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Review Article

GLOBAL PREVALENCE OF FELINE CORONAVIRUS INFECTION (FCOV) IN DOMESTIC CATS: SYSTEMATIC META-ANALYSIS

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ABSTRACT

The aim of this study was to conduct a systematic meta-analysis on global prevalence of Feline Coronavirus (FCoV) infection. According to the guidelines of PRISMA, the meta-analysis was performed. After compete search, data extraction and selection of studies, data were analyzed using comprehensive meta-analysis software program. The results of meta-analysis were95% confidence intervals, effect size, heterogeneity, weight, and publication bias. In the finally selected studies (54 articles), the overall prevalence of FCoV was 32.42 %,wherein, a total of 13,639 cats out of 42,076 were found to be positive for FCoV. The prevalence of infection was most prevalent in Europe (47.6%), but less prevalent in North and M/ Central America (3.88%). The lowest infection rate was recorded in the USA, but the highest was recorded in Germany (0.6% vs 100%). Results of meta-analysis for fixed effect showeda Z value of -30.213 (p=0.00), but for random effect, the z value was -0.310 (P = 0.756). The degree of heterogeneity in the selected study on both fixed and random effect was measured and demonstrated by the forest plot (I-squared: 99.046; Q-value: 5453.144 and P value: 0.000. The output of the Egger regression test was intercept (1.82), confidence interval (-1.72- 5.37), t-value (1.03) and p-value (0.30). However, the result of Begg and Mazumdar rank correlation test was Kendall's Tau (0.00), z-value for Tau (0.00) and P value (0.5). In conclusion, the present results indicate that the FCoV infection is globally widespread.Therefore, strict prevention and control policies should be formulated.

Keywords: Epidemiology, cat, Coronavirus, Prevalence, Meta-analysis.

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INTRODUCTION

Feline coronaviruses (FCoV), a member of family Coronaviridae, are single-stranded, positive-sense ribonucleic acid (RNA) viruses (Hagemeijer, Rottier, and Haan 2012; González *et al*. 2003). Coronaviruses infect humans as well as many other mammalian and avian species, generally causing variably severe intestinal, respiratory, neurologic, or systemic disease syndromes (Gnirs *et al*. 2016; Addie and Jarrett 2001). Infection with the avirulentpathotype of FCoV usually causes no clinical signs or only mild enteritis. But, fatal syndrome of feline infectious peritonitis (FIP) has been reported in up to 12% of the cats infected with a highly virulent mutant of FCoV(Addie and Jarrett 1992; Pedersen 2009).

Genetic recombination between FECV serotype I and canine enteric coronavirus CCoV serotype II results in emergence of feline enteric coronavirus (FECV) serotype II with subsequent confirmation of Cross-species transmission(Terada *et al*. 2014). Likewise, the emergence of canine coronavirus variants with spike protein N-terminal domains that are largely homologous to swine transmissible gastroenteritis virus (TGEV)(Decaro *et al*. 2009). Therefore, zoonotic potential of such virus has been recorded (Fan *et al*. 2019). In the framework of the concept of "One Health," a more thorough understanding of the coronaviruses of companion animals, their biological properties, their ability to recombine and to acquire new biological attributes, and their capacity for cross-species transmission has the potential to improve prevention and control measures for future emerging zoonotic coronaviruses(Cui, Li, and Shi 2019).

FCoV is widely distributed in most multi-cat environments; consequently, it is essential to identify FCoV shedders in these situations (Kipar *et al*. 1998; Addie and Jarrett 2001; Drechsler *et al*. 2011). An inherited predisposition to FCoV has been demonstrated in pedigree cats (Foley and Pedersen 1996), but trials to select resistant breeds have failed (Pedersen *et al*. 2016). The prevalence of FCoV infection in cats has been studied in several countries by reverse transcriptase polymerase chain reaction (RT-PCR), and the results have been variable (Li *et al*. 2019b; Herrewegh *et al*. 1997; Paris *et al*. 2014; Paltrinieri, Rossi, and Giordano 2014; Paltrinieri *et al*. 2007; Soma *et al*. 2013b; McKay *et al*. 2020b; Sharif *et al*. 2009; Kiss, Kecskemeti, *et al*. 2000; Sabshin *et al*. 2012; Andersen *et al*. 2018; Polak *et al*. 2014; Pedersen *et al*. 2004; Fish *et al*. 2018). Overcrowding and sharing of litter boxes have been proposed as risk factors of FCoV infection(Klein-Richers *et al*. 2020).

Meta-analysis is defined as a quantitative, formal, an epidemiological study used to evaluate earlier studies to obtain a conclusion about such studies (Israel and Richter 2011). Subsequently, a consolidated and quantitative review of such large, and complex studies will be obtained (Haidich 2010).The examination of variability or heterogeneity results obtained by previous studies is also a critical outcome of the meta-analysis(Higgins *et al*. 2003). To the best of author's knowledge, there is no available meta-analysis studies on the prevalence of feline coronavirus infection. Therefore, we conducted a systematic meta-analysis on the global infection offeline coronavirus in domestic cats. All tests regarding the meta-analysis were employed to analyze data based on previous surveys.

MATERIALS AND METHODS

Ethical approval: Analyses of all papers were completed by the authors following the guidelines and regulations of PRISMA. Therefore, ethical approval for use of animals in scientific tests was not required in this study.

Selected studies: This meta-analysis considered all papers on reference prevalence of feline coronavirus infection in domestic cats.

Inclusion and exclusion criteria:

Inclusion criteria

- Accessibility to English version of the reports in the case of foreign-language papers.
- Studies carried out on domesticated cats
- Cross sectional and case-control studies
- Pooled prevalence of repeated examination of the same catteries

Exclusion criteria

- Studies carried out on wild cats.
- Experimental studies
- Non-English published Papers

Search strategy and selection of studies:The authors searched the PubMed, Ovid, Sage, BESCO, CAB, Scopus, and ISI web of knowledge database with a combination of the following search terms FELINE CORONAVIRUS (title/ abstract) AND ("PREVALENCE") (title/abstract) OR ("Domestic Cats") (title/ abstract) from the earliest data available until December 31, 2022. This process was complemented by reviewing citations, searching with Google Scholar, expert recommendations, and hand-searching. We combined the outputs from the databases using a referencing program, EndNote (version X9; Thomson Reuters). The articles included in this study were shown in **Figure 1**.

Data extraction and analysis: The following data were extracted: the year of study, sample size, country, used technique, and positive cases with reported summary statistics (i.e. prevalence, standard error, variance, and confidence interval at 95%). Continent, country, examination technique was added onto a data extraction form.

Quality assurance: The present systematic meta-analysis was conducted according to the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA**) (Moher *et al.* 2009)**. All available published papers prevalence of feline coronavirus infection in domesticated cats were included, to minimize publication bias.

Statistical analysis: Firstly, the overall pooled prevalence was expressed as the number of positive cases divided by the number of total tested animals. The variables meta-analysis used for the assessment of the prevalence of feline coronavirus infection included fixed and random effect models, 95% confidence intervals, effect size, heterogeneity, weight and publication bias. Effect size was conducted using a standardized Z-statistic and p value (Duffield, Rabiee, and Lean 2008).Heterogeneity was assessed using Cochrane's Q test with a significant value of $p \leq 0.05$, and the I^2 statistic was used to define the % of true heterogeneity among analyses. I^2 statistic was used to estimate the degree of heterogeneity which describe the total variation which depend on Q-statistic and the number of trial (K), In fact, negative value of I^2 put equal to zero, consequently I^2 statistic lay between 0 to 100% and equal or more than 50% is considered heterogeneous (Chen *et al*. 2011).With values of 25%, 50%, and 75%, low, moderate, and high degrees of heterogeneity were identified, respectively (Higgins *et al*. 2003).Study weight was calculated as base inverse square of standard error of the effect of each trial. Forest plot

used to present the means and their confidence intervals in a graphic manner and heterogeneous degree were explored. Potential publication bias and sensitivity analysis of the overall prevalence of feline coronavirus infection were assessed using Begg's rank correlation and Egger's linear regression test. Furthermore, funnel plots were used to visually predict results discordance(Egger *et al*. 1997). Begg's rank correlation analysis usually assesses the publication bias at fixed effect. The fail-safe N was used to calculate the number of studies with a zero effect size that are necessary to eliminate the funnel plot's overall effect size. All data analyses were performed using a commercial specified Meta-Analysis software program (Comprehensive Meta-Analysis software version 2, Biostat, Englewood, NJ, USA). Additionally, a chi square test was performed to explore the statistical significance of FCoV infection among continents.

RESULTS

Search results and eligible studies: A total of 121itemswere found from databases and published articles. After exclusion, 53 eligible studies were included in this meta-analysis (Table 1, Figure 1).

Results of meta-analysis: In all 54 articles, the overall prevalence of FCoVwas 32.42%. A total of 42,076 cats were examined, of which 13,639cats were found to be positive for FCoV. Feline coronavirus infection was more prevalent in Europe (47.6%), but less prevalent in North and middle America (3.88%). The lowest prevalence was recorded by Pesteanu-somogyi *et al*. 2006 in USA (0.6%) However, the highest prevalence was recorded by Emmler *et al*. 2020 in Germany (100%). Norway showed the lowest infection rate, but Italy showed the highest prevalence of 95.8% (Table 2). Molecular technique was used in 38 (71.69%) studies, but traditional methods were used in 15 studies (Table 1).

Table 3 shows the final Meta-analysis model of the effect of size and test of null for prevalence of FCoV globally at fixed and random effect. Fixed effect shows Z value of -30.213 (p=0.00), but at random effect shows z value of -0.310 (P = 0.756).

Publication bias: The degree of heterogeneity in the selected studies on both fixed and random effect was measured and demonstrated in a forest plot (Figure 2). Additionally, the result of weight logit on both fixed and random effect was presented (Figure 3). The final variables of heterogenicity were Q-value (5453.144), I-squared (99.046), and P value (0.000). Moreover, the Tau-squared was 1.36 with Standard Error of 0.826 (Table 4).

Publication bias is presented in funnel plots with standard error and precision by logit event rate for both fixed and random effect (Figure 4,5). The output of the Egger regression test was intercept (1.82), confidence interval (-1.72- 5.37), t-value (1.03) and p-value (0.30). However, the result of Begg and Mazumdar rank correlation test was Kendall's *Tau* (0.00), z-value for Tau (0.00) and P valuem (0.5).The fail-safe N suggested that 1656.00 missing studies are needed for the result of this meta-analysis to be non-significant (p-value > 0.05).

Table 1. Descriptive statistics for the global prevalence of feline coronavirus infection in domestic cats.

Study	Positive	Sample size	Prevalence	Country	Technique
(Marshall *et al*. 1987)	2	208	0.96	Australia	Negative Staining Electron Microscopy
(Hohdatsu *et al*. 1992)	647	1079	59.96	Japan	ELISA
(Addie *et al*. 1995)	73	820	8.9	UK	PCR
(Herrewegh *et al*. 1995)	14	18	77.77	The Netherlands	RT-nPCR
(Foley *et al*. 1997)	24	275	8.7	USA	Coronavirus Antibody Titers
(Kiss *et al*. 1998)	31	102	30.4	Urban areas of Eastern Hungary	PCR
(Kiss, Kecskeméti, *et al*. 2000)	34	113	30.1	Urban areas of Eastern Hungary	PCR
(Addie *et al*. 2004)	25	148	16.9	UK	PCR
(Benetka *et al*. 2004)	74	94	78.7	Vienna, Austria	RT-PCR
(Bannasch and Foley 2005)	218	573	38.0	California, USA	PCR
(Kummrow *et al*. 2005)	530	639	82.9	Switzerland	Indirect IFA
(Lickey *et al*. 2005)	22	30	73.3	Petèn region of Guatemala	ELISA
(Bell *et al*. 2006)	104	306	33.98	Sydney, Australia	ELISA
(Holst *et al*. 2006)	209	423	49.4	Sweden	Indirect IFA

(Pesteanu-Somogyi, Radzai, and Pressler 2006)	60	9511	0.6	USA	ELISA
(Shiba *et al*. 2007)	50	79	63.3	Japan	VN Virus neutralization test
(Pratelli 2008)	115	120	95.8	Southern Italy	ELISA&IFAT
(Akkan and Karaca 2009)	38	70	54.3	Turkey	ELISA
(Duarte, Veiga, and Tavares 2009)	57	120	47.5	Portugal	RT-PCR
(Lin *et al*. 2009)	222	663	33.5	Taiwan	RT-PCR
(Pratelli *et al*. 2009)	21	100	21	Bursa Province, Turkey	ELISA
(Sharif *et al*. 2009)	37	44	84.1	Malaysia	RT-PCR
(Chang *et al*. 2010)	20	28	71.4	Utrecht, the Netherlands	RT-PCR
(Sharif *et al*. 2010)	25	28	89.3	Malaysia	RT-PCR
(An *et al*. 2011)	29	212	13.7	Korea	RT-PCR
(Amer *et al*. 2012)	40	42	95.2	Northern Taiwan	RT-PCR
(Fischer, Sauter-Louis, and Hartmann 2012)	497	851	58.4	Germany	Rivalta test
(Lund, Rimstad, and Eggertsdóttir 2012)	1	102	0.98	Norway	PCR
(Taharaguchi, Soma, and Hara 2012)	6433	17392	36.98	Japan	RT-PCR
(Barker *et al*. 2013)	13	20	65	UK	RT-qPCR
(Oguzoglu *et al*. 2013)	91	200	45.5	Ankara, Turkey	PCR
(Soma *et al*. 2013a)	531	854	62.2	Japan	RT-PCR
(Wang *et al*. 2013)	13	46	28.3	Taiwan	RT-nPCR
(Rypula *et al*. 2014)	620	676	91.7	South-Western Poland	PCR
(Wang, Chueh, and Wan 2014)	22	26	84.6	Taiwan	IFA
(Tekelioglu *et al*. 2015)	24	32	75	Istanbul, Turkey	IFA
(Fish *et al*. 2018)	9	205	4.4	Southern California	RT-PCR
(Li *et al*. 2019a)	126	169	74.5	China	RT-PCR
(Emmler *et al*. 2020)	20	20	100	Germany	RT-PCR
(Klein-Richers *et al*. 2020)	137	179	76.5	Germany	RT-qPCR
(Guan *et al*. 2020)	189	1523	12.4	Harbin, Northeast China	RT-PCR
(McKay *et al*. 2020a)	86	185	46.5	Western Canada	PCR
(Luo *et al*. 2020)	47	81	58.0	Taiwan	Immunofluorescence Staining & RT-PCR &Viral RNAs
(Hosie *et al*. 2021)	1	22	4.5	China	RT-PCR
(Kobialka *et al*. 2021)	22	39	56.4	Germany	RT-PCR
(Mūrniece *et al*. 2021)	27	40	67.5	Latvia	RT-PCR
(Oh *et al*. 2021)	1380	1620	85.2	Republic of Korea	PCR
(Zhou *et al*. 2021)	139	173	80.3	Southwest China	RT-nPCR
(Adler *et al*. 2022)	103	1005	10.2	Germany	RT-PCR
(Felten *et al*. 2022)	144	234	61.5	Germany	RT-qPCR
(Lin *et al*. 2022)	109	120	90.8	China	PCR
(Ouyang *et al*. 2022)	34	81	41.97	Central China	PCR
(Vojtkovska *et al*. 2022)	44	70	62.8	District of Moravia in the Czech Republic	RIM&RT-PCR
(Amoroso *et al*. 2022)	56	266	21.5	Italy	PCR

Table 2. Global Prevalence and pooled prevalence of feline coronavirus infection in domestic cats.

Continent	Country	Number of studies	Total examined	Total positive	Pooled prevalence	Minimum (%)	Maximum (%)
Asia		**19**	**24254**	**10074**	**41.5**	**4.54**	**95.23**
	China	6	2088	598	28.6	4.54	90.83
	Taiwan	5	858	344	40.1	28.26	95.23
	Japan	4	19404	7661	39.5	36.98	63.29
	Malaysia	2	72	62	86.1	84.09	89.28
	Korea	2	1832	1409	76.9	13.67	85.18
Europe		**27**	**6529**	**3036**	**46.5**	**0.98**	**100**
	Germany	6	2328	923	39.6	10.25	100
	Turkey	4	402	174	43.3	21	75
	UK	3	988	111	11.2	8.9	65
	Netherlands	2	46	34	73.9	71.42	77.77
	Hungary	2	215	65	30.2	30.08	30.39
	Austria	1	94	74	78.7	-	-
	Switzerland	1	639	530	82.9	-	-
	Sweden	1	423	209	49.4	-	-
	Italy	2	386	171	44.3	21.5	95.83
	Portugal	1	120	57	47.5	-	-
	Norway	1	102	1	0.98	-	-
	Poland	1	676	620	91.7	-	-
	Czech Republic	1	70	40	57.1	-	-
	Latvia	1	40	27	67.5	-	-
North and Middle America		**6**	**10779**	**419**	**3.88**	**0.63**	**46.48**
	USA	4	10564	311	2.94	0.63	38.04
	Canada	1	185	86	46.5	-	-
	Guatemala	1	30	22	73.3	-	-
Australia							
	Australia	**2**	**514**	**106**	**20.6**	**0.96**	**33.98**

Table3. Final Meta-analysis model of the effect of size and test of null (2-tail) for 53 studies on prevalence of feline coronavirus infection in domestic cats.

Model	Effect size and 95% interval				Test of null (2-Tail)	
	Number of studies	Point estimate	Lower limit	Upper limit	Z-value	P-value
Fixed	54	0.406	0.400	0.412	-30.83	0.000
Random	54	0.481	0.401	0.561	-0.467	0.756

Table 4.Heterogenicity and Tau-squared for 53 studies on prevalence of feline coronavirus infection in domestic cats.

Model	Heterogeneity					Tau-squared	
	Number of studies	Q-value	df (Q)	P-value	I-squared	Tau-squared	Standard Error
Fixed	54	5492.5	53	0.000	99.046	1.36	0.826
Random	54	-	-	-	-	-	-

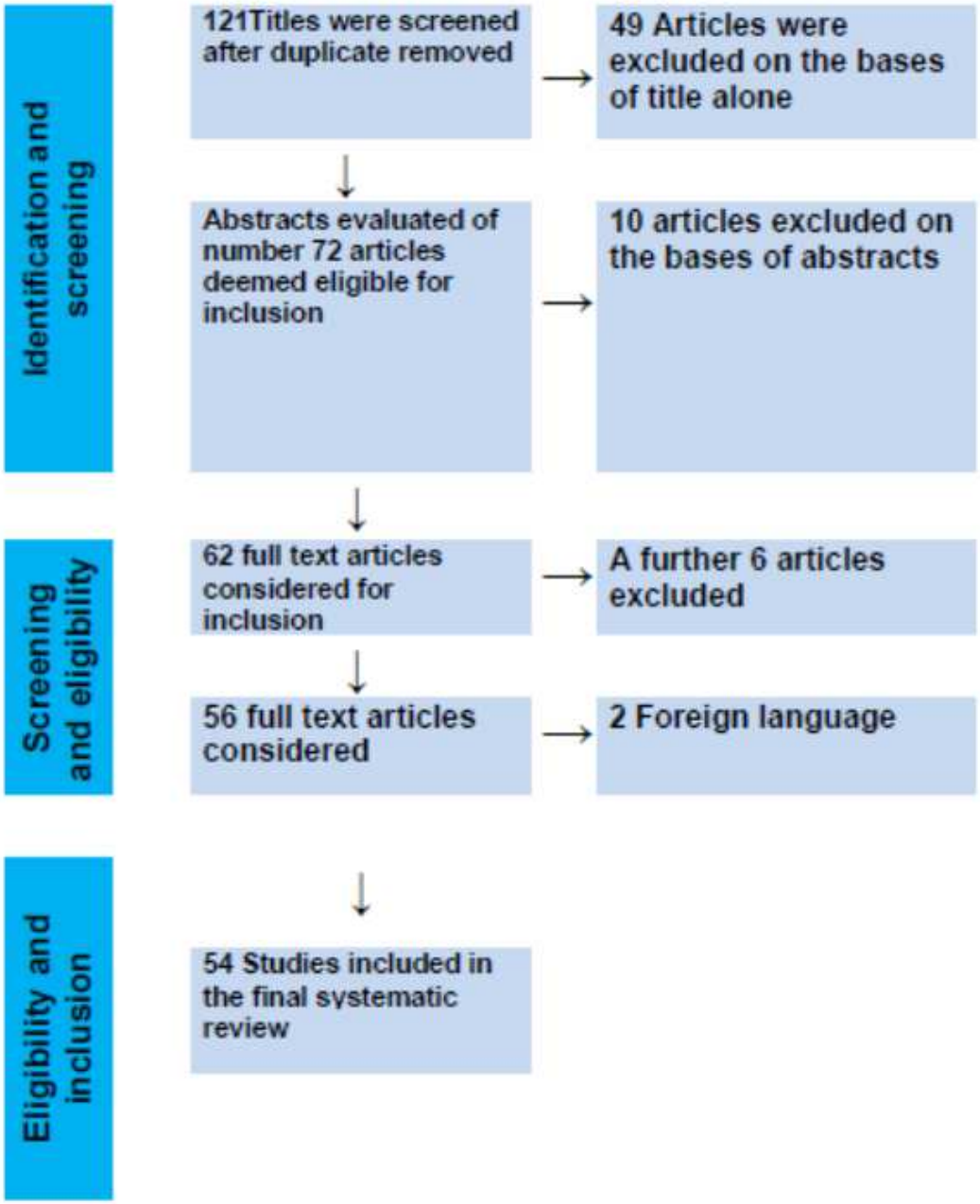

Figure 1. Descriptive diagram of studies selection strategy for Feline coronavirus infection (FCoV).

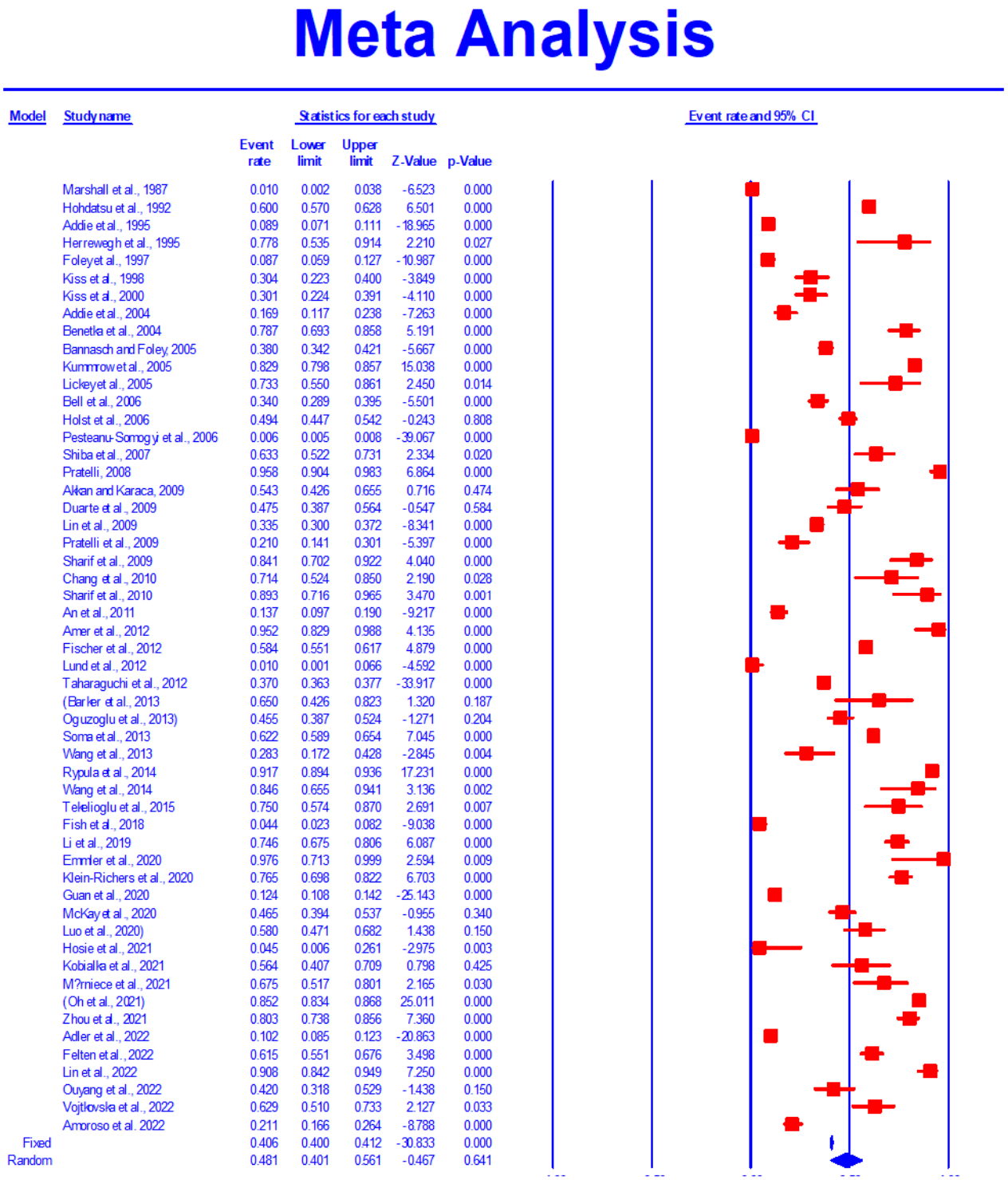

Figure 2 .Forest Plot of the prevalence of Feline coronavirus infection (FCoV) shows the event rate, confidence interval, Z value and p value of 54 studies.

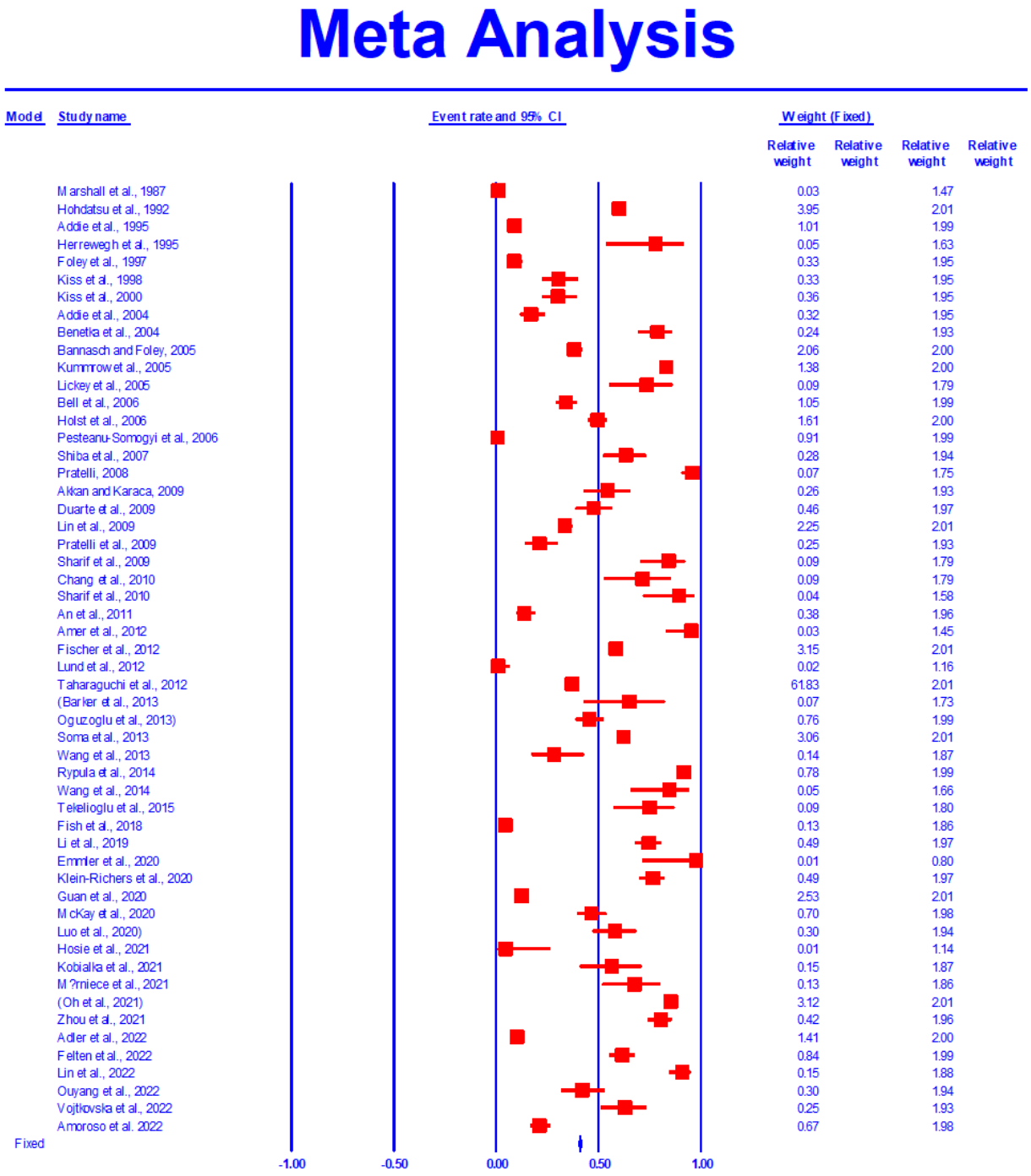

Figure 3 . Forest Plot of the prevalence of Feline coronavirus infection (FCoV) shows relative weight on both fixed and random effect of 54 studies.

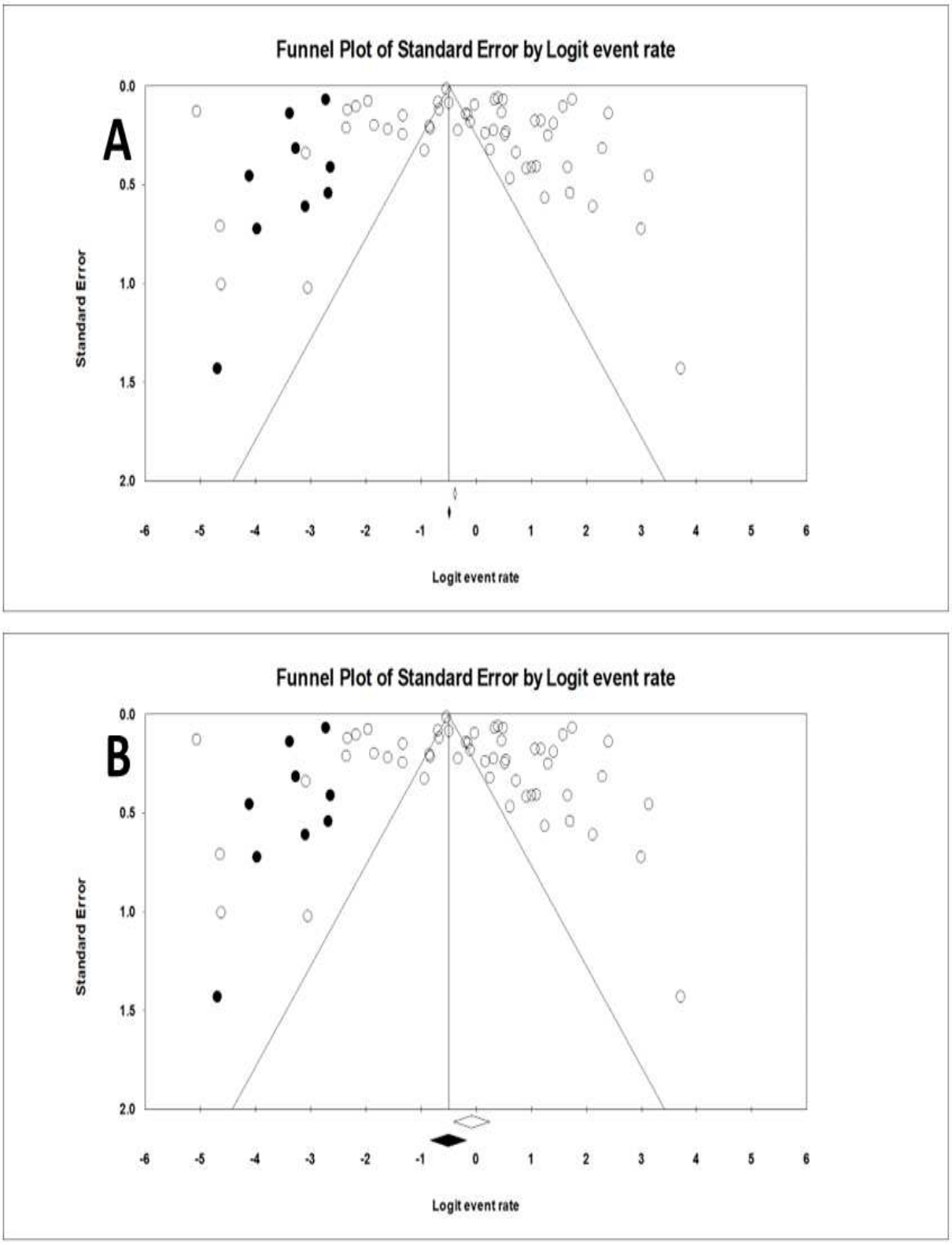

Figure 4. Funnel plot of prevalence of Feline Coronavirus infection (FCoV) shows the publication bias and standard error by logit event rate.

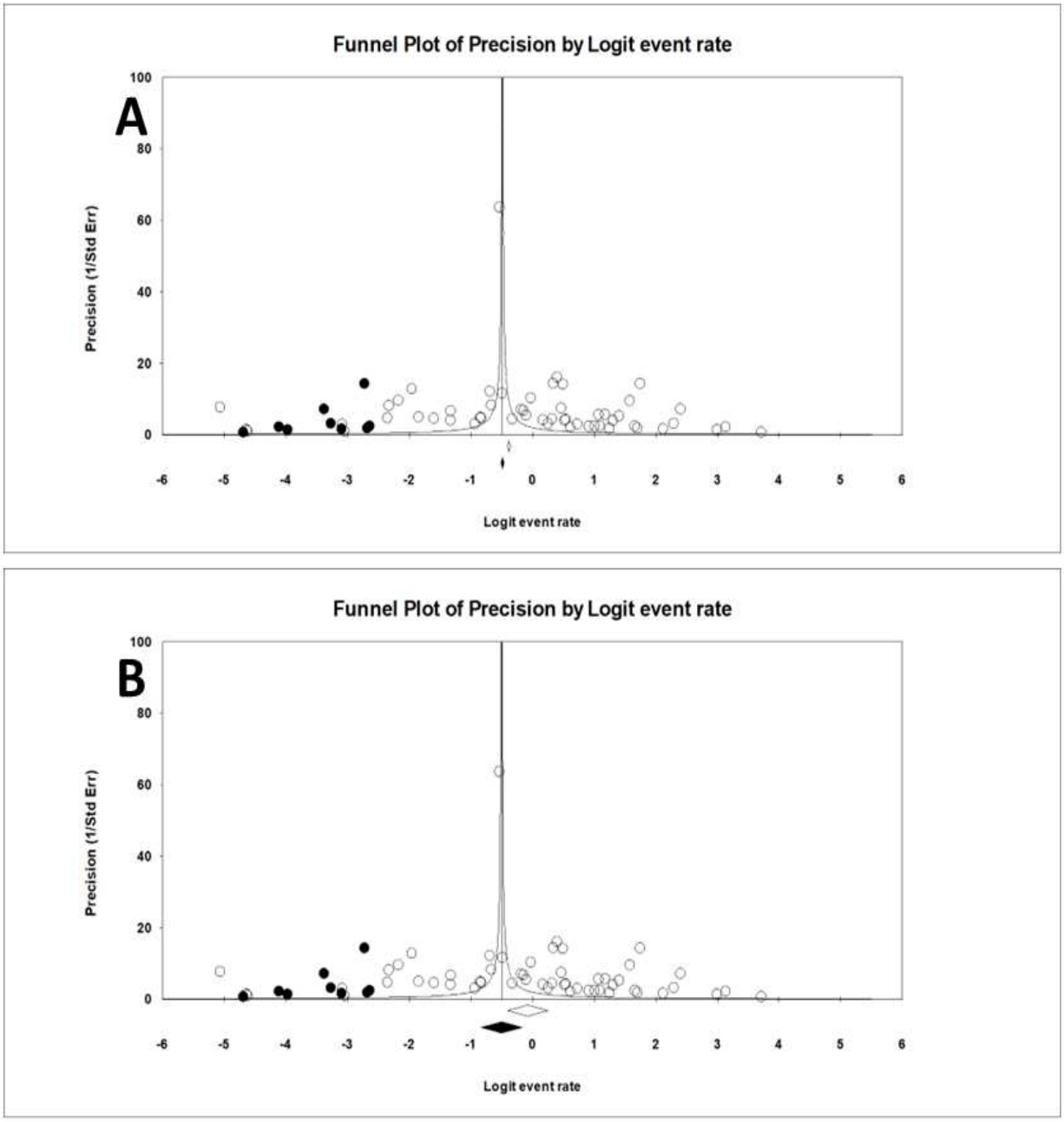

Figure 5. Funnel plot of prevalence of Feline Coronavirus infection (FCoV) shows the precision by logit event rate.

DISCUSSION

Domesticated cats, an important companion animal, have extensive contact to humans (Franklin and White 2001; Krahn, Tovar, and Miller 2015), and play a crucial role in transmission of zoonotic diseases (Kahn, Kaplan, and Steele 2007; Cantas and Suer 2014). The aim of the present meta-analyses was to assess the pooled prevalence of global FCoV infection in domestic cats. Therefore, the present systematic meta-analysis was conducted according to the rules established by PRISMA to minimize the publication bias.

FCoV is a virus with high prevalence that circulates worldwide. Infection is mainly common in environments with large numbers of cats(Jähne *et al*. 2022). The virus is present in 75–100% of domestic cats living in environments with many cats(Pedersen 1995). In the present study, by considering the prevalence of infection using traditional and molecular techniques, both fixed and random effects were assessed. According to 54

articles thatmet the criteria, the overall prevalence of FCoVof 32.42 %was found in the 42,076 cats examined.

The present meta-analysis indicates that there is a great variation in the prevalence of FCoV infection on different continents.The analysis results based on national subgroup showed that the European countries (27 studies) have the highest pooled prevalence (46.5%; 0.98-100%). However, countriesof north, and middle America recorded the lowest prevalence (3.88%). In Germany, the study carried out by Emmler *et al*., 2020 recorded the highest prevalence (100%, CI at 95%: 0.71-0.99). On the other hand, the analysis results based on national subgroup showed that the prevalence of FCoVinfection inUSAwas the lowest. The study of Pesteanu-Somogyi *et al*., 2006 recorded the lowest prevalence (0.6%; Confidence interval at 95%: 0.005-0.008).The prevalence of FCoV infection in cats has been studied in several countries and the results were variable (Li *et al*. 2019b; Herrewegh *et al*. 1997; Paris *et al*. 2014; Paltrinieri, Rossi, and Giordano 2014; Paltrinieri *et al*. 2007; Soma *et al*. 2013b; McKay *et al*. 2020b; Sharif *et al*. 2009; Kiss, Kecskemeti, *et al*. 2000; Sabshin *et al*. 2012; Andersen *et al*. 2018; Polak *et al*. 2014; Pedersen *et al*. 2004; Fish *et al*. 2018). High prevalence of FCoV infection may be due to overcrowding and sharing of the litter boxes (Klein-Richers *et al*. 2020).

Publication bias or reporting bias implies absence of information produced by either non-publication of complete studies (missing studies), or selective resultsfound in published studies (missing outcomes).The publication bias is more significant in randomized clinical trials than continuous results.In the present study, the output of the Egger regression test consists of intercept (1.82), confidence interval: -1.72-5.37, t-value: 1.03 and p-value: 0.30, suggesting that there is no evidence of publication bias.The Egger regression test can describe the intensity of funnel plot asymmetry as determined by the intercept from regression of standard normal deviates against precision(Egger *et al*. 1997). Interestingly, the result indicates symmetry of the funnel plot with no evidence of publication bias.

The result of Begg and Mazumdar rank correlation test is Kendall's *Tau*= 0.00, z-value for Tau= 0.00 and P value = 0.5. This finding supports the results of Egger regression test with no evidence of publication bias. The Begg and Mazumdar rank correlation test applies the correlation between the ranks of effect sizes and the ranks of their variances (Begg and Mazumdar 1994). Bothe Egger regression and Begg and Mazumdar rank correlation are the best statistics to support the results of funnel plot. However, a report indicates that funnel plots are not a good way to investigate publication bias (Sedgwick 2013). Other reasons for production of asymmetrical funnel plot are Poor methodological design, reporting bias, chance and study heterogenicity(Sterne *et al*. 2011).

The fail-safe N or file drawer number is an alternativeformula to counteract publication bias. (Rosenthal 1979)**.** It indicates that it is possible to calculate the actual number of missing studies and argues that finding studies to include in a meta-analysis is necessary before determining whether the p value is significant. The use of fail-safe N assumes that the main effect of missing studies has no effect. The present meta-analysis incorporates data from 54 studies, which yield a z-value of -11.02681 and corresponding 2-tailed p-value of 0.00000. The fail-safe N is 1656which means that we would need to locate and include 1656 'null' studies for the combined 2-tailed *P*-value to exceed 0.050. Contradictory, in spite of being frequently used in meta-analysis applications, these publication bias tests may have high type I error rate or low power in certain simulation settings(Sterne, Gavaghan, and Egger 2000; Terrin *et al*. 2003; Peters *et al*. 2006, 2007; Rücker, Schwarzer, and Carpenter 2008).

Generally, to minimize the limitations of the current study, the protocol was conducted according to the rules of PRISMA. However, to study the prevalence globally, data concerned with African and south American countries should be presented. Unfortunately, there is no available publication of prevalence of FCoV infection in such countries. Therefore, we included published peer-reviewed publications, which could have limited the number of studies included in the meta-analysis (54 studies).

Conclusion: The results of the present study indicate that the FCoVinfection is more prevalent in European and Asian countries. To the best of our knowledge, this is the first meta-analysis estimating the prevalence of FCoV in domesticated cats. More attention to epidemiology, pathophysiology or immunology associated with this virus and its behavior as a pathogen should be given. In the framework of the concept of "One Health," a more rigorous understanding of the feline coronaviruses, their biological properties, their ability to recombine and to acquire new biological attributes, and their capability for cross-species transmission will play a crucial role to improve prevention and control measures for future emerging zoonotic coronaviruses.

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acquisition, M.M. All authors have read and agreed to the published version of the manuscript."

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