	65
Asian dominant	Pre	3	0.31	0.18–0.54	**0.0001**	0.62	0	202	992	73.5	Robust	2	0.36	0.20–0.67	**0.001**	0.95	0
Asian allele	Post	2	0.39	0.24–0.63	**0.0001**	0.68	0	101	644	46.3	Robust	2	0.39	0.25–0.62	**0.0001**	0.64	0
Did not survive Bonferroni-correction ‡																	
Non-ARDS controls (A1)																	
Overall allele	Post	9	0.85	0.74–0.97	**0.02**	0.10	40	754	1437	**99.4**	Non-robust	6	0.97	0.67–1.41	0.88	0.0006	77
HWE recessive	Post	7	0.64	0.48–0.85	**0.002**	0.12	41	812	1696	**99.7**	Non-robust	–	–	–	–	–	–
Caucasian allele	Post	7	0.81	0.68–0.97	**0.02**	0.11	42	470	741	**92.4**	Non-robust	3	0.83	0.40–1.70	0.60	0.0009	86
Asian recessive	Pre	3	0.54	0.37–0.78	**0.001**	0.10	56	310	866	**85.5**	Non-robust	3	0.79	0.49–1.28	0.34	0.84	0
Adults recessive	Post	4	0.61	0.44–0.83	**0.002**	0.40	0	378	892	**90.3**	Non-robust	–	–	–	–	–	–
Children dominant	Post	5	0.64	0.42–0.99	**0.04**	0.38	5	282	451	74.9	Non-robust	–	–	–	–	–	–
Healthy controls (A2)																	
Overall recessive	Post	6	0.68	0.52–0.88	**0.003**	0.12	43	291	2838	**90.1**	Non-robust	5	0.79	0.47–1.33	0.37	0.004	74
Overall dominant	Post	6	1.39	1.04–1.87	**0.03**	0.42	0	291	1032	**85.3**	Non-robust	5	1.05	0.60–1.83	0.86	0.00	75
HWE dominant	Post	4	1.83	1.22–2.72	**0.003**	0.73	0	190	524	65.5	Robust	–	–	–	–	–	–
Mortality outcomes (A3)																	
Overall recessive	Post	5	1.79	1.24–2.57	**0.002**	0.13	42	347	883	**88.4**	Robust	4	0.61	0.21–1.75	0.36	0.01	74
HWE recessive	Post	5	1.74	1.01–2.99	**0.04**	0.10	48	507	696	**92.8**	Non-robust	–	–	–	–	–	–
HWE dominant	Post	5	0.47	0.29–0.75	**0.002**	0.11	47	507	696	**92.8**	Robust	–	–	–	–	–	–
Caucasian recessive	Post	5	1.96	1.31–2.95	**0.001**	0.11	47	347	647	**85.1**	Robust	2	1.25	0.58–2.67	0.57	0.21	35
Asian recessive	Post	2	0.22	0.08–0.58	**0.003**	0.42	0	209	518	68.3	Non-robust	2	0.21	0.08–0.55	**0.002**	0.42	0

ARDS: acute respiratory distress syndrome; HWE: Hardy-Weinberg Equilibrium; * analysis model for all comparisons in this study was fixed-effects; † analysis model for all Matsuda comparisons were random-effects; ‡ refers to this study; n: number of studies; OR: odds ratio; CI: confidence interval; P[a]: P-value for association; P_{het}: P-value for heterogeneity; I^2: measure of variability; ASP: aggregate statistical power ($\alpha = 0.05$, OR 1.5); values in bold indicate significant Pa values and statistically powered comparisons (> 80%).

Table 5
Meta-regression analysis of the core outcomes on Bonferroni-suriving outcomes show the influence of publication year, age of the subjects, quality of the studies (assessed by the Clark-Baudouin Scale) and sample size on the pooled ORs. Decimal numbers (columns two-five) indicate coefficient, upper and lower confidence limits and *P*-values.

Covariates	Overall	Caucasian	Children	Overall
Genetic model	Recessive	Recessive	Recessive	Dominant
Comparison	A1	A1	A1	A3
I^2	24%	9%	46%	36%
year				
Coefficient	0.002	−0.029	−0.246	−0.034
Upper confidence limit	0.057	0.053	0.228	0.006
Lower confidence limit	−0.053	−0.112	−0.721	−0.074
P-value	0.947	0.487	0.309	0.100
age				
Coefficient	−0.003	0.016	1.531	−0.054
Upper confidence limit	0.002	0.034	4.29	−0.006
Lower confidence limit	−0.009	−0.002	−1.228	−0.102
P-value	0.221	0.076	0.277	**0.028**
methodological quality				
Coefficient	−0.057	0.277	0.353	0.262
Upper confidence limit	0.069	0.514	0.718	0.500
Lower confidence limit	−0.183	0.041	−0.012	0.023
P-value	0.377	**0.021**	0.058	**0.032**
sample size				
Coefficient	0.000	0.004	0.002	−0.001
Upper confidence limit	0.001	0.008	0.012	0.003
Lower confidence limit	−0.002	0.000	−0.008	−0.005
P-value	0.585	**0.037**	0.673	0.566

A1: ARDS versus non-ARDS; A3: mortality outcome; I^2: measure of variability; all four comparisons were post-outlier; values in bold indicate significance.

the outlier-derived A2 and A1 outcomes in the recessive model was contributed to increasing the evidence for associations. Using A3 (mortality outcome) facilitated comparisons with previous meta-analyses (Matsuda et al., 2012; Tsantes et al., 2013).

4.2. Gene-gene, gene-environment interactions

Despite the evidence for associations, the complexity of ALI/ARDS involves interactions between genetic and nongenetic factors allowing for the possibility of environmental involvement. Four of the 16 articles mentioned gene-environment interactions (Adamzik et al., 2007; Salnikova et al., 2013; Tsantes et al., 2013; Villar et al., 2008) and four mentioned haplotypes (Cardinal-Fernandez et al., 2013; Marshall et al., 2002a; Salnikova et al., 2013; Villar et al., 2008).

4.3. Novelty of the findings

We identified six novelties in our study: First, in life stage sub-grouping, the childhood stage was implicated in the genetics of *ACE* I/D-ALI/ARDS associations. Second, outlier treatment generated significance and eliminated heterogeneity. Third, previous nonsignificant ($P^a > 0.05$) comparisons (Matsuda et al., 2012) became significant ($P^a < 0.05$) in our study (Table 4), likely due to the greater number of studies resulting in elevated ASP. Fourth, an umbrella review of previous meta-analyses (Table S4) showed improvement of accumulated knowledge on *ACE* I/D-ALI/ARDS associations. Fifth, meta-regression examined the influence of covariates on pooled ORs. Sixth, interaction analysis improved the significant mortality outcome with Asians being implicated in the allelic model. These novelties render our study the most comprehensive to date, with, three accomplishments: (1) filling the gaps and updating meta-analysis knowledge on the *ACE* I/D-ALI/ARDS associations; (2) minimizing the methodological problems that beset primary studies, which include limited statistical power, unrecognized confounding factors and stratification of populations (Clark and Baudouin, 2006) and (3) implicating our findings within the clinical/epidemiological dimensions of the COVID-19 pandemic.

4.4. ACE I/D-ARDS-COVID-19 associations

The *ACE* I/D polymorphism is posited to have a role in the variable prevalence of COVID-19 infections (Bandyopadhyay et al., 2020). While *ACE* I/D-ALI/ARDS associations have been studied extensively, research findings on association between *ACE* I/D and COVID-19 are only

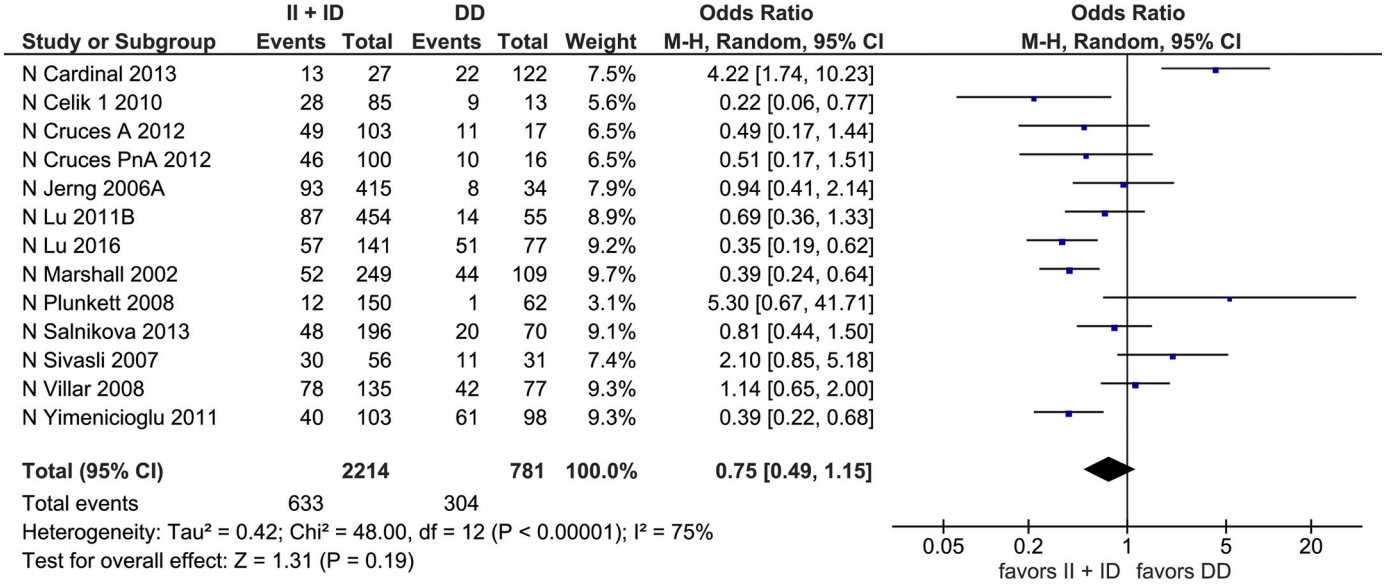

Fig. 2. Overall analysis in the recessive model with non-ARDS controls pre-outlier.
ACE: *angiotensin converting enzyme* gene; ARDS: acute respiratory distress syndrome; I/D: polymorphism;
DD: homozygote genotypes; Diamond denotes the pooled odds ratio (OR) of 0.75. Squares indicate the OR in each study. Horizontal lines on either side of each square represent the 95% confidence intervals (CI). The Z test for overall effect was not significant ($P^a = 0.19$). I^2: a measure of variability expressed in %. The χ2-test shows the presence of heterogeneity ($P_{het} < 0.00001$, $I^2 = 75\%$).

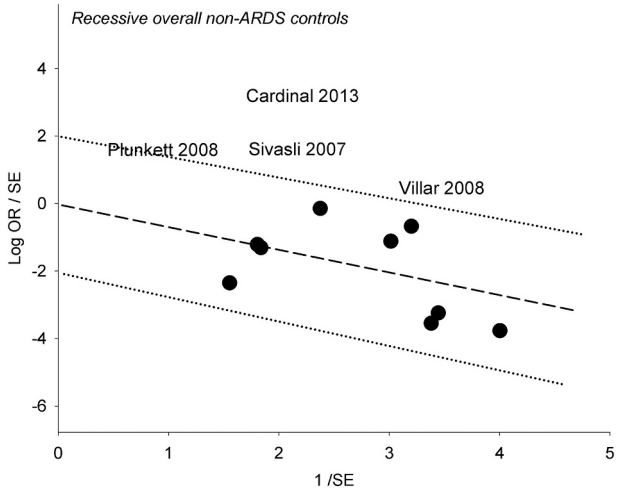

Fig. 3. Galbraith plot analysis for the recessive model with non-ARDS controls. ARDS: acute respiratory distress syndrome; Log OR: logarithm of odds ratio; SE: standard error.

emerging, covering two areas of inquiry, geography and life stage (adults/children). The *ACE* I/D-COVID-19 connection has been studied across the pandemic swath of geographical locations. (Hatami et al., 2020) found that the I/D allele ratio differed significantly between populations in Europe and Asia ($P = 0.027$). (Saab et al., 2007) found that *ACE* I allele frequencies correlated strongly with longitude. This suggests the role of genetic factors in high case-fatality rates of COVID-19 (Livingston and Bucher, 2020). The strong negative correlation between *ACE* II genotype frequency and the number of cases, as well as deaths from COVID-19 suggests a role for *ACE* II in the clinical outcome of COVID-19 and may be a predictive marker for COVID-19 risk (Yamamoto et al., 2020). At the opposing end of the *ACE* genotype spectrum, (Delanghe et al., 2020a) reported a correlation between increasing D alleles and decreasing COVID-19 morbidity/mortality. Nevertheless, these findings tend to be confounded by social and public health factors such as economic power and testing (Saadat, 2020). The risk for COVID-19 mortality has been shown to heavily impact elderly people (Borges do Nascimento et al., 2020; Liu et al., 2020). A recent review invoked the immune response and renin-angiotensin system (RAS) to explain why children are less impacted by COVID-19 than adults. Entry of the COVID-19 virus into the human body involves the transmembrane protein, ACE2, levels of which are higher in children compared to adults. High levels of ACE2 help maintain RAS balance, and genetic polymorphisms including *ACE* impact upon RAS imbalance (Krogh-Jensen et al., 2020). In the clinical milieu, *ACE* I/D was found to be associated with changes in circulating and tissue concentrations of ACE, and deletion has been associated with reduced expression of ACE2 (Delanghe et al., 2020b). Moreover, two paradoxical implication in ALI/ARDS may occur for *ACE1* DD homozygotes: (i) limit of viral replication and (ii) enhanced lung injury. Such speculation warrants further investigation.

4.5. Comparison with other meta-analyses

Four published meta-analyses examined the *ACE* I/D-ALI/ARDS associations (Deng et al., 2015; Hu et al., 2010; Matsuda et al., 2012; Tsantes et al., 2013) are shown in Tables 1 and S4. The earliest meta-analysis (2010) reported a significant 1.6-fold association of the DD genotype with ARDS based on five articles, though without reference to any genetic model (Hu et al., 2010). Two years later (2012), a second meta-analysis generated forest plots from the same sources showing no overall associations for any genetic model (Matsuda et al., 2012). This meta-analysis, however, did find significant associations of *ACE* I/D with mortality among Asians in any genetic model from two studies (Jerng et al., 2006; Lu et al., 2011), which was replicated in our study (Table 4). A year later (2013), (Tsantes et al., 2013) showed a significant recessive association indicating a two-fold (95% CI 1.16–3.77) risk of death in patients with ALI/ARDS, which concurred with our significant ($P^a = 0.002$) 1.8-fold finding for the recessive model (95% CI 1.24–2.57) (Table 4). In 2015, a fourth meta-analysis indicated a significant 1.6-fold recessive effect based on 10 articles obtained under high heterogeneity (Deng et al., 2015). A summary of these four meta-analyses indicates variability in the associative effects of the *ACE* I/D polymorphism and heterogeneity, both of which have been underexplored.

4.6. Strengths and limitations

The limitations of our study include the following: (i) we were unable to examine sex as a factor; and (ii) the pathological conditions of some cases were diluted, whereby ALI/ARDS comprised only part of the patients' condition. On the other hand, the strengths are as follows: (i) combined sample sizes of the overall sample and subgroups translated to high statistical power in most (14/21: 67%) of the significant

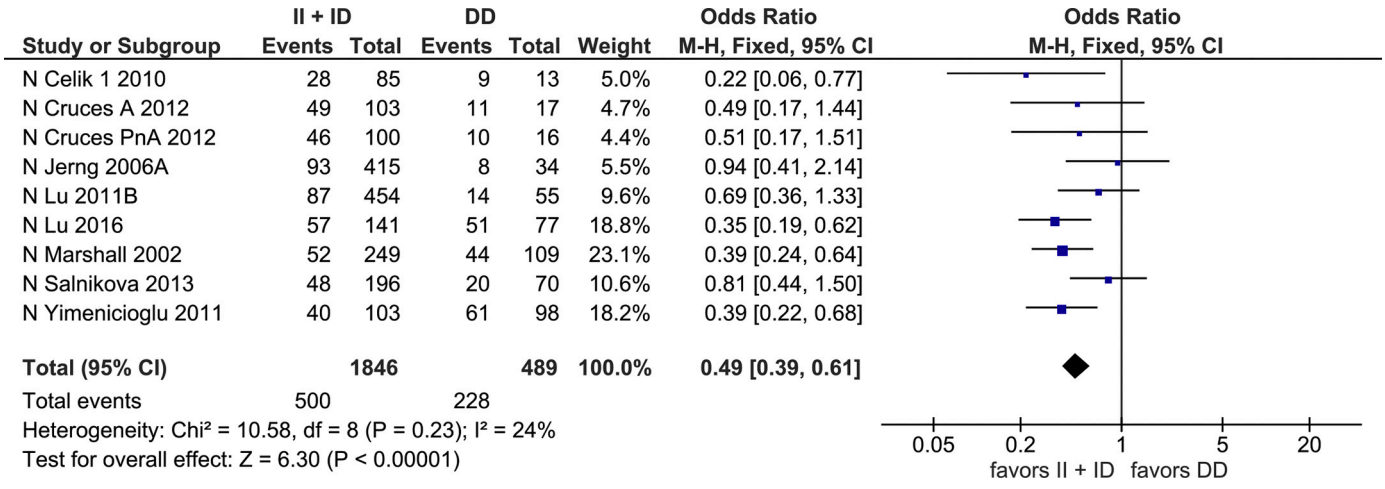

Fig. 4. Overall analysis in the recessive model with non-ARDS controls post-outlier.
ARDS: acute respiratory distress syndrome; I/D: polymorphism; DD: homozygote genotypes; Diamond denotes the pooled odds ratio (OR) of 0.49. Squares indicate the OR in each study. Horizontal lines on either side of each square represent the 95% confidence intervals (CI). The Z test for overall effect was significant ($P^a < 0.00001$). I^2: a measure of variability expressed in %. The χ2-test shows low-level heterogeneity ($P_{het} = 0.23$, $I^2 = 24\%$).

comparisons (Table 4); (ii) outlier and meta-regression treatments resulted in the core outcomes and minimized bias, respectively; (iii) likelihood of Type 1 and Type II errors were minimized with corrective procedures and statistically powered outcomes, respectively; (iv) six (86%) of the seven Bonferroni-filtered outcomes were robust.

5. Conclusions

In summary, the *ACE* I/D polymorphism may be a useful prognostic marker for ALI/ARDS. It would be interesting for future studies to examine the role of *ACE* I/D in ALI/ARDS- positive and ALI/ARDS-negative COVID-19 patients. This may clarify the role of *ACE* genotypes and the likelihood of their clinical utility in ALI/ARDS therapy for COVID-19- patients.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2020.104682.

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