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Title: Prevalence of Accessory Transverse Foramen in the Dried Cervical Vertebrae of Human Population and its' Clinical Significance: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Variations in number, location, size & shape of foramen transversarium affect the anatomical course of the vertebral vessels, which may cause pathological conditions like vertebro-basilar insufficiency. Knowledge of such variations of the presence of accessory transverse foramina in the cervical vertebrae would be useful in planning the cervical spine surgery, and avoiding postoperative complications. Investigations in the magnitude and types of such variation may thus be important for the relevant clinical practices. The aim of this study is to assess the pooled prevalence and clinical importance of accessory transverse foramen among the dried cervical vertebrae of global human population.

Methods: This review is carried out in accordance with the protocol of Systematic reviews and Meta-Analyses (PRISMA) guidelines. Condition, context and population framework approach was used. Articles were searched from PubMed, Scopus, EMBASE, CINAHL and Web of Science. Grey literature from Google and Google scholar were hand-searched. In addition to the above databases searches, a hand search of the major anatomical journals was carried out in the reference lists of all the eligible and selected articles for systematic review. Data is clearly summarised and presented in tabular and narrative forms. In addition, meta-analyses was performed on methodologically comparable studies regarding to the study design, primary, and secondary outcomes.

Results: Twenty studies with a total of 3848 dried cervical vertebrae of human population were included for this systematic review and meta-analysis. The pooled global prevalence of the accessory transverse cervical foramen was 17.54 % (95% CI: 13.30-21.77). In this study, heterogeneity was found across the studies as revealed by I^2 statistic ($I^2 = 93.6\%$, $p\text{-value} < 0.005$). The subgroup analysis showed that the prevalence of unilateral accessory transverse cervical foramen was 66.27% (95 % CI: 58.94-73.60), and that of bilateral accessory transverse cervical foramen was found to be 33.73% (95 % CI: 26.40,41.06), anterior accessory transverse cervical foramen was found to be 30.50% (95 % CI: -0.46,61.47), posterior accessory transverse cervical foramen was found to be 62.83% (95 % CI: 22.67,103.00), complete accessory transverse cervical foramen was found to be 63.22% (95 % CI: 56.27,70.17), and that of incomplete accessory transverse cervical foramen of cervical vertebrae was found to be 36.78% (95 % CI: 29.83,43.73). Eggers' and Beggs' test revealed the presence of statistically significant publication bias, $p > 0.05$ which was also supported by the funnel plot.

Conclusions and Recommendation: The pooled global level prevalence of accessory transverse cervical foramen was found to be high. Among these, anterior, complete and unilateral accessory transverse cervical foramen was found to be more prevalent than their counterparts. Knowledge of variations in the presence of accessory FT in the cervical vertebrae would be useful in planning the cervical spine surgery, as well as avoiding postoperative complications. Awareness of such large variations may thus be interesting for Neurologists, Neurosurgeons and Medical community in general.

Keywords: Foramen transversarium, cervical vertebrae, vertebral artery

INTRODUCTION

Background: The adult cervical vertebrae are characterized by the presence of foramen transversarium (FT) in their transverse processes, which differentiates them from other vertebrae. The vertebral artery, vertebral vein and sympathetic nerves from inferior cervical ganglion pass through these foramina, except the seventh. The vertebral artery enters in its vertebral course at the level of FT of sixth cervical vertebra. The FT of seventh cervical vertebra transmits only vein and is small or even some time absent. [1] An accessory transverse foramen is seen as a smaller foramen in size than the primary foramen and generally found in the sixth cervical vertebra, and less frequently in the adjacent vertebrae.(2) Variation in number, size & shape of foramen transversarium affects the anatomical course of the vertebral vessels, which may cause pathological conditions like vertebra-basilar insufficiency. Since, inner ear derive it's blood supply from vertebral and basilar arteries, any spasm of these arteries due to irritation of sympathetic plexus, may cause labyrinthine or hearing disturbances along with neurological symptoms.(3)

In a study that examined 480 FT, 34 (7.08%) vertebrae with duplication of FT were found in the Indian population[4]. In a similar study by Kaya et al. that was carried out in an Ancient Byzantine Jewish population, five out of 22 vertebrae which account for 22.73 % double FT were observed. These double transverse foramina were unilateral in three (13.63%) and bilateral in two (9.09%) of all the vertebrae considered.[5] Additionally, 15 out of 222 vertebrae with bilateral duplication of FT which accounts for 6.76% were also observed in Turkish population(6). A recent study by Sangari in 71 vertebrae of unknown race 17 vertebrae (24%) with unilateral duplication and one vertebra (1.04 %) with bilateral duplication of the foramen were reported. (7)

Such significant observations of variations in the cervical FT in different human populations may necessitate further studies for compiling the different studies for a better understanding of the magnitude of the occurrence of the variations. This study is aimed at measuring the pooled prevalence of individual studies on the accessory cervical transverse foramen in the dried cervical vertebrae of human population. The study also reviewed the distribution and variation of accessory cervical transverse foramen among different subgroups. Knowing the prevalence and the clinical significance of the accessory cervical transverse foramen is important for the development of science in the areas of accessory cervical transverse foramen. It also alerts

clinicians to consider the accessory cervical transverse foramen during their clinical examination and surgeries of cervical spine, so that they can minimize risks associated with accessory cervical transverse foramen.

METHODS

Study Setting and Design

This systematic review and meta-analysis was carried out to determine the pooled prevalence and clinical importance of accessory transverse foramen among the dried cervical vertebrae of global human population.

Search strategies

The systematic review and meta-analysis was conducted in accordance with the protocol of Systematic reviews and Meta-Analyses (PRISMA) guideline. (Fig.1). All literatures accessible until 2022 were included in the review. To determine the scope of the research and to identify the key concepts to be used in search strategy, and to guide which papers are being searched for this study condition, context and population (CO-Co-Pop) approach model was used (Table 1). The Co-Co-Pop framework has been used to identify the possible searching terms. Key words of the searching terms for the anatomical variations of the transverse foramen in dried cervical vertebrae and its clinical importance are adapted from different articles conducted on the anatomical variations of transverse foramen of cervical vertebrae. This framework is prevalence or incidence model. Prevalence or incidence reviews are important in the description of a variable and the variation between subgroups. The Co-Co-Pop framework has been used to identify the possible searching terms. In this study, we searched for potentially applicable papers, such as PubMed / MEDLINE, the Science Web, EMBASE, CINAHL, HINARI, Google Scholar, Science Direct, and Cochrane Library. This review included all articles published in peer-reviewed journals, which were written in the English language. Also, Gray literatures of observational studies were used. The search of the literature was conducted from the 1st of August, 2022 up to October 30, 2023. All papers published until October 30, 2022 was considered. The Electronic databases were searched by medical subject headings (MeSH) terms and using the following keywords “prevalence”, “clinical importance”, “clinical relevance”, “accessory foramen transversarium”, “accessory foramen of transverse process” ,

“dried cervical vertebrae” and “preserved cervical vertebra”. We used the search terms independently and/or in combination using Boolean operators like “OR” or “AND”.

Eligibility criteria

Inclusion criteria

Study area: studies conducted globally were considered.

Population: studies done on dried cervical vertebrae of men and female of all ages were included.

Publication condition: published articles were considered.

Study design: All observational studies reporting the prevalence and clinical importance of accessory transverse foramen among the dried cervical vertebrae of human population were considered.

Language: Articles reported only in English language were considered.

Exclusion criteria

The following were excluded: Articles which were not fully accessible, Case reports, Studies of expert opinion, Conference abstracts, Letters of the editor, and published studies reporting missing, unclear, or incomplete results. Furthermore, unsuccessful attempts to contact the authors of the original study for clarification after at least two emails were also excluded.

Measurement of outcome variables

The main aim of this meta- analysis was to determine the pooled global prevalence and clinical importance of accessory transverse foramen among the dried cervical vertebrae of human population.

Data extraction and quality assessment

Data were extracted using a standardized data extraction spreadsheet format in Microsoft Excel. The data extraction format includes author/s name, year of publication, study region, sample size, the prevalence and clinical significance of accessory transverse cervical foramen, various types or pattern of accessory transverse cervical foramen (Table 3). All published primary studies those written in the English language and conducted anywhere in the world were included. The data were extracted by two independent authors (Tsegaab and professor Mekbebe). Accessory transverse foramen referenced to the normal anatomy of the transverse foramen in the cervical vertebrae will be the comparison group.

Data processing and analysis

After extracting the data obtained from the studies using Microsoft Excel 2016 format, we imported the data to statistical program STATA version 11.0 (STATA Corporation, College Station Texas) software for further analysis. The researchers calculated the proportion of accessory transverse cervical foramen (ATF), standard error of prevalence of ATF, prevalence of Unilateral and bilateral ATF, incomplete ATF and complete ATF and anterior and posterior ATF for each original article using the binomial distribution formula. Meta-analyses were performed on comparable studies reporting main outcomes. A random effects model was considered to estimate the Der Simonian and Laird's pooled effect. In order to identify the heterogeneity between the studies, Cochrane's Q statistics (Chi-square), inverse variance (I^2) and p-values were assessed. Potential publication bias was also assessed subjectively by funnel plot (Fig 9.) and objectively using Egger's weighted correlation and Begg's regression intercept tests at 5% significance level (Table 4). The funnel plot which was plotted by effect or prevalence estimate versus standard error of effect estimate was done. Accordingly, Egger's and Begg's tests, with the p-value, less than 5% indicates the presence of publication bias. In addition, subgroup analysis was done in order to reduce the random heterogeneity between the estimates of the primary studies. Forest plot was also done. In the forest plot, the size of each box indicated the weight of the study, while each crossed line refers to a 95% confidence interval.

RESULTS

Study selection and data extraction

This systematic review and meta-analysis is reported by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Fig.1). Initially, 701 articles related to the prevalence and clinical significance of accessory transverse cervical foramen were found from the electronic databases of PubMed / MEDLINE, the Science Web, EMBASE, CINAHL, HINARI, Google Scholar, Science Direct, Cochrane Library, reference lists of selected articles. After excluding 132 articles because of duplication, the remaining articles were screened based on the pre-set eligibility criteria. Then, after reviewing the titles and abstracts of 569 studies, 113 full-text articles were assessed by two independent reviewers for the eligibility of articles for the inclusion of the review and meta-analysis. From these, a total of 20 articles were found relevant for this systematic review and meta-analysis. Finally, the data extraction formats were prepared

based on the first author, publication year, country of study, the number of studied subjects, patterns and types of variation.

Characteristics of included studies

A total of 20 accessible studies (3848 cervical vertebrae) were included for this systematic review and meta-analysis. All the studies were conducted on dried cervical vertebrae of human population. The numbers of studied cervical vertebrae specimens varied from 52 to 865 in individual studies. Most of the studies (85%) were conducted on dried cervical vertebrae of Indian population and the remaining was conducted in Turkey and New York populations. (Table 3).

Meta-analysis

The prevalence of accessory transverse cervical foramen

The lowest prevalence rate of accessory transverse cervical foramen was 2% observed in a study conducted in India and the highest was 71% observed in a study conducted in New York. Based on the random effect analysis, the pooled global level prevalence rate of accessory transverse cervical foramen was 17.54 % (95% CI: 13.30-21.77). (Fig. 2)

Sub- Group Analysis

In addition, in this meta-analysis, subgroup analysis was performed based on the unilateral or bilateral presence of accessory transverse cervical foramen. Accordingly, the highest prevalence of ATF of cervical vertebrae was found to be unilateral 66.27% (95 % CI: 58.94-73.60), (Fig. 3) while the prevalence of bilateral ATF of cervical vertebrae was found to be 33.73% (95 % CI: 26.40,41.06) (Fig. 4), anterior ATF of cervical vertebrae was found to be 30.50% (95 % CI: -0.46,61.47) (Fig. 5), posterior ATF of cervical vertebrae was found to be 62.83% (95 % CI: 22.67,103.00) (Fig. 6), complete ATF of cervical vertebrae was found to be 63.22% (95 % CI: 56.27,70.17) (Fig. 7), incomplete ATF of cervical vertebrae was found to be 36.78% (95 % CI: 29.83,43.73) (Fig. 8).

Heterogeneity and publication bias

The I^2 (variation in ES attributable to heterogeneity) test result showed that there was a considerable heterogeneity among the studies ($I^2 = 97.5\%$, $p = 0.000$). The existence of publication bias was evaluated by visual examination of the funnel plot and Egger's and Begg's

test. Visual examination of the funnel plot indicated asymmetrical distribution of included studies. Egger's and Begg's test showed that there was statistical evidence of publication bias at p-value less than 0.05. (Fig.9 and Table 4). Considering the presence of publication bias, trim and fill analysis was done. However, based on this analysis no significant change was shown as compared with the main meta-analysis.

DISCUSSIONS

This meta-analysis study conducted on anatomical variation of accessory transverse cervical foramina is the first estimate of pooled prevalence of accessory transverse cervical foramina. In this study, the pooled prevalence of the accessory cervical transverse foramina was assessed in 3848 dried cervical vertebrae of human specimen. The overall pooled prevalence of ATF among 20 studies was 17.54 % (95% CI: 13.30-21.77). This finding was slightly higher than a study conducted in Spanish population on computed tomography of cervical scans of 300 human subjects which reported 11.2% of double transverse foramina of cervical vertebrae. It was also higher than the study conducted in Turkish population on three dimensional CT scan of cervical vertebrae which reported 8.91%. (8)

There could be several reasons for the inconsistency between the finding of current systematic review and meta-analysis and the above mentioned studies. These includes the difference in study design, multi-centeredness and sample size may have contributed for the higher prevalence rates in the current study and relatively low prevalence in the other studies.

Additionally, the subgroup analysis were performed in regards to the prevalence of the various types/patterns of ATF such as the unilateral or bilateral presence of ATF of cervical vertebrae specimen, location of the accessory transverse cervical foramen in relation to the main transverse cervical foramen and complete or incompleteness of the accessory transverse cervical foramen. Accordingly, the most prevalent types of ATF of cervical vertebrae was found to be unilateral 66.27% (95 % CI: 58.94-73.60) than that of bilateral ATF of cervical vertebrae which was found to be 33.73% (95 % CI: 26.40, 41.06). This was supported by the findings from the study conducted in Spanish and Turkish populations on computed tomography of cervical scans of human subjects which reported higher prevalence of unilateral ATF of cervical vertebrae than that of bilateral ATF of cervical vertebrae. It was also reported in this study that complete ATF

of cervical vertebrae was found to be 63.22% (95 % CI: 56.27, 70.17) where as that of incomplete ATF of cervical vertebrae was found to be 36.78% (95 % CI: 29.83, 43.73). In contrary to the current study ,it was reported that incomplete accessory transverse cervical foramen of cervical vertebrae was more prevalent than the complete ATF of cervical vertebrae in the study conducted in Turkish population on computed tomography of cervical scans of human subjects.(9)

The findings of the current study indicated that the prevalence of anterior ATF of cervical vertebrae was found to be 30.50% (95 % CI: -0.46, 61.47) and that of posterior ATF of cervical vertebrae was found to be 62.83% (95 % CI: 22.67, 103.00).

Regarding the clinical significance, the presence of a FT (foramen transversum) in the transverse process is the identification feature for cervical vertebrae. In all cervical vertebrae, the FT normally transmits the vertebral artery and vein and a branch from cervico-thoracic ganglion (vertebral nerve) except seventh cervical vertebra where there is no vertebral artery [10]. Normally, there is one cervical transverse foramen on either side. Occasionally, it is either absent or duplicated unilaterally or bilaterally. Cervical vertebrae are smaller and more delicate than those of the other regions of human vertebral column. Variations of the FT of cervical vertebrae cause pathologic conditions related with the compression of the vertebral arteries which lead to vertebra-basilar insufficiency during neck movements and may cause headache, migraine, fainting attacks and hearing disturbances [11]

Anatomically, the transverse foramen is described to be divided by a fibrous or bony ridge separating the artery and the vein. (12) Double transverse foramina could mean duplication of vertebral artery. Embryo-logically, the vertebral artery is developed from the fusion of the longitudinal anastomosis that link the cervical inter-segmental arteries which branch off from the dorsal division of somatic inter-segmental artery in the region of the neck. These inter-segmental arteries eventually regress except for the seventh artery which forms the proximal portion of the subclavian artery and the beginning of vertebral arteries. (13)

Sometimes there occurs failure of the controlled regression of this portion of the primitive dorsal aorta along with the two inter segmental arteries which leads to the double origin and duplication of the vertebral arteries. The bilateral occurrence of these failures is the reason behind the

bilateral duplication of the vertebral arteries. The vertebral vessels are responsible for the formation of the transverse foramen. It can be assumed that variations in the course of vertebral vessels will cause variations in the transverse foramen. It is stated that maintaining the vertebral artery intact constitutes an important concern to neurosurgeons while performing surgeries on the cervical spine since minor accidental damage to vertebral artery can lead to grave consequences and even death. (14) Hence, the knowledge of all kind of variations in the anatomy and morphology of accessory FT in cervical vertebrae may be helpful to concerned practitioners in preventing vascular catastrophes due to accidental damage of vertebral artery.

Conclusions and Recommendation: The pooled global level prevalence of accessory transverse cervical foramen was found to be high. Regarding the types of accessory transverse cervical foramina; anterior, complete and unilateral accessory transverse cervical foramen were found to be more prevalent than their counterparts. Knowledge of variations of the presence of accessory FT in the cervical vertebrae could be useful in planning the cervical spine surgery and as well as avoiding postoperative complications. Awareness of such variation in the accessory transverse cervical foramen may be important for Neurologists, Neurosurgeons and Medical community in general.

Abbreviations

TT: Tsegaab Temsegen; **MA:** Mekbeb Afework **ATF** :Accessory transverse foramina

CV: Cervical Vertebrae **CO-Co-Pop:** Condition, context and population **DFT:** Double Foramen transversum **FT:** Foramen transversarium **SE:** Standard Error

Declaration

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

We have confirmed that we have no competing interests.

Funding

No funding was obtained for this study.

Authors' contributions

TT and MA: developed the study design and protocol, literature review, selection of studies, quality assessment, data extraction, statistical analysis, and interpretation of the data and developing the initial drafts of the manuscript.

TT and MA: Involved in statistical analysis and interpretation, quality assessment, prepared the final draft of the manuscript. Both authors read and approved the final manuscript

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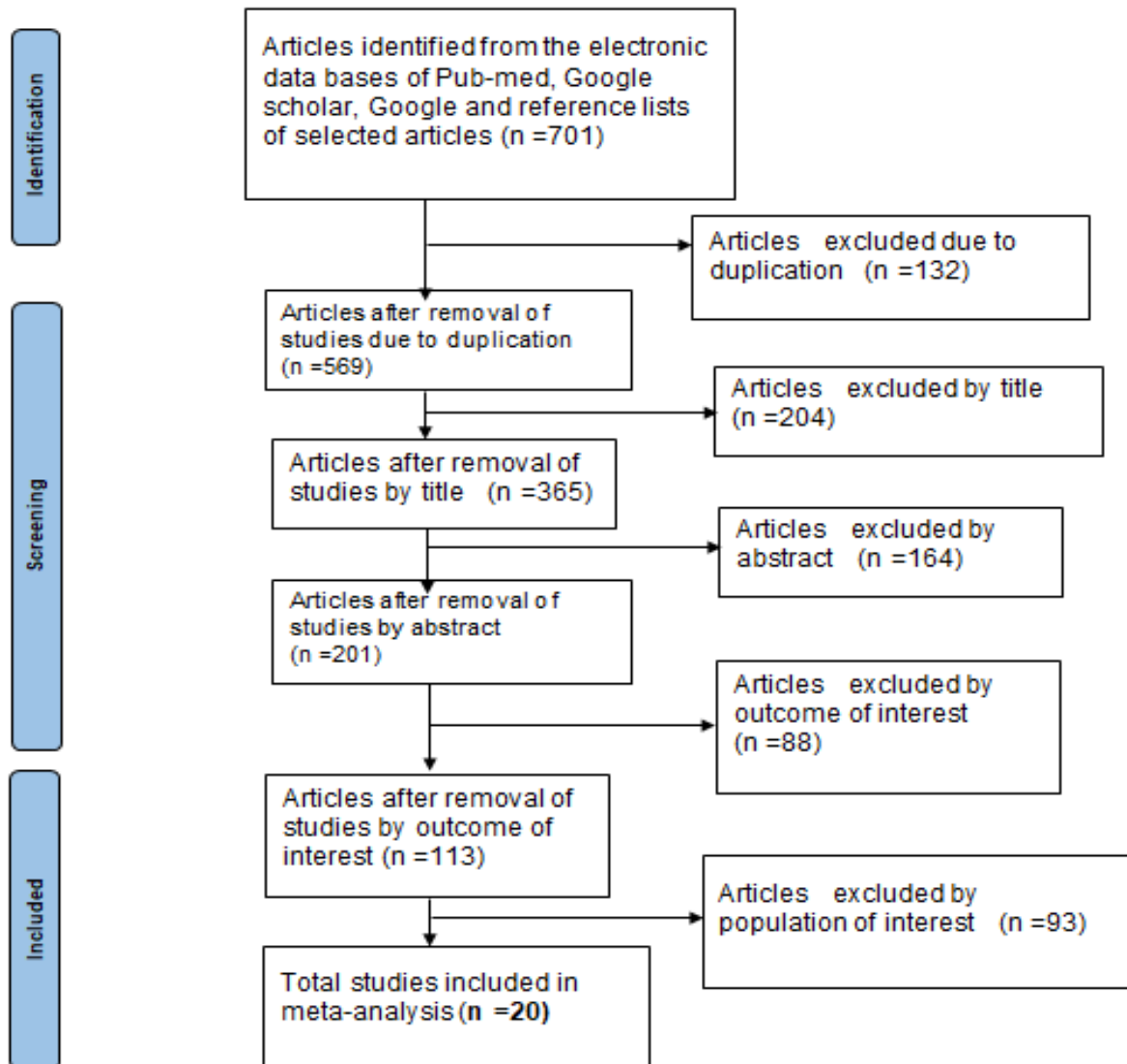


Figure 1 Flow diagram showing the procedure of selecting studies for the prevalence of AFT, systematic review and meta-analysis, 2023.

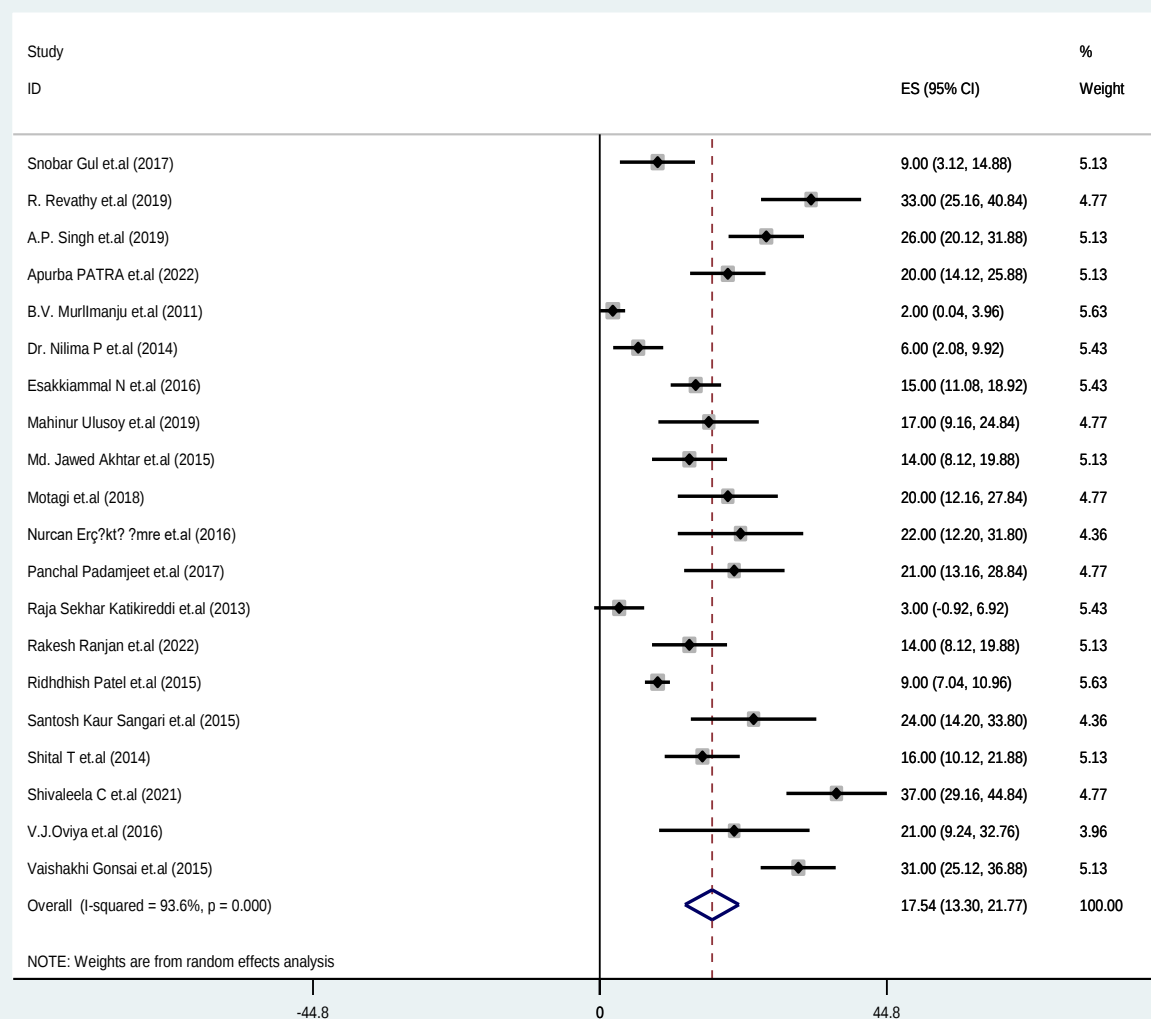


Fig. 2 Forest plot of the pooled prevalence of ATF among the dried cervical vertebrae of human population, 2023

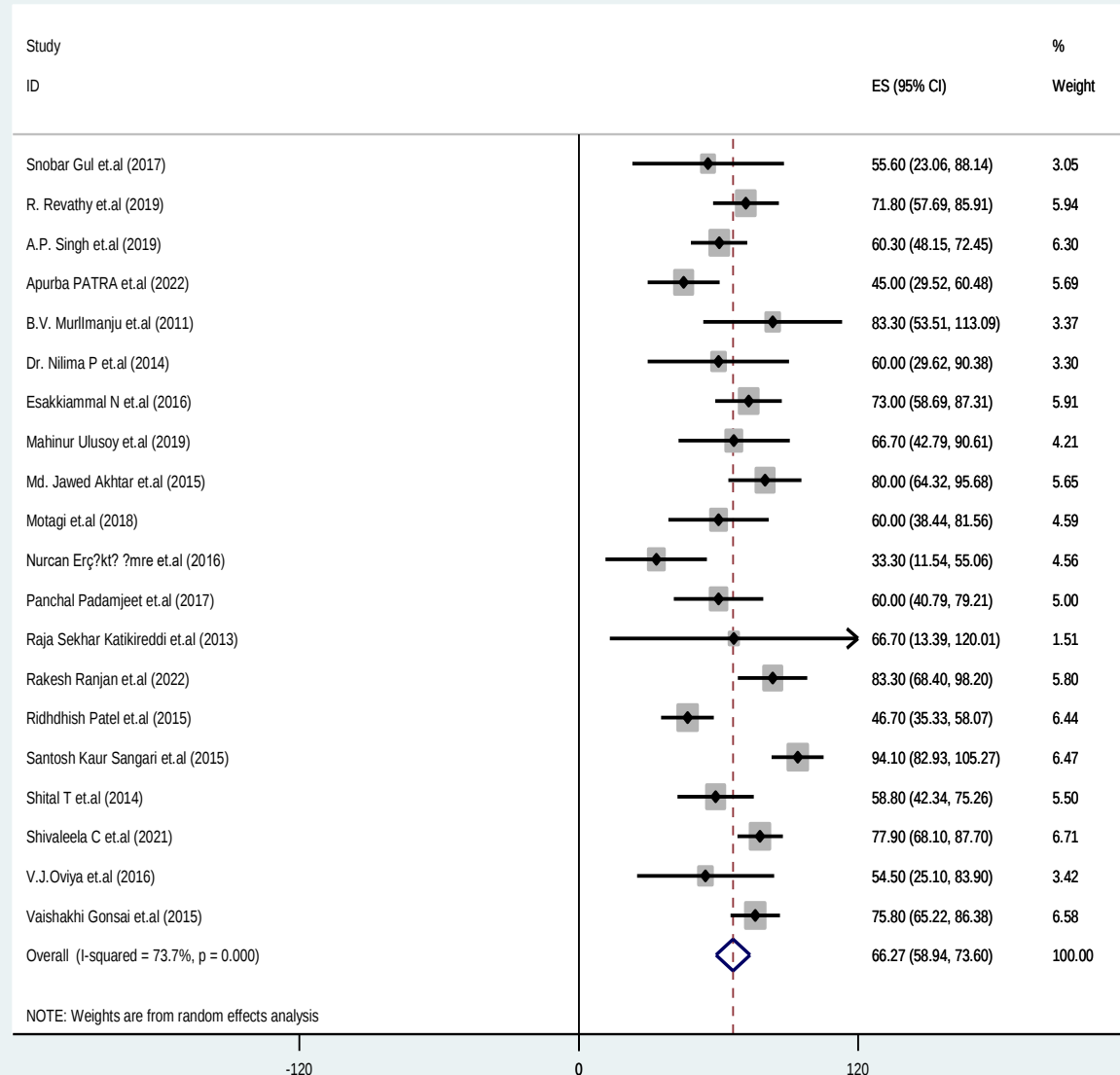


Fig. 3 Forest plot of the sub - group analysis of prevalence of unilateral ATF among the dried cervical vertebrae of human population, 2023

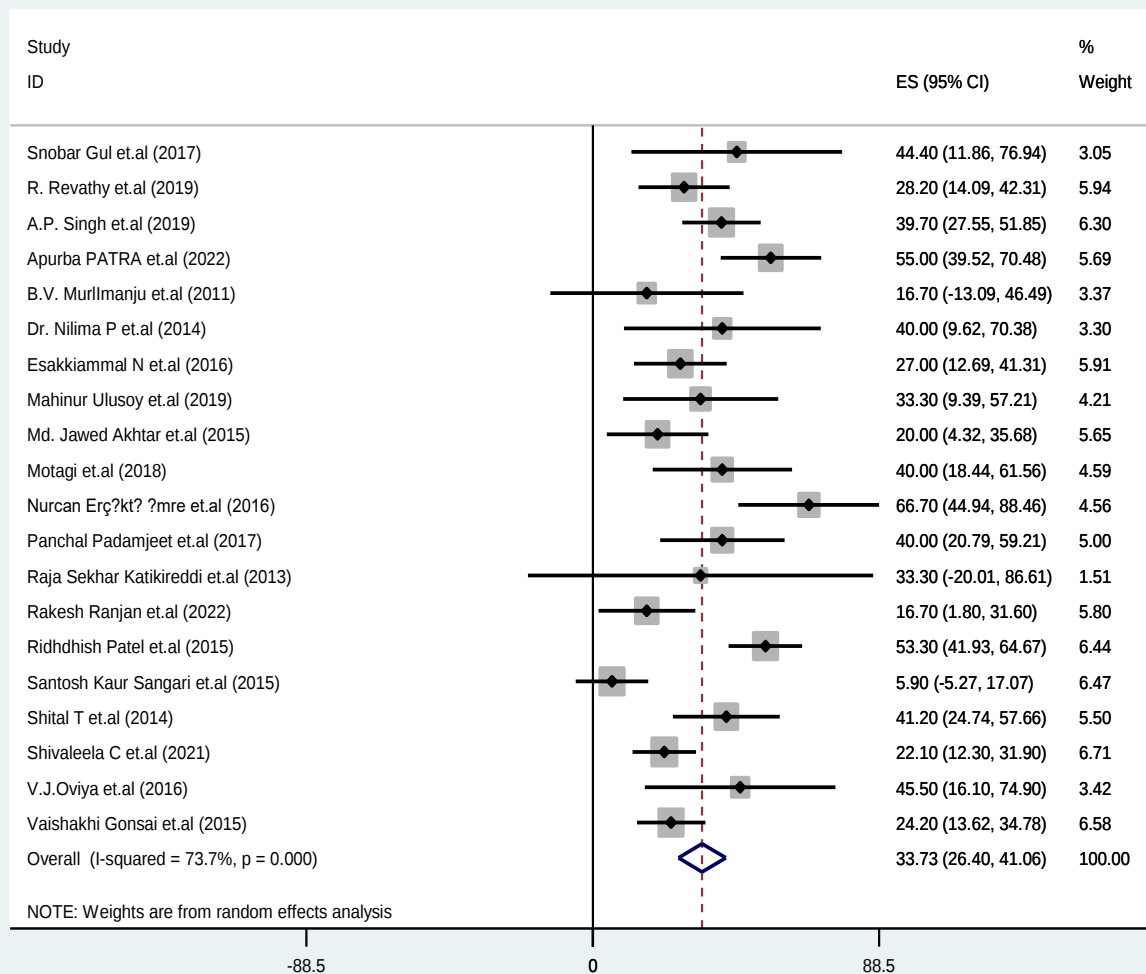


Fig. 4 Forest plot of the sub - group analysis of prevalence of bilateral ATF among the dried cervical vertebrae of human population, 2023

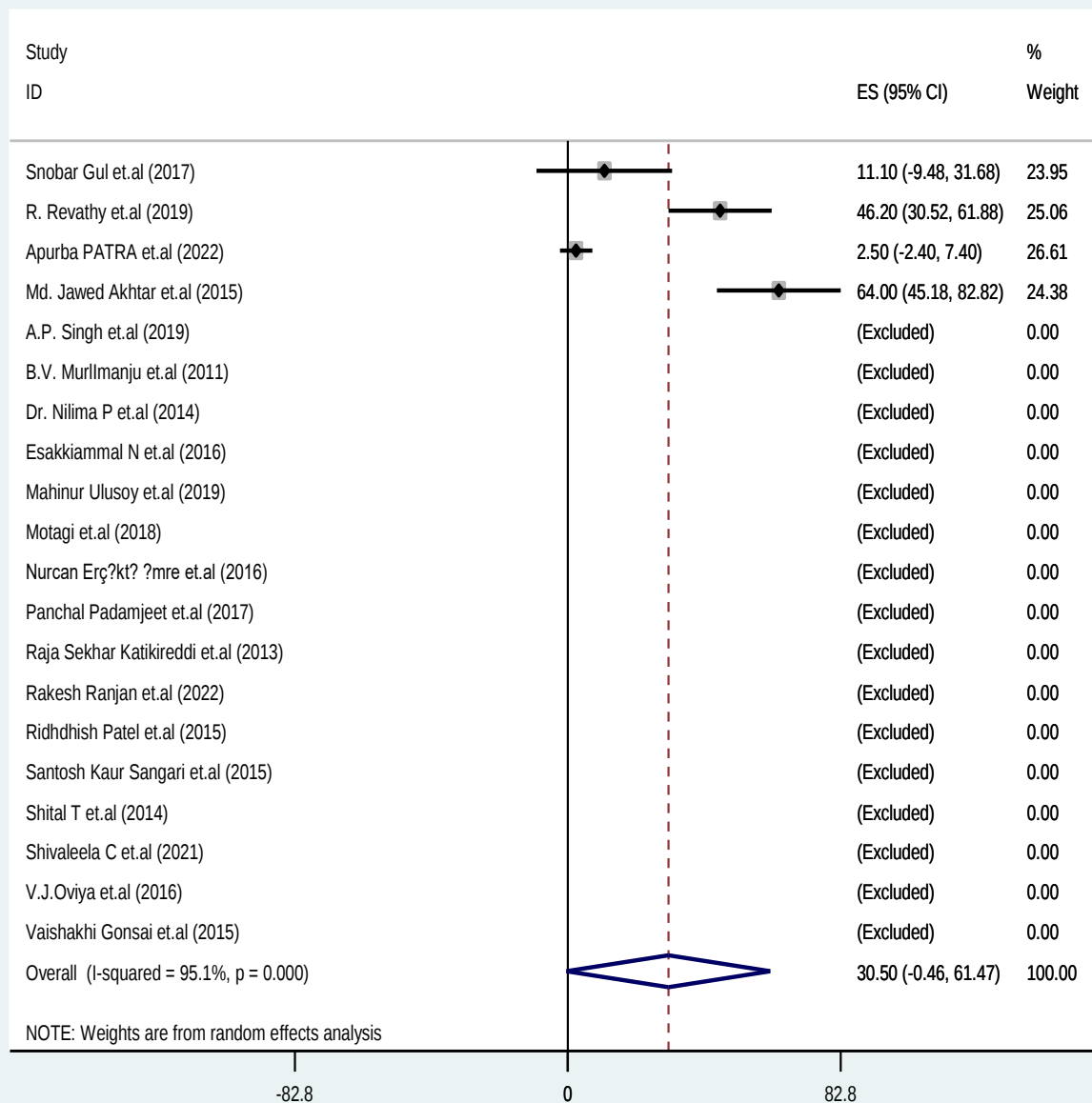


Fig. 5 Forest plot of the sub - group analysis of prevalence of anterior ATF among the dried cervical vertebrae of human population, 2023

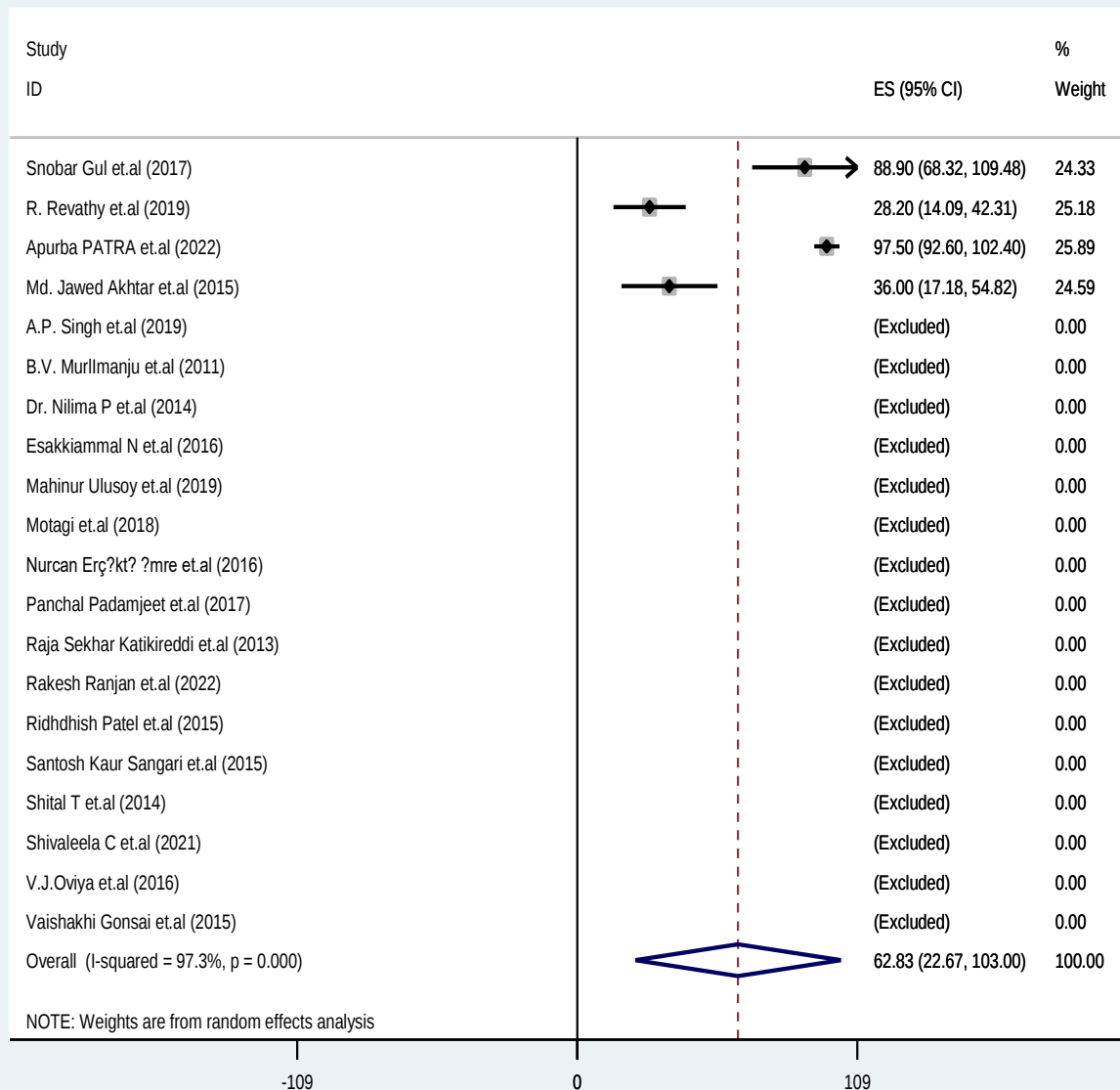


Fig. 6 Forest plot of the sub - group analysis of prevalence of posterior ATF among the dried cervical vertebrae of human population, 2023

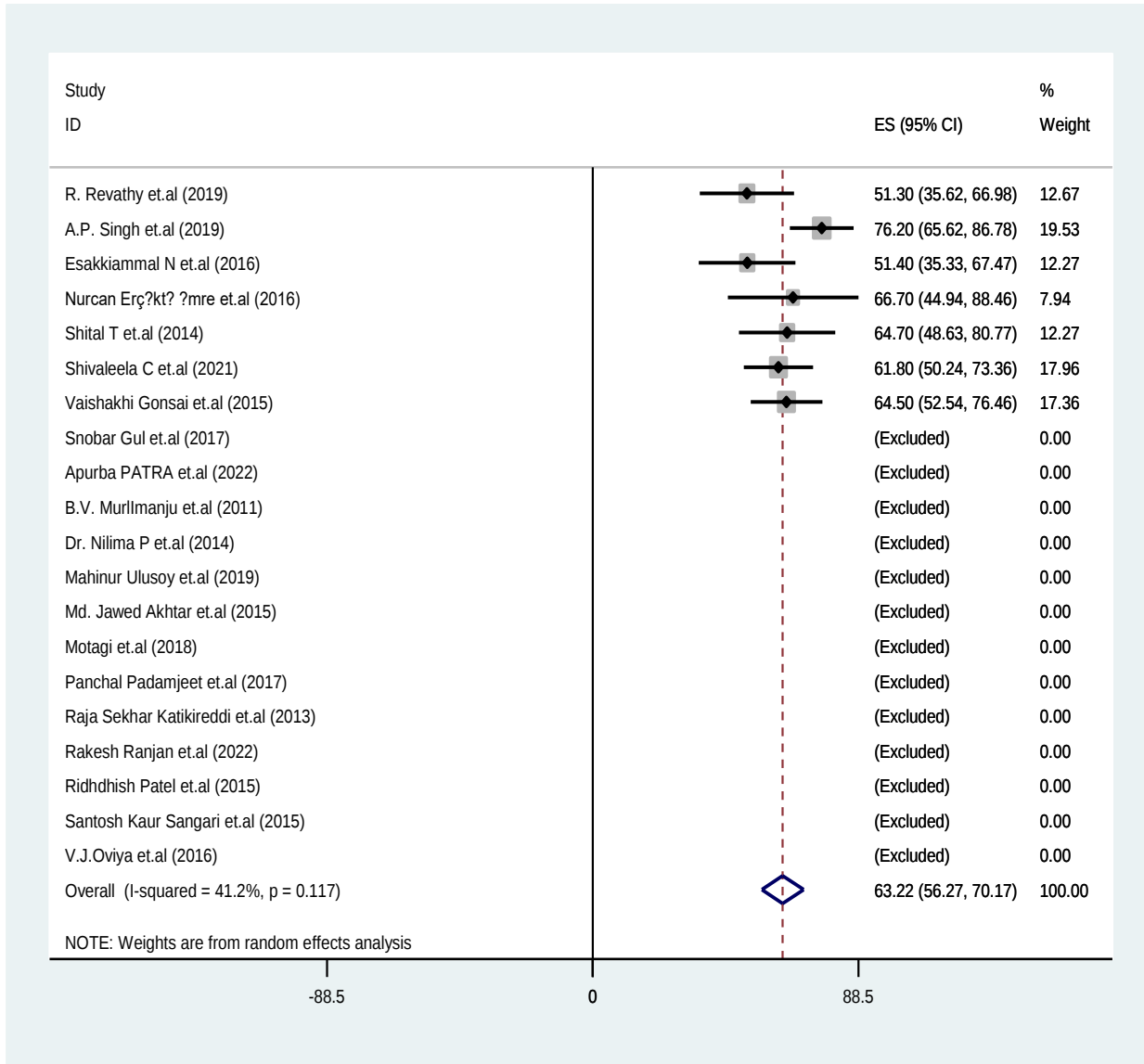


Fig. 7 Forest plot of the sub - group analysis of prevalence of complete ATF among the dried cervical vertebrae of human population, 2023

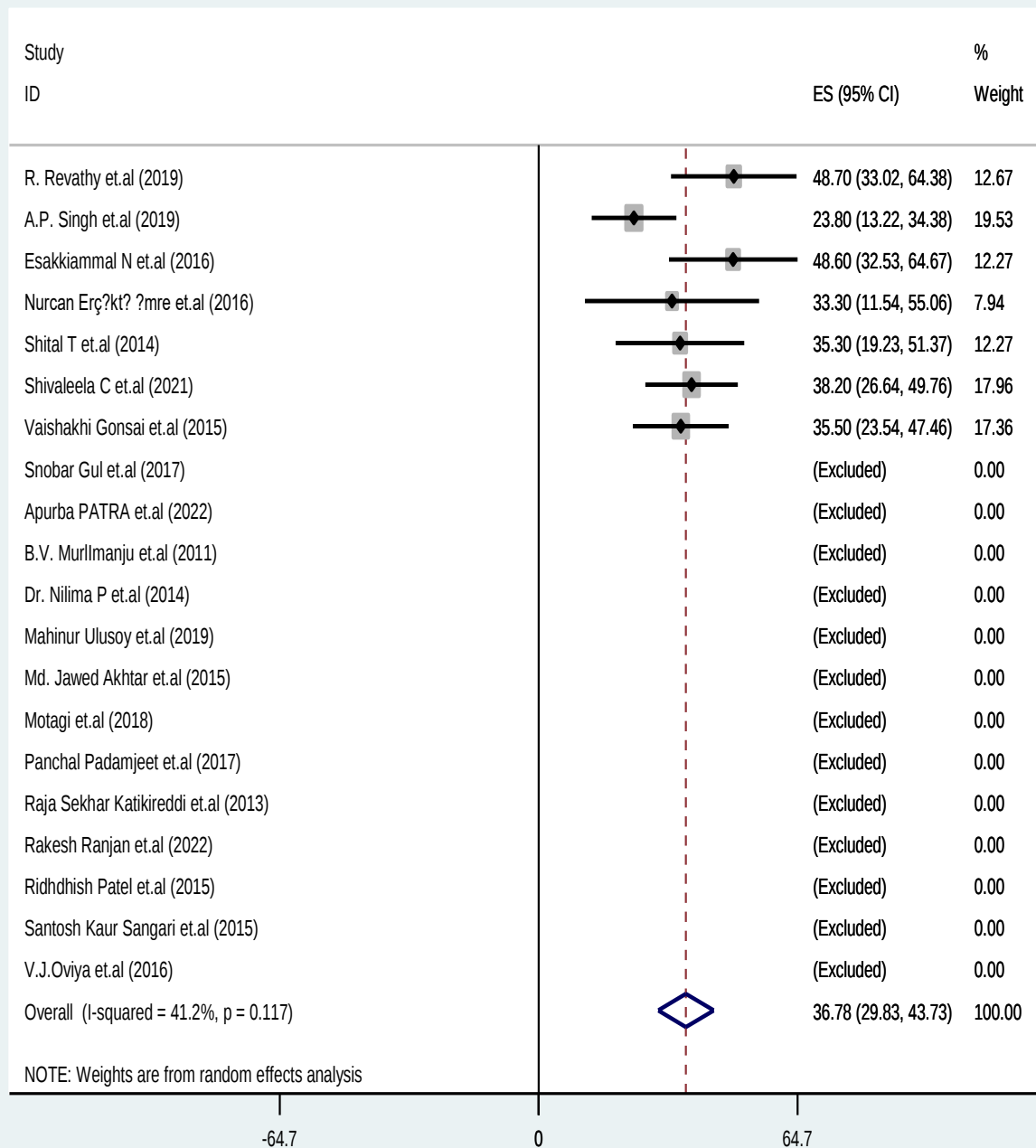


Fig. 8 Forest plot of the sub - group analysis of prevalence of incomplete ATF among the dried cervical vertebrae of human population, 2023

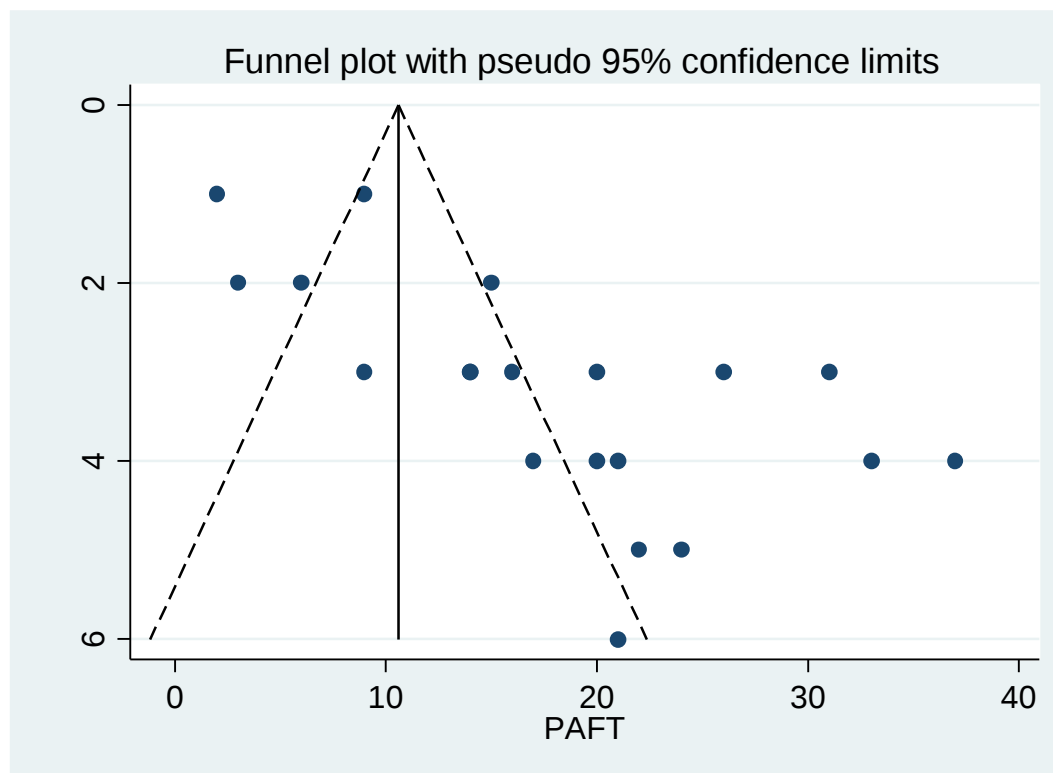


Fig. 9 Funnel plot showing the presence of publication bias among articles conducted on ATF among the dried cervical vertebrae of human population, 2023

Table 4.CoCoPo framework for the Prevalence of accessory transverse foramen among the dried cervical vertebrae of human population and its' clinical importance

Condition	Context	Population
Prevalence	transverse foramen	cervical vertebrae
Clinical importance		

Table 5. Logic grid for searching terms on the prevalence of accessory transverse foramen among the dried cervical vertebrae of human population and its' clinical importance

Condition	Context	Population
Prevalence clinical importance clinical significance clinical implications clinical relevance	accessory transverse foramen foramentransversarium accessory transverse foramina accessory foramen of transverse process accessory foramen processu transversi accessory foramen vertebra-arteriale accessory vertebra-arterial foramen accessory foramina transversaria	dried cervical vertebra preserved cervical vertebra

Table 6 Characteristics of Published studies on the prevalence of AFT in dried the cervical vertebrae, 2023

Author	Publication year	Origin of population	No. of cervical vertebrae	Prevalence of AFT	Bilateral AFT	Unilateral AFT	Anterior AFT	Posterior AFT	Complete AFT	Incomplete AFT
Snobar et.al	2017	India	100	9	4	5	1	8	0	0
R. Revathy et.al	2019	India	120	39	11	28	18	11	20	19
A.P. Singh et.al	2019	India	240	63	25	38	0	0	48	15
Apurba et.al	2022	India	200	40	22	18	1	39	0	0
B.V. Murlimanju et.al	2011	India	363	6	1	5	0	0	0	0
Dr.Nilima P et.al	2014	India	175	10	4	6	0	0	0	0
Esakki ammala N et.al	2016	India	241	37	10	27	0	0	19	18
Mahinur et.al	2019	Turkey	86	15	5	10	0	0	0	0
Md.	2015	India	174	25	5	20	16	9	0	0

Jawed et.al										
Motagi et.al	2018	Indian	100	20	8	12	0	0	0	0
Nurcan et.al	2016	Turkey	82	18	12	6	0	0	12	6
Pancha l et.al	2017	India	117	25	10	15	0	25	0	0
Raja et.al	2013	India	100	3	1	2	0	0	0	0
Rakesh et.al	2022	India	170	24	4	20	0	24	0	0
Ridhdh ish et.al	2015	India	865	75	40	35	0	0	0	0
Santos h et.al	2015	New York	71	17	1	16	0	0	0	0
Shital T et.al	2014	India	210	34	14	20	0	0	22	12
Shivale ela C et.al	2021	India	182	68	15	53	0	0	42	26
V.J.Ovi ya et.al	2016	India	52	11	5	6	0	0	0	0
Vaisha khiGon sai et.al	2015	India	200	62	15	47	0	0	40	22

Table 4: showing eggers test analysis of meta-analysis showing the presence of publication bias among articles conducted on ATF among the dried cervical vertebrae of human population, 2023

Egger's test						
std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
slope	-.5895432	2.574888	-0.23	0.821	-5.999183	4.820096
bias	5.777167	1.144024	5.05	0.000	3.373662	8.180671