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Research article

Prevalence of feline panleukopenia (FPL) in domestic cats: A systematic meta-analysis

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Abstract

Feline panleukopenia (FPL) is a fatal, transmissible disease in cats and other members of the *Felidae* family. A meta-analysis was performed to determine the worldwide prevalence of FPL infections in domesticated cats. This meta-analysis was finalized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. After a competent search, data extraction and identification of qualified articles were performed. Data were analyzed using a specific software program for meta-analysis, and the results included weight, effect size, publication bias, and heterogeneity. A total of 5820 domesticated cats from 36 accepted studies were investigated for FPLV infections. Of all, 2928 cats were found positive for FPLV infection, with a prevalence of 50.30%. The prevalence of FPL in cats varied significantly between countries ($p < 0.001$). The highest prevalence was recorded in Germany (15.81%), whereas the lowest prevalence was recorded in Korea (2 %). The Z-values were -10.935 ($P = 0.000$) and -2.903 ($P = 0.004$) for fixed and random effects, respectively. The Q-value (948.37), I-squared (96.309), and P (0.000) were the final heterogeneity variables. Moreover, the Tau-squared value was 0.888 with an SE of 0.316. Egger's linear regression test for asymmetry did not indicate publication bias (intercept: -0.75382; 95% CI: -4.63013 to 3.122; t-value:0.395; p=0.695). The classic fail-safe N proposed that 1031 missing studies were required to conclude that the study result was significant ($p = 0.000$). The results of this meta-analysis indicated a high global prevalence of FPLV infection in cats. Wide variation in the prevalence of FPLV infection among countries may indicate the failure of preventive programs. The results also necessitate more attention to associated risk factors and strict control measures.

Keywords: FPLV, Incidence, Systematic review.

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INTRODUCTION

Feline panleukopenia (FPL) is a highly contagious viral disease that can be fatal to cats and other members of the *Felidae* family (Kruse et al., 2010; Kabir et al., 2023). Although FPL can affect cats of all ages, it is particularly severe and devastating in kittens (Truyen et al., 1994). FPLV infection can manifest with various common symptoms such as severe diarrhea, vomiting, nasal discharge, and leukopenia (Parrish, 1995). The severity of these clinical signs can vary based on factors such as age, immune status, and presence of concurrent infections (Foley et al., 1999). Feline panleukopenia is caused by feline panleukopenia virus (FPLV). This virus belongs to the *Protoparvovirus* genus of the *Parvoviridae* family (Cotmore et al., 2019). FPLV has a linear genome composed of a single strand of DNA (Balboni et al., 2018). Under an electron microscope, FPLV have a round or hexagonal shape without a capsule structure (Reed et al., 1988). The full length of the FPLV genome is approximately 5200 nt, and it contains two open reading frames (ORFs) that encode structural proteins (VP1 and VP2) and nonstructural proteins (NS1 and NS2) (Christensen and Tattersall, 2002). In FPLV, the VP2 protein is the result of translation of the VP2 gene and the primary building block of the viral capsid, whereas the NS protein primarily controls the expression and replication of viral genes following viral infection (Govindasamy et al., 2003). FPLV may replicate in a variety of tissues in felines, including the lymph nodes, thymus, spleen, and intestinal epithelium, with significant quantities of the virus shed in the feces (Truyen and Parrish, 1992; Haynes and Holloway, 2012). FPLV infection leads to immunosuppression by targeting lymphoid tissues and causes cellular depletion. This depletion not only results from direct lymphocyte destruction and subsequent lymphopenia, but also from the migration of lymphocytes into tissues (Parrish, 1995). Meanwhile, the destructive impact of FPLV on intestinal cells, particularly in the villi, leads to diarrhea, as it interferes with the absorption of nutrients and increases permeability (Stuetzer and Hartmann, 2014). Because FPLV is shed from all bodily fluids during the active stages of the disease, direct contact between vulnerable animals and infected cats or their secretions is the most typical way in which the virus spreads horizontally (Cotmore et al., 2019). Fleas, however, may be involved in the spread (Vobis et al., 2003). The virus can spread vertically during pregnancy and affect the developing fetus. This can lead to several problems in the early stages of pregnancy, including fetal mortality, resorption, abortion, and mummification (Garigliany et al., 2016). The FPLV may harm neural tissue in the later stages of pregnancy, specifically resulting in fetal cerebellar hypoplasia (Aeffner et al., 2006). In contaminated surroundings, FPLV can persist for weeks or even months and exhibit a remarkable level of resilience to both chemical and physical agents (Uttenthal et al., 1999).

Ensuring a prompt diagnosis of FPLV infection is crucial for the isolation of infected cats and prevention of secondary infections among susceptible animals. To facilitate a quick field diagnosis, several point-of-care tests can provide a convenient and rapid means of diagnosing the presence of FPLV. These tests utilize either an enzyme-linked immunosorbent assay (ELISA) or immunochromatographic technology (ICT). Several laboratory techniques have been used to detect FPLV in infected cats. These include hemagglutination inhibition (HI), which is widely regarded as the gold standard for measuring antibodies against FPLV (Yang et al., 2021), other techniques include conventional polymerase chain reaction (cPCR) (Hasırcıoglu et al., 2023), real-time PCR (Rehme et al., 2022b), and multiplex PCR (Zhang et al., 2019) have been also used.

Feline panleukopenia is a globally distributed disease with varying prevalence rates in different regions. In Iran, a study using ICT test found that the prevalence rate of FPLV among diarrheal cats was 34.3% (Mosallanejad et al., 2009). In Egypt, another study using conventional PCR found a prevalence rate of 45.45% for FPLV infection (Awad et al., 2018). In Germany, the prevalence of FPLV

infection is 28% using quantitative PCR (Rehme et al., 2022b). On the other hand, in China, the prevalence rate of FPL was 61.44% using PCR (Yan et al., 2023).

A meta-analysis is an epidemiological study designed to systematically assess the results of previous investigations to reach a conclusion about this research topic (Haidich, 2010). This includes a combined and quantitative review of a large, frequently complex, and occasionally conflicting body of literature (Moher et al., 2010). Additionally, the results of the meta-analysis may provide a more accurate estimation of the effects of risk factors or treatment for specific diseases or other outcomes than any individual study participating in the pooled analysis (Moher et al., 2009).

Several meta-analytical studies have been conducted on the viral diseases in cats (Ludwick and Clymer, 2019; Bezerra et al., 2024; Hu et al., 2024). However, there are no systematic reviews or meta-analyses on FPLV infection in cats. Therefore, the objective of this study was to conduct a systematic meta-analysis of the global prevalence of feline panleukopenia in domesticated cats.

Methodology

Ethical approval

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Consequently, it was not necessary to obtain approval from the ethical committee for animal use in scientific research.

Selected studies and reference cats

This meta-analysis included all published studies describing the prevalence of FPL in cats using different techniques.

Selection criteria

Inclusion criteria

- Only papers in English language.
- Publications on prevalence of FPLV infection in domestic cats.
- A reputable journal publication.
- Papers with case-control and cross-sectional studies.
- Studies imply the prevalence of using any diagnostic technique.

Exclusion criteria

- Papers described only techniques for identifying FPLV.
- Experimental studies on FPLV infection.
- Languages of publications other than English.
- Preprint and review articles.

Study selection

The objective of this study was to identify all publications on the prevalence of FPLV infection in domesticated cats. We searched PubMed, Web of Science, Sage, BESCO, Ovid, CABI, Scopus, and other databases. The following search terms were used: ("CATS" "FELINE PANLEUKOPENIA") (title and abstract) ("FELINE PANLEUKOPENIA") (title/abstract) ("CATS") (title / abstract) AND ("PREVALANCE" "INCIDENCE") (title/abstract). The preliminary screening of the articles was based on the title and abstract from the earliest data available by March 2024. This procedure was supplemented by manual searching, Google Scholar search, expert recommendations, and citation reviews. Database outputs were integrated using the EndNote software. The standard identification, selection, and eligibility criteria of the selected studies are shown in Figure 1.

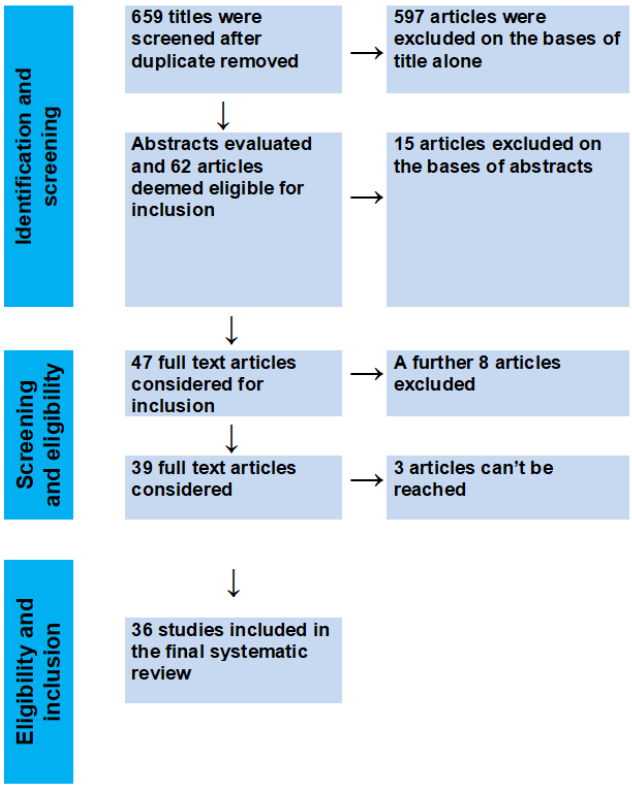

Figure 1 Articles included regarding the global prevalence of FPLV infection in cats.

Data extraction and analysis

The extracted data included the year of publication, study area, diagnostic method, sample size, and positive cases with summary statistics (Table 1).

Data analysis

First, the prevalence of FPL was calculated for all cats examined in the accepted studies. The Chi-square test was used to assess significant variation among countries (GraphPad Prism for Windows version 9, USA). Commercial Meta-Analysis software was used (Comprehensive Meta-Analysis software version 2, Biostat, Englewood, NJ, USA). In both random- and fixed effects models, effect size, 95% confidence intervals, variance, heterogeneity, relative weight, and publication bias were the main tests. The effect size was expressed by both *P* and standardized Z-statistics. Cochran's Q test was conducted to assess heterogeneity, and the I^2 statistic was used to determine the proportion of heterogeneity (Duffield et al., 2008). A funnel plot was generated to assess the degree of publication bias (Higgins et al., 2011). Egger's linear regression intercept (Egger et al., 1997) and the Begg–Mazumdar rank correlation tests were also applied (Begg and Mazumdar, 1994).

Table 1 Descriptive data regarding the global prevalence of Feline Panleukopenia Virus (FPLV) in domesticated cats.

Authors	Country	Total samples	Positive (%)	Technique
(Goto et al., 1981)	Japan	226	130 (57.52 %)	Hemagglutination-inhibition
(Neuerer et al., 2008)	Germany	52	10 (19.23%)	Electron microscopy
(Levy et al., 2008)	The Republic of Ecuador	52	34 (65.38%)	Indirect ELISA
(Abd-Eldaim et al., 2009)	USA	97	55 (56.7%)	Antigen ELISA
(Mosallanejad et al., 2009)	Iran	67	23 (34.32%)	Immunochromatography assay test
(Suntz et al., 2010)	Germany	302	152 (50.33%)	An indirect immunoperoxidase method
(Islam et al., 2010)	Bangladesh	58	13 (22.41%)	A chromatographic immunoassay for the qualitative detection of panleukopenia antigen in feline feces
(Uhart et al., 2012)	Argentina	40	4 (10%)	The hemagglutination inhibition (HI)
(DiGangi et al., 2012)	USA	348	138 (39.65%)	Hemagglutination inhibition assay, PCR
(Kim et al., 2013)	Korea	200	4 (2%)	
(Parthiban et al., 2014)	India	60	22 (36.66%)	The hemagglutination inhibition (HI), PCR
(Mende et al., 2014)	Germany	347	245 (70.60%)	The hemagglutination inhibition (HI)
(Paris et al., 2014)	United Kingdom	1088	240 (22.05%)	ImmunoComb Feline VacciCheck real-time PCR
(Sibel and AVDATEK, 2016)	Turkey	151	24 (15.89%)	FPLV Indirect ELISA
(Bayati, 2016)	Iraq	84	32 (30.09 %)	Chromatographic immunoassay, PCR
(Raheena et al., 2017)	India	27	10 (37.04 %)	Immunochromatographic strips, Hemagglutination, PCR
(Miranda et al., 2017)	Portugal	31	18 (58.06%)	Conventional PCR
(Awad et al., 2018)	Egypt	165	66 (40.0%)	Direct ELISA, PCR
(Koç et al., 2018)	Turkey	68	13 (19.11 %)	PCR
(Bukar-Kolo et al., 2018)	Nigeria	200	27 (13.5 %)	Immunochromatography Assay
(Zhang et al., 2019)	CHINA	197	73 (18.78 %)	Multiplex PCR
(Dall'Ara et al., 2019)	Italy	151	69 (45.69 %)	Indirect Elisa
(Zenad and Radhy, 2020)	Iraq	180	40 (22.22%)	Immunochromatography assay test, indirect ELISA
(Liu et al., 2020)	China	18	1 (5.55%)	PCR
(Riya et al., 2020)	INDIA	40	34 (85 %)	PCR
(Jacobson et al., 2021)	Canada	145	55 (37.93 %)	qPCR
(Chowdhury et al., 2021)	Bangladesh	98	8 (8.16%)	Immunochromatography, PCR
(Abayli et al., 2021)	Turkey	93	9 (9.67%)	PCR
(Rehme et al., 2022b)	Germany,	150	42 (28 %)	qPCR
(Amoroso et al., 2022)	Italy	257	189 (73.54 %)	Real-Time PCR
(Yang et al., 2022)	Korea	200	185 (92.5 %)	The hemagglutination inhibition (HI)
(Tajbiur-Abir, 2022)	Bangladesh	61	30 (49.18 %)	Feline Panlekopenia Antigen FPV Ag test, Manufacturer: Hangzhou Testsea Biotechnology Co. Ltd.)
(Cao et al., 2023)	China	304	187 (61.51 %)	PCR
(Dishow et al., 2023)	Iraq	100	66 (66.0 %)	Indirect enzyme immunosorbent assay, c-PCR technique
(Xue et al., 2023a)	China	80	30 (37.5 %)	PCR
(Xue et al., 2023b)	China	83	64 (77.1 %)	NanoPCR, Conventional PCR

RESULTS

After the complete search, 659 items were identified. According to the inclusion and exclusion criteria, 36 studies were eligible for this meta-analysis (Table 1, Figure 1). The overall prevalence of FPLV infection in domesticated cats was 50.30% in all the studies. Examination of 5820 diseased domestic cats revealed that 2928 cats were positive for FPLV infection. Two studies in Korea reported the lowest (2%) and the highest (92.5%) prevalence of the disease.

The results of the size effect and weight regarding the prevalence of FPLV in domesticated cats are presented in Table 2 and Figure 2-3. At random, the effect had a Z-value of -2.903 (P = 0.004) as opposed to the fixed effect's Z-value of -10.935.

Table 2 Final Meta-analysis model of the effect of size and test of null (2-tail) for 36 observed studies on the prevalence of feline panleukopenia (FPL) in domesticated cats.

Model	Effect size and 95% Confidence Interval				Test of null (2-Tail)	
	Number of studies	Point estimate	Lower limit	Upper limit	Z-value	*P*
Fixed	36	0.418	0.404	0.433	**-10.935**	0.000
Random	36	0.383	0.310	0.461	-2.903	0.004

Z-value: result of Z-test
P: P-value

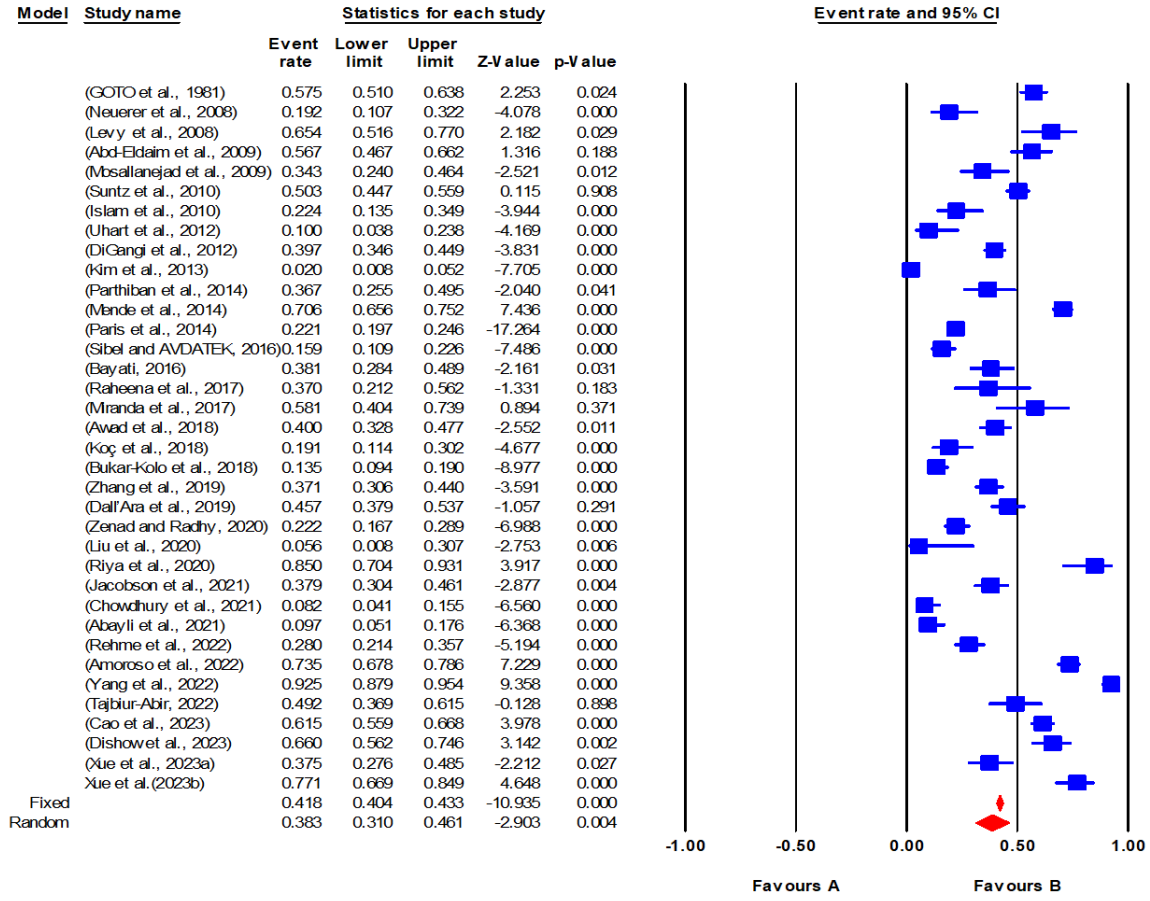

Figure 2 Forest plot describes the heterogenicity of meta-analysis on global prevalence of FPLV infection in cats.

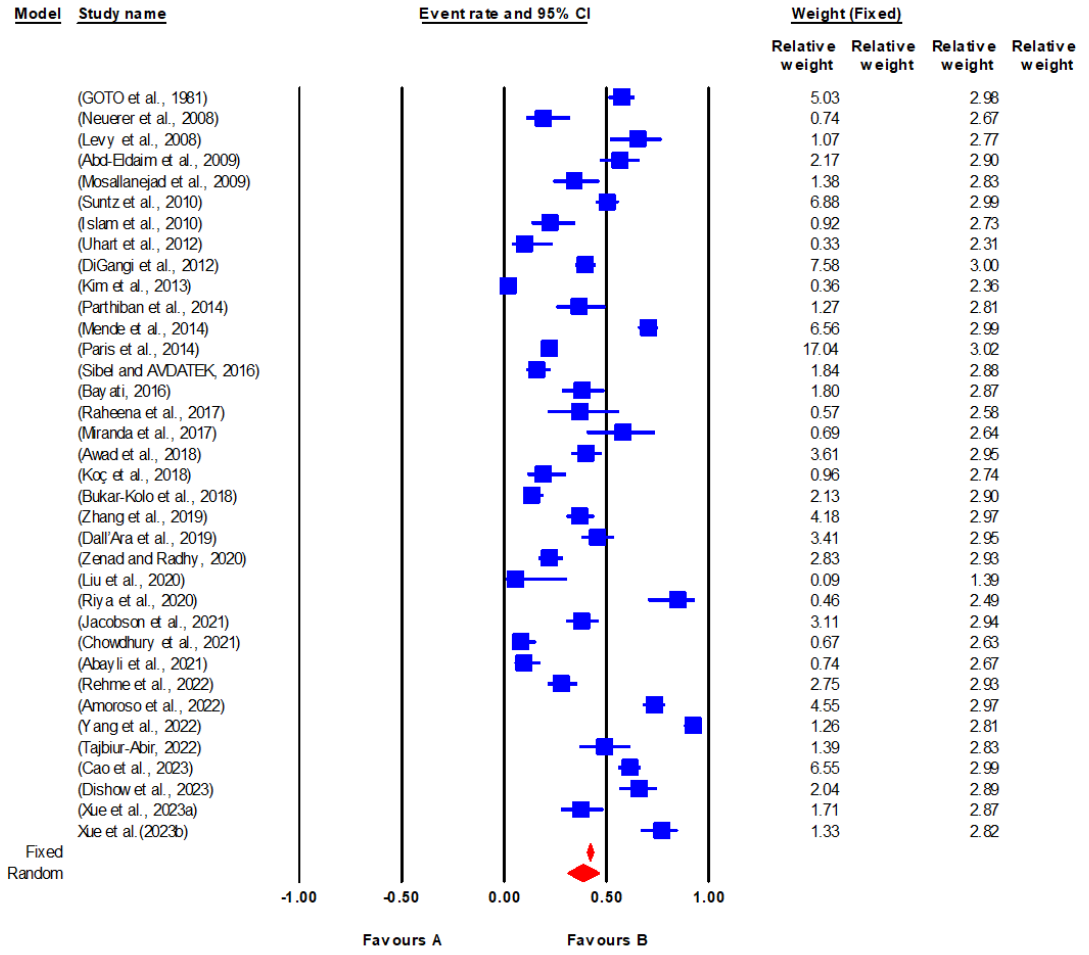

Figure 3 Forest plot showing the event rate and weight regarding prevalence of FPLV infection in cats.

Degree of Heterogeneity

A forest plot was used to evaluate and illustrate the degree of heterogeneity in the selected studies for both fixed and random effects (Figure 4). The Q-value (948.378), I-squared (96.309), and *P* (0.000) were the final heterogeneity variables. Additionally, the Tau-squared value was 0.888 with a Standard Error (Table 3).

Table 3 Heterogeneity and Tau-squared for the 36 observed studies on the prevalence of Feline Panleukopenia (FPL) in domesticated cats.

Model	Heterogeneity					Tau-squared	
	Number of studies	Q-value	DF (Q)	*P*	I-squared	Tau-squared	Standard Error
Fixed	36	948.378	35	0.000	96.309	0.888	0.316
Random	36	-	-	-	-	-	-

DF: degree of freedom, Q-Value: Cochran's Q test, I-squared: heterogenicity test

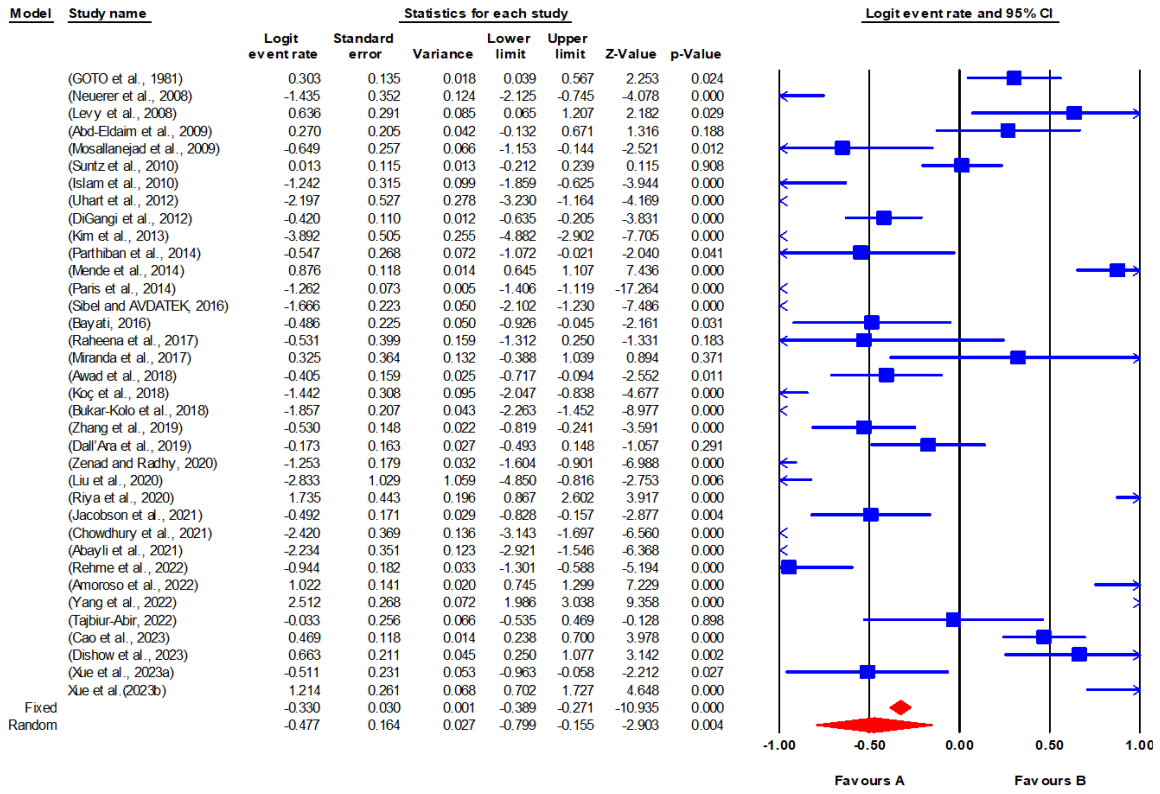

Figure 4 Forest plot showing the event rate and weight regarding prevalence of FPLV infection in cats.

Publication bias

The results of the publication bias are presented in funnel plots for both fixed and random effects (Figure 5,6). Egger's linear regression test for asymmetry did not indicate publication bias, intercept (-0.75382), 95% confidence interval (from -4.63013 to 3.12249), t-value (0.39521), df = 34.00. The *P* (1-tailed) (recommended) was 0.34758 and *P* (2-tailed) was 0.69516.

The outcome of Kendall's tau without continuity correction (-0.17778), Z-value for tau (1.52554), *P* (1- tailed) (recommended) of 0.06356, and *P* (2 -tailed) of 0.12712. The outcome of Kendall's tau with continuity correction (-0.17619), Z-value for tau (1.51192), *P* (1-tailed) (recommended) of 0.06528, and *P* (2-tailed) of 0.13055.

Duval and Tweedie's trim-and-fill method (no studies trimmed) resulted in an adjusted correlation from 0.40392 to 0.43270 (95% CI) for fixed effects and from 0.31031 to 0.46136 (95% CI) for random effects. For the fixed and random effects, the Q-value was 948.37828.

The fail-safe N expected 1031.00 missing studies are needed for the result of this meta-analysis to be non-significant (*P* >.050), and the number of observed studies was approximately 36.00. Orwin's fail-safe N was 0.41824, and in missing studies, it was 0.500.

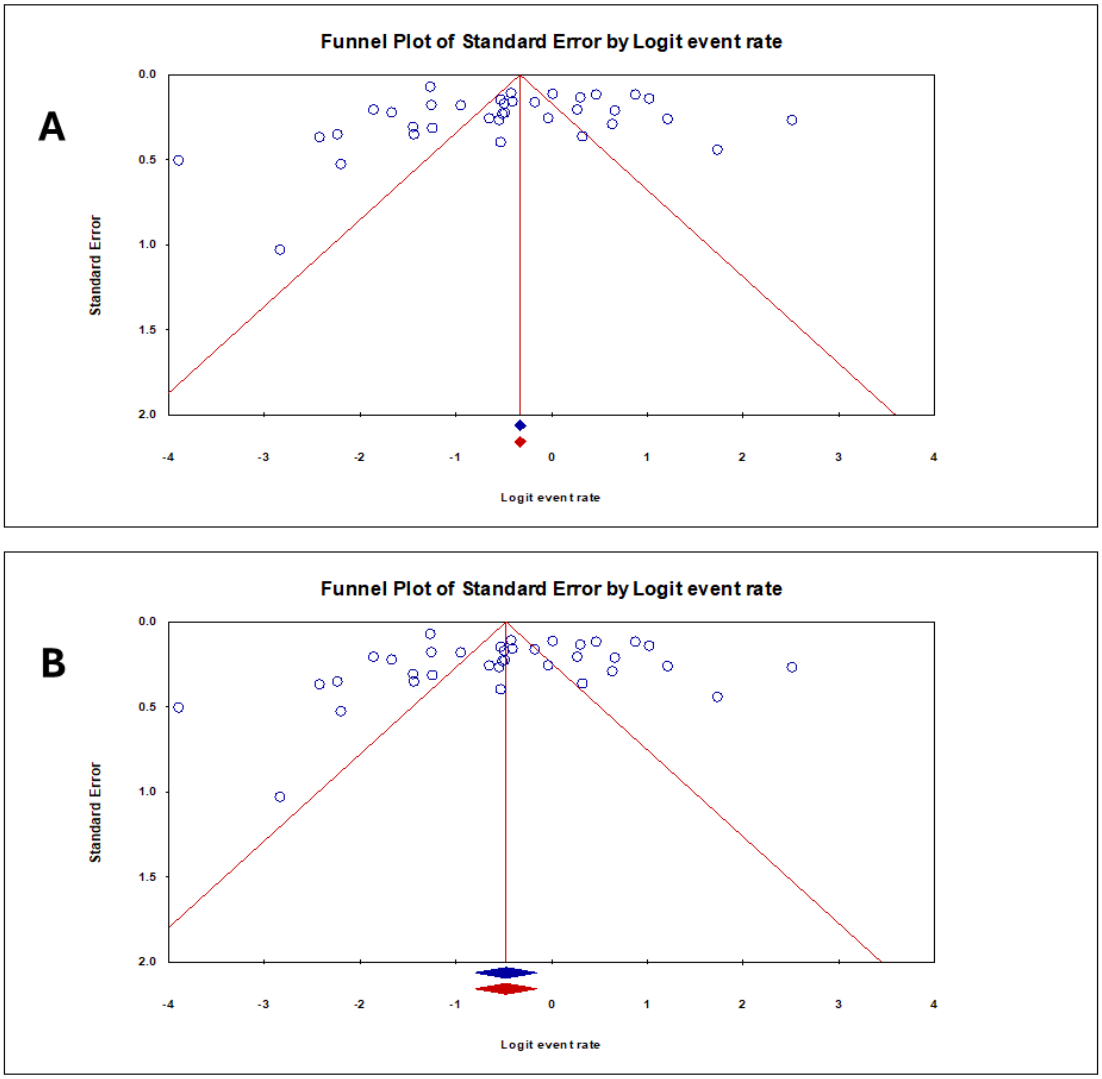

Figure 5 Funnel plot on the global prevalence of FPLV infection in cats showing publication bias on both random (B) and fixed (A) effects of 36 analyzes.

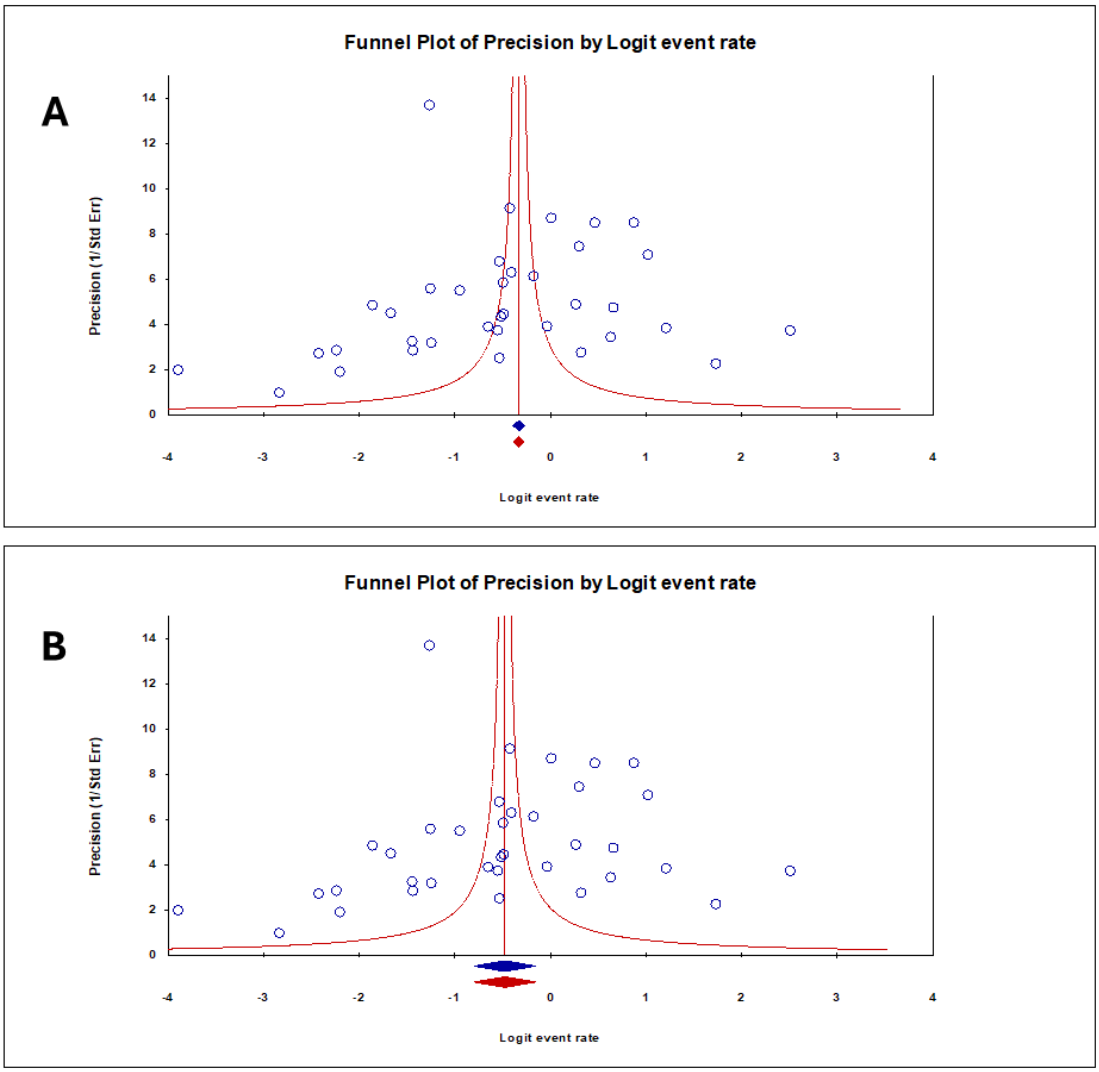

Figure 6 Funnel plot on the global prevalence of FPLV infection in cats showing the precision by logit in both random (B) and foxed (A) effects of 36 analyzes.

DISCUSSION

In the present meta-analysis, thirty-six studies were deemed eligible for inclusion. examination of 5820 domesticated cats revealed that 2928 cats were positive for FPLV. The prevalence of FPLV infection was determined to be 50.30%. The prevalence of the disease varies among countries and even within studies in the same country. Collectively, the lowest (2%) (Kim et al., 2013) and highest (92.5%) (Yang et al., 2022) prevalence of the disease was recorded in Korea. In North America, the prevalence of the disease in Canada was higher than that in the USA. Among European countries, Germany has the highest prevalence (70.60 %) (Mende et al., 2014). In Africa, Egypt has the highest prevalence (Awad et al., 2018). The high prevalence of the disease may be attributed to several contributing factors such as improper vaccination, poor management, and sanitation.

The prevalence of FPLV infection has been found to be associated with many factors, such as the management system (Rehme et al., 2022a), age (Kabir et al., 2023) and vaccination programs (Jacobson et al., 2022). Poor hygiene measures and insufficient disinfection have been found to be important risk factors for FPLV

infection (Möstl et al., 2013; Addie et al., 2015). Also, vaccination plays a crucial role for prevention of the disease, where non-vaccinated cats were found more susceptible to the disease than vaccinated ones at 4-6 weeks of age (Day et al., 2016). Cats less than 2 years of age were found to be more susceptible to FPLV infection than older cats because of the decline in maternal antibodies necessary for protection (Rehme et al., 2022b). Moreover, an increasing seasonal incidence of FPLV infection has been documented, in which the disease is prevalent during the summer and autumn seasons (Litster and Benjanirut, 2014; Barrs, 2019)

Based on the findings of meta-analysis, the results of Paris et al. (Paris et al., 2014) provided high relative weight (17.04%), whereas small studies carried out by Liu et al. (2020), Raheena et al. (2017), and Uhart et al. (2012) provided a low relative weight. It is known that the common effect can be assessed by large studies but not by small studies. Studies with small sample sizes had a negligible effect on the total value. The present meta-analysis provided Z-value of -10.93 (P = 0.00), and -2.90 (P = 0.004). However, the Z-value here does not add to the results, as it is not the effect size but only indicates the data distribution (Hak et al., 2016).

Regarding heterogeneity, the Q-statistics and I^2 for this study were 948.378 and 96.309, respectively (P < 0.00). The Q-statistics include the observed dispersion, while the null hypothesis for heterogeneity proposes that studies assign a common effect size. Consequently, it is assumed that the degrees of freedom are equal to the Q-statistic (Thompson, 1994). However, if the Q-statistic provides no effect size dispersion, I^2 and tau-squared can provide alternative interpretations (Schulz et al., 1995). In this study, the tau-squared value was 0.888, which denotes variance and was used to determine the weights. It has been stated that the I^2 is usually used successfully to measure the extent of heterogeneity in meta-analytical studies (Huedo-Medina et al., 2006).

Heterogeneity analysis usually proves that the effect width varies among the studies. This statistical test explains the differences among studies due to differences between studies or sampling errors (Borenstein et al., 2021). Heterogeneity tests were performed to determine the conformity of the normal distribution of effect sizes. Considering heterogeneity, the null hypothesis is that the effect is zero for both fixed and random effects. The Hedges' g/standard error for the relevant model is usually used to determine the Z-value, which is used to check the null hypothesis (Higgins JP, 2019). It has also been stated that the (P) is not an effect size and, therefore, is not a measure of the magnitude of heterogeneity. In this case, a low (P) indicates that there is probably some (unidentified) degree of heterogeneity (Duffield et al., 2008).

Regarding publication bias, studies with low power, small sample sizes, and absence of differences among groups are thought to affect publication bias by increasing the effect size (Joober et al., 2012). Thus, detection bias is an important issue, as publication bias can result in inaccurate conclusions in systematic meta-analyses (Sutton et al., 2000). In meta-analyses, funnel plots are frequently used to detect heterogeneity and/or publication bias. In this plot, the effect size is usually shown against standard errors or precision (Light and B. Pillemer, 1986). In the present study, as the funnel plot was asymmetric and there was a distinction between studies with lower and higher accuracy, there was no indication of publication bias. Moreover, the results of the Egger's linear regression test confirmed absence of publication bias, intercept (-0.75382), 95% confidence interval (from -4.63013 to 3.12249), t-value (0.39521), df = 34.00. The P (1-tailed) (recommended) was 0.34758 and P (2-tailed) was 0.69516. It has been stated that in meta-analysis, the weighted regression slope is expected to be zero in the absence of publication bias (Rothstein, 2005). If the Begg and Mazumdar rank correlation test has a strong correlation, it indicates the presence of publication bias (Begg and Mazumdar, 1994). In the present study, Kendall's tau with continuity correction was (-0.17778), and the Z-value for tau (1.52554), with P (1- tailed) (recommended) of 0.06356 and P (2 -tailed) of 0.12712. This finding provided the Egger regression test results with no indication of publication bias. Egger's

regression test is a statistical tool for measuring funnel plot asymmetry through standardized effect sizes on their precision, and in the absence of publication bias, the regression intercept is expected to be zero (Egger et al., 1997).

The trim and fill test is an additional test that evaluates the total effect size and tests publication bias (Duval and Tweedie, 2000). A repetitive procedure was used to exclude small studies at the margin of the positive end of the funnel plot. The trimming and filling processes were repeated until the funnel plot was symmetric with regard to effect size (Duval, 2005). The results of the present 36 studies indicated that the confidence interval for adjusted correlation was 0.40 - 0.43 for fixed effects and 0.31-0.46 for random effects. The fail-safe N test suggests that 1031.00 missing studies were required to conclude that the results of the study were significant ($p = 0.000$). The present results are supported by the findings of a previous study (Rosenthal, 1979a). Calculation of the number of missing studies was possible in the meta-analysis to determine whether *P* was significant. In addition, in observed studies, Orwin's fail-safe N proposed a 0.41824 event rate, but in missing studies, it proposed a mean event rate of 0.500. Although they are typically applied in meta-analytical studies, they may have different types of errors (Sterne et al., 2000; Terrin et al., 2003; Peters et al., 2006; Peters et al., 2007; Rücker et al., 2008). Fail-safe N is an alternative tool for counteracting publication bias (Rosenthal, 1979b). The test suggested that 1031 missing studies were required to obtain non-significant results ($p > 0.05$). However, these tests may provide low power or high type-I error rates (Sterne et al., 2000; Terrin et al., 2003; Peters et al., 2006; Peters et al., 2007; Rücker et al., 2008).

CONCLUSIONS

The results of this meta-analysis indicated a high global prevalence of FPLV infection in cats. Wide variation in the prevalence of FPLV infection among countries may indicate the failure of preventive programs. The results also necessitate more attention to associated risk factors and strict control measures.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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