### <u>Review Article</u>

### Peste Des Petits Ruminants in Atypical Hosts and Wildlife: Systematic Review and Meta-Analysis of the Prevalence between 2001 and 2021

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#### Abstract

Peste des petits ruminants (PPR) or goat plague is considered a leading, highly contagious, and most lethal infectious viral disease of small ruminants affecting the worldwide livestock economy and international animal trade. Although sheep and goats are the primarily affected, the PPR Virus (PPRV) host range has expanded to other livestock (large ruminants) and wildlife animals over the last few decades, resulting in serious concern to the ongoing PPR global eradication program, which is primarily optimized, designed, and targeted towards accessible sheep and goat population. A systematic review and meta-analysis study was conducted to estimate the prevalence and spill-over infection of PPRV in large ruminants (bovine and camel) and wildlife. Published articles from 2001 to October 2021 on the "PPR" were searched in four electronic databases of PubMed, Scopus, Science direct, and Google Scholars. The articles were then selected using inclusion criteria (detection/prevalence of PPRV in bovine, camel, and wildlife population), exclusion criteria (only sheep or goats, lack of prevalence data, experimental trial, test evaluation, and reviews written in other languages or published before 2001), and the prevalence was estimated by random effect meta-analysis model. In the current study, all published articles belonged to Africa and Asia. The overall pooled prevalence of PPR estimates was 24% (95% CI: 15-33), with 30% in Asia (95% CI: 14-49) and 20% in Africa (95% CI: 11-30). The overall estimated pooled prevalence at an Africa-Asia level in bovine and camel was 13% (95% CI: 8-19), and in wildlife, it was 52% (95% CI: 30-74) with significant heterogeneity ( $I^2 = 97\%$ ) in most pooled estimates with a high prevalence in atypical hosts and wildlife across Asia and Africa. Over the last two decades, the host range has increased drastically in the wildlife population, even for prevalent PPR in the unnatural hosts only for a short time, contributing to virus persistence in multi-host systems with an impact on PPR control and eradication program. This observation on the epidemiology of the PPRV in unnatural hosts demands appropriate intervention strategies, particularly at the livestock-wildlife interface.

Keywords: PPR; Bovine; Camel; Wildlife; Systemic Review; Meta-analysis, Prevalence

### 1. Context

Peste des petits ruminants (PPR) as 'small ruminants plague' is one of the leading and most lethal infectious viral diseases of small ruminants, caused by *small ruminant morbillivirus (SRMV)* otherwise known as PPR Virus

(PPRV), belonging to the genus *Morbillivirus* in the *Paramyxoviridae* family (http://ictvonline.org/virusTaxonomy.asp). Highly contagious nature results in classifying as Transboundary Animal Disease by Office International des Epizooties.

PPR also has high morbidity and mortality rates with a high number of outbreaks per year; therefore, a threat is to sustainable agricultural growth causing a severe socioeconomic impact on the livestock industry, especially in developing and underdeveloped countries. Furthermore, PPR was first described in 1942 in the Republic Côte d'Ivoire in West Africa and then spread to more than 70 countries, such as Africa, the Middle East, the parts of Asia; in addition, the parts of Europe together have confirmed PPR affecting ~1.7 billion of the global sheep and goat population (4, 5). Considering the importance of small ruminants in ensuring food security and socio-economic growth in many parts of the world, mainly in Africa and Asia the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE) launched the PPR global eradication program (PPR-GEP) with the adoption of PPR Global Control and Eradication Strategy (GCES) for the global eradication of PPRV by 2030.

Sheep and goats are primary hosts for PPRV due to their highly contagious nature and ability to crossspecies barrier similar to other members of morbillivirus (Rinderpest virus, Measles virus) with the mechanism for adapting to new hosts. In the last few decades, an increase was in reports on PPRV interspecies transmission to unnatural hosts. Such unknown mechanism of PPRV's propensity to transmit, expansion of susceptible hosts, and their epidemiological role raises concerns on the successful implementation of the PPR-GEP. Among the livestock, some reports are for confirmed PPRV infection with seroprevalence in large ruminants- in Asia and Africa (cattle, water buffalo, and camel) (11-14). Other than unusual livestock (bovine and camel), PPR is extensively reported in various wildlife and the first natural infection of PPR in wild Dorcas gazelle was reported by Furley, Taylor (17). The huge fatality documented in Mongolian wildlife (18) and mountain ungulates from the Middle East, South, and East Asia exemplifies the impact of PPR on the wildlife population (19-22). As per the literature based on antibody and viral detection, African wildlife often seems exposed to PPRV due to its large wildlife population density, compared to Asia (23-25).

Over the past few decades, the role of livestock and wildlife in PPR epidemiology is becoming clearer, with the majority of data supporting the effective disease transmission between livestock and wildlife with some gaps in knowledge (29, 30). PPRV spillover from a domestic source was observed in Tanzania's Serengeti habitat, with greater antibody prevalence in wild ungulates/cattle and without clinical symptoms or death (18, 19, 25). Furthermore, PPRV circulation in animals, even if only for a short time, can contribute to virus persistence in multi-host systems which increase virus propagation, and affect the intervention program (37). The current study aimed to conduct a systematic meta-analysis to determine the evidence of PPRV infection in atypical hosts (bovine and camel) and wildlife.

### 2. Evidence Acquisition

### 2.1. Literature Search Strategy

Preferred Reporting Items for Systematic Reviews and guidelines Meta-Analysis (PRISMA) of Cochran collaborations were used for systematic review and subsequently meta-analysis (38-40). A literature survey was systematically conducted to collect all relevant literature on the prevalence of PPRV in the bovine, camel, and wildlife. The published information was collected from the various electronic web database engines, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (www.scopus.com), ScienceDirect (https://www.sciencedirect.com/), and Google Scholars (https://scholar.google.com/). Some of the articles were added by the authors using hand-searching of references from the reviewed materials. Initial search string resulted in 552 articles from January 2001 to October 2021 using the different combinations of keywords "Prevalence OR Incidence OR Frequency OR Detection OR Occurrence OR Identification OR Isolation OR Characterization OR Investigation OR Survey OR Rate" AND "PPR OR Peste des petits ruminants OR Goat plague OR Kata OR ovine rinderpest OR Caprine rinderpest" AND "Large Ruminant OR Bovine OR Cattle OR Buffalo OR Camel Or Camelus OR Wild OR Wildlife OR feral Or unnatural host OR unusual host" (Table 1). Rayyan QCRI (the systematic reviews web app) was used for systematic reviews and compilations (40). Initially, a blind screening was performed by the two investigators independently and followed by resolving the conflict in the software (Rayyan QCRI). The reference management software Zotero desktop (version 5.0.96.3) was used to manage full articles and selected references. Furthermore, country and continent-wise distribution of PPR in atypical hosts and wildlife were depicted in the map using QGIS software (version 3.20.1), QGIS team, Switzerland.

### 2.2. Study Selection and Data Extraction

The schematic representation of the systematic review on the prevalence of PPR was depicted in figure 1. Out of 552 studies compiled during the literature search from the databases and duplicated entries, 153 articles were removed by screening titles and citation details. In the preliminary screening phase, studies were excluded based on irrelevance (n=357) (i.e., non-PPR study, nonbovine/camel/wildlife, lack of temporal and spatial information, lack of full text, article related to only sheep or goat, experimental trial, and articles in other languages than English). In total, seven articles were removed based on full-text screening due to lack of data on the sample tested, the test used, and species tested. Subsequently, three relevant articles were identified through a reference search based on the author's knowledge without an appearance in the search list. Accordingly, 48 studies were selected for the full-text reviews and subjected to the quality of bias assessment. Finally, a total of 37 articles were used for the metaanalysis and the determinants, such as the author, publication year, region, and species (wildlife, bovine, and camel); moreover, region and number of the sample tested, the number of positive samples, and tests used for the analysis were extracted from the selected articles.

### 2.3. Quality Assessment of Studies

The quality of the studies was assessed by two investigators independently, and the investigator used seven items with a 5-point Likert scale to judge the quality of each research paper. The maximum score of 5 indicates a likely and unlikely article. The scores of the investigators were further used to calculate the coefficient of the validity with the Aiken value (44-46).

### 2.4. Meta-Analysis

Meta-analysis was conducted using R open-source scripting software (Comprehensive R Archive Network; version 3.2.5) and the R package used was "meta" as reported earlier (48). The graphical representation of the effect size was done through a forest plot or confidence interval plot. In a metaanalysis, predominantly fixed effect and random effect models were used based on the variation in the studies and heterogeneity [I<sup>2</sup>] values. The random-effect model was used when the heterogeneity among the studies was statistically significant in combining with inconsistency indices. The heterogeneity of the studies was calculated using Cochran's Q statistic, Tau square, H-value, and *P*-values obtained, and results are given in the last line of the forest plot (40, 44).

Meta-regression was conducted to analyze the influence of included studies and estimate variation in the studies (50). To predict the effect of a hypothesized moderator, a weighted linear regression model was applied in which the effect size (samples) was regressed onto the moderator (48, 51). The moderators in univariate meta-regression include the test, geographic region, years, species, and total. The variables with P < 0.05 in univariate meta-regression were used for further subgroup analysis, and only factors significant at  $P \le 0.05$  were retained in the final model. Meta-regression reduces the number of tests and estimations; therefore, the power of analysis is greater and the probability of false-positives findings is reduced (50).

Subgroup analysis was conducted to assess the heterogeneity in the region (Asia and Africa), sample size, and the test included along with species (51). Sensitivity analysis was performed to identify the studies contributing to overall heterogeneity and measure the robustness of meta-analysis findings. The extent of publication bias in the selected studies was measured and demonstrated in a funnel plot with the Y-axis representing the standard error of each study and the X-axis representing the arcsine transformation of the proportion of the study (51).

Study	Year	Country	Continent	Animal	Species	Genus Species
*Roger, Yesus (6)	1995	Ethiopia	Africa	*Camel	Camel	Camelus dromedarius
		Sudan	Africa	*Camel	Camel	Camelus dromedarius
*Haroun, Hajer (7)	2002	United Arab Emirates	Asia	Bovine	Cattle	Bos primigenius taurus
Ozkul, Akca (10)	1999-2000	Turkey	Asia	Bovine	Cattle	Bos primigenius taurus
*Ogunsanmi, Awe (15)	Nil	Nigeria	Africa	*Wildlife	African grey duiker	Sylvicapra grimmia
Elzein, Housawi (26)	2002	Kingdom of Saudi	Asia	Wildlife	Dorcas gazelles	Gazella dorcus
*1 1 11 101 0 11 1 (20)	1007 1000	Alabia (KSA)	A :	*D :	Thomsons gazelles	Gazella thomsoni
*Lundervold, Milner-Gulland (28)	1997-1998	Kazaknstan	Asia	*Bovine	Cattle	Bos primigenius taurus
*Haque, Habib (35)	1997-1998	Bangladesh	Asia	*Bovine	Cattle	Bos primigenius taurus
*Abraham, Sintayehu (41)	2001	Ethiopia	Africa	*Camel	Camel	Cameius aromedarius
-				*Bovine	Cattle	Bos primigenius taurus
Couacy-Hymann, Bodjo (23)	2005	Côte d'Ivoire	Africa	Wildlife	African buffalo	Syncerus caffer
					Defassa waterbuck	Kobus defassa
Khan, Siddique (42)	2008	Pakistan	Asia	Bovine	Cattle	Bos primigenius taurus
					Buffalo	Bubalus bubalis
*Maillard, Van (43)	Nil	Vietnam	Asia	*Bovine	Buffalo	Bubalus bubalis
					Cattle	Bos primigenius taurus
*Rashid, Asim (47)	Nil	Pakistan	Asia	*Bovine	Cattle	Bos primigenius taurus
*Albayrak and Gur (49)	2009	Turkey	Asia	*Bovine	Cattle	Bos primigenius taurus
*Gur and Albayrak (52)	2010	Turkey	Asia	*Wildlife	Goitered gazella	Gazella subgutturosa
*Kwiatek, Ali (53)	2000-2009	Sudan	Africa	*Camel	Camel	Camelus dromedarius
*Bao, Wang (54)	2007-2008	China	Asia	*Wildlife	Bharals	Pseudois nayaur
*Rajneesh, Kataria (55)	Nil	India	Asia	*Camel	Camel	Camelus dromedarius
*Balamurugan, Krishnamoorthy	2009-2010	India	Asia	*Bovine	Buffalo	Bubalus bubalis
(11)		India		Dorme	Cattle	Bos primigenius taurus
Hoffmann, Wiesner (56)	2010-2011	Iraq	Asia	Wildlife	Wild goat	Capra aegagrus
Sen, Saravanan (76)	2012	India	Asia	Wildlife	Lion	Panthera leo persica
*Balamurugan, Krishnamoorthy	2011	India	Asia	*Bovine	Buffalo	Bubalus bubalis
(58)	2011			*••••	Cattle	Bos primigenius taurus
*Lembo, Oura (59)	2011	Tanzania	Africa	*Bovine	Cattle	Bos primigenius taurus
El-Dakhly (60)	Nil	Libya	Africa	Camel	Camel	Camelus dromedarius
Abdul-Dahiru, Baba (61)	Nil	Nigeria	Africa	Bovine	Cattle	Bos primigenius taurus
		6		Camel	Camel	Camelus dromedarius
					African buffalo	Syncerus caffer
*Mahapatra, Sayalel (25)	2014	Tanzania	Africa	*Wildlife	Grant's gazelle	Nanger granti
1 2 2 2					Wildebeest	Connochaetes gnou
					Impala	Aepyceros melampus
*Woma, Kalla (62)	2014	Nigeria	Africa	*Camel	Camel	Camelus dromedarius
*Saeed, Ali (63)	2002-2011	Sudan	Africa	*Camel	Camel	Camelus dromedarius
					Argali	Ovis ammon
*Li, Li (20)	2013-2016	China	Asia	*Wildlife	Ibex	Capra ibex sibirica
					Goitered gazella	Gazella subgutturosa
*Abubakar, Mahapatra (64)	2015	Pakistan	Asia	*Bovine	Buffalo	Bubalus bubalis
					Cattle	Bos primigenius taurus
				Bovine	Cattle	Bos primigenius taurus
*Intisar, Ali (65)	2008-2012	Sudan	Africa	*Wildlife	Dorcas gazelles	Gazella dorcus
				*Camel	Camel	Camelus dromedarius
*Jaisree, Aravindhbabu (66)	Nil	India	Asia	*Wildlife	Chowsingha	Tetracerus quadricornis
*Zhou, Wang (67)	2016	China	Asia	*Wildlife	Water deer	Hydropotes inermis
Ali, Osman (68)	2015-2016	Sudan	Asia	Bovine	Cattle	Bos primigenius taurus
Bello, Kazeem (70)	Nil	Nigeria	Africa	Camel	Camel	Camelus dromedarius
*Omani, Gitao (71)	2018	Kenya	Africa	*Camel	Camel	Camelus dromedarius

### Table 1. Evidence of PPRV infection in bovine, camel, and wildlife published during 2001-2021

1592

Study	Year	Country	Continent	Animal	Species	Genus Species
*Asil, Ludlow (1)	2018	Sudan	Africa	*Wildlife	Dorcas gazelles	Gazella dorcus
*Li, Cao (2)	2018	China	Asia	*Wildlife	Przewalski's gazelle	Procapra przewalskii
*Herzog, de Glanville (3)	2016	Tanzania	Africa	*Bovine	Cattle	Bos primigenius taurus
*Vj, Gitao (8)	Nil	Kenya	Africa	*Camel	Camel	Camelus dromedarius
*Agga, Raboisson (9)	2005-2006	Ethiopia	Africa	*Bovine	Cattle	Bos primigenius taurus
Hekal, Al-Gaabary (16)	2016-2018	Sudan	Africa	Bovine	Cattle	Bos primigenius taurus
*Abubakar, Sattorov (27)	2014	Pakistan	Asia	*Bovine	Yak	Bos grunniens
					Ibex	Capra ibex
*Pruvot, Fine (18)	2017	Mongolia	Asia	*Wildlife	Goitered gazella	Gazella subgutturosa
					Saiga antelope	Saiga tatarica
					Elephant	Loxodonta africana
*Fernandez Aguilar, Mahapatra (31)	2013-2017	Sudan	Africa	*Wildlife	Tiang	Damaliscus lunatus tiang
		Uganda	A fries	-	African buffalo	Syncerus caffer
			Anica		Uganda kob	Kobus kob thomasi
*Cosseddu, Doumbia (32)	2013	Mauritania	Africa	Bovine	Cattle	Bos primigenius taurus
*Liu, Liu (33)	2021	China	Asia	Wildlife	Alpacas	Vicugna pacos
					Kongoni	Alcelaphus buselaphus
		Tonzonio	Africa		Grant's gazelle	Nanger granti
		Talizailla	Amea		African buffalo	Syncerus caffer
	_			_	Торі	Damaliscus lunatus
					African buffalo	Syncerus caffer
*Iones Mahapatra (34)	2015-2016			Wildlife	Wildebeest	Connochaetes gnou
Jones, Manapatra (34)	2013-2010			windine	Grant's gazelle	Nanger granti
		Kenva	Africa		Impala	Aepyceros melampus
		Kenya	Antea		Thomsons gazelles	Gazella thomsoni
					Warthog	Phacochoerus africanus
					Gerenuk	Litocranius walleri
*Prajapati, Shrestha (36)	2021	Nepal	Asia	Bovine	Cattle	Bos primigenius taurus

\* Study and animal included in the meta-analysis after exclusion of studies due to inter-rater disagreement



Figure 1. PRISMA checklist flow diagram of the selection of eligible studies for inclusion in the meta-analysis

### 3. Results

# **3.1. Information on the Included Studies and** Quality of Bias Assessment

Out of 552 studies, a total of 48 studies (Table 1) were selected for full-text reviews and subjected to the quality of bias assessment. For the selection of articles, inter-rater agreement and consensus using Aiken's Vvalue index were performed to reduce bias. Additionally, the quality of the studies was assessed based on the score given by the two independent authors to seven items using the Likert scale. Based on the ratings calculated, Aiken's V-value for all the studies was more than 0.75, indicating the acceptable quality of the study. Finally, 37 articles were selected for meta-analysis (1-3, 6-9, 11, 15, 18, 20, 24, 28, 31-36, 41, 43, 47, 49, 52-55, 58-59, 62-68, 71, 83) (Table 1) with the details presented in the PRISMA flow chart (Figure 1). The prevalence of PPRV was calculated using a total sample size of 12,337 out of which Bovine alone contributed to 7,962 cases followed by camel (n=3,577) and wildlife (n=798).

### **3.2. Publication Bias**

Publication bias is a critical problem in systematic review and meta-analysis, affecting the validity and generalization of conclusions (57). In this study, funnel plot-based methods include a visual examination of a funnel plot, regression, and rank test used to assess publication bias. A funnel plot was plotted with arcsine transformation proportion in the X-axis and standard error in Y-axis. The arcsine-based transformation has the important advantage of stabilizing variance (57) which is likely the main reason included in our study. In figure 2, most of the studies were scattered and a few of the studies fall into the funnel, showing the publication bias. Moreover, the presence of asymmetry in the funnel plot was tested using Begg's rank correlation test and Egger's regression test. To deal with the presence of publication bias, the meta-regression was employed with sample size as the risk of bias factor, proving the non-significance (P>0.05) nullifying the effect of publication bias on the study.



**Figure 2.** Funnel plot for the examination of publication bias of the prevalence estimates of PPR in bovine, camel, and wildlife during 2001-2021

## **3.3.** Meta-Regression to Identify the Factors Affecting the Heterogeneity

Univariate meta-regression was used to identify potential covariates likely the magnitude and direction of the overall estimate of heterogeneity. The result of the meta-regression (Table 2) revealed that detection techniques had a significant impact on the overall heterogeneity at a 5% level. Variables, such as test, species, sample sizes, and year were statistically significant, and the estimated results revealed that the subgroup analysis and sensitivity analysis were required for further fine-tuning of prevalence rates of PPR.

### 3.4. Subgroup and Sensitivity Analysis

Subgroup analysis was conducted for the covariates, such as antigen/antibody test with a level of sample size further based on region and animal group due to the effect on heterogeneity (Table 3). Subgroup analysis of antigen/antibody test revealed the percentage prevalence of 90% with  $I^2 = 88\%$  and  $\tau 2 = 0.1882$  (95% CI: 0.67-1.0) in PCR assay, followed by antibody prevalence of 25.71% (Figure 3).

Predictors	Estimate	SE	z value	τ2	I <sup>2</sup> (%)	$H^2$	R <sup>2</sup> (%)	Qm	P- Value
Region	0.45	0.07	6.19	0.10	99.11	112.59	0.00	0.99	0.3192
Test	0.29	0.16	1.76	0.05	97.87	46.86	45.89	40.53	0.0001***
Species	0.33	0.07	4.66	0.07	98.71	77.62	27.31	17.28	0.0002***
Sample Size	0.56	0.06	9.16	0.09	98.90	90.76	5.22	3.72	0.0538
Year	-38.99	17.15	-2.27	0.08	98.97	97.09	9.06	5.30	0.0214*

Table 2. Univariate meta-regression analysis of PPR in large ruminants and wildlife

Where\* indicates the 5% level of significance, \*\*\* 0.1% level of significance

Table 3. Estimated pooled prevalence of PPR in large ruminants and wildlife

Group	Variables	No. of study	No. of animal sampled	No. of positive animal	Pooled estimate %	95% CI	Heterogeneity chi-squared (τ <sup>2</sup> )	I <sup>2</sup> %	<i>P</i> -value
Continent	Africa	18	8811	1025	20	11-30	0.0684	98	< 0.01
Continent	Asia	19	3526	527	30	14-49	0.1599	95	< 0.01
	Bovine	14	7962	900	11	8-14	0.0090	94	< 0.01
	Camel	10	3577	425	15	4-31	0.0936	99	< 0.01
Animal	Estimate Livestock (Bovine and camel)	23	11539	1325	13	8-19	0.0403	98	<0.01
	Wildlife	15	798	227	52	30-74	0.1568	91	< 0.01
	Livestock in 2001-2010	10	3426	336	15	5-28	0.0642	97	< 0.01
	Wildlife in 2001-2010	3	124	17	24	2-61	0.0952	74	< 0.02
	Estimate livestock and wildlife 2001- 2010	13	3550	353	16	7-27	0.0601	97	<0.01
Study years	Livestock in 2011-2021	13	8113	989	12	7-19	0.0272	98	< 0.01
	Wildlife in 2011-2021	12	674	210	60	35-83	0.1580	92	< 0.01
	Estimate livestock and wildlife 2011- 2021	24	8787	1199	29	16-44	0.1298	97	<0.01
Overal	lestimate	37	12337	1552	24	15-33	0.1005	97	< 0.01

Study	Events	Total		Proportion	95%-CI	Weight
TEST = Antibody_ELISA Abubakar et al 2017 Balamurugan et al 2014 Haque et al 2004 Random effects model Heterogeneity: $l^2 = 95\%$ , $r^2$ =	_Bovine 58 137 131 = 0.0096, j	_Asia_ 480 1037 500 2017 p < 0.01	Group1(≻median)	0.12 0.13 0.26 0.17	[0.09; 0.15] [0.11; 0.15] [0.22; 0.30] [0.09; 0.26]	2.9% 2.9% 2.9% 8.6%
TEST = PCR Kwiatek et al 2011 Omani et al 2019 Li et al 2017 Bao et al 2017 Asii et al 2019 Zhou et al 2018 Balamurugan et al 2012a Li et al 2019 Jaisree et al 2018 Random effects model Heterogenety. <sup>24</sup> = 91%, <sup>24</sup> =	38 1 13 3 1 1 1 1 1 1	49 25 13 4 6 1 1 104 p < 0.01		0.78 0.04 1.00 - 0.75 - 0.75 0.17 1.00 1.00 1.00 1.00 0.74	[0.63; 0.88] [0.00; 0.20] [0.75; 1.00] [0.19; 0.99] [0.00; 0.64] [0.03; 1.00] [0.03; 1.00] [0.03; 1.00] [0.39; 0.97]	2.7% 2.6% 2.4% 1.8% 1.8% 0.8% 0.8% 0.8% 0.8% 0.8% 15.7%
TEST = Antigen Test/ELI Saeed et al 2015 Intisar et al 2017 Pruvot et al 2020 Random effects model Heterogeneity: $l^2 = 92\%$ , $r^2 =$	SA 214 74 17 = 0.0730.	474 220 20 714 p < 0.01	*	0.45 0.34 0.85 0.54	[0.41; 0.50] [0.27; 0.40] [0.62; 0.97] [0.24; 0.83]	2.9% 2.8% 2.5% 8.3%
TEST = Antibody_ELISA Haroun et al 2002 Chemweno et al 2019 Roger et al 2001 Random effects model Heterogeneity: $l^2$ = 86%, $r^2$ =	_Camel_ 14 12 7	Africa 100 380 90 570 p < 0.01	_Group2( <median)< td=""><td>0.14 0.03 0.08 0.07</td><td>[0.08; 0.22] [0.02; 0.05] [0.03; 0.15] [0.02; 0.15]</td><td>2.8% 2.9% 2.8% 8.5%</td></median)<>	0.14 0.03 0.08 0.07	[0.08; 0.22] [0.02; 0.05] [0.03; 0.15] [0.02; 0.15]	2.8% 2.9% 2.8% 8.5%
TEST = Antibody_ELISA Abraham et al 2005 Herzog et al 2019 Random effects model Heterogeneity: $I^2$ = 97%, $\tau^2$ =	_Bovine 46 339 = 0.0066,	_Afric: 910 2997 3907 p < 0.01	a_Group1(>median)	0.05 0.11 0.08	[0.04; 0.07] [0.10; 0.12] [0.03; 0.15]	2.9% 2.9% 5.7%
TEST = Antibody_ELISA Abraham et al 2005 Woma et al 2015 Random effects model Heterogeneity: $I^2$ = 83%, $\tau^2$ =	_Camel 10 51 = 0.0014, ;	_Africa 628 1517 2145 p = 0.01	_Group1(>median) ■ ●	0.02 0.03 0.02	[0.01; 0.03] [0.03; 0.04] [0.01; 0.05]	2.9% 2.9% 5.7%
TEST = Antibody_ELISA Intisar et al 2017 Mahapatra et al 2015 Ogunsanmi et al 2003 Random effects model Heterogeneity: $l^2 = 94\%$ , $r^2 =$	_Wild_A 5 29 4 = 0.0929, j	frica_G 23 45 38 106 p < 0.01	iroup2(≮median)	0.22 0.64 0.11 0.30	[0.07; 0.44] [0.49; 0.78] [0.03; 0.25] [0.05; 0.66]	2.6% 2.7% 2.7% 8.0%
TEST = Antibody_ELISA Lembo et al 2013 Cosseddu et al 2021 Agga et al 2019 Random effects model Heterogeneity: $l^2$ = 87%, $r^2$ =	_Bovine 46 15 49 = 0.0048, j	_Afric: 266 118 613 997 p < 0.01	a_Group2( <median)< td=""><td>0.17 0.13 0.08 0.12</td><td>[0.13; 0.22] [0.07; 0.20] [0.06; 0.10] [0.07; 0.18]</td><td>2.9% 2.8% 2.9% 8.5%</td></median)<>	0.17 0.13 0.08 0.12	[0.13; 0.22] [0.07; 0.20] [0.06; 0.10] [0.07; 0.18]	2.9% 2.8% 2.9% 8.5%
TEST = Antibody_ELISA Albayrak and Gur 2010 Prajapati et al 2021 Maillard et al 2008 Abubakar et al. 2019 Lundervoid et al 2008 Random effects model Heterogenety. / <sup>2</sup> = 85%, r <sup>2</sup> =	_Bovine 22 15 9 23 6 4 = 0.0083, j	_Asia_ 122 255 85 250 279 50 1041 p < 0.01	Group2( <median)< td=""><td>0.18 0.06 0.11 0.09 0.02 0.08 0.08</td><td>[0.12; 0.26] [0.03; 0.10] [0.05; 0.19] [0.06; 0.13] [0.01; 0.05] [0.02; 0.19] [0.04; 0.13]</td><td>2.8% 2.8% 2.8% 2.9% 2.7% 16.9%</td></median)<>	0.18 0.06 0.11 0.09 0.02 0.08 0.08	[0.12; 0.26] [0.03; 0.10] [0.05; 0.19] [0.06; 0.13] [0.01; 0.05] [0.02; 0.19] [0.04; 0.13]	2.8% 2.8% 2.8% 2.9% 2.7% 16.9%
TEST = Antibody_ELISA Gur and Albayrak 2010 Liu et al 2021 Random effects model Heterogeneity: $l^2 = 91\%$ , $t^2 =$	_Wild_A 10 71 = 0.0201, j	sia 82 246 328 p < 0.01	-	0.12 0.29 0.20	[0.06; 0.21] [0.23; 0.35] [0.07; 0.39]	2.8% 2.8% 5.6%
TEST = Antibody_ELISA Aguilar et al 2020 Jones et al 2021 Random effects model Heterogeneity: / <sup>2</sup> = 48%, r <sup>2</sup>	_Wild_A 42 26 = 0.0017, j	frica_G 216 98 314 p = 0.17	Group1(>median) 	0.19 0.27 0.22	[0.14; 0.25] [0.18; 0.36] [0.16; 0.29]	2.8% 2.8% 5.6%
TEST = Antibody_ELISA Rajneesh et al 2011 Random effects model Heterogeneity: not applicable	_Camel_ 4	Asia 94 94	•	<b>0.04</b> 0.04	[0.01; 0.11] [0.01; 0.09]	<b>2.8%</b> 2.8%
Random effects model Heterogeneity: $l^2 = 97\%$ , $t^2 = 7\%$	= 0.0970, j	12337 p < 0.01		0.23	[0.15; 0.32]	100.0%

**Figure 3.** Forest plot of the subgroup and sensitivity analysis of PPR in bovine, camel and wildlife during 2001-2021

### 3.5. Region and Animal Species Reported

A total of 37 articles covering 16 countries in two continents (Asia and Africa) were included in this study. The number of articles published (mentioned in parenthesis) from African countries was: Ethiopia (3), Kenya (3), Mauritania (1), Nigeria (2), Sudan (6), Tanzania (4), Uganda (1), and from Asian countries was Bangladesh (1), China (5), India (4), Kazakhstan (1), Mongolia (1), Nepal (1), Pakistan (3), Turkey (2), and Vietnam (1) from 2001 to 2021 (Table 1 and Figure 4). Totally, 29 animal species among which livestock species included in the study, were Cattle (Bos primigenius taurus), Water Buffalo (Bubalus bubalis), Yak (Bos grunniens), and Camel (Camelus dromedarius), and among the wildlife, African buffalo (Syncerus caffer), African grey duiker (Sylvicapra grimmia), Alpacas (Vicugna pacos), Argali (Ovis ammon), Bharals (Pseudois nayaur), Chowsingha (Tetracerus quadricornis), Dorcas gazelles (Gazella dorcus), Elephant (Loxodonta africana), Gerenuk (Litocranius walleri), Goitered gazella (Gazella subgutturosa), Grant's gazelle (Nanger granti), Ibex (Capra ibex and Capra ibex sibirica), Impala (Aepyceros melampus), Kongoni (Alcelaphus buselaphus), Lion (Panthera leo persica), Przewalski's gazelle (Procapra przewalskii), Saiga antelope (Saiga tatarica), Thomsons gazelles (Gazella thomsoni), Tiang (Damaliscus lunatus tiang), Topi (Damaliscus lunatus), Uganda kob (Kobus kob thomasi), Warthog (Phacochoerus africanus), Water deer (Hydropotes inermis). and Wildebeest (Connochaetes gnou) (Table 1 and Figure 4).

#### 3.6. Prevalence Estimates

The random effect meta-analysis of bovine, camel, and wildlife showed that pooled prevalence of PPR was 24% (95% CI: 15-33) with heterogeneity  $I^2 =97\%$ ,  $\tau 2=0.1005$ , P<0.01 (Table 3, Figure 5). Furthermore, in the case of the specific region, the studies showed that the prevalence of PPRV in Asia was 30% (95% CI: 0.14-0.49) followed by Africa with 20% (95% CI: 0.11-0.30) (Figures 6). Animal species category wise pooled prevalence showed 11% (95% CI: 8-14) for bovine (cattle and buffaloes), 15% (95% CI: 4-31) for camel, and 52% (95% CI: 30-74) for wildlife (Figure 7). However, the pooled prevalence of livestock (bovine and camel combined) was 13%. Furthermore, the articles were sub grouped into the studied period (2001-2010 and 2011-2021) to understand the prevalence of PPR in

the last two decades. From 2001 to 2010, the estimated prevalence was 15% (95% CI: 5-28) and 24% (95% CI: 2-61) for livestock and wildlife, respectively, with an overall estimated pooled prevalence of 16% (95% CI: 7-27) during 2001-2010.

Similarly, from 2011 to 2021, the prevalence was 12% (95% CI: 7-19) and 60% (95% CI: 35-83) for livestock and wildlife, respectively, and overall estimate pooled prevalence showed 29% (95% CI: 16-44) during 2011-2021.



Figure 4. A. PPR affected countries in Asia and Africa to bovine, camel, and wildlife animals and animal species distribution. B. Graph depicting the number of species described in the year-wise publication, and the frequency of new or unique species described for the first time.

								Weight	Weight
Study	Events	Total				Proportion	95%-CI	(fixed)	(random)
Abubakar et al 2017	58	480	+			0.12	[0.09; 0.15]	3.9%	3.0%
Balamurugan et al 2014	137	1037	100			0.13	[0.11: 0.15]	8.4%	3.0%
Kwiatek et al 2011	38	49	1			0.78	[0.63; 0.88]	0.4%	2.9%
Saeed et al 2015	214	474				0.45	[0.41; 0.50]	3.8%	3.0%
Haroun et al 2002	14	100				0.14	[0.08; 0.22]	0.8%	3.0%
Abraham et al 2005	56	1538				0.04	[0.03; 0.05]	12.5%	3.0%
Intisar et al 2017	79	243				0.33	[0.27; 0.39]	2.0%	3.0%
Omani et al 2019	1	25	+			0.04	[0.00; 0.20]	0.2%	2.8%
Lembo et al 2013	46	266				0.17	[0.13: 0.22]	2.2%	3.0%
Albavrak and Gur 2010	22	122	- (++			0.18	[0.12: 0.26]	1.0%	3.0%
Li et al 2017	13	13	1		-	1.00	[0.75; 1.00]	0.1%	2.5%
Bao et al 2011	3	4	-			0.75	[0.19: 0.99]	0.0%	1.9%
Asil et al 2019	3	4	1 -			0.75	[0.19; 0.99]	0.0%	1.9%
Gur and Albayrak 2010	10	82				0.12	[0.06; 0.21]	0.7%	2.9%
Zhou et al 2018	1	6	÷			0.17	[0.00; 0.64]	0.0%	2.1%
Balamurugan et al 2012a	1	1				1.00	[0.03; 1.00]	0.0%	0.9%
Pruvot et al 2020	17	20	1		. <u> </u>	0.85	[0.62; 0.97]	0.2%	2.7%
Cosseddu et al 2021	15	118	+			0.13	[0.07; 0.20]	1.0%	3.0%
Li et al 2019	1	1				1.00	[0.03; 1.00]	0.0%	0.9%
Liu et al 2021	71	246	1.8	-		0.29	[0.23; 0.35]	2.0%	3.0%
Mahapatra et al 2015	29	45	1		·	0.64	[0.49; 0.78]	0.4%	2.9%
Aguilar et al 2020	42	216	+			0.19	[0.14; 0.25]	1.8%	3.0%
Jones et al 2021	26	98		·		0.27	[0.18: 0.36]	0.8%	3.0%
Prajapati et al 2021	15	255	+			0.06	[0.03; 0.10]	2.1%	3.0%
Maillard et al 2008	9	85	+			0.11	[0.05; 0.19]	0.7%	3.0%
Herzog et al 2019	339	2997				0.11	[0.10; 0.12]	24.3%	3.0%
Chemweno et al 2019	12	380	*			0.03	[0.02; 0.05]	3.1%	3.0%
Agga et al 2019	49	613	÷.			0.08	[0.06; 0.10]	5.0%	3.0%
Abubakar et al. 2019	23	250	*			0.09	[0.06; 0.13]	2.0%	3.0%
Woma et al 2015	51	1517				0.03	[0.03; 0.04]	12.3%	3.0%
Rajneesh et al 2011	4	94	+			0.04	[0.01; 0.11]	0.8%	3.0%
Lundervold et al 2004	6	279	•			0.02	[0.01; 0.05]	2.3%	3.0%
Hague et al 2004	131	500	1	*		0.26	[0.22; 0.30]	4.1%	3.0%
Rashid et al 2008	4	50	+			0.08	[0.02; 0.19]	0.4%	2.9%
Ogunsanmi et al 2003	4	38		-		0.11	[0.03; 0.25]	0.3%	2.9%
Roger et al 2001	7	90	+			0.08	[0.03; 0.15]	0.7%	3.0%
Jaisree et al 2018	1	1	+			1.00	[0.03; 1.00]	0.0%	0.9%
Fixed effect model		12337				0.11	[0.10; 0.12]	100.0%	
Random effects model	- 0 1005			>		0.24	[0.15; 0.33]		100.0%
neterogeneity. / = 9/%, t	- 0.1000,	p < 0.01	0.	0.4 0	0.6 0.8	1			

Figure 5. Forest plot of the prevalence estimates of PPR in bovine, camel, and wildlife during 2001-2021



Figure 6. A. Estimated pooled prevalence of PPR in studied animals in Asia and Africa

B. Showing reported countries for PPR in sheep and goats (as per OIE 2018), bovine, camel, and wildlife





### 4. Conclusions

Contagious viral infection of PPRV has been reported in different parts of the world, including Asia, Africa, and some parts of Europe (18-22). However, for the meta-analysis, only 37 articles were selected from 48 eligible articles due to inter-rater disagreement. All 48 articles on bovine, camel, and wildlife from 2001 to 2021 were listed in table 1. An article published in 2001 by Roger, Yesus (6) based on the study conducted in 1995 was also included, and the systemic review and meta-analysis summarize the prevalence of PPR in bovine, camels, and wildlife based on the population size (n=12,337). An earlier meta-analysis study by Ahaduzzaman (69) using the random-effect model on PPR prevalence in sheep and goats from 34 countries shows an overall estimated pooled prevalence of 39.46% so that all data included in the study belonged to Asia and Africa with the prevalence of 38.63% and

1598

40.16%, respectively. In the present study, the overall estimated pooled prevalence was 24% in three groups of unnatural hosts bovine, camel, and wildlife, which is lower than the prevalence of the primary host sheep and goat observed by Ahaduzzaman (69). The prevalence in bovine, camel, and wildlife was significantly higher in Asia (30%) and Africa (20%) (Table 3, Figures 6), which was contrary to the continent wise prevalence in compared to sheep and goats observed by Ahaduzzaman (69).

The present study under PCR assay grouping had I<sup>2</sup>=91% and  $\tau$ 2=0.2286 with a high prevalence of 74% (95 % CI: 39-97) (Figure 3). The chance of positivity was attributed to the low sample size as the outbreak samples were collected only in case of the onset of animal deaths and analyzed by RT-PCR. Furthermore, subgroup analyses of the enzyme-linked immunosorbent assay were classified by PPRV antigen and antibody detection with species, continents, and sample size above or below the median for better understanding. The result of antibody detection had a wide range of prevalence from 2 % above-median in camels from Africa to 30% below-median in the wildlife of Africa.

PPR in sheep and goats is reported from more than 70 countries, mostly of African and Asian origin (Figure 6) (4, 69). In the present review, PPR in the atypical/unnatural hosts (bovine, camel) and wildlife were observed in 22 countries from Africa (9) and Asia (13) (Table 1, Figure 4); however, the pooled prevalence was estimated for only 16 countries in the present meta-analysis. Only three enzootic countries, such as Nigeria, Sudan, and India were reported for all three groups of animals (bovine, camel, and wildlife) in the study period (Figure 6). Moreover, Bangladesh, Ethiopia, Kazakhstan, Libya, Mauritania, Nepal, Pakistan, and United Arab Emirates (UAE) were only reported in the atypical hosts (bovine and camel), and Côte d'Ivoire, Iraq, Saudi Arabia, Mongolia, China, and Uganda were reported only wildlife (Table 1, Figure 6B). Evidence of PPRV was in bovine in Vietnam without any official OIE reports on the prevalence of PPR in sheep and goats. Apart from these countries listed in this review, other reports conducted to detect the PPRV in wildlife were in Pakistan (72), Kurdistan, Iran (21, 56), UAE (73), and Egypt (74) as reviewed earlier (19, 22). Out of 70 countries with PPR in sheep and goats, only about 22 countries (31%) studied or reported the prevalence of PPR in atypical and wildlife hosts, showing a huge knowledge gap in understanding the role of these animals in the PPR spread and transmission.

In the present study, overall estimated pooled prevalence rates of 11%, 15%, and 52% were observed for bovine, camel, and wildlife, respectively. Prevalence in wildlife was higher than that in the bovine and camel, leading to concerns; however, the study population size of the wildlife was only 798, compared to 7,962 in bovine and 3,577 in camel as these low numbers are attributed to the lack of systematic study, limiting to outbreaks responses and lack of reporting in the wildlife setup.

A significant difference was also observed between the number of studies and prevalence of PPR in wildlife in two decades, 24% (3 studies) in 2001-2010 and 60% (12 studies) in 2011-2021 (Table 3). A cumulative time-scale map of the reported countries for PPR in the atypical hosts (bovine and camel) and wildlife during 2001-2021 is shown in figures 8 indicating the significance of wildlife recognized in recent years and the increasing frequency of PPR in wildlife.

Furthermore, large ruminants, such as cattle, water buffalo, and yaks are reported for seroconversion to PPRV in Asia and Africa; however, Govindarajan, Koteeswaran (13) observed rare clinical infection with high case fatality (96%) in bovine with fever, conjunctival congestion, hypersalivation, and depression. Experimental clinical infection was established in buffalo calves, whereas cattle were susceptible without clinical signs (75, 76). The cattle are also considered dead-end hosts for PPRV as no evidence of virus shedding was observed in body secretion and excretions (9, 14); however, transmission by water buffalo cannot be ruled out (13, 14). Clinical PPRV infection and seroconversion in camels are frequently reported from Africa and Asia. Here, clinical signs have been similar to sheep and goats (14, 77, 78), and the signs include fever, diarrhea, conjunctivitis with ocular discharges, loss of body condition, and general weakness, resembling PPR in small ruminants consequently. Additionally, evidence supporting viral shedding in faces and nasal discharges is considered as source of infection. It should be noted that the possible risk of camel transmission needs more studies. Both bovine and camel PPRV infections are attributed to the cohabitation of sheep and goats (14).



**Figure 8.** Cumulative reported countries for PPR in atypical hosts -bovine and camel- for the period 2001-2005, 2001-2010, 2001-2015 and 2001-2021 (A), in wildlife for the period 2001-2005, 2001-2010, 2001-2015 and 2001-2021 (B)

Hamdy and Dardiri (79) first reported in 1976 that wild ruminants were also sensitive to PPRV. Since then most reports of PPRV-related deaths focused on wild ruminants, such as bharals, wild goats, dorcas gazelles, bubal hartebeests, and waterbucks (22, 80). Before 2001, PPR was reported in cattle, water buffalo, camel, and in a few wildlife species, including Gazella dorcass (*Dorcas gazelles*), Nubian ibex (*Capra nubiana*), White-tailed deer (*Odocoileus virginianus*), Asinus (*Equus asinus*), Gemsbok (*Oryx gazella*), Laristan sheep (*Ovis gmelina*), and Nilgai (*Boselaphus tragocamelus*) (14, 17, 19, 22, 79, 81).

Since 2001, a drastic increase in the reports of atypical hosts and wildlife, and around 25 new species of animals (mostly in the wildlife) are reported, (Figure 4B). Prevalence of PPR in 25 wildlife species was covered in the present systematic review in Asia and Africa (Figure 4A) that include Aepyceros melampus (25), Alcelaphus buselaphus (34, 82), Capra ibex (18, 20), Connochaetes spp. (25), Damaliscus lunatus tiang (31), Defassa waterbuck (23), Eudorcas thomsonii, Phacochoerus africanus Litocranius walleri (34), Gazella subgutturosa (20, 26, 52), Gazella thomsoni (52), Kobus kob leucotis, Kobus kob thomasi, Loxodonta africana (31), Nanger granti (25, 34), Ovis ammon (20), Panthera leo persica (76), Procapra przewalskii (2), Saiga tatarica (18), Syncerus caffer (59), Vicugna pacos (33), Capra aegagrus (56), Hydropotes inermis (67), Sylvicapra grimmia (15), and Tetracerus quadricornis (66). Apart from these, PPR was also reported in other wildlife species, including Gazella gazella cora (Arabian mountain gazelle), Antidorcas marsupialis (Springbuck), Gazella gazella (Arabian gazelle), Ammotragus lervia (Barbary), Tragelaphus scriptus (Bushbuck), Capra falconeri (Afghan Markhor goat) (73), and Ovis orientalis (wild sheep) (21) without any data regarding prevalence in these reports. There is also reports with evidence of PPRV detection in lions (76) and elephant (31) from Asia and Africa, respectively. The frequency of PPR reporting in new hosts increased over the years and the year-wise species diversity and detection of new hosts

are shown in figure 4B. Due to high animal density, most of the enzootic regions of Asia and Africa are likely to have a higher risk of PPR, for eg. the countries like Sudan, Kenya, and Tanzania have the highest species diversity. Moreover, because of a vast host range and heterogeneities in different host ranges and animal population density, the difference in susceptibility of the host to PPRV infection, disease control, and eradication seem cumbersome. As a result, the strategies employed cannot solely rely on or be limited to the vaccination of sheep and goats.

In the PPR GCES of the "Global Program-Transboundary Animal Diseases (GF-TADs)", the focus is considered vital on the prevention of crossspecies and transmission from the typical hosts to wildlife unnatural hosts. including through strengthened disease surveillance, coupled with appropriate diagnostics and vaccination. More research on the pathogenesis of PPR in wildlife species is needed to explain this phenomenon; additionally, the function of infective strains, migration, stress, coinfections, environmental conditions, and other ecological elements of the disease must be thoroughly examined. However, wild ruminants can sustain and bridge viruses between wildlife and livestock (80), thereby eradicating PPRV may be hindered. For effective eradication, the program should focus on understanding the transmission of PPRV among the atypical hosts/wildlife. Modern molecular tools should also help in understanding virus virulence, an adapted ability for diverse hosts (80).

The limitation of the present analysis is that most of the studies on unnatural hosts, such as large ruminants and wildlife, were based on few samples, leading to high positivity. The systematic review was conducted on articles only from countries of Africa and Asia within the search range. Demographic characteristics (age, gender) and risk factors were also absent or not uniform in the selected articles. The review excluded some kinds of articles, including non-English, unpublished articles, retro perspective, methodvalidation articles, and also experimental-trial results. Finally, heterogeneity in models was significant that showed other ignored factors might have substantial effects.

To the best of our knowledge, this paper is the first study to estimate the prevalence of PPR among unusual hosts (bovine, camel) and wildlife using systematic review and meta-analysis. The estimated pooled prevalence was high and different between the two continents, which was contrary to observation on sheep and goats in Asia than Africa. The results show that the host range is widening over time and the frequency of discovery of new hosts has increased in recent years; moreover, the screening tests for PPR, effective preventive, and control measures should be routinely conducted in all susceptible animals (livestock and wildlife) in regions with a high disease prevalence to control the spill-over outbreaks. The outbreak in unnatural hosts may cause morbidity and mortality in economically important livestock and be also fatal to the wildlife populations in the sanctuaries and national parks. Controlling disease transmission to other unnatural hosts from sheep and goats is as much important as in sheep and goats. Furthermore, epidemiological surveillance is needed for estimating the disease burden and its elimination in many regions, in which the virus may be circulating in multiple hosts. Additionally, the contributing factors to the prevalence heterogeneity should be handled suitably in the survey for an accurate estimate. The findings of the current study are significant as Asia and Africa are responsible for the majority of the world's bovine, camel, and wildlife populations. Due to human activities and global climate change, wildlife has less access to food and water, resulting in poor nutritional status and habitat disturbance, increasing the probability of wildlife-livestock interactions. This interaction either directly or indirectly via other livestock animal persistence transmission can jeopardize the ongoing control program in the sheep and goat population. Therefore, surveillance mechanisms should be

considered at the interface between the livestock and wildlife to identify the spillover mechanism of the PPRV infection. Furthermore, the surveillance should be strengthened to ensure mild clinical cases as PPR reported in sheep and goat vaccinated regions (due to the impact of vaccination, changing pattern of the disease in sheep and goats). Syndromic surveillance should be also used for knowing the status of clinical diseases, if any in the interface, and identifying the undetected mild cases during the PPR control and eradication program.

### **Authors' Contribution**

S. S. K. carried out the literature search, analysis of data, and wrote the rough draft of the manuscript. K. V. K. and P. P. B. interpreted the data, wrote the draft, and prepared the GIS map, figures, and tables. S. S. K., B. A. P., and A. N. analyzed the data and carried out the meta-analysis in R software. K. P. S. designed, analyzed, and interpreted the data. BRS provided guidance and support to carry out the research. V. B. designed and conceptualized the idea, interpreted the data, rewritten the draft, and edited the manuscript. All authors read and approved the final edited manuscript.

### **Conflict of Interest**

The authors declare that they have no conflict of interest.

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